(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
02 December 2021 (02.12.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/243301 A2

(51) International Patent Classification:
C12N 15/67 (2006.01) *C12N 15/11* (2006.01)

(21) International Application Number:
PCT/US2021/035015

(22) International Filing Date:
28 May 2021 (28.05.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/032,008 29 May 2020 (29.05.2020) US

(71) Applicant: **FLAGSHIP PIONEERING INNOVATIONS VI, LLC.** [US/US]; 55 Cambridge Parkway, 8th Floor, Suite 800E, Cambridge, MA 02142 (US).

(72) Inventors: **ANASTASSIADIS, Theonie**; 10 Emerson Place, Apt. 9B, Boston, MA 02114 (US). **BERRY, David, Arthur**; 55 Cambridge Parkway, 8th Floor, Suite 800E, Cambridge, MA 02142 (US). **HAJDIN, Christine, Elizabeth**; 55 Cambridge Parkway, 8th Floor, Suite 800E, Cambridge, MA 02142 (US). **AFEYAN, Noubar, Boghos**; 55 Cambridge Parkway, 8th Floor, Suite 800E, Cambridge, MA 02142 (US). **BUTLER, David, Charles, Donnell**; 55 Cambridge Parkway, 8th Floor, Suite 800E, Cambridge, MA 02142 (US). **LI, Qingyi**; 55 Cambridge Parkway, 8th Floor, Suite 800E, Cambridge, MA 02142 (US).

(74) Agent: **LARKIN, Angelyn**; Lando & Anastasi, LLP, 60 State Street, 23rd Floor, Boston, MA 02109 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

(54) Title: TREM COMPOSITIONS AND METHODS RELATING THERETO

(57) Abstract: The disclosure relates generally to uses of tRNA-based effector molecules having a non-naturally occurring modification.

WO 2021/243301 A2

TREM COMPOSITIONS AND METHODS RELATING THERETO

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 63/032,008, filed on May 29, 2020, the entire contents of which is hereby incorporated by reference.

BACKGROUND

Transfer RNAs (tRNAs) are complex, naturally occurring RNA molecules that possess a number of functions including initiation and elongation of proteins.

SUMMARY

The present disclosure features modified tRNA-based effector molecules (TREMs, e.g., a TREM, TREM core fragment, or TREM fragment), as well as related compositions and uses thereof. The inventors have discovered that a TREM composition can be used, *inter alia*, to: (1) modulate a production parameter of an RNA, or a protein encoded by an RNA, wherein the RNA has a contextually-rare codon ("con-rare codon"); and/or (2) to modulate tRNA pools in a cell or a subject. Accordingly, in an aspect, provided herein is a method of modulating a tRNA pool in a cell comprising an endogenous open reading frame (ORF), which ORF comprises a codon having a first sequence, comprising: optionally, acquiring knowledge of the abundance of one or both of (i) and (ii), e.g., acquiring knowledge of the relative amounts of: (i) and (ii) in the cell, wherein (i) is a tRNA moiety having an anticodon that pairs with the codon of the ORF having a first sequence (the first tRNA moiety) and (ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the codon having the first sequence (the second tRNA moiety) in the cell; contacting the cell with a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, wherein the TREM, TREM core fragment or TREM fragment has an anticodon that pairs with: (a) the codon having the first sequence; or (b) the codon other than the codon having the first sequence, in an amount and/or for a time sufficient to modulate the relative amounts of the first tRNA moiety and the second tRNA moiety in the cell, thereby modulating the tRNA pool in the cell.

In an embodiment, the TREM comprises an anticodon that pairs with (a). In an embodiment, the TREM comprises an anticodon that pairs with (b).

In another aspect, provided herein is a method of modulating a tRNA pool in a subject having an endogenous open reading frame (ORF), which ORF comprises a codon having a first sequence, comprising: optionally, acquiring knowledge of the abundance of one or both of (i) and (ii), e.g., acquiring knowledge of the relative amounts of: (i) and (ii) in the subject, wherein (i) is a tRNA moiety having an anticodon that pairs with the codon of the ORF having a first sequence (the first tRNA moiety) and (ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the codon having the first sequence (the second tRNA moiety) in the subject; contacting the subject with a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, wherein the TREM, TREM core fragment or TREM fragment has an anticodon that pairs with: (a) the codon having the first sequence; or (b) the codon other than the codon having the first sequence, in an amount and/or for a time sufficient to modulate the relative amounts of the first tRNA moiety and the second tRNA moiety in the subject, thereby modulating the tRNA pool in the subject.

In an embodiment, the TREM comprises an anticodon that pairs with (a). In an embodiment, the TREM comprises an anticodon that pairs with (b).

In an embodiment, the method comprises acquiring knowledge of (i). In an embodiment, the method comprises acquiring knowledge of (ii). In an embodiment, the method comprises acquiring knowledge of (i) and (ii).

In an embodiment, acquiring knowledge of (i) comprises acquiring a value for the abundance, e.g., relative amounts, of (i); and/or acquiring knowledge of (ii) comprises acquiring a value for the abundance, e.g., relative amounts, of (ii). In an embodiment, responsive to said value, the cell or subject is contacted with the TREM composition having an anticodon that pairs with (a) or (b).

In one aspect, the disclosure provides, a method of evaluating a tRNA pool in a cell or subject, comprising an endogenous open reading frame (ORF), which ORF comprises a codon having a first sequence, comprising acquiring, e.g., directly or indirectly acquiring, knowledge of the abundance of one or both of (i) and (ii), e.g., acquiring knowledge of the relative amounts of (i) and (ii) in the cell or subject wherein:

(i) is a tRNA moiety having an anticodon that pairs with the codon of the ORF having a first sequence (the first tRNA moiety); and

(ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the codon having the first sequence (the second tRNA moiety) in the cell or subject,

thereby evaluating the tRNA pool in the cell or subject.

In an embodiment, the method comprises acquiring knowledge of (i). In an embodiment, the method comprises acquiring knowledge of (ii). In an embodiment, the method comprises acquiring knowledge of (i) and (ii).

In an embodiment, acquiring knowledge of (i) comprises acquiring a value for the abundance, e.g., relative amount, of (i); and/or acquiring knowledge of (ii) comprises acquiring a value for the abundance, e.g., relative amount, of (ii). In an embodiment, responsive to said value, the method comprises administering a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, wherein the TREM, TREM core fragment or TREM fragment has an anticodon that pairs with: (a) the codon having the first sequence; or (b) the codon other than the codon having the first sequence, in an amount and for a time sufficient to modulate the relative amounts of the first tRNA moiety and the second tRNA moiety.

In yet another aspect, provided herein is a method of modulating a tRNA pool in a subject or cell having an endogenous open reading frame (ORF) comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

providing a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, wherein the TREM, TREM core fragment or TREM fragment comprises an isoacceptor tRNA moiety comprising an anticodon sequence that pairs with the SMC (the TREM);

contacting the subject or cell with the TREM composition in an amount and/or for a time sufficient to modulate the tRNA pool in the subject or cell,

thereby modulating the tRNA pool in the subject or cell.

In an embodiment, the method comprises acquiring knowledge of the abundance of one or both of (i) and (ii) e.g., acquiring knowledge of the relative amounts of (i) and (ii) wherein (i) is a tRNA moiety having an anticodon that pairs with the SMC (the first tRNA moiety) and (ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the SMC (the second tRNA moiety), in the subject or cell.

In one aspect, the disclosure provides a method of treating a subject having an endogenous open reading frame (ORF) comprising a codon having a first sequence, comprising:

(i) acquiring, e.g., directly or indirectly acquiring, a value for the status of the codon having the first sequence in the subject, wherein said value comprises a measure of the presence or absence of the codon having the first sequence in a sample from the subject; and identifying the subject as having the codon having the first sequence; and

(ii) responsive to said value, administering a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, wherein the TREM, TREM core fragment or TREM fragment comprises an isoacceptor tRNA moiety having an anticodon that pairs with the codon having the first sequence, to the subject,

thereby treating the subject.

In yet another aspect, provided herein is a method of treating a subject having an endogenous open reading frame (ORF) comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

(i) acquiring, e.g., directly or indirectly acquiring, a value for the SMC status of the subject, wherein said value comprises a measure of the presence or absence of SMC in a sample from the subject, and identifying the subject as having a SMC; and

(ii) responsive to said value, administering a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, wherein the TREM, TREM core fragment or TREM fragment comprises comprising an isoacceptor tRNA moiety having an anticodon that pairs with the SMC, to the subject,

thereby treating the subject.

In an aspect, the disclosure provides a method of evaluating a subject having an endogenous open reading frame (ORF) comprising a codon having a first sequence, comprising:

acquiring, e.g., directly or indirectly acquiring, a value for the status of the codon having the first sequence in the subject, wherein said value comprises a measure of the presence or absence of the codon having the first sequence in a sample from the subject; and

identifying the subject as having a codon having the first sequence,

thereby evaluating the subject.

In another aspect, provided herein is a method of evaluating a subject having an endogenous open reading frame (ORF) comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

acquiring, e.g., directly or indirectly acquiring, a value for the SMC status of the subject, wherein said value comprises a measure of the presence or absence of SMC in a sample from the subject; and

identifying the subject as having a SMC,

thereby evaluating the subject.

In an embodiment of any of the methods disclosed herein, the TREM, TREM core fragment or TREM fragment does not comprise an anticodon that pairs with a stop codon.

In an embodiment of any of the methods disclosed herein, (a) the ORF codon having the first sequence; or (b) the SMC; is other than a stop codon, e.g., TAA, TGA or TAG.

In an embodiment, (a) the ORF codon having the first sequence; or (b) the SMC; in the absence of contact with the composition comprising a TREM, is associated with a phenotype, e.g., an unwanted phenotype, e.g., a disorder or symptom, e.g., a disorder or symptom chosen from Table 1. In an embodiment, the disorder or symptom is chosen from a disease group provided in Table 1, e.g., cardiovascular, dermatology, endocrine, immunology, neurology, oncology, ophthalmology, or respiratory.

In one aspect, disclosed herein is a method of modulating a production parameter of an RNA, or a protein encoded by an RNA, in a target cell or tissue, comprising:

providing, *e.g.*, administering, to the target cell or tissue, or contacting the target cell or tissue with, an effective amount of a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, which TREM, TREM core fragment or TREM fragment corresponds to a contextually-rare codon ("con-rare codon") of the RNA,

thereby modulating the production parameter of the RNA, or protein encoded by the RNA in the target cell or tissue.

In an embodiment, the target cell or tissue is obtained from a subject.

In an embodiment, the method comprises administering the TREM composition to a subject.

In an embodiment, the method comprises contacting the TREM composition with the target tissue or cell ex vivo.

In an embodiment, the method comprises introducing the ex vivo-contacted target tissue or cell into a subject, *e.g.*, an allogeneic or autologous subject.

In an embodiment, the target cell or tissue is a specific or selected target cell or tissue, *e.g.*, a cell or tissue type in a particular developmental stage; a cell or tissue type in a particular disease state; or a cell present in a particular extracellular milieu.

In an embodiment of any of the methods disclosed herein, the production parameter comprises an expression parameter or a signaling parameter, *e.g.*, as described herein. In an embodiment, the production parameter of the RNA is modulated, *e.g.*, an RNA that can be translated into a polypeptide, *e.g.*, a messenger RNA. In an embodiment, the production parameter of the RNA is increased or decreased. In an embodiment, the production parameter of the protein encoded by the RNA is modulated. In an embodiment, the production parameter of the protein is increased. In an embodiment, the production parameter of the protein is decreased.

In another aspect, provided herein is a method of determining the presence of a nucleic acid sequence, *e.g.*, a DNA or RNA, having a contextually-rare codon ("con-rare codon nucleic acid sequence"), comprising:

acquiring knowledge of the presence of the con-rare codon nucleic acid sequence in a sample from a subject, *e.g.*, a target cell or tissue sample,

wherein responsive to the acquisition of knowledge of the presence of the con-rare codon nucleic acid sequence:

(1) the subject is classified as being a candidate to receive administration of an effective amount of a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, which TREM, TREM core fragment or TREM fragment corresponds to a contextually-rare codon ("con-rare codon") of the nucleic acid sequence; or

(2) the subject is identified as likely to respond to a treatment comprising the TREM composition.

In yet another aspect, the disclosure provides a method of treating a subject having a disease associated with a contextually-rare codon ("con-rare codon"), comprising:

acquiring knowledge of the presence of a nucleic acid sequence, *e.g.*, a DNA or RNA, having the con-rare codon ("con-rare codon nucleic acid sequence") in a target cell or tissue sample from the subject; and

administering to the subject an effective amount of a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, which TREM, TREM core fragment or TREM fragment corresponds to the con-rare codon of the nucleic acid sequence,

thereby treating the disease in the subject.

In an aspect, provided herein is a method of providing a tRNA effector molecule (TREM) to a subject, comprising:

providing, *e.g.*, administering, to the subject, an effective amount of a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, which TREM, TREM core fragment or TREM fragment corresponds to a contextually-rare codon ("con-rare codon") for a nucleic acid sequence in a target cell or tissue in the subject,

thereby providing a TREM composition to the subject.

In an embodiment of any of the methods disclosed herein, the method comprises acquiring a value for a con-rare codon in the nucleic acid sequence, *e.g.*, DNA or RNA, wherein the value is a function of one or more of the following factors, *e.g.*, by evaluating or determining one or more of the following factors:

(1) the sequence of the codon;

(2) the availability of a corresponding tRNA, *e.g.*, charged tRNA, for that con-rare codon in a target cell or tissue, *e.g.*, one or more iso-acceptor tRNA molecules;

(3) the expression profile (or proteomic properties) of the target cell or tissue (*e.g.*, the abundance of expression of other proteins which include the con-rare codon);

(4) the proportion of the tRNAs corresponding to the con-rare codon which are charged; and

(5) the iso-decoder isotype of the tRNA corresponding to the con-rare codon;

In an embodiment, (1) comprises determining the presence or absence of a con-rare codon.

In an embodiment, a determination of the availability of a tRNA comprises acquiring a measure of one, two, three or all of the following parameters:

(a) level of a tRNA corresponding to the con-rare codon ("con-rare codon tRNA") compared to a tRNA corresponding to a different codon;

(b) function, *e.g.*, polypeptide chain elongation function, of a con-rare codon tRNA compared to a tRNA corresponding to a different codon;

(c) modification, *e.g.*, aminoacylation or post-transcriptional modification, of a con-rare codon tRNA compared to a tRNA corresponding to a different codon; and/or

(d) sequence of a con-rare codon tRNA.

In an embodiment of any of the methods disclosed herein, the method comprises acquiring a value of the knowledge of the abundance of e.g., acquiring knowledge of the relative amounts of: (i) a tRNA moiety having an anticodon that pairs with the con-rare codon (the first tRNA moiety).

In an embodiment of any of the methods disclosed herein, the method comprises acquiring a value of the knowledge of the abundance of e.g., acquiring knowledge of the relative amounts of: (ii) an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the con-rare codon (the second tRNA moiety).

In an embodiment, the method comprises acquiring a value of the knowledge (i) and (ii).

In an embodiment of any of the methods disclosed herein, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the TREMs, TREM core fragments or TREM fragments in the TREM composition correspond to a con-rare codon.

In an embodiment of any of the methods disclosed herein, the TREM composition comprises TREMs, TREM core fragments or TREM fragments that correspond to a plurality of con-rare codons.

In an embodiment of any of the methods disclosed herein, the TREM composition comprises: a first TREM which corresponds to a first con-rare codon; and an additional TREM which corresponds to a different con-rare codon.

In an embodiment of any of the methods disclosed herein, the TREM composition comprises: a first TREM which corresponds to a first con-rare codon; and a second TREM which corresponds to a second con-rare codon.

In an embodiment of any of the methods disclosed herein, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the TREMs in the composition are charged.

In an embodiment of any of the methods disclosed herein, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the TREMs in the composition are of the same iso-decoder isotype.

In an embodiment of any of the methods disclosed herein, the cell is a host cell. In an embodiment, the cell is a host cell chosen from: a HeLa cell, a HEK293T cell (*e.g.*, a Freestyle 293-F cell), a HT-1080 cell, a PER.C6 cell, a HKB-11 cell, a CAP cell, a HuH-7 cell, a BHK 21 cell, an MRC-S cell, a MDCK cell, a VERO cell, a WI-38 cell, or a Chinese Hamster Ovary (CHO) cell.

In an embodiment of any of the methods disclosed herein, the cell comprises an exogenous nucleic acid sequence. In an embodiment, the cell is autologous to the exogenous nucleic acid sequence. In an embodiment, the cell is allogeneic to the exogenous nucleic acid sequence. In an embodiment, the exogenous nucleic acid sequence (*e.g.*, DNA or RNA) comprises a con-rare codon.

In an embodiment, administration of a TREM composition corresponding to the con-rare codon to the cell, modulates a production parameter, *e.g.*, expression parameter or signaling parameter, of a product, *e.g.*, RNA or polypeptide, of the exogenous nucleic sequence.

In an aspect, provided herein is a TREM comprising a sequence of Formula A:

[L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2],

wherein independently, [L1] and [VL Domain], are optional; and one of [L1], [ASt Domain1], [L2]-[DH Domain], [L3], [ACH Domain], [VL Domain], [TH Domain], [L4], and [ASt Domain2] comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, the TREM: (a) retains the ability to: support protein synthesis, be charged by a synthetase, be bound by an elongation factor, introduce an amino acid into a peptide chain, support elongation, or support initiation; (b) comprises at least X contiguous nucleotides without a non-naturally occurring modification, wherein X is greater than 10;(c) comprises at least 3, but less than all of the nucleotides of a type (e.g., A, T, C, G or U) comprise the same non-naturally occurring modification;(d) comprises at least X nucleotides of a type (e.g., A, T, C, G or U) that do not comprise a non-naturally occurring modification, wherein X=1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50; (e)

comprises no more than 5, 10, or 15 nucleotides of a type (e.g., A, T, C, G or U) that comprise a non-naturally occurring modification; and/or (f) comprises no more than 5, 10, or 15 nucleotides of a type (e.g., A, T, C, G or U) that do not comprise a non-naturally occurring modification.

In an embodiment, the TREM comprises feature (a). In an embodiment, the TREM comprises feature (b). In an embodiment, the TREM comprises feature (c). In an embodiment, the TREM comprises feature (d). In an embodiment, the TREM comprises feature (e). In an embodiment, the TREM comprises feature (f). In an embodiment, the TREM comprises all of features (a)-(f) or a combination thereof.

In an embodiment, the TREM Domain comprising the non-naturally occurring modification retains a function, e.g., a domain function described herein.

In an aspect, provided herein is a TREM core fragment comprising a sequence of Formula B:

$[L1]_y$-[ASt Domain1]$_x$-$[L2]_y$-[DH Domain]$_y$-$[L3]_y$-[ACH Domain]$_x$-[VL Domain]$_y$-[TH Domain]$_y$-$[L4]_y$-[ASt Domain2]$_x$,

wherein x=1 and y=0 or 1; and one of [ASt Domain1], [ACH Domain], and [ASt Domain2] comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, the TREM retains the ability to support protein synthesis. In an embodiment, the TREM retains the ability to be able to be charged by a synthetase. In an embodiment, the TREM retains the ability to be bound by an elongation factor. In an embodiment, the TREM retains the ability to introduce an amino acid into a peptide chain. In an embodiment, the TREM retains the ability to support elongation. In an embodiment, the TREM retains the ability to support initiation.

In an embodiment, the [ASt Domain 1] and/or [ASt Domain 2] comprising the non-naturally occurring modification retains the ability to initiate or elongate a polypeptide chain.

In an embodiment, the [ACH Domain] comprising the non-naturally occurring modification retains the ability to mediate pairing with a codon.

In an embodiment, y=1 for any one, two, three, four, five, six, all or a combination of [L1], [L2], [DH Domain], [L3], [VL Domain], [TH Domain], [L4].

In an embodiment, y=0 for any one, two, three, four, five, six, all or a combination of [L1], [L2], [DH Domain], [L3], [VL Domain], [TH Domain], [L4].

In an embodiment, y=1 for linker [L1], and L1 comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, y=1 for linker [L2], and L2 comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, y=1 for [DH Domain (DHD)], and DHD comprises a nucleotide having a non-naturally occurring modification. In an embodiment, the DHD comprising the non-naturally occurring modification retains the ability to mediate recognition of aminoacyl-tRNA synthetase.

In an embodiment, y=1 for linker [L3], and L3 comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, y=1 for [VL Domain (VLD)], and VLD comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, y=1 for [TH Domain (THD)], and THD comprises a nucleotide having a non-naturally occurring modification. In an embodiment, the THD comprising the non-naturally occurring modification retains the ability to mediate recognition of the ribosome.

In an embodiment, y=1 for linker [L4], and L4 comprises a nucleotide having a non-naturally occurring modification.

In another aspect, the disclosure provides a TREM fragment comprising a portion of a TREM, wherein the TREM comprises a sequence of Formula A:

[L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2], and wherein the TREM fragment comprises a non-naturally occurring modification.

In an embodiment, the TREM fragment comprises one, two, three or all or any combination of the following: (a) a TREM half (*e.g.*, from a cleavage in the ACH Domain, *e.g.*, in the anticodon sequence, *e.g.*, a 5'half or a 3' half); (b) a 5' fragment (*e.g.*, a fragment comprising the 5' end, *e.g.*, from a cleavage in a DH Domain or the ACH Domain); (c) a 3' fragment (*e.g.*, a fragment comprising the 3' end, *e.g.*, from a cleavage in the TH Domain); or (d) an internal fragment (*e.g.*, from a cleavage in any one of the ACH Domain, DH Domain or TH Domain).

In an embodiment, the TREM fragment comprise (a) a TREM half which comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, the TREM fragment comprise (b) a 5' fragment which comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, the TREM fragment comprise (c) a 3' fragment which comprises a nucleotide having a non-naturally occurring modification.

In an embodiment, the TREM fragment comprise (d) an internal fragment which comprises a nucleotide having a non-naturally occurring modification.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the TREM Domain comprises a plurality of nucleotides each having a non-naturally occurring modification.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the non-naturally occurring modification is a modification in a base or a backbone of a nucleotide, e.g., a modification chosen from any one of Tables 5, 6, 7, 8 or or 9.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the non-naturally occurring modification is a base modification chosen from a modification listed in Table 5.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the non-naturally occurring modification is a base modification chosen from a modification listed in Table 6.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the non-naturally occurring modification is a base modification chosen from a modification listed in Table 7.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the non-naturally occurring modification is a backbone modification chosen from a modification listed in Table 8.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the non-naturally occurring modification is a backbone modification chosen from a modification listed in Table 9.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the TREM, TREM core fragment, or TREM fragment is encoded by a sequence provided in Table 4, e.g., any one of SEQ ID NOs 1-451.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the TREM, TREM core fragment, or TREM fragment is encoded by a consensus sequence chosen from any one of SEQ ID NOs: 562-621.

In another aspect, the disclosure provides a pharmaceutical composition comprising a TREM, a TREM core fragment, or a TREM fragment disclosed herein.

In another aspect, the disclosure provides a method of making a TREM, a TREM core fragment, or a TREM fragment disclosed herein, comprising linking a first nucleotide to a second nucleotide to form the TREM.

In an embodiment, the TREM, TREM core fragment or TREM fragment is synthetic.

In an embodiment, the TREM, TREM core fragment or TREM fragment is made by cell-free solid phase synthesis.

In an embodiment of any of the TREMs, TREM core fragments, or TREM fragments disclosed herein, the TREM Domain comprises a plurality of nucleotides each having a non-naturally occurring modification. In an embodiment, the non-naturally occurring modification comprises a nucleobase modification, a sugar (e.g., ribose) modification, or a backbone modification. In an embodiment, tbe non-naturally occurring modification is a sugar (e.g., ribose) modification. In an embodiment, tbe non-naturally occurring modification is 2'-ribose modification, e.g., a 2'-OMe, 2'-halo (e.g., 2'-F), 2'-MOE, or 2'-deoxy modification. In an embodiment, tbe non-naturally occurring modification is a backbone modification, e.g., a phosphorothioate modification.

Additional features of any of the aforesaid TREMs, TREM core fragments, TREM fragments, TREM compositions, preparations, methods of making TREM compositions and preparations, and methods of using TREM compositions and preparations include one or more of the following enumerated embodiments.

Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following enumerated embodiments.

Other features, objects, and advantages of the invention will be apparent from the Examples, Description, Figures, and Claims.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

BRIEF DESCRIPTIONS OF THE DRAWINGS

Fig. 1A depicts the mRNA and protein sequence, and the endogenous tRNA pool for a non-SNP subject. The sequence of the second codon is GTG (depicted by the open triangle) encoding for the amino acid valine. Two Valine isoacceptor tRNA species are shown. Each of the two tRNA species recognize different Valine codons. The two species have different abundances. The species that recognize the wildtype codon, GTG, are not shaded and are in higher abundance. The shaded species, which has a lower abundance, does not pair with the wildtype codon. Thus, the Valine isoacceptor tRNA species that corresponds to the codon used (GTG) is abundant.

Fig. 1B depicts the mRNA and protein sequence, and the endogenous tRNA pool for a subject having a single nucleotide polymorphism (SNP) at the third position of the second codon (shown with a closed triangle) in the depicted mRNA sequence. The composition of the endogenous tRNA pool is the same as described for **Fig. 1A**. However, incorporation of Valine at the second codon now depends on the use of a less abundant tRNA species (the shaded species). As a consequence, as shown in **Fig. 1B**, translation is compromised. Other consequences of using a less abundant tRNA species may also be, e.g., interruption of the elongation of the peptide chain, lower protein production, protein misfolding, protein mislocalization, altered protein function, or altered mRNA transcript stability.

Fig. 1C depicts the same mRNA sequence as in **Fig. 1B**, which includes a SNP at the third position of the second codon. The endogenous tRNAs of the pool are the same as in **Figs. 1A** and **1B**, but the pool is supplemented with exogenous TREMs which increase the abundance of species that will pair with the SNP codon. This can result in an improvement in the translation of the mRNA.

Fig. 2A depicts the mRNA and protein sequence, and the endogenous tRNA pool for a non-SNP subject. The sequence of the second codon is GTG (depicted by the open triangle)

encoding for the amino acid Valine. Two Valine isoacceptor tRNA species are shown. Each of the two tRNA species recognize different Valine codons. The two species have different abundances. The species that recognize the wildtype codon, GTG, are not shaded and are in higher abundance. The shaded species, which has a lower abundance, does not pair with the wildtype codon. Thus, the Valine isoacceptor tRNA species that corresponds to the codon used (GTG) is abundant. This results in translation of the mRNA sequence into the corresponding protein as depicted.

Fig. 2B depicts the mRNA and protein sequence, and the endogenous tRNA pool for a subject having a single nucleotide polymorphism (SNP) at the third position of the second codon (shown with a closed triangle) in the depicted mRNA sequence. The composition of the endogenous tRNA pool is the same as described for **Fig. 2A**. However, incorporation of Valine at the second codon now depends on the use of a less abundant tRNA species (the shaded species). As a consequence, as shown in **Fig. 2B**, translation of the mRNA sequence into the corresponding protein is compromised.

Fig. 2C depicts the same mRNA sequence as in **Fig. 2B**, which includes a SNP at the third position of the second codon (shown with a closed triangle). The endogenous tRNAs of the pool are the same as in **Figs. 2A** and **2B**, but the pool is supplemented with exogenous TREMs which increase the abundance of species that will pair with the SNP codon. As a consequence, translation of the mRNA sequence into the corresponding protein is not compromised and is similar to that of a non-SNP subject.

Fig. 3 The top row depicts the endogenous tRNA pool and, movingto the right, the mRNA and protein sequence, for a non-SNP subject. The sequence of the second codon is GTG (depicted by the open triangle) encoding for the amino acid Valine. Two Valine isoacceptor tRNA species are shown. Each of the two tRNA species recognize different Valine codons. The two species have different abundances. The species that recognize the wildtype codon, GTG, are not shaded and are in higher abundance. The shaded species, which has a lower abundance, does not pair with the wildtype codon. Thus, the Valine isoacceptor tRNA species that corresponds to the codon used (GTG) is abundant. This results in translation of the mRNA sequence into the corresponding protein as depicted. Using a more abundant tRNA species may also have an impact on transcript stability, protein expression, protein function, protein folding, or protein localization.

Fig. 3 The middle row depicts the endogenous tRNA pool and the mRNA and protein sequence for a subject having a single nucleotide polymorphism (SNP) at the third position of the second codon (shown with a closed triangle) in the depicted mRNA sequence. The composition of the endogenous tRNA pool is the same as described for **Fig. 3 top row.** However, incorporation of Valine at the second codon now depends on the use of a less abundant tRNA species (the shaded species). As a consequence, as shown in **Fig. 3 middle row**, translation of the mRNA sequence into the corresponding protein is compromised. Using a less abundant tRNA species may also reduce transcript stability, reduce protein expression, change protein function, change protein folding, or change protein localization.

Fig. 3 bottom row depicts the same mRNA sequence as in **Fig. 3 middle row**, which includes a SNP at the third position of the second codon (shown with a closed triangle). The endogenous tRNAs of the pool are the same as in the **top row** and the **middle row**, but the pool is supplemented with exogenous TREMs which increase the abundance of species that can pair with the SNP codon. As a consequence, translation of the mRNA sequence into the corresponding protein is not compromised.

Fig. 4 is a table provided a list of exemplary synonymous SNPs and related genes and diseases. The column titled "New codon" refers to the new codon created by the SNP. The columns titled "Fold change" and "Log2 fold change" refer to the fold change/Log2 fold change in codon usage based on genome codon usage, respectively.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

The present disclosure features uses of tRNA-based effector molecules (TREMs) comprising a non-naturally occurring modification to modulate tRNA pools in a cell or a subject. Also disclosed herein are methods of treating a disorder or ameliorating a symptom of a disorder by administering a composition comprising a TREM or a pharmaceutical composition comprising a TREM. Further disclosed herein are uses of TREMs comprising a non-naturally occurring modification to modulate a production parameter of an RNA, or a protein encoded by an RNA, wherein the RNA has a contextually-rare codon ("con-rare codon").

As disclosed herein, TREMs are complex molecules which can mediate a variety of cellular processes. TREMs of the disclosure include TREMs, TREM core fragments and TREM fragments. TREMs, TREM core fragments or TREM fragments can be modified with non-

naturally occurring modifications to, e.g., increase the level and/or activity (e.g., stability) of the TREM. Pharmaceutical TREM compositions, e.g., TREMs comprising a non-naturally occurring modification, can be administered to a cell, a tissue, or to a subject to modulate these functions, *e.g.*, *in vitro* or *in vivo*. Disclosed herein are TREMs, TREM core fragments or TREM fragments comprising non-naturally occurring modifications, TREM compositions, preparations, methods of making TREM compositions and preparations, and methods of using the same.

Definitions

A "contextually rare codon" or "con-rare codon", as those terms are used herein, refer to a codon which, in a target cell or tissue, is limiting for a production parameter, *e.g.*, an expression parameter, for a nucleic acid sequence having a con-rare codon ("con-rare codon nucleic acid sequence"), *e.g.*, because the availability of a tRNA corresponding to the con-rare codon is limiting for a production parameter. Contextual rareness or con-rarity can be identified or evaluated by determining if the addition of a tRNA corresponding to a con-rare codon modulates, typically increases, a production parameter for a nucleic acid sequence, *e.g.*, gene. By way of example, the method of Example 3, can be used, or adapted to be used, to evaluate con-rarity. Con-rarity as a property of a codon, is a function of, and can be identified or evaluated on the basis of, one, two, three, four, five, six, or all of the following factors:

(1) the sequence of the con-rare codon, or candidate con-rare codon;

(2) the availability of a corresponding tRNA for the con-rare, or candidate con-rare, -codon in a target cell or tissue Availability as a parameter can comprise or be a function of, one or both of the observed or predicted abundance or availability of a tRNA that corresponds to the con-rare codon. In an embodiment, abundance can be evaluated by quantifying tRNAs present in a target cell or tissue. See, *e.g.*, Example 12;

(3) the contextual demand (the demand in a target cell or tissue) for a tRNA, *e.g.*, a con-rare tRNA, or a candidate con-rare tRNA. This can be identified or evaluated by use of a parameter, a contextual demand-parameter, which comprises or is a function of, the demand or usage of a con-rare tRNA by one, some, or all of the nucleic acid sequences having con-rare codons in a target tissue or cell, *e.g.*, the other nucleic acid sequences in a target cell or tissue which have a con-rare codon. A demand parameter can comprise of, or be a function of one or more, or all of:

(a) the expression profile (or proteomic properties) in the target cell or tissue (*e.g.*, the abundance of expression) of one, some, or all of the nucleic acid sequences in the target cell or tissue which have a con-rare codon (*e.g.*, for one or more, a subset of, or all of the expressed con-rare codon nucleic acid sequences in the target cell or tissue). In an embodiment, the expression profile (or proteomic properties) can be evaluated by evaluating proteins expressed in a target cell or tissue. See, *e.g.*, Example 13;

(b) a measure which comprises or is a function of the frequency or proportion of appearance of the con-rare codon in an expressed nucleic acid sequence (*e.g.*, for one or more, a subset of, or all of the expressed con-rare codon nucleic acid sequences in the target cell or tissue); or

(c) a parameter that is a function of (3)(a) and (3)(b);

(4) a parameter (or use-parameter) related to the con-rare codon usage in a con-rare codon nucleic acid sequence, and can include one or more of:

(a) the expression profile (or proteomic properties) in the target cell or tissue (*e.g.*, the abundance of expression) of one, some, or all of the nucleic acid sequences in the target cell or tissue which have a con-rare codon, or a candidate nucleic acid sequence having a con-rare codon, (*e.g.*, for one or more, a subset of, or all of the expressed con-rare codon nucleic acid sequences(s) in the target cell or tissue). In an embodiment, the expression profile (or proteomic properties) can be evaluated by evaluating proteins expressed in a target cell or tissue. See, *e.g.*, Example 2;

(b) a measure which comprises or is a function of the frequency or proportion of appearance of the con-rare codon in a nucleic acid sequence having a con-rare codon (*e.g.*, for one or more, a subset of, or all of the expressed con-rare codon nucleic acid sequence(s) in the target cell or tissue); or

(c) a parameter that is a function of (4)(a) and (4)(b);

(5) the proportion of the tRNAs corresponding to the con-rare codon which are charged;

(6) the iso-decoder isotype of the tRNA corresponding to the con-rare codon; and

(7) one or more post-transcriptional modifications of the con-rare tRNA, or candidate con-rare tRNA; and

In an embodiment, a con-optimized nucleic acid sequence has one less or one more con-rare codon than a reference sequence, *e.g.*, a parental sequence, a naturally occurring sequence, a wildtype sequence, or a conventionally optimized sequence.

In an embodiment, con-rarity can be identified or evaluated by: (i) direct determination of whether a con-rare codon or candidate con-rare codon is limiting for a production parameter, *e.g.*, in an assay analogous to that of Example 3; (ii) whether a con-rare or candidate con-rare codon meets a predetermined value, *e.g.*, a standard or reference value (*e.g.*, as described herein), of one or more, or all of factors (1)-(7); or (i) and (ii).

In an embodiment, con-rarity can be identified or evaluated by a production parameter, *e.g.*, an expression parameter or a signaling parameter, *e.g.*, as described herein.

In an embodiment, con-rarity is a function of normalized proteome codon count and tRNA abundance in a target tissue or cell. In an embodiment, con-rarity is a measure of codon frequency that is contextually dependent on tRNA abundance levels in a target tissue or cell.

Thus, the identification of a codon as a con-rare codon can involve a multi-parameter function of (1)-(7). In an embodiment, the con-rare codon meets a reference value for at least one of (1)-(7). In an embodiment, the con-rare codon meets a reference value for at least one of (1)-(7). In an embodiment, the con-rare codon meets a reference value for at least two of (1)-(7). In an embodiment, the con-rare codon meets a reference value for at least three of (1)-(7). In an embodiment, the con-rare codon meets a reference value for at least four of (1)-(7). In an embodiment, the con-rare codon meets a reference value for at least five of (1)-(7). In an embodiment, the con-rare codon meets a reference value for at least six of (1)-(7). In an embodiment, the con-rare codon meets a reference value for at all of (1)-(7). In an embodiment the reference value is a pre-determined or pre-selected value, *e.g.*, as described herein.

In an embodiment, the identity of a con-rare codon is the DNA sequence which encodes for the codon in the nucleic acid sequence, *e.g.*, gene.

In an embodiment, a con-rare codon is a function of the prevalence of the codon in the open reading frame (ORF) of protein coding genes in an organism, *e.g.*, the proteome.

The availability, *e.g.*, abundance, of tRNAs that correspond to a con-rare codon can be measured using an assay known in the art or as described herein, *e.g.*, Nanopore sequencing, *e.g.*, as described in Example 1. In an embodiment, a con-rare codon nucleic acid sequence has a low

abundance of a tRNA corresponding to the con-rare codon, *e.g.*, as compared to the abundance of a tRNA corresponding to a different/second codon.

The expression profile or proteomic property of a target cell or tissue refers to the protein expression, *e.g.*, level of protein expression, from all of the protein coding genes in a target cell or tissue. The expression profile or proteomic property of a target cell or tissue can be measured using an assay known in the art or as described herein, *e.g.*, a mass spectrometry based method, *e.g.*, a SILAC based method as described in Example 13. In an embodiment, a protein coding gene in a target cell or tissue is a function of tissue or cell type specific regulation, *e.g.*, a promoter element, an enhancer element, epigenetic regulation, and/or transcription factor control.

A "contextually-modified nucleic acid sequence" (sometimes referred to herein as a "con-modified nucleic acid sequence") refers to a nucleic acid sequence in which the con-rarity of a codon of the con-modified nucleic acid sequence has been altered. *E.g.*, a con-rare codon is replaced with a con-abundant codon and/or a con-abundant codon is replaced with a con-rare codon. In an embodiment, the con-modified nucleic acid sequence has one more or one less, *e.g.*, two more or two lesser, con-rare codons, than a reference nucleic acid sequence. In an embodiment, the con-modified nucleic acid sequence has a codon with con-rarity that differs from the con-rarity of the corresponding codon in a reference nucleic acid sequence.

The reference nucleic acid sequence can be, *e.g.*, any selected sequence, a parental sequence, a starting sequence, a wildtype or naturally occurring sequence that encodes the same amino acid at the corresponding codon, a wildtype or naturally occurring sequence that encodes the same polypeptide, or a conventionally codon-optimized sequence. In an embodiment, the reference nucleic acid sequence encodes the same polypeptide sequence as the con-modified nucleic acid sequence. In an embodiment, the reference nucleic acid sequence encodes a polypeptide sequence that differs from the con-modified nucleic acid sequence at a position other than the con-rare modified sequence. In an embodiment, a con-modified nucleic acid sequence results in a different production parameter, *e.g.*, an expression parameter or signaling parameter, compared to that seen with expression of a reference nucleic acid sequence.

In an embodiment, a con-modified nucleic acid sequence refers to a nucleic acid sequence which has one more or one less, *e.g.*, two more or two lesser, con-rare codons, than a reference sequence, wherein the con-modified nucleic acid sequence encodes a polypeptide that comprises the reference sequence.

A "contextually-rare tRNA" or "con-rare tRNA," is a tRNA that corresponds to a con-rare codon.

A "contextually-abundant codon" or "con-abundant codon" as those terms are used herein, refer to a codon other than a con-rare codon.

A "con-rare codon nucleic acid sequence," or a "nucleic acid sequence having a con-rare codon" as those terms are used herein, refer to a nucleic acid sequence, *e.g.*, DNA, or RNA, or gene, comprising a con-rare codon. In an embodiment, in such con-rare codon nucleic acid sequences, modulation of a production parameter, *e.g.*, an expression parameter or signaling parameter, can be mediated by altering the availability, *e.g.*, abundance of a con-rare tRNA. In an embodiment, the con-rare codon is in a translated region of the con-rare codon nucleic acid sequence, *e.g.*, in an open reading frame (ORF) or coding sequence (CDS).

A "con-rare codon RNA," as that term is used herein, refers to an RNA sequence comprising a con-rare codon. In an embodiment, a con-rare codon RNA comprises a messenger RNA or an RNA that can be translated into a polypeptide or protein. In an embodiment, a con-rare codon RNA is transcribed from a complementary DNA sequence which comprises said con-rare codon. In an embodiment, the con-rare codon RNA is transcribed in vivo. In an embodiment, the con-rare codon RNA is transcribed in vitro.

A "codon-value" as that term is used herein, is a function of the con-rarity of a sequence-codon in a sequence. Con-rarity of a codon is a function of one or more factors as described in the definition of "con-rare codon" above. In an embodiment, a codon-value is the identity of a codon, *e.g.*, a replacement codon selected to replace the sequence-codon. In an embodiment, when the replacement codon is a con-abundant codon, the sequence codon is a con-rare codon. In an embodiment, when the replacement codon is a con-rare codon, the sequence-codon is a con-abundant codon.

A "sequence-codon" as that term is used herein, refers to a codon in a nucleic acid sequence for which a codon-value is acquired.

A "production parameter," refers to an expression parameter and/or a signaling parameter. In an embodiment a production parameter is an expression parameter. An expression parameter includes an expression parameter of a polypeptide or protein encoded by the con-rare codon nucleic acid sequence; or an expression parameter of an RNA, *e.g.*, messenger RNA,

encoded by the con-rare codon nucleic acid sequence. In an embodiment, an expression parameter can include:

(a) protein translation;

(b) expression level (*e.g.*, of polypeptide or protein, or mRNA);

(c) post-translational modification of polypeptide or protein;

(d) folding (*e.g.*, of polypeptide or protein, or mRNA),

(e) structure (*e.g.*, of polypeptide or protein, or mRNA),

(f) transduction (*e.g.*, of polypeptide or protein),

(g) compartmentalization (*e.g.*, of polypeptide or protein, or mRNA),

(h) incorporation (*e.g.*, of polypeptide or protein, or mRNA) into a supermolecular structure, *e.g.*, incorporation into a membrane, proteasome, or ribosome,

(i) incorporation into a multimeric polypeptide, *e.g.*, a homo or heterodimer, and/or

(j) stability.

In an embodiment, a production parameter is a signaling parameter. A signaling parameter can include:

(1) modulation of a signaling pathway, *e.g.*, a cellular signaling pathway which is downstream or upstream of the protein encoded by the con-rare codon nucleic acid sequence;

(2) cell fate modulation;

(3) ribosome occupancy modulation;

(4) protein translation modulation;

(5) mRNA stability modulation;

(6) protein folding and structure modulation;

(7) protein transduction or compartmentalization modulation; and/or

(8) protein stability modulation.

An "isoacceptor," as that term is used herein, refers to a plurality of tRNA molecule or TREMs wherein each molecule of the plurality comprises a different naturally occurring anticodon sequence and each molecule of the plurality mediates the incorporation of the same amino acid and that amino acid is the amino acid that naturally corresponds to the anticodons of the plurality.

A "tRNA pool," as that term is used herein, refers to the pool of all species, e.g., endogenous tRNAs and TREMS, which can function as tRNAs. The endogenous tRNA pool for

a cell or subject that has not been administered a TREM includes only endogenous tRNAs. A TREM can be added to modulate a tRNA pool comprising only endogenous tRNAs, but can also be administered to a cell or subject that has a tRNA pool that includes TREMs that have been administered previously. In an embodiment, the TREM which is administered to a cell or a subject, mediates initiation or elongation by incorporating the amino acid (the cognate amino acid) associated in nature with a particular anticodon. In an embodiment, the TREM which is administered has an anticodon other than a stop codon.

A "nucleotide," as that term is used herein, refers to an entity comprising a sugar, typically a pentameric sugar; a nucleobase; and a phosphate linking group. In an embodiment, a nucleotide comprises a naturally occurring, e.g., naturally occurring in a human cell, nucleotide, e.g., an adenine, thymine, guanine, cytosine, or uracil nucleotide.

A "modification," as that term is used herein with reference to a nucleotide, refers to a modification of the chemical structure, e.g., a covalent modification, of the subject nucleotide. The modification can be naturally occurring or non-naturally occurring. In an embodiment, the modification is non-naturally occurring. In an embodiment, the modification is naturally occurring. In an embodiment, the modification is a synthetic modification. In an embodiment, the modification is a modification provided in Tables 5, 6, 7 , 8 or 9.

A "non-naturally occurring modification," as that term is used herein with reference to a nucleotide, refers to a modification that: (a) a cell, e.g., a human cell, does not make on an endogenous tRNA; or (b) a cell, e.g., a human cell, can make on an endogenous tRNA but wherein such modification is in a location in which it does not occur on a native tRNA, e.g., the modification is in a domain, linker or arm, or on a nucleotide and/or at a position within a domain, linker or arm, which does not have such modification in nature. In either case, the modification is added synthetically, e.g., in a cell free reaction, e.g., in a solid state or liquid phase synthetic reaction. In an embodiment, the non-naturally occurring modification is a modification that is not present (in identity, location or position) if a sequence of the TREM is expressed in a mammalian cell, e.g., a HEK293 cell line. Exemplary non-naturally occurring modifications are found in Tables 5, 6, 7, 8 or 9.

A "non-naturally modified nucleotide," as that term is used herein, refers a nucleotide comprising a non-naturally occurring modification on or of a sugar, nucleobase, or phosphate moiety.

A "non-naturally occurring sequence," as that term is used herein, refers to a sequence wherein an Adenine is replaced by a residue other than an analog of Adenine, a Cytosine is replaced by a residue other than an analog of Cytosine, a Guanine is replaced by a residue other than an analog of Guanine, and a Uracil is replaced by a residue other than an analog of Uracil. An analog refers to any possible derivative of the ribonucleotides, A, G, C or U. In an embodiment, a sequence having a derivative of any one of ribonucleotides A, G, C or U is a non-naturally occurring sequence.

A "naturally occurring nucleotide," as that term is used herein, refers to a nucleotide that does not comprise a non-naturally occurring modification. In an embodiment, it includes a naturally occurring modification.

A "tRNA-based effector molecule" or "TREM," as that term is used herein, refers to an RNA molecule comprising a structure or property from (a)-(v) below, and which is a recombinant TREM, a synthetic TREM, or a TREM expressed from a heterologous cell. The TREMs described in the present invention are synthetic molecules and are made, e.g., in a cell free reaction, e.g., in a solid state or liquid phase synthetic reaction. TREMs are chemically distinct, e.g., in terms of primary sequence, type or location of modifications from the endogenous tRNA molecules made in cells, e.g., in mammalian cells, e.g., in human cells. A TREM can have a plurality (*e.g.*, 2, 3, 4, 5, 6, 7, 8, 9) of the structures and functions of (a)-(v).

In an embodiment, a TREM is non-native, as evaluated by structure or the way in which it was made.

In an embodiment, a TREM comprises one or more of the following structures or properties:

(a') an optional linker region of a consensus sequence provided in the "Consensus Sequence" section, *e.g.*, a Linker 1 region;

(a) an amino acid attachment domain that binds an amino acid, *e.g.*, an acceptor stem domain (AStD), wherein an AStD comprises sufficient RNA sequence to mediate, *e.g.*, when present in an otherwise wildtype tRNA, acceptance of an amino acid, *e.g.*, its cognate amino acid or a non-cognate amino acid, and transfer of the amino acid (AA) in the initiation or elongation of a polypeptide chain. Typically, the AStD comprises a 3'-end adenosine (CCA) for acceptor stem charging which is part of synthetase recognition. In an embodiment the AStD has at least 75, 80, 85, 85, 90, 95, or 100% identity with a naturally occurring AStD, *e.g.*, an AStD encoded

by a nucleic acid in Table 4. In an embodiment, the TREM can comprise a fragment or analog of an AStD, *e.g.*, an AStD encoded by a nucleic acid in Table 4, which fragment in embodiments has AStD activity and in other embodiments does not have AStD activity. (One of ordinary skill can determine the relevant corresponding sequence for any of the domains, stems, loops, or other sequence features mentioned herein from a sequence encoded by a nucleic acid in Table 4. *E.g.*, one of ordinary skill can determine the sequence which corresponds to an AStD from a tRNA sequence encoded by a nucleic acid in Table 4.)

In an embodiment the AStD falls under the corresponding sequence of a consensus sequence provided in the "Consensus Sequence" section, or differs from the consensus sequence by no more than 1, 2, 5, or 10 positions;

In an embodiment, the AStD comprises residues R_1-R_2-R_3-R_4 -R_5-R_6-R_7 and residues R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71} of Formula I $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the AStD comprises residues R_1-R_2-R_3-R_4 -R_5-R_6-R_7 and residues R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71} of Formula II $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the AStD comprises residues R_1-R_2-R_3-R_4 -R_5-R_6-R_7 and residues R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71} of Formula III $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

(a'-1) a linker comprising residues R_8-R_9 of a consensus sequence provided in the "Consensus Sequence" section, *e.g.*, a Linker 2 region;

(b) a dihydrouridine hairpin domain (DHD), wherein a DHD comprises sufficient RNA sequence to mediate, *e.g.*, when present in an otherwise wildtype tRNA, recognition of aminoacyl-tRNA synthetase, *e.g.*, acts as a recognition site for aminoacyl-tRNA synthetase for amino acid charging of the TREM. In embodiments, a DHD mediates the stabilization of the TREM's tertiary structure. In an embodiment the DHD has at least 75, 80, 85, 85, 90, 95, or 100% identity with a naturally occurring DHD, *e.g.*, a DHD encoded by a nucleic acid in Table 4. In an embodiment, the TREM can comprise a fragment or analog of a DHD, *e.g.*, a DHD encoded by a nucleic acid in Table 4, which fragment in embodiments has DHD activity and in other embodiments does not have DHD activity.

In an embodiment the DHD falls under the corresponding sequence of a consensus sequence provided in the "Consensus Sequence" section, or differs from the consensus sequence by no more than 1, 2, 5, or 10 positions;

In an embodiment, the DHD comprises residues R_{10}-R_{11}-R_{12}-R_{13}-R_{14} R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28} of Formula I $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the DHD comprises residues R_{10}-R_{11}-R_{12}-R_{13}-R_{14} R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28} of Formula II $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the DHD comprises residues R_{10}-R_{11}-R_{12}-R_{13}-R_{14} R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28} of Formula III $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

(b'-1) a linker comprising residue R_{29} of a consensus sequence provided in the "Consensus Sequence" section, *e.g.*, a Linker 3 region;

(c) an anticodon that binds a respective codon in an mRNA, *e.g.*, an anticodon hairpin domain (ACHD), wherein an ACHD comprises sufficient sequence, *e.g.*, an anticodon triplet, to mediate, *e.g.*, when present in an otherwise wildtype tRNA, pairing (with or without wobble) with a codon; In an embodiment the ACHD has at least 75, 80, 85, 85, 90, 95, or 100% identity with a naturally occurring ACHD, *e.g.*, an ACHD encoded by a nucleic acid in Table 4. In an embodiment, the TREM can comprise a fragment or analog of an ACHD, *e.g.*, an ACHD encoded by a nucleic acid in Table 4, which fragment in embodiments has ACHD activity and in other embodiments does not have ACHD activity.

In an embodiment the ACHD falls under the corresponding sequence of a consensus sequence provided in the "Consensus Sequence" section, or differs from the consensus sequence by no more than 1, 2, 5, or 10 positions;

In an embodiment, the ACHD comprises residues -R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}-R_{43}-R_{44}-R_{45}-R_{46} of Formula I $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the ACHD comprises residues -R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}-R_{43}-R_{44}-R_{45}-R_{46} of Formula II $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the ACHD comprises residues -R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}-R_{43}-R_{44}-R_{45}-R_{46} of Formula III $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

(d) a variable loop domain (VLD), wherein a VLD comprises sufficient RNA sequence to mediate, *e.g.*, when present in an otherwise wildtype tRNA, recognition of aminoacyl-tRNA synthetase, *e.g.*, acts as a recognition site for aminoacyl-tRNA synthetase for amino acid charging of the TREM. In embodiments, a VLD mediates the stabilization of the TREM's tertiary structure. In an embodiment, a VLD modulates, *e.g.*, increases, the specificity of the TREM, *e.g.*, for its cognate amino acid, *e.g.*, the VLD modulates the TREM's cognate adaptor function. In an embodiment the VLD has at least 75, 80, 85, 85, 90, 95, or 100% identity with a naturally occurring VLD, *e.g.*, a VLD encoded by a nucleic acid in Table 4. In an embodiment, the TREM can comprise a fragment or analog of a VLD, *e.g.*, a VLD encoded by a nucleic acid in Table 4, which fragment in embodiments has VLD activity and in other embodiments does not have VLD activity.

In an embodiment the VLD falls under the corresponding sequence of a consensus sequence provided in the "Consensus Sequence" section.

In an embodiment, the VLD comprises residue -$[R_{47}]_x$ of a consensus sequence provided in the "Consensus Sequence" section, wherein x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271);

(e) a thymine hairpin domain (THD), wherein a THD comprises sufficient RNA sequence, to mediate, *e.g.*, when present in an otherwise wildtype tRNA, recognition of the ribosome, *e.g.*, acts as a recognition site for the ribosome to form a TREM-ribosome complex during translation. In an embodiment the THD has at least 75, 80, 85, 85, 90, 95, or 100% identity with a naturally occurring THD, *e.g.*, a THD encoded by a nucleic acid in Table 4. In an embodiment, the TREM can comprise a fragment or analog of a THD, *e.g.*, a THD encoded by a nucleic acid in Table 4, which fragment in embodiments has THD activity and in other embodiments does not have THD activity.

In an embodiment the THD falls under the corresponding sequence of a consensus sequence provided in the "Consensus Sequence" section, or differs from the consensus sequence by no more than 1, 2, 5, or 10 positions;

In an embodiment, the THD comprises residues -R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64} of Formula I $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the THD comprises residues -R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64} of Formula II $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

In an embodiment, the THD comprises residues -R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64} of Formula III $_{ZZZ}$, wherein ZZZ indicates any of the twenty amino acids;

(e'1) a linker comprising residue R_{72} of a consensus sequence provided in the "Consensus Sequence" section, *e.g.*, a Linker 4 region;

(f) under physiological conditions, it comprises a stem structure and one or a plurality of loop structures, *e.g.*, 1, 2, or 3 loops. A loop can comprise a domain described herein, *e.g.*, a domain selected from (a)-(e). A loop can comprise one or a plurality of domains. In an embodiment, a stem or loop structure has at least 75, 80, 85, 85, 90, 95, or 100% identity with a naturally occurring stem or loop structure, *e.g.*, a stem or loop structure encoded by a nucleic acid in Table 4. In an embodiment, the TREM can comprise a fragment or analog of a stem or loop structure, *e.g.*, a stem or loop structure encoded by a nucleic acid in Table 4, which fragment in embodiments has activity of a stem or loop structure, and in other embodiments does not have activity of a stem or loop structure;

(g) a tertiary structure, *e.g.*, an L-shaped tertiary structure;

(h) adaptor function, i.e., the TREM mediates acceptance of an amino acid, *e.g.*, its cognate amino acid and transfer of the AA in the initiation or elongation of a polypeptide chain;

(i) cognate adaptor function wherein the TREM mediates acceptance and incorporation of an amino acid (*e.g.*, cognate amino acid) associated in nature with the anti-codon of the TREM to initiate or elongate a polypeptide chain;

(j) non-cognate adaptor function, wherein the TREM mediates acceptance and incorporation of an amino acid (*e.g.*, non-cognate amino acid) other than the amino acid

associated in nature with the anti-codon of the TREM in the initiation or elongation of a polypeptide chain;

(k) a regulatory function, *e.g.*, an epigenetic function (*e.g.*, gene silencing function or signaling pathway modulation function), cell fate modulation function, mRNA stability modulation function, protein stability modulation function, protein transduction modulation function, or protein compartmentalization function;

(l) a structure which allows for ribosome binding;

(m) a post-transcriptional modification, e.g., a naturally occurring post-trasncriptional modification;

(n) the ability to inhibit a functional property of a tRNA, *e.g.*, any of properties (h)-(k) possessed by a tRNA;

(o) the ability to modulate cell fate;

(p) the ability to modulate ribosome occupancy;

(q) the ability to modulate protein translation;

(r) the ability to modulate mRNA stability;

(s) the ability to modulate protein folding and structure;

(t) the ability to modulate protein transduction or compartmentalization;

(u) the ability to modulate protein stability; or

(v) the ability to modulate a signaling pathway, *e.g.*, a cellular signaling pathway.

In an embodiment, a TREM comprises a full-length tRNA molecule or a fragment thereof.

In an embodiment, a TREM comprises the following properties: (a)-(e).

In an embodiment, a TREM comprises the following properties: (a) and (c).

In an embodiment, a TREM comprises the following properties: (a), (c) and (h).

In an embodiment, a TREM comprises the following properties: (a), (c), (h) and (b).

In an embodiment, a TREM comprises the following properties: (a), (c), (h) and (e).

In an embodiment, a TREM comprises the following properties: (a), (c), (h), (b) and (e).

In an embodiment, a TREM comprises the following properties: (a), (c), (h), (b), (e) and (g).

In an embodiment, a TREM comprises the following properties: (a), (c), (h) and (m).

In an embodiment, a TREM comprises the following properties: (a), (c), (h), (m), and (g).

In an embodiment, a TREM comprises the following properties: (a), (c), (h), (m) and (b).

In an embodiment, a TREM comprises the following properties: (a), (c), (h), (m) and (e).

In an embodiment, a TREM comprises the following properties: (a), (c), (h), (m), (g), (b) and (e).

In an embodiment, a TREM comprises the following properties: (a), (c), (h), (m), (g), (b), (e) and (q).

In an embodiment, a TREM comprises:

(i) an amino acid attachment domain that binds an amino acid (*e.g.*, an AStD, as described in (a) herein; and

(ii) an anticodon that binds a respective codon in an mRNA (*e.g.*, an ACHD, as described in (c) herein).

In an embodiment the TREM comprises a flexible RNA linker which provides for covalent linkage of (i) to (ii).

In an embodiment, the TREM mediates protein translation.

In an embodiment a TREM comprises a linker, *e.g.*, an RNA linker, *e.g.*, a flexible RNA linker, which provides for covalent linkage between a first and a second structure or domain. In an embodiment, an RNA linker comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 ribonucleotides. A TREM can comprise one or a plurality of linkers, *e.g.*, in embodiments a TREM comprising (a), (b), (c), (d) and (e) can have a first linker between a first and second domain, and a second linker between a third domain and another domain.

In an embodiment, the TREM comprises a sequence of Formula A: [L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2].

In an embodiment, a TREM comprises an RNA sequence at least 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99% identical with, or which differs by no more than 1, 2, 3, 4, 5, 10, 15, 20, 25, or 30 ribonucleotides from, an RNA sequence encoded by a DNA sequence listed in Table 4, or a fragment or functional fragment thereof. In an embodiment, a TREM comprises an RNA sequence encoded by a DNA sequence listed in Table 4, or a fragment or functional fragment thereof. In an embodiment, a TREM comprises an RNA sequence encoded by a DNA sequence at least 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99% identical with a DNA sequence listed in Table 4, or a fragment or functional fragment thereof. In an embodiment, a TREM comprises a TREM domain, *e.g.*, a domain described herein, comprising at least 60, 65, 70, 75,

80, 85, 90, 95, 96, 97, 98, or 99% identical with, or which differs by no more than 1, 2, 3, 4, 5, 10, or 15, ribonucleotides from, an RNA encoded by a DNA sequence listed in Table 4, or a fragment or a functional fragment thereof. In an embodiment, a TREM comprises a TREM domain, *e.g.*, a domain described herein, comprising an RNA sequence encoded by DNA sequence listed in Table 4, or a fragment or functional fragment thereof. In an embodiment, a TREM comprises a TREM domain, *e.g.*, a domain described herein, comprising an RNA sequence encoded by DNA sequence at least 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98 or 99% identical with a DNA sequence listed in Table 4, or a fragment or functional fragment thereof.

In an embodiment, a TREM is 76-90 nucleotides in length. In embodiments, a TREM or a fragment or functional fragment thereof is between 10-90 nucleotides, between 10-80 nucleotides, between 10-70 nucleotides, between 10-60 nucleotides, between 10-50 nucleotides, between 10-40 nucleotides, between 10-30 nucleotides, between 10-20 nucleotides, between 20-90 nucleotides, between 20-80 nucleotides, 20-70 nucleotides, between 20-60 nucleotides, between 20-50 nucleotides, between 20-40 nucleotides, between 30-90 nucleotides, between 30-80 nucleotides, between 30-70 nucleotides, between 30-60 nucleotides, or between 30-50 nucleotides.

In an embodiment, a TREM is aminoacylated, *e.g.*, charged, with an amino acid by an aminoacyl tRNA synthetase.

In an embodiment, a TREM is not charged with an amino acid, *e.g.*, an uncharged TREM (uTREM).

In an embodiment, a TREM comprises less than a full length tRNA. In embodiments, a TREM can correspond to a naturally occurring fragment of a tRNA, or to a non-naturally occurring fragment. Exemplary fragments include: TREM halves (*e.g.*, from a cleavage in the ACHD, *e.g.*, in the anticodon sequence, *e.g.*, 5'halves or 3' halves); a 5' fragment (*e.g.*, a fragment comprising the 5' end, *e.g.*, from a cleavage in a DHD or the ACHD); a 3' fragment (*e.g.*, a fragment comprising the 3' end, *e.g.*, from a cleavage in the THD); or an internal fragment (*e.g.*, from a cleavage in one or more of the ACHD, DHD or THD).

A "TREM core fragment," as that term is used herein, refers to a portion of the sequence of Formula B: $[L1]_y$-$[ASt\ Domain1]_x$-$[L2]_y$-$[DH\ Domain]_y$-$[L3]_y$-$[ACH\ Domain]_x$-$[VL\ Domain]_y$-$[TH\ Domain]_y$-$[L4]_y$-$[ASt\ Domain2]_x$, wherein: x=1 and y=0 or 1.

A "TREM fragment," as used herein, refers to a portion of a TREM, wherein the TREM comprises a sequence of Formula A: [L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2].

A "cognate adaptor function TREM," as that term is used herein, refers to a TREM which mediates initiation or elongation with the AA (the cognate AA) associated in nature with the anti-codon of the TREM.

"Decreased expression," as that term is used herein, refers to a decrease in comparison to a reference, *e.g.*, in the case where altered control region, or addition of an agent, results in a decreased expression of the subject product, it is decreased relative to an otherwise similar cell without the alteration or addition.

An "exogenous nucleic acid," as that term is used herein, refers to a nucleic acid sequence that is not present in or differs by at least one nucleotide from the closest sequence in a reference cell, *e.g.*, a cell into which the exogenous nucleic acid is introduced. In an embodiment, an exogenous nucleic acid comprises a nucleic acid that encodes a TREM.

An "exogenous TREM," as that term is used herein, refers to a TREM that:

(a) differs by at least one nucleotide or one post transcriptional modification from the closest sequence tRNA in a reference cell, *e.g.*, a cell into which the exogenous nucleic acid is introduced;

(b) has been introduced into a cell other than the cell in which it was transcribed;

(c) is present in a cell other than one in which it naturally occurs; or

(d) has an expression profile, *e.g.*, level or distribution, that is non-wildtype, *e.g.*, it is expressed at a higher level than wildtype. In an embodiment, the expression profile can be mediated by a change introduced into a nucleic acid that modulates expression or by addition of an agent that modulates expression of the RNA molecule. In an embodiment an exogenous TREM comprises 1, 2, 3 or 4 of properties (a)-(d).

A "GMP-grade composition," as that term is used herein, refers to a composition in compliance with current good manufacturing practice (cGMP) guidelines, or other similar requirements. In an embodiment, a GMP-grade composition can be used as a pharmaceutical product.

As used herein, the terms "increasing" and "decreasing" refer to modulating that results in, respectively, greater or lesser amounts of function, expression, or activity of a particular

metric relative to a reference. For example, subsequent to administration to a cell, tissue or subject of a TREM described herein, the amount of a marker of a metric (*e.g.*, protein translation, mRNA stability, protein folding) as described herein may be increased or decreased by at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 98%, 2X, 3X, 5X, 10X or more relative to the amount of the marker prior to administration or relative to the effect of a negative control agent. The metric may be measured subsequent to administration at a time that the administration has had the recited effect, *e.g.*, at least 12 hours, 24 hours, one week, one month, 3 months, or 6 months, after a treatment has begun.

"Increased expression," as that term is used herein, refers to an increase in comparison to a reference, *e.g.*, in the case where altered control region, or addition of an agent, results in an increased expression of the subject product, it is increased relative to an otherwise similar cell without the alteration or addition.

A "non-cognate adaptor function TREM," as that term is used herein, refers to a TREM which mediates initiation or elongation with an AA (a non-cognate AA) other than the AA associated in nature with the anti-codon of the TREM. In an embodiment, a non-cognate adaptor function TREM is also referred to as a mischarged TREM (mTREM).

A "pharmaceutical TREM composition," as that term is used herein, refers to a TREM composition that is suitable for pharmaceutical use. Typically, a pharmaceutical TREM composition comprises a pharmaceutical excipient. In an embodiment the TREM will be the only active ingredient in the pharmaceutical TREM composition. In embodiments the pharmaceutical TREM composition is free, substantially free, or has less than a pharmaceutically acceptable amount, of host cell proteins, DNA, *e.g.*, host cell DNA, endotoxins, and bacteria.

"Post-transcriptional processing," as that term is used herein, with respect to a subject molecule, *e.g.*, a TREM, RNA or tRNAs, refers to a covalent modification of the subject molecule. In an embodiment, the covalent modification occurs post-transcriptionally. In an embodiment, the covalent modification occurs co-transcriptionally. In an embodiment the modification is made *in vivo, e.g.*, in a cell used to produce a TREM. In an embodiment the modification is made *ex vivo*, *e.g.*, it is made on a TREM isolated or obtained from the cell which produced the TREM.

A "subject," as this term is used herein, includes any organism, such as a human or other

animal. In embodiments, the subject is a vertebrate animal (e.g., mammal, bird, fish, reptile, or amphibian). In embodiments, the subject is a mammal, e.g., a human. In embodiments, the method subject is a non-human mammal. In embodiments, the subject is a non-human mammal such as a non-human primate (e.g., monkeys, apes), ungulate (e.g., cattle, buffalo, sheep, goat, pig, camel, llama, alpaca, deer, horses, donkeys), carnivore (e.g., dog, cat), rodent (e.g., rat, mouse), or lagomorph (e.g., rabbit). In embodiments, the subject is a bird, such as a member of the avian taxa Galliformes (e.g., chickens, turkeys, pheasants, quail), Anseriformes (e.g., ducks, geese), Paleaognathae (e.g., ostriches, emus), Columbiformes (e.g., pigeons, doves), or Psittaciformes (e.g., parrots). The subject may be a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle–aged adult, or senior adult)). A non–human subject may be a transgenic animal.

A "synthetic TREM," as that term is used herein, refers to a TREM which was synthesized other than in or by a cell having an endogenous nucleic acid encoding the TREM, *e.g.*, a synthetic TREM is synthetized by cell-free solid phase synthesis. A synthetic TREM can have the same, or a different, sequence, or tertiary structure, as a native tRNA.

A "recombinant TREM," as that term is used herein, refers to a TREM that was expressed in a cell modified by human intervention, having a modification that mediates the production of the TREM, *e.g.*, the cell comprises an exogenous sequence encoding the TREM, or a modification that mediates expression, *e.g.*, transcriptional expression or post-transcriptional modification, of the TREM. A recombinant TREM can have the same, or a different, sequence, set of post-transcriptional modifications, or tertiary structure, as a reference tRNA, *e.g.*, a native tRNA.

A "tRNA", as that term is used herein, refers to a naturally occurring transfer ribonucleic acid in its native state.

A "TREM composition," as that term is used herein, refers to a composition comprising a plurality of TREMs, a plurality of TREM core fragments and/or a plurality of TREM fragments. A TREM composition can comprise one or more species of TREMs, TREM core fragments or TREM fragments. In an embodiment, the composition comprises only a single species of TREM, TREM core fragment or TREM fragment. In an embodiment, the TREM composition comprises a first TREM, TREM core fragment or TREM fragment species; and a second TREM, TREM core fragment or TREM fragment species. In an embodiment, the TREM composition

comprises X TREM, TREM core fragment or TREM fragment species, wherein X=2, 3, 4, 5, 6, 7, 8, 9, or 10. In an embodiment, the TREM, TREM core fragment or TREM fragment has at least 70, 75, 80, 85, 90, or 95, or has 100%, identity with a sequence encoded by a nucleic acid in Table 4. A TREM composition can comprise one or more species of TREMs, TREM core fragments or TREM fragments. In an embodiment, the TREM composition is at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 95 or 99% dry weight TREMs (for a liquid composition dry weight refers to the weight after removal of substantially all liquid, *e.g.*, after lyophilization). In an embodiment, the composition is a liquid. In an embodiment, the composition is dry, *e.g.*, a lyophilized material. In an embodiment, the composition is a frozen composition. In an embodiment, the composition is sterile. In an embodiment, the composition comprises at least 0.5 g, 1.0 g, 5.0 g, 10 g, 15 g, 25 g, 50 g, 100 g, 200 g, 400 g, or 500 g (*e.g.*, as determined by dry weight) of TREM.

In an embodiment, at least X% of the TREMs in a TREM composition has a non-naturally occurring modification at a selected position, and X is 80, 90, 95, 96, 97, 98, 99, or 99.5.

In an embodiment, at least X% of the TREMs in a TREM composition has a non-naturally occurring modification at a first position and a non-naturally occurring modification at a second position, and X, independently, is 80, 90, 95, 96, 97, 98, 99, or 99.5. In embodiments, the modification at the first and second position is the same. In embodiments, the modification at the first and second position are different. In embodiments, the nucleiotide at the first and second position is the same, e.g., both are adenine. In embodiments, the nucleiotide at the first and second position are different, e.g., one is adenine and one is thymine.

In an embodiment, at least X% of the TREMs in a TREM composition has a non-naturally occurring modification at a first position and less than Y% have a non-naturally occurring modification at a second position, wherein X is 80, 90, 95, 96, 97, 98, 99, or 99.5 and Y is 20, 20, 5, 2, 1, .1, or .01. In embodiments, the nucleotide at the first and second position is the same, e.g., both are adenine. In embodiments the nucleotide at the first and second position are different, e.g., one is adenine and one is thymine.

"Pairs with" or "pairing," as those terms are used herein, refer to the correspondence of a codon with an anticodon and includes fully complementary codon:anticodon pairs as well as "wobble" pairing, in which the third position need not be complementary. Fully complementary

pairing refers to pairing of all three positions of the codon with the corresponding anticodon according to Watson-Crick base pairing. Wobble pairing refers to complementary pairing of the first and second positions of the codon with the corresponding anticodon according to Watson-Crick base pairing, and flexible pairing at the third position of the codon with the corresponding anticodon.

The terms modified, replace, derived and similar terms, when used or applied in reference to a product, refer only to the end product or structure of the end product, and are not restricted by any method of making or manufacturing the product, unless expressly provided as such in this disclosure.

Headings, titles, subtitles, numbering or other alpha/numeric hierarchies are included merely for ease of reading and absent explicit language to the contrary do not indicate order of performance, order of importance, magnitude or other value.

Contextually-rare codons ("con-rare codons")

Disclosed herein, inter alia, is the observation that a production parameter of an RNA, or a protein encoded by an RNA having a con-rare codon, can be modulated by administration of a TREM composition comprising a TREM, TREM core fragment or TREM fragment, e.g., as described herein, corresponding to said con-rare codon. Accordingly, this disclosure provides, *inter alia*, methods of identifying a contextually rare codon ("con-rare codon"), compositions of TREMs corresponding to a con-rare codon and uses of said TREM compositions.

A con-rare codon is a codon that is limiting for a production parameter, *e.g.*, an expression parameter or a signaling parameter, for a nucleic acid sequence, *e.g.*, a DNA or an RNA, or a protein encoded by a nucleic acid sequence, *e.g.*, a DNA or an RNA. Contextual rareness or con-rarity can be identified or evaluated by determining if the addition of a tRNA corresponding to a con-rare codon modulates, typically increases, a production parameter for a target nucleic acid sequence, *e.g.*, target, *e.g.*, gene. In an embodiment, con-rarity as a property of a codon, is a function of, one, two, three, four, all of the following factors:

(1) the sequence of the codon;

(2) the availability of a corresponding tRNA, *e.g.*, charged tRNA, for that con-rare codon in a target cell or tissue, *e.g.*, one or more iso-acceptor tRNA molecules;

(3) the expression profile (or proteomic properties) of the target cell or tissue (*e.g.*, the abundance of expression of other proteins which include the con-rare codon);

(4) the proportion of the tRNAs corresponding to the con-rare codon which are charged; and

(5) the iso-decoder isotype of the tRNA corresponding to the con-rare codon.

In an embodiment, con-rarity is a function of normalized proteome codon count and tRNA abundance in a target tissue or cell. In an embodiment, con-rarity is a measure of codon frequency that is contextually dependent on tRNA abundance levels in a target tissue or cell. In an embodiment, con-rarity can be identified or evaluated by a production parameter, *e.g.*, an expression parameter or a signaling parameter, *e.g.*, as described herein.

An exemplary method of evaluating con-rarity and identifying a con-rare codon is provided in Example 3.

Exemplary reference values for evaluating con-rarity

In an embodiment, con-rarity is a function of normalized proteome codon count and the tRNA profile, *e.g.*, as described herein. In an embodiment, con-rarity is determined by dividing the normalized proteome codon count by the tRNA profile determined by Nanopore or other tRNA sequencing experiment. This provides a measure of codon usage that is contextually dependent on the tRNA profile, *e.g.*, tRNA abundance levels.

In an embodiment, a codon is determined to be contextually rare (con-rare) if the con-rarity meets a reference value, *e.g.*, a pre-determined or pre-selected reference value, *e.g.*, a threshold, *e.g.*, an internal threshold, *e.g.*, as described herein. In an embodiment, the reference value is a value under which *e.g.*, 1.5X sigma of the normally fit distribution to that codon frequency.

In an embodiment, a codon is con-rare if the value of a normalized proteome codon count divided by the tRNA profile value for a particular tRNA meets a reference value, *e.g.*, a pre-determined or pre-selected reference value, *e.g.*, a threshold, *e.g.*, an internal threshold.

In an embodiment, a codon is con-rare if the value of a normalized proteome codon count divided by the tRNA profile value for a particular tRNA is in the top 5%, 10%, 20%, 30%, or 40% of values for normalized proteome codon count divided by the tRNA profile value for all codons measured, *e.g.*, wherein all 64 codons are measured. In an embodiment, a codon is con-

rare if the value of a normalized proteome codon count divided by the tRNA profile value for a particular tRNA is in the top 5% of values for normalized proteome codon count divided by the tRNA profile value for all codons measured. In an embodiment, a codon is con-rare if the value of a normalized proteome codon count divided by the tRNA profile value for a particular tRNA is in the top 10% of values for normalized proteome codon count divided by the tRNA profile value for all codons measured. In an embodiment, a codon is con-rare if the value of a normalized proteome codon count divided by the tRNA profile value for a particular tRNA is in the top 20% of values for normalized proteome codon count divided by the tRNA profile value for all codons measured. In an embodiment, a codon is con-rare if the value of a normalized proteome codon count divided by the tRNA profile value for a particular tRNA is in the top 30% of values for normalized proteome codon count divided by the tRNA profile value for all codons measured. In an embodiment, a codon is con-rare if the value of a normalized proteome codon count divided by the tRNA profile value for a particular tRNA is in the top 40% of values for normalized proteome codon count divided by the tRNA profile value for all codons measured.

In an embodiment, a codon is con-rare if for the value of a normalized proteome codon count divided by the tRNA profile value for a particular tRNA, the value for the normalized proteome codon count is below the value for all codons measured and the value for tRNA profile, is above the value for all codons measured, *e.g.*, wherein all 64 codons are measured.

In an embodiment, a codon is a con-rare codon if it is in the upper left quadrant of a plot of normalized proteome codon count (y-axis) vs tRNA profile (x-axis), with equal number of codons in each quadrant, *e.g.*, wherein all 64 codons are measured.

In an embodiment, a codon is a con-rare codon if it is in a quadrant other than the lower right quadrant of a plot of normalized proteome codon count (y-axis) vs tRNA profile (x-axis), with equal number of codons in each quadrant, *e.g.*, wherein all 64 codons are measured.

Methods of modulating a production parameter of an RNA, or a protein encoded by an RNA having a con-rare codon with a TREM composition

A production parameter of an RNA, or a protein encoded by an RNA having a con-rare codon, can be modulated by administration of a TREM composition comprising a TREM, a TREM core fragment, or TREM fragment, e.g., as described herein, corresponding to said con-rare codon.

In an aspect, provided herein is a method of method of modulating a production parameter of an RNA, or a protein encoded by an RNA, in a target cell or tissue, comprising:

providing, *e.g.*, administering, to the target cell or tissue, or contacting the target cell or tissue with, an effective amount of a TREM composition comprising a TREM, a TREM core fragment, or TREM fragment, which TREM, TREM core fragment or TREM fragment corresponds to a contextually-rare codon ("con-rare codon") of the RNA,

thereby modulating the production parameter of the RNA, or protein encoded by the RNA in the target cell or tissue.

The TREM composition can be administered to the subject or the target cell or tissue can be contacted ex vivo with the TREM composition. In an embodiment, the target cell or tissue which has been contacted ex vivo with the TREM composition can be introduced into a subject, *e.g.*, an allogeneic subject or an autologous subject.

Modulation of a production parameter of an RNA, or a protein encoded by an RNA having a con-rare codon by administration of a TREM composition (*e.g.*, comprising a TREM, TREM core fragment or TREM fragment corresponding to the con-rare codon) comprises modulation of an expression parameter or a signaling parameter, *e.g.*, as described herein.

For example, administration of a TREM composition to a target cell or tissue can result in an increase or decrease in any one or more of the following expression parameters for the con-rare codon RNA:

(a) protein translation;

(b) expression level (*e.g.*, of polypeptide or protein, or mRNA);

(c) post-translational modification of polypeptide or protein;

(d) folding (*e.g.*, of polypeptide or protein, or mRNA),

(e) structure (*e.g.*, of polypeptide or protein, or mRNA),

(f) transduction (*e.g.*, of polypeptide or protein),

(g) compartmentalization (*e.g.*, of polypeptide or protein, or mRNA),

(h) incorporation (*e.g.*, of polypeptide or protein, or mRNA) into a supermolecular structure, *e.g.*, incorporation into a membrane, proteasome, or ribosome,

(i) incorporation into a multimeric polypeptide, *e.g.*, a homo or heterodimer, and/or

(j) stability.

As another example, administration of a TREM composition to a target cell or tissue can result in an increase or decrease in any one or more of the following signaling parameters for the con-rare codon RNA:

(1) modulation of a signaling pathway, *e.g.*, a cellular signaling pathway which is downstream or upstream of the protein encoded by the con-rare codon RNA;

(2) cell fate modulation;

(3) ribosome occupancy modulation;

(4) protein translation modulation;

(5) mRNA stability modulation;

(6) protein folding and structure modulation;

(7) protein transduction or compartmentalization modulation; and/or

(8) protein stability modulation.

A production parameter (*e.g.*, an expression parameter and/or a signaling parameter) may be modulated, *e.g.*, by at least 5% (*e.g.*, at least 10%, 15%, 20%, 25%, 30%, 40%. 50%. 60%. 70%, 80%, 90%, 100%, 150%, 200% or more) compared to a reference nucleic acid sequence, *e.g.*, parental, wildtype or conventionally optimized nucleic acid sequence.

Synonymous SNPs and method of modulating tRNA pool

A single nucleotide polymorphism (SNP) is a mutation that is found in the genome. A SNP can occur anywhere in the genome, e.g., in a coding sequence (e.g., an exon), or in a regulatory region (e.g., in an intron, a promoter element, an enhancer), or in a non-coding sequence.

A SNP that occurs in a coding sequence, e.g., an exon, can affect the corresponding polypeptide by altering a codon to specify a different amino acid, e.g., a different amino acid compared to that specified by the non-mutated codon.

A SNP that occurs in a coding sequence which alters a codon but does not change the amino acid specified by said mutated codon will not change the amino acid that is incorporated into the corresponding polypeptide at that position. This is possible due to the degeneracy of the genetic codon (i.e. more than one codon specifying one amino acid). Codon degeneracy is supported by "wobble" base pairing at the first base of the tRNA anticodon. For example, if a wildtype CTT codon which specifies the amino acid leucine is mutated to a CTC codon which

specifies the same amino acid Leucine, no change to the corresponding protein with respect to its composition at that particular position is expected. Both codons CTT and CTC are recognized by tRNAs that specify the amino acid Leucine. These different species of tRNAs are referred to as isoacceptor tRNAs.

A mutation which changes a codon but does not change the corresponding amino acid specified by the mutated codon is called a synonymous SNP. Synonymous SNPs are also known as silent SNPs.

Synonymous SNPs found in the human population are linked to certain diseases. Since synonymous SNPs are not expected to alter the composition of the polypeptide chain, without wishing to be bound by theory, is it believed that the effect of a synonymous SNP is linked to bias in codon usage. For example, a synonymous SNP may result in reduced protein translation, altered protein folding, altered protein localization or altered protein function. The relationship between codon usage and tRNA abundance is currently being investigated.

In an embodiment, the amount of a tRNA in a cell is correlated with codon usage. In an embodiment, a tRNA which pairs with a codon that is highly used is more abundant than a tRNA which pairs with a codon that is not highly used. In an embodiment, a tRNA which pairs with a codon that is not highly used is less abundant than a tRNA which pairs with a codon that is highly used.

As defined herein, the tRNA pool in a cell is the tRNA pool of all species, e.g., endogenous tRNAs and TREMS, which can function as tRNAs. The endogenous tRNA pool for a cell or subject that has not been administered a TREM includes only endogenous tRNAs. The tRNA pool for a cell or subject that has been administered a TREM includes endogenous tRNAs and the TREM.

Without wishing to be bound by theory, it is believed that the tRNA pool in a cell or subject can be altered by administering a composition comprising a TREM to the cell or subject. In an embodiment, the tRNA pool in a cell or subject that has been administered a Composition comprising a TREM comprises endogenous tRNAs and the administered TREM.

In an aspect, disclosed herein is a TREM composition comprising a TREM, a TREM core fragment or TREM fragment (e.g., a pharmaceutical composition comprising a TREM as described herein) for use in modulating a tRNA pool in a cell or subject, e.g., as described herein.

In embodiments, a TREM composition (e.g., a pharmaceutical composition comprising a TREM) described herein is contacted with a cell or tissue, or administered to a subject in need thereof, in an amount and for a time sufficient to modulate (increase or decrease) the tRNA pool. In embodiments, the tRNA pool comprises a first tRNA moiety and an additional tRNA moiety, e.g., a second tRNA moiety. In an embodiment, a tRNA moiety comprises an endogenous tRNA and/or a TREM.

In an embodiment, TREM composition descriebd herein (e.g., a pharmaceutical composition comprising a TREM as described herein) can be used to treat a subject having an endogenous ORF comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC).

A TREM composition (e.g., a pharmaceutical composition comprising a TREM as described herein) can also be used to modulate a function in a cell, tissue or subject. In embodiments, a TREM composition (e.g., a pharmaceutical composition comprising a TREM) described herein is contacted with a cell or tissue, or administered to a subject in need thereof, in an amount and for a time sufficient to modulate (increase or decrease) one or more of the following parameters: adaptor function (e.g., cognate or non-cognate adaptor function), e.g., the rate, efficiency, robustness, and/or specificity of initiation or elongation of a polypeptide chain; ribosome binding and/or occupancy; regulatory function (e.g., gene silencing or signaling); cell fate; mRNA stability; protein localization; protein folding; protein stability; protein transduction; or protein compartmentalization.

A parameter may be modulated, e.g., by at least 5% (e.g., at least 10%, 15%, 20%, 25%, 30%, 40%. 50%. 60%. 70%, 80%, 90%, 100%, 150%, 200% or more) compared to a reference tissue, cell or subject (e.g., a healthy, wild-type or control cell, tissue or subject).

In an embodiment, a subject or a cell having a synonymous SNP has a tRNA pool which has a lower abundance of the tRNA that pairs with the SNP codon. In an embodiment, administration of a TREM that pairs with the SNP codon to the subject or cell, increases the amount of the isoaccepting tRNA pool in the subject or cell, e.g., increase the amount of amino acid specifying molecule that can pair with the SNP codon.

Exemplary synonymous SNPs and related genes are provided in Tables 1 and Fig. 4 . In Table 1, the column with the heading “codon from/to” describes a wildtype codon for a particular transcript and the mutated codon. In Fig. 4, the column with the heading “original

codon" describes a wildtype codon for a particular transcript, while the mutated codon is listed in the column entitled "new codon." Information in these tables was derived from publicly available databases, such as MyVariant.info, MyGene.info, each of which is provided by The Scripps Research Institute; RefSeq (https://www.ncbi.nlm.nih.gov/refseq/); and CoCoPUTs (https://hive.biochemistry.gwu.edu/dna.cgi?cmd=tissue_codon_usage&id=586358&mode=cocoputs).

In an embodiment, a cell or subject described in a method of treatment, a method of modulating a tRNA pool, or a method of evaluation disclosed herein has a SNP provided in Table 1 or Fig. 4. In an embodiment, a cell or subject described in a method of treatment, a method of modulating a tRNA pool, or a method of evaluation disclosed herein has a disease listed in Table 1 or Fig. 4. In an embodiment, a cell or subject described in a method of treatment, a method of modulating a tRNA pool, or a method of evaluation disclosed herein has a SNP and the corresponding disease listed in Table 1 or Fig. 4.

Table 1: Exemplary SNPs and correlated diseases

Disease Group	Disease	Transcript	Codon from/To	Anticodon from/to	Ratio of tRNA frequency (from/to)
Cardiovascular	Cardiac hypertrophy	ENST00000357596	CTA/CTC	TAG/GAG	19.3
Cardiovascular	Cardiac hypertrophy	ENST00000357596	CTA/CTG	TAG/CAG	4.8
Cardiovascular	Cardiac hypertrophy	ENST00000378319	CTA/CTC	TAG/GAG	19.3
Cardiovascular	Cardiac hypertrophy	ENST00000378319	CTA/CTG	TAG/CAG	4.8
Cardiovascular	Cardiac hypertrophy	ENST00000442195	CTA/CTC	TAG/GAG	19.3
Cardiovascular	Cardiac hypertrophy	ENST00000442195	CTA/CTG	TAG/CAG	4.8
Cardiovascular	Cardiac hypertrophy	ENST00000465045	CTA/CTC	TAG/GAG	19.3
Cardiovascular	Cardiac hypertrophy	ENST00000465045	CTA/CTG	TAG/CAG	4.8
Cardiovascular	Cardiac hypertrophy	ENST00000485919	CTA/CTC	TAG/GAG	19.3
Cardiovascular	Cardiac hypertrophy	ENST00000485919	CTA/CTG	TAG/CAG	4.8
Cardiovascular	Cardiac hypertrophy	ENST00000488958	CTA/CTC	TAG/GAG	19.3
Cardiovascular	Cardiac hypertrophy	ENST00000488958	CTA/CTG	TAG/CAG	4.8
Cardiovascular	Cardiac hypertrophy	ENST00000496623	CTA/CTC	TAG/GAG	19.3
Cardiovascular	Cardiac hypertrophy	ENST00000496623	CTA/CTG	TAG/CAG	4.8
Cardiovascular	Coronary artery disease	ENST00000375377	CAC/CAT	GTG/ATG	4.8
Cardiovascular	Coronary artery disease	ENST00000375377	CAC/CAT	GTG/ATG	4.8
Cardiovascular	Coronary artery disease	ENST00000413988	GGC/GGT	GCC/ACC	2235.1
Cardiovascular	Hypertension	ENST00000229768	GGA/GGG	TCC/CCC	1.2
Cardiovascular	Hypertension	ENST00000563726	CCA/CCT	TGG/AGG	16.7
Cardiovascular	Hypertension	ENST00000563726	CCA/CCG	TGG/CGG	2.2
Cardiovascular	Obesity-related traits	ENST00000318130	ATC/ATT	GAT/AAT	1443.7
Cardiovascular	Obesity-related traits	ENST00000367512	ATC/ATT	GAT/AAT	1443.7

Cardiovascular	Obesity-related traits	ENST00000439962	ATC/ATT	GAT/AAT	1443.7
Cardiovascular	Type 1 diabetes	ENST00000261340	AGC/AGT	GCT/ACT	400.5
Cardiovascular	Type 1 diabetes	ENST00000290855	AGC/AGT	GCT/ACT	400.5
Cardiovascular	Type 1 diabetes	ENST00000325960	AGC/AGT	GCT/ACT	400.5
Cardiovascular	Type 1 diabetes	ENST00000430909	AGC/AGT	GCT/ACT	400.5
Cardiovascular	Type 1 diabetes	ENST00000444971	AGC/AGT	GCT/ACT	400.5
Cardiovascular	Type 1 diabetes	ENST00000476198	AGC/AGT	GCT/ACT	400.5
Cardiovascular	Type 1 diabetes	ENST00000479877	AGC/AGT	GCT/ACT	400.5
Cardiovascular	Type 1 diabetes	ENST00000536355	AGC/AGT	GCT/ACT	400.5
Cardiovascular	Type 1 diabetes	ENST00000543300	AGC/AGT	GCT/ACT	400.5
Cardiovascular	Type 1 diabetes	ENST00000544322	AGC/AGT	GCT/ACT	400.5
Cardiovascular	Type 1 diabetes	ENST00000263125	CGA/AGA	TCG/TCT	0.9
Cardiovascular	Type 1 diabetes	ENST00000397176	CGA/AGA	TCG/TCT	0.9
Cardiovascular	Type 1 diabetes	ENST00000539722	CGA/AGA	TCG/TCT	0.9
Cardiovascular	Type 1 diabetes	ENST00000610727	CGA/AGA	TCG/TCT	0.9
Cardiovascular	Type 2 diabetes	ENST00000226760	AAC/AAT	GTT/ATT	655.6
Cardiovascular	Type 2 diabetes	ENST00000503569	AAC/AAT	GTT/ATT	655.6
Dermatology	Psoriasis	ENST00000289431	TGC/TGT	GCA/ACA	111.3
Dermatology	Psoriasis	ENST00000422556	TGC/TGT	GCA/ACA	111.3
Endocrine	Endometriosis	ENST00000381434	TAC/TAT	GTA/ATA	268.1
Endocrine	Endometriosis	ENST00000417746	TAC/TAT	GTA/ATA	268.1
Endocrine	Endometriosis	ENST00000456383	TAC/TAT	GTA/ATA	268.1
Endocrine	Endometriosis	ENST00000611532	TAC/TAT	GTA/ATA	268.1
Immunology	Chronic inflammatory diseases (ankylosing spondylitis, Crohn's disease, psoriasis, primary sclerosing cholangitis, ulcerative colitis) (pleiotropy)	ENST00000171111	GAC/GAT	GTC/ATC	238.2

Immunology	Chronic inflammatory diseases (ankylosing spondylitis, Crohn's disease, psoriasis, primary sclerosing cholangitis, ulcerative colitis) (pleiotropy)	ENST00000393623	GAC/GAT	GTC/ATC	238.2
Immunology	Chronic inflammatory diseases (ankylosing spondylitis, Crohn's disease, psoriasis, primary sclerosing cholangitis, ulcerative colitis) (pleiotropy)	ENST00000592478	GAC/GAT	GTC/ATC	238.2
Immunology	Crohn's disease	ENST00000300590	ATC/ATT	GAT/AAT	1443.7
Immunology	Crohn's disease	ENST00000330943	ATC/ATT	GAT/AAT	1443.7
Immunology	Crohn's disease	ENST00000423026	ATC/ATT	GAT/AAT	1443.7
Immunology	Crohn's disease	ENST00000568993	ATC/ATT	GAT/AAT	1443.7
Immunology	Crohn's disease	ENST00000610485	ATC/ATT	GAT/AAT	1443.7
Immunology	Graves' disease	ENST00000561890	CAC/CAT	GTG/ATG	4.8
Neurology	Alzheimer disease and age of onset	ENST00000356711	AAG/AAA	CTT/TTT	2.1
Neurology	Alzheimer disease and age of onset	ENST00000357550	AAG/AAA	CTT/TTT	2.1
Neurology	Alzheimer disease and age of onset	ENST00000457511	AAG/AAA	CTT/TTT	2.1
Neurology	Alzheimer's disease or family history of Alzheimer's disease	ENST00000198536	AGG/CGG	CCT/CCG	1.3

Neurology	Alzheimer's disease or family history of Alzheimer's disease	ENST00000350573	AGG/CGG	CCT/CCG	1.3
Neurology	Alzheimer's disease or family history of Alzheimer's disease	ENST00000394000	AGG/CGG	CCT/CCG	1.3
Neurology	Alzheimer's disease or family history of Alzheimer's disease	ENST00000432297	AGG/CGG	CCT/CCG	1.3
Neurology	Alzheimer's disease or family history of Alzheimer's disease	ENST00000453419	AGG/CGG	CCT/CCG	1.3
Neurology	Major depressive disorder	ENST00000292591	CTG/TTG	CAG/CAA	1.4
Neurology	Major depressive disorder	ENST00000337755	CTG/TTG	CAG/CAA	1.4
Neurology	Major depressive disorder	ENST00000519836	CTG/TTG	CAG/CAA	1.4
Neurology	Major depressive disorder	ENST00000520918	CTG/TTG	CAG/CAA	1.4
Neurology	Major depressive disorder	ENST00000373352	TGC/TGT	GCA/ACA	111.3
Neurology	Major depressive disorder	ENST00000373371	TGC/TGT	GCA/ACA	111.3
Neurology	Major depressive disorder	ENST00000430147	TGC/TGT	GCA/ACA	111.3
Neurology	Major depressive disorder	ENST00000451404	TGC/TGT	GCA/ACA	111.3
Neurology	Major depressive disorder	ENST00000610552	TGC/TGT	GCA/ACA	111.3
Neurology	Migraine	ENST00000348159	AAC/AAT	GTT/ATT	655.6
Neurology	Migraine	ENST00000360595	AAC/AAT	GTT/ATT	655.6
Neurology	Migraine	ENST00000368240	AAC/AAT	GTT/ATT	655.6
Neurology	Migraine	ENST00000475587	AAC/AAT	GTT/ATT	655.6
Neurology	Parkinson's disease	ENST00000262407	GTC/GTT	GAC/AAC	725.5
Neurology	Parkinson's disease	ENST00000587295	GTC/GTT	GAC/AAC	725.5
Neurology	Parkinson's disease	ENST00000648408	GTC/GTT	GAC/AAC	725.5
Neurology	Parkinson's disease	ENST00000398238	AAG/AAA	CTT/TTT	2.1
Neurology	Parkinson's disease	ENST00000465370	AAG/AAA	CTT/TTT	2.1

Neurology	Parkinson's disease	ENST00000575068	AAG/AAA	CTT/TTT	2.1
Neurology	Parkinson's disease	ENST00000576346	AAG/AAA	CTT/TTT	2.1
Neurology	Schizophrenia	ENST00000304743	CTG/CTC	CAG/GAG	4.0
Neurology	Schizophrenia	ENST00000439984	CTG/CTC	CAG/GAG	4.0
Oncology	Adverse response to chemotherapy (neutropenia/leucopenia) (all antimicrotubule drugs)	ENST00000282849	GTG/GTA	CAC/TAC	5.2
Oncology	Breast cancer	ENST00000360962	GTG/GTC	CAC/GAC	1.2
Oncology	Breast cancer	ENST00000525449	GTG/GTC	CAC/GAC	1.2
Oncology	Breast cancer	ENST00000525908	GTG/GTC	CAC/GAC	1.2
Oncology	Breast cancer	ENST00000527634	GTG/GTC	CAC/GAC	1.2
Oncology	Breast cancer	ENST00000532565	GTG/GTC	CAC/GAC	1.2
Oncology	Breast cancer	ENST00000540737	GTG/GTC	CAC/GAC	1.2
Oncology	Breast cancer	ENST00000642265	GTG/GTC	CAC/GAC	1.2
Oncology	Breast cancer	ENST00000359435	AAG/AAA	CTT/TTT	2.1
Oncology	Breast cancer	ENST00000447614	AAG/AAA	CTT/TTT	2.1
Oncology	Breast cancer	ENST00000595632	AAG/AAA	CTT/TTT	2.1
Oncology	Breast cancer	ENST00000598188	AAG/AAA	CTT/TTT	2.1
Oncology	Breast cancer	ENST00000601043	AAG/AAA	CTT/TTT	2.1
Oncology	Breast cancer (early onset)	ENST00000399503	ACC/ACT	GGT/AGT	1099.1
Oncology	Breast cancer (early onset)	ENST00000399503	ACC/ACT	GGT/AGT	1099.1
Oncology	Carboplatin disposition in epthelial ovarian cancer	ENST00000370449	CAC/CAT	GTG/ATG	4.8
Oncology	Carboplatin disposition in epthelial ovarian cancer	ENST00000647814	CAC/CAT	GTG/ATG	4.8
Oncology	Clostridium difficile infection in multiple myeloma	ENST00000335385	CTC/CTT	GAG/AAG	90.2

Oncology	Colorectal cancer	ENST00000349830	CCC/CCG	GGG/CGG	3.4
Oncology	Colorectal cancer	ENST00000349830	CCC/CCT	GGG/AGG	25.7
Oncology	Colorectal cancer	ENST00000398564	CCC/CCG	GGG/CGG	3.4
Oncology	Colorectal cancer	ENST00000398564	CCC/CCT	GGG/AGG	25.7
Oncology	Colorectal cancer	ENST00000518288	CCC/CCG	GGG/CGG	3.4
Oncology	Colorectal cancer	ENST00000518288	CCC/CCT	GGG/AGG	25.7
Oncology	Colorectal cancer	ENST00000520359	CCC/CCG	GGG/CGG	3.4
Oncology	Colorectal cancer	ENST00000520359	CCC/CCT	GGG/AGG	25.7
Oncology	Colorectal cancer	ENST00000522435	CCC/CCG	GGG/CGG	3.4
Oncology	Colorectal cancer	ENST00000522435	CCC/CCT	GGG/AGG	25.7
Oncology	Endometrial cancer ((endometrioid histology)	ENST00000247270	AGC/AGT	GCT/ACT	400.5
Oncology	Esophageal squamous cell cancer (length of survival)	ENST00000269187	CTG/TTG	CAG/CAA	1.4
Oncology	Esophageal squamous cell cancer (length of survival)	ENST00000440549	CTG/TTG	CAG/CAA	1.4
Oncology	Esophageal squamous cell cancer (length of survival)	ENST00000586829	CTG/TTG	CAG/CAA	1.4
Oncology	Esophageal squamous cell cancer (length of survival)	ENST00000590986	CTG/TTG	CAG/CAA	1.4
Oncology	Esophageal squamous cell carcinoma	ENST00000330794	GTG/GTC	CAC/GAC	1.2
Oncology	Esophageal squamous cell carcinoma	ENST00000330794	GTG/GTA	CAC/TAC	5.2
Oncology	Esophageal squamous cell carcinoma	ENST00000510817	GTG/GTC	CAC/GAC	1.2
Oncology	Esophageal squamous cell carcinoma	ENST00000510817	GTG/GTA	CAC/TAC	5.2
Oncology	Glioblastoma	ENST00000320521	CTC/CTT	GAG/AAG	90.2

Oncology	Lung cancer in ever smokers	ENST00000326828	TAC/TAT	GTA/ATA	268.1
Oncology	Lung cancer in ever smokers	ENST00000348639	TAC/TAT	GTA/ATA	268.1
Oncology	Lung cancer in ever smokers	ENST00000559658	TAC/TAT	GTA/ATA	268.1
Oncology	Macrophage Migration Inhibitory Factor levels	ENST00000344836	GTG/GTC	CAC/GAC	1.2
Oncology	Macrophage Migration Inhibitory Factor levels	ENST00000381886	GTG/GTC	CAC/GAC	1.2
Oncology	Oral cavity and pharyngeal cancer	ENST00000209665	AGG/AGA	CCT/TCT	1.1
Oncology	Oral cavity and pharyngeal cancer	ENST00000437033	AGG/AGA	CCT/TCT	1.1
Oncology	Oral cavity and pharyngeal cancer	ENST00000476959	AGG/AGA	CCT/TCT	1.1
Oncology	Oral cavity and pharyngeal cancer	ENST00000482593	AGG/AGA	CCT/TCT	1.1
Oncology	Pancreatic cancer	ENST00000162330	CTC/CTT	GAG/AAG	90.2
Oncology	Pancreatic cancer	ENST00000393420	CTC/CTT	GAG/AAG	90.2
Oncology	Pancreatic cancer	ENST00000393422	CTC/CTT	GAG/AAG	90.2
Oncology	Pancreatic cancer	ENST00000418647	CTC/CTT	GAG/AAG	90.2
Oncology	Pancreatic cancer	ENST00000420641	CTC/CTT	GAG/AAG	90.2
Oncology	Pancreatic cancer	ENST00000535626	CTC/CTT	GAG/AAG	90.2
Oncology	Pancreatic cancer	ENST00000538440	CTC/CTT	GAG/AAG	90.2
Oncology	Pancreatic cancer	ENST00000542031	CTC/CTT	GAG/AAG	90.2
Ophthalmology	Myopia	ENST00000358540	GTG/GTA	CAC/TAC	5.2
Ophthalmology	Myopia	ENST00000396166	GTG/GTA	CAC/TAC	5.2
Ophthalmology	Myopia	ENST00000396168	GTG/GTA	CAC/TAC	5.2
Ophthalmology	Myopia	ENST00000396170	GTG/GTA	CAC/TAC	5.2

Ophthalmology	Myopia	ENST00000477854	GTG/GTA	CAC/TAC	5.2
Ophthalmology	Myopia (pathological)	ENST00000336812	ACG/ACT	CGT/AGT	190.9
Ophthalmology	Myopia (pathological)	ENST00000336812	ACG/ACT	CGT/AGT	190.9
Respiratory	Asthma	ENST00000427077	CTA/TTA	TAG/TAA	2.0
Respiratory	Asthma	ENST00000346243	TCC/TCT	GGA/AGA	5.7
Respiratory	Asthma	ENST00000346872	TCC/TCT	GGA/AGA	5.7
Respiratory	Asthma	ENST00000350532	TCC/TCT	GGA/AGA	5.7
Respiratory	Asthma	ENST00000351680	TCC/TCT	GGA/AGA	5.7
Respiratory	Asthma	ENST00000377944	TCC/TCT	GGA/AGA	5.7
Respiratory	Asthma	ENST00000377945	TCC/TCT	GGA/AGA	5.7
Respiratory	Asthma	ENST00000377952	TCC/TCT	GGA/AGA	5.7
Respiratory	Asthma	ENST00000377958	TCC/TCT	GGA/AGA	5.7
Respiratory	Asthma	ENST00000394189	TCC/TCT	GGA/AGA	5.7
Respiratory	Asthma	ENST00000439016	TCC/TCT	GGA/AGA	5.7
Respiratory	Asthma	ENST00000439167	TCC/TCT	GGA/AGA	5.7
Respiratory	Asthma	ENST00000467757	TCC/TCT	GGA/AGA	5.7
Respiratory	Asthma	ENST00000535189	TCC/TCT	GGA/AGA	5.7
Respiratory	Asthma	ENST00000583368	TCC/TCT	GGA/AGA	5.7
Respiratory	Asthma	ENST00000623724	TCC/TCT	GGA/AGA	5.7
Respiratory	Post bronchodilator FEV1/FVC ratio in COPD	ENST00000225275	AAC/AAT	GTT/ATT	655.6
Respiratory	Post bronchodilator FEV1/FVC ratio in COPD	ENST00000240335	CCC/CCA	GGG/TGG	1.5
Respiratory	Post bronchodilator FEV1/FVC ratio in COPD	ENST00000240335	CCC/CCG	GGG/CGG	3.4
Respiratory	Post bronchodilator FEV1/FVC ratio in COPD	ENST00000240335	CCC/CCT	GGG/AGG	25.7
Respiratory	Post bronchodilator FEV1/FVC ratio in COPD	ENST00000393853	CCC/CCA	GGG/TGG	1.5

Respiratory	Post bronchodilator FEV1/FVC ratio in COPD	ENST00000393853	CCC/CCG	GGG/CGG	3.4
Respiratory	Post bronchodilator FEV1/FVC ratio in COPD	ENST00000393853	CCC/CCT	GGG/AGG	25.7
Respiratory	Post bronchodilator FEV1/FVC ratio in COPD	ENST00000642491	CCC/CCA	GGG/TGG	1.5
Respiratory	Post bronchodilator FEV1/FVC ratio in COPD	ENST00000642491	CCC/CCG	GGG/CGG	3.4
Respiratory	Post bronchodilator FEV1/FVC ratio in COPD	ENST00000642491	CCC/CCT	GGG/AGG	25.7
Respiratory	Post bronchodilator FEV1/FVC ratio in COPD	ENST00000644296	CCC/CCA	GGG/TGG	1.5
Respiratory	Post bronchodilator FEV1/FVC ratio in COPD	ENST00000644296	CCC/CCG	GGG/CGG	3.4
Respiratory	Post bronchodilator FEV1/FVC ratio in COPD	ENST00000644296	CCC/CCT	GGG/AGG	25.7

TREM, TREM core fragment and TREM fragment

A "tRNA-based effector molecule" or "TREM" refers to an RNA molecule comprising one or more of the properties described herein. A TREM can comprise a non-naturally occurring modification, e.g., as provided in Tables 4, 5, 6 or 7.

In an embodiment, a TREM includes a TREM comprising a sequence of Formula A; a TREM core fragment comprising a sequence of Formula B; or a TREM fragment comprising a portion of a TREM which TREM comprises a sequence of Formula A.

In an embodiment, a TREM comprises a sequence of Formula A: [L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2]. In an embodiment, [VL Domain] is optional. In an embodiment, [L1] is optional.

In an embodiment, a TREM core fragment comprises a sequence of Formula B: $[L1]_y$-$[ASt\ Domain1]_x$-$[L2]_y$-[DH Domain]$_y$-$[L3]_y$-[ACH Domain]$_x$-[VL Domain] $_y$-[TH Domain] $_y$-$[L4]_y$-$[ASt\ Domain2]_x$, wherein: x=1 and y=0 or 1. In an embodiment, y=0. In an embodiment, y=1.;

In an embodiment, a TREM fragment comprises a portion of a TREM, wherein the TREM comprises a sequence of Formula A: [L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2], and wherein the TREM fragment comprises: one, two, three or all or any combination of the following: a TREM half (*e.g.*, from a cleavage in the ACH Domain, *e.g.*, in the anticodon sequence, *e.g.*, a 5'half or a 3' half); a 5' fragment (*e.g.*, a fragment comprising the 5' end, *e.g.*, from a cleavage in a DH Domain or the ACH Domain); a 3' fragment (*e.g.*, a fragment comprising the 3' end, *e.g.*, from a cleavage in the TH Domain); or an internal fragment (*e.g.*, from a cleavage in any one of the ACH Domain, DH Domain or TH Domain). Exemplary TREM fragments include TREM halves (*e.g.*, from a cleavage in the ACHD, *e.g.*, 5'TREM halves or 3' TREM halves), a 5' fragment (*e.g.*, a fragment comprising the 5' end, *e.g.*, from a cleavage in a DHD or the ACHD), a 3' fragment (*e.g.*, a fragment comprising the 3' end of a TREM, *e.g.*, from a cleavage in the THD), or an internal fragment (*e.g.*, from a cleavage in one or more of the ACHD, DHD or THD).

In an embodiment, a TREM, a TREM core fragment or a TREM fragment can be charged with an amino acid (*e.g.*, a cognate amino acid); charged with a non-cognate amino acid (*e.g.*, a mischarged TREM (mTREM)); or not charged with an amino acid (*e.g.*, an uncharged TREM (uTREM)). In an embodiment, a TREM, a TREM core fragment or a TREM fragment can be

charged with an amino acid selected from alanine, arginine, asparagine, aspartate, cysteine, glutamine, glutamate, glycine, histidine, isoleucine, methionine, leucine, lysine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine.

In an embodiment, the TREM, TREM core fragment or TREM fragment is a cognate TREM. In an embodiment, the TREM, TREM core fragment or TREM fragment is a non-cognate TREM. In an embodiment, the TREM, TREM core fragment or TREM fragment recognizes a codon provided in Table 2 or Table 3.

Table 2: List of codons

AAA	CUG
AAC	CUU
AAG	GAA
AAU	GAC
ACA	GAG
ACC	GAU
ACG	GCA
ACU	GCC
AGA	GCG
AGC	GCU
AGG	GGA
AGU	GGC
AUA	GGG
AUC	GGU
AUG	GUA
AUU	GUC
CAA	GUG
CAC	GUU
CAG	UAA
CAU	UAC
CCA	UAG
CCC	UAU
CCG	UCA
CCU	UCC
CGA	UCG
CGC	UCU
CGG	UGA
CGU	UGC
CUA	UGG
CUC	UGU

UUA	UUG
UUC	UUU

Table 3: Amino acids and corresponding codons

Amino Acid	mRNA codons
Alanine	GCU, GCC, GCA, GCG
Arginine	CGU, CGC, CGA, CGG, AGA, AGG
Asparagine	AAU, AAC
Aspartate	GAU, GAC
Cysteine	UGU, UGC
Glutamate	GAA, GAG
Glutamine	CAA, CAG
Glycine	GGU, GGC, GGA, GGG
Histidine	CAU, CAC
Isoleucine	AUU, AUC, AUA
Leucine	UUA, UUG, CUU, CUC, CUA, CUG
Lysine	AAA, AAG
Methionine	AUG
Phenylalanine	UUU, UUC
Proline	CCU, CCC, CCA, CCG
Serine	UCU, UCC, UCA, UCG, AGU, AGC
Stop	UAA, UAG, UGA
Threonine	ACU, ACC, ACA, ACG
Tryptophan	UGG
Tyrosine	UAU, UAC
Valine	GUU, GUC, GUA, GUG

In an embodiment, a TREM comprises a ribonucleic acid (RNA) sequence encoded by a deoxyribonucleic acid (DNA) sequence disclosed in Table 4, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 4. In an embodiment, a TREM comprises an RNA sequence at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to an RNA sequence encoded by a DNA sequence provided in Table 4, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 4. In an embodiment, a TREM comprises an RNA sequence encoded by a DNA sequence at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to a DNA sequence provided in Table 4, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 4.

In an embodiment, a TREM, a TREM core fragment, or TREM fragment comprises at least 5, 10, 15, 20, 25, or 30 consecutive nucleotides of an RNA sequence encoded by a DNA sequence disclosed in Table 4, *e.g.*, at least 5, 10, 15, 20, 25, or 30 consecutive nucleotides of an RNA sequence encoded by any one of SEQ ID NOs: 1-451 disclosed in Table 4. In an embodiment, a TREM, a TREM core fragment, or TREM fragment comprises at least 5, 10, 15, 20, 25, or 30 consecutive nucleotides of an RNA sequence at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to an RNA sequence encoded by a DNA sequence provided in Table 4, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 4. In an embodiment, a TREM, a TREM core fragment, or TREM fragment comprises at least 5, 10, 15, 20, 25, or 30 consecutive nucleotides of an RNA sequence encoded by a DNA sequence at least 60%, 65%, 70%, 75%, 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, or 99% identical to a DNA sequence provided in Table 4, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 4.

In an embodiment, a TREM core fragment or a TREM fragment comprises at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of an RNA sequence encoded by a DNA sequence provided in Table 4, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 4. In an embodiment, a TREM core fragment or a TREM fragment comprises at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of an RNA sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to an RNA sequence encoded by a DNA sequence provided in Table 4, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 4. In an embodiment, a TREM core fragment or a TREM fragment comprises at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% of an RNA sequence encoded by a DNA sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to a DNA sequence provided in Table 4, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 4.

In an embodiment, a TREM core fragment or a TREM fragment comprises at least 5 ribonucleotides (nt), 10 nt, 15 nt, 20 nt, 25 nt, 30 nt, 35 nt, 40 nt, 45 nt, 50 nt, 55 nt or 60 nt (but less than the full length) of an RNA sequence encoded by a DNA sequence disclosed in Table 4, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 4. In an embodiment, a TREM core fragment or a TREM fragment comprises at least 5 ribonucleotides (nt), 10 nt, 15 nt, 20 nt, 25 nt,

30 nt, 35 nt, 40 nt, 45 nt, 50 nt, 55 nt or 60 nt (but less than the full length) of an RNA sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to an RNA sequence encoded by a DNA sequence provided in Table 4, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 4. In an embodiment, a TREM core fragment or a TREM fragment comprises at least 5 ribonucleotides (nt), 10 nt, 15 nt, 20 nt, 25 nt, 30 nt, 35 nt, 40 nt, 45 nt, 50 nt, 55 nt or 60 nt (but less than the full length) of an RNA sequence encoded by a DNA sequence with at least 80%, 82%, 85%, 87%, 88%, 90%, 92%, 95%, 96%, 97%, 98%, 99% or 100% identity to a DNA sequence provided in Table 4, *e.g.*, any one of SEQ ID NOs: 1-451 disclosed in Table 4.

In an embodiment, a TREM core fragment or a TREM fragment comprises a sequence of a length of between 10-90 ribonucleotides (rnt), between 10-80 rnt, between 10-70 rnt, between 10-60 rnt, between 10-50 rnt, between 10-40 rnt, between 10-30 rnt, between 10-20 rnt, between 20-90 rnt, between 20-80 rnt, 20-70 rnt, between 20-60 rnt, between 20-50 rnt, between 20-40 rnt, between 30-90 rnt, between 30-80 rnt, between 30-70 rnt, between 30-60 rnt, or between 30-50 rnt.

***Table 4**: List of tRNA sequences*

SEQ ID NO	tRNA name	tRNA sequence
1	Ala_AGC_chr6:28763741-28763812 (-)	GGGGGTATAGCTCAGTGGTAGAGCGCGTGCTTAGCATGCACGAGGTCC TGGGTTCGATCCCCAGTACCTCCA
2	Ala_AGC_chr6:26687485-26687557 (+)	GGGGAATTAGCTCAAGTGGTAGAGCGCTTGCTTAGCACGCAAGAGGTA GTGGGATCGATGCCCACATTCTCCA
3	Ala_AGC_chr6:26572092-26572164 (-)	GGGGAATTAGCTCAAATGGTAGAGCGCTCGCTTAGCATGCGAGAGGTA GCGGGATCGATGCCCGCATTCTCCA
4	Ala_AGC_chr6:26682715-26682787 (+)	GGGGAATTAGCTCAAGTGGTAGAGCGCTTGCTTAGCATGCAAGAGGTA GTGGGATCGATGCCCACATTCTCCA
5	Ala_AGC_chr6:26705606-26705678 (+)	GGGGAATTAGCTCAAGCGGTAGAGCGCTTGCTTAGCATGCAAGAGGTA GTGGGATCGATGCCCACATTCTCCA
6	Ala_AGC_chr6:26673590-26673662 (+)	GGGGAATTAGCTCAAGTGGTAGAGCGCTTGCTTAGCATGCAAGAGGTA GTGGGATCAATGCCCACATTCTCCA
7	Ala_AGC_chr14:89445442-89445514 (+)	GGGGAATTAGCTCAAGTGGTAGAGCGCTCGCTTAGCATGCGAGAGGTA GTGGGATCGATGCCCGCATTCTCCA
8	Ala_AGC_chr6:58196623-58196695 (-)	GGGGAATTAGCCCAAGTGGTAGAGCGCTTGCTTAGCATGCAAGAGGTA GTGGGATCGATGCCCACATTCTCCA
9	Ala_AGC_chr6:28806221-28806292 (-)	GGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTAGCATGCACGAGGCCC CGGGTTCAATCCCCGGCACCTCCA
10	Ala_AGC_chr6:28574933-28575004 (+)	GGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTAGCATGTACGAGGTCC CGGGTTCAATCCCCGGCACCTCCA
11	Ala_AGC_chr6:28626014-28626085 (-)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTAGCATGCATGAGGTCC CGGGTTCGATCCCCAGCATCTCCA
12	Ala_AGC_chr6:28678366-28678437 (+)	GGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTAGCATGCACGAGGCCC TGGGTTCAATCCCCAGCACCTCCA
13	Ala_AGC_chr6:28779849-28779920 (-)	GGGGGTATAGCTCAGCGGTAGAGCGCGTGCTTAGCATGCACGAGGTCC TGGGTTCAATCCCCAATACCTCCA

14	Ala_AGC_chr6:28687481-28687552 (+)	GGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTAGCATGCACGAGGCCC CGGGTTCAATCCCTGGCACCTCCA
15	Ala_AGC_chr2:27274082-27274154 (+)	GGGGGATTAGCTCAAATGGTAGAGCGCTCGCTTAGCATGCGAGAGGTA GCGGGATCGATGCCCCGCATCCTCCA
16	Ala_AGC_chr6:26730737-26730809 (+)	GGGGAATTAGCTCAGGCGGTAGAGCGCTCGCTTAGCATGCGAGAGGTA GCGGGATCGACGCCCCGCATTCTCCA
17	Ala_CGC_chr6:26553731-26553802 (+)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTCGCATGTATGAGGTCC CGGGTTCGATCCCCCGGCATCTCCA
18	Ala_CGC_chr6:28641613-28641684 (-)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTCGCATGTATGAGGCCC CGGGTTCGATCCCCCGGCATCTCCA
19	Ala_CGC_chr2:157257281-157257352 (+)	GGGGATGTAGCTCAGTGGTAGAGCGCGCGCTTCGCATGTGTGAGGTCC CGGGTTCAATCCCCCGGCATCTCCA
20	Ala_CGC_chr6:28697092-28697163 (+)	GGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTCGCATGTACGAGGCCC CGGGTTCGACCCCCGGCTCCTCCA
21	Ala_TGC_chr6:28757547-28757618 (-)	GGGGGTGTAGCTCAGTGGTAGAGCGCATGCTTTGCATGTATGAGGTCC CGGGTTCGATCCCCGGCACCTCCA
22	Ala_TGC_chr6:28611222-28611293 (+)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTTGCATGTATGAGGTCC CGGGTTCGATCCCCGGCATCTCCA
23	Ala_TGC_chr5:180633868-180633939 (+)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTTGCATGTATGAGGCCC CGGGTTCGATCCCCGGCATCTCCA
24	Ala_TGC_chr12:125424512-125424583 (+)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTTGCACGTATGAGGCCC CGGGTTCAATCCCCGGCATCTCCA
25	Ala_TGC_chr6:28785012-28785083 (-)	GGGGGTGTAGCTCAGTGGTAGAGCGCATGCTTTGCATGTATGAGGCCT CGGGTTCGATCCCCGACACCTCCA
26	Ala_TGC_chr6:28726141-28726212 (-)	GGGGGTGTAGCTCAGTGGTAGAGCACATGCTTTGCATGTGTGAGGCCC CGGGTTCGATCCCCGGCACCTCCA
27	Ala_TGC_chr6:28770577-28770647 (-)	GGGGGTGTAGCTCAGTGGTAGAGCGCATGCTTTGCATGTATGAGGCCT CGGTTCGATCCCCCGACACCTCCA
28	Arg_ACG_chr6:26328368-26328440 (+)	GGGCCAGTGGCGCAATGGATAACGCGTCTGACTACGGATCAGAAGATT CCAGGTTCGACTCCTGGCTGGCTCG
29	Arg_ACG_chr3:45730491-45730563 (-)	GGGCCAGTGGCGCAATGGATAACGCGTCTGACTACGGATCAGAAGATT CTAGGTTCGACTCCTGGCTGGCTCG

30	Arg_CCG_chr6:28710729-28710801 (-)	GGCCGCGTGGCCTAATGGATAAGGCGTCTGATTCCGGATCAGAAGATT GAGGGTTCGAGTCCCTTCGTGGTCG
31	Arg_CCG_chr17:66016013-66016085 (-)	GACCCAGTGGCCTAATGGATAAGGCATCAGCCTCCGGAGCTGGGGATT GTGGGTTCGAGTCCCATCTGGGTCG
32	Arg_CCT_chr17:73030001-73030073 (+)	GCCCCAGTGGCCTAATGGATAAGGCACTGGCCTCCTAAGCCAGGGATT GTGGGTTCGAGTCCCACCTGGGGTA
33	Arg_CCT_chr17:73030526-73030598 (-)	GCCCCAGTGGCCTAATGGATAAGGCACTGGCCTCCTAAGCCAGGGATT GTGGGTTCGAGTCCCACCTGGGGTG
34	Arg_CCT_chr16:3202901-3202973 (+)	GCCCCGGTGGCCTAATGGATAAGGCATTGGCCTCCTAAGCCAGGGATT GTGGGTTCGAGTCCCACCCGGGGTA
35	Arg_CCT_chr7:139025446-139025518 (+)	GCCCCAGTGGCCTAATGGATAAGGCATTGGCCTCCTAAGCCAGGGATT GTGGGTTCGAGTCCCATCTGGGGTG
36	Arg_CCT_chr16:3243918-3243990 (+)	GCCCCAGTGGCCTGATGGATAAGGTACTGGCCTCCTAAGCCAGGGATT GTGGGTTCGAGTTCCACCTGGGGTA
37	Arg_TCG_chr15:89878304-89878376 (+)	GGCCGCGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAGAAGATT GCAGGTTCGAGTCCTGCCGCGGTCG
38	Arg_TCG_chr6:26323046-26323118 (+)	GACCACGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAGAAGATT GAGGGTTCGAATCCCTCCGTGGTTA
39	Arg_TCG_chr17:73031208-73031280 (+)	GACCGCGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAGAAGATT GAGGGTTCGAGTCCCTTCGTGGTCG
40	Arg_TCG_chr6:26299905-26299977 (+)	GACCACGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAGAAGATT GAGGGTTCGAATCCCTTCGTGGTTA
41	Arg_TCG_chr6:28510891-28510963 (-)	GACCACGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAGAAGATT GAGGGTTCGAATCCCTTCGTGGTTG
42	Arg_TCG_chr9:112960803-112960875 (+)	GGCCGTGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAAAAGATT GCAGGTTTGAGTTCTGCCACGGTCG
43	Arg_TCT_chr1:94313129-94313213 (+)	GGCTCCGTGGCGCAATGGATAGCGCATTGGACTTCTAGAGGCTGAAGG CATTCAAAGGTTCCGGGTTCGAGTCCCGGCGGGAGTCG
44	Arg_TCT_chr17:8024243-8024330 (+)	GGCTCTGTGGCGCAATGGATAGCGCATTGGACTTCTAGTGACGAATAG AGCAATTCAAAGGTTGTGGGTTCGAATCCCACCAGAGTCG
45	Arg_TCT_chr9:131102355-131102445 (-)	GGCTCTGTGGCGCAATGGATAGCGCATTGGACTTCTAGCTGAGCCTAG TGTGGTCATTCAAAGGTTGTGGGTTCGAGTCCCACCAGAGTCG

46	Arg_TCT_chr11:59318767-59318852 (+)	GGCTCTGTGGCGCAATGGATAGCGCATTGGACTTCTAGATAGTTAGAG AAATTCAAAGGTTGTGGGTTCGAGTCCCACCAGAGTCG
47	Arg_TCT_chr1:159111401-159111474 (-)	GTCTCTGTGGCGCAATGGACGAGCGCGCTGGACTTCTAATCCAGAGGT TCCGGGTTCGAGTCCCGGCAGAGATG
48	Arg_TCT_chr6:27529963-27530049 (+)	GGCTCTGTGGCGCAATGGATAGCGCATTGGACTTCTAGCCTAAATCAA GAGATTCAAAGGTTGCGGGTTCGAGTCCCTCCACAGAGTCG
49	Asn_GTT_chr1:161510031-161510104 (+)	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGGT TGGTGGTTCGATCCCACCCAGGGACG
50	Asn_GTT_chr1:143879832-143879905 (-)	GTCTCTGTGGCGCAATCGGCTAGCGCGTTTGGCTGTTAACTAAAAGGTT GGCGGTTCGAACCCACCCAGAGGCG
51	Asn_GTT_chr1:144301611-144301684 (+)	GTCTCTGTGGTGCAATCGGTTAGCGCGTTCCGCTGTTAACCGAAAGCTT GGTGGTTCGAGCCCACCCAGGGATG
52	Asn_GTT_chr1:149326272-149326345 (-)	GTCTCTGTGGCGCAATCGGCTAGCGCGTTTGGCTGTTAACTAAAAAGTT GGTGGTTCGAACACACCCAGAGGCG
53	Asn_GTT_chr1:148248115-148248188 (+)	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGGT TGGTGGTTCGAGCCCACCCAGGGACG
54	Asn_GTT_chr1:148598314-148598387 (-)	GTCTCTGTGGCGCAATCGGTTAGCGCATTCGGCTGTTAACCGAAAGGT TGGTGGTTCGAGCCCACCCAGGGACG
55	Asn_GTT_chr1:17216172-17216245 (+)	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGAT TGGTGGTTCGAGCCCACCCAGGGACG
56	Asn_GTT_chr1:16847080-16847153 (-)	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACTGAAAGGTT GGTGGTTCGAGCCCACCCAGGGACG
57	Asn_GTT_chr1:149230570-149230643 (-)	GTCTCTGTGGCGCAATGGGTTAGCGCGTTCGGCTGTTAACCGAAAGGT TGGTGGTTCGAGCCCATCCAGGGACG
58	Asn_GTT_chr1:148000805-148000878 (+)	GTCTCTGTGGCGTAGTCGGTTAGCGCGTTCGGCTGTTAACCGAAAAGTT GGTGGTTCGAGCCCACCCAGGAACG
59	Asn_GTT_chr1:149711798-149711871 (-)	GTCTCTGTGGCGCAATCGGCTAGCGCGTTTGGCTGTTAACTAAAAGGTT GGTGGTTCGAACCCACCCAGAGGCG
60	Asn_GTT_chr1:145979034-145979107 (-)	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACTGAAAGGTT AGTGGTTCGAGCCCACCCGGGGACG
61	Asp_GTC_chr12:98897281-98897352 (+)	TCCTCGTTAGTATAGTGGTTAGTATCCCCGCCTGTCACGCGGGAGACCG GGGTTCAATTCCCCGACGGGGAG

62	Asp_GTC_chr1:161410615-161410686 (-)	TCCTCGTTAGTATAGTGGTGAGTATCCCCGCCTGTCACGCGGGAGACC GGGGTTCGATTCCCCGACGGGGAG
63	Asp_GTC_chr6:27551236-27551307 (-)	TCCTCGTTAGTATAGTGGTGAGTGTCCCCGTCTGTCACGCGGGAGACC GGGGTTCGATTCCCCGACGGGGAG
64	Cys_GCA_chr7:149007281-149007352 (+)	GGGGGCATAGCTCAGTGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CTGGTTCAAATCCAGGTGCCCCCT
65	Cys_GCA_chr7:149074601-149074672 (-)	GGGGGTATAGCTCAGGGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CTGGTTCAAATCCAGGTGCCCCCC
66	Cys_GCA_chr7:149112229-149112300 (-)	GGGGGTATAGCTTAGCGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CCGGTTCAAATCCGGGTGCCCCCT
67	Cys_GCA_chr7:149344046-149344117 (-)	GGGGGTATAGCTTAGGGGTAGAGCATTTGACTGCAGATCAAAAGGTCC CTGGTTCAAATCCAGGTGCCCCTT
68	Cys_GCA_chr7:149052766-149052837 (-)	GGGGGTATAGCTCAGGGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CCAGTTCAAATCTGGGTGCCCCCT
69	Cys_GCA_chr17:37017937-37018008 (-)	GGGGGTATAGCTCAGGGGTAGAGCATTTGACTGCAGATCAAGAAGTCC CCGGTTCAAATCCGGGTGCCCCCT
70	Cys_GCA_chr7:149281816-149281887 (+)	GGGGGTATAGCTCAGGGGTAGAGCATTTGACTGCAGATCAAGAGGTCT CTGGTTCAAATCCAGGTGCCCCCT
71	Cys_GCA_chr7:149243631-149243702 (+)	GGGGGTATAGCTCAGGGGTAGAGCACTTGACTGCAGATCAAGAAGTCC TTGGTTCAAATCCAGGTGCCCCCT
72	Cys_GCA_chr7:149388272-149388343 (-)	GGGGATATAGCTCAGGGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CCGGTTCAAATCCGGGTGCCCCCC
73	Cys_GCA_chr7:149072850-149072921 (-)	GGGGGTATAGTTCAGGGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CTGGTTCAAATCCAGGTGCCCCCT
74	Cys_GCA_chr7:149310156-149310227 (-)	GGGGGTATAGCTCAGGGGTAGAGCATTTGACTGCAAATCAAGAGGTCC CTGATTCAAATCCAGGTGCCCCCT
75	Cys_GCA_chr4:124430005-124430076 (-)	GGGGGTATAGCTCAGTGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CCGGTTCAAATCCGGGTGCCCCCT
76	Cys_GCA_chr7:149295046-149295117 (+)	GGGCGTATAGCTCAGGGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CCAGTTCAAATCTGGGTGCCCCCT
77	Cys_GCA_chr7:149361915-149361986 (+)	GGGGGTATAGCTCACAGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CCGGTTCAAATCTGGGTGCCCCCT

78	Cys_GCA_chr7:149253802-149253871 (+)	GGGCGTATAGCTCAGGGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CCAGTTCAAATCTGGGTGCCCA
79	Cys_GCA_chr7:149292305-149292376 (-)	GGGGGTATAGCTCACAGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CCGGTTCAAATCCGGTTACTCCCT
80	Cys_GCA_chr7:149286164-149286235 (-)	GGGGGTATAGCTCAGGGGTAGAGCACTTGACTGCAGATCAAGAGGTCC CTGGTTCAAATCCAGGTGCCCCCT
81	Cys_GCA_chr17:37025545-37025616 (-)	GGGGGTATAGCTCAGTGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CTGGTTCAAATCCGGGTGCCCCCT
82	Cys_GCA_chr15:80036997-80037069 (+)	GGGGGTATAGCTCAGTGGGTAGAGCATTTGACTGCAGATCAAGAGGTC CCCGGTTCAAATCCGGGTGCCCCCT
83	Cys_GCA_chr3:131947944-131948015 (-)	GGGGGTGTAGCTCAGTGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CTGGTTCAAATCCAGGTGCCCCCT
84	Cys_GCA_chr1:93981834-93981906 (-)	GGGGGTATAGCTCAGGTGGTAGAGCATTTGACTGCAGATCAAGAGGTC CCCGGTTCAAATCCGGGTGCCCCCT
85	Cys_GCA_chr14:73429679-73429750 (+)	GGGGGTATAGCTCAGGGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CCGGTTCAAATCCGGGGTGCCCCCT
86	Cys_GCA_chr3:131950642-131950713 (-)	GGGGGTATAGCTCAGGGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CTGGTTCAAATCCAGGGTGCCCCCT
87	Gln_CTG_chr6:18836402-18836473 (+)	GGTTCCATGGTGTAATGGTTAGCACTCTGGACTCTGAATCCAGCGATCC GAGTTCAAATCTCGGTGGGAACCT
88	Gln_CTG_chr6:27515531-27515602 (-)	GGTTCCATGGTGTAATGGTTAGCACTCTGGACTCTGAATCCAGCGATCC GAGTTCAAGTCTCGGTGGGAACCT
89	Gln_CTG_chr1:145963304-145963375 (+)	GGTTCCATGGTGTAATGGTGAGCACTCTGGACTCTGAATCCAGCGATC CGAGTTCGAGTCTCGGTGGGAACCT
90	Gln_CTG_chr1:147737382-147737453 (-)	GGTTCCATGGTGTAATGGTAAGCACTCTGGACTCTGAATCCAGCGATC CGAGTTCGAGTCTCGGTGGAACCT
91	Gln_CTG_chr6:27263212-27263283 (+)	GGTTCCATGGTGTAATGGTTAGCACTCTGGACTCTGAATCCGGTAATCC GAGTTCAAATCTCGGTGGAACCT
92	Gln_CTG_chr6:27759135-27759206 (-)	GGCCCCATGGTGTAATGGTCAGCACTCTGGACTCTGAATCCAGCGATC CGAGTTCAAATCTCGGTGGGACCC
93	Gln_CTG_chr1:147800937-147801008 (+)	GGTTCCATGGTGTAATGGTAAGCACTCTGGACTCTGAATCCAGCCATCT GAGTTCGAGTCTCTGTGGAACCT

94	Gln_TTG_chr17:47269890-47269961 (+)	GGTCCCATGGTGTAATGGTTAGCACTCTGGACTTTGAATCCAGCGATCC GAGTTCAAATCTCGGTGGGACCT
95	Gln_TTG_chr6:28557156-28557227 (+)	GGTCCCATGGTGTAATGGTTAGCACTCTGGACTTTGAATCCAGCAATCC GAGTTCGAATCTCGGTGGGACCT
96	Gln_TTG_chr6:26311424-26311495 (-)	GGCCCCATGGTGTAATGGTTAGCACTCTGGACTTTGAATCCAGCGATC CGAGTTCAAATCTCGGTGGGACCT
97	Gln_TTG_chr6:145503859-145503930 (+)	GGTCCCATGGTGTAATGGTTAGCACTCTGGGCTTTGAATCCAGCAATCC GAGTTCGAATCTTGGTGGGACCT
98	Glu_CTC_chr1:145399233-145399304 (-)	TCCCTGGTGGTCTAGTGGTTAGGATTCGGCGCTCTCACCGCCGCGGCCC GGGTTCGATTCCCGGTCAGGGAA
99	Glu_CTC_chr1:249168447-249168518 (+)	TCCCTGGTGGTCTAGTGGTTAGGATTCGGCGCTCTCACCGCCGCGGCCC GGGTTCGATTCCCGGTCAGGAAA
100	Glu_TTC_chr2:131094701-131094772 (-)	TCCCATATGGTCTAGCGGTTAGGATTCCTGGTTTTTCACCCAGGTGGCCC GGGTTCGACTCCCGGTATGGGAA
101	Glu_TTC_chr13:45492062-45492133 (-)	TCCCACATGGTCTAGCGGTTAGGATTCCTGGTTTTTCACCCAGGCGGCCC GGGTTCGACTCCCGGTGTGGGAA
102	Glu_TTC_chr1:17199078-17199149 (+)	TCCCTGGTGGTCTAGTGGCTAGGATTCGGCGCTTTTCACCGCCGCGGCCC GGGTTCGATTCCCGGCCAGGGAA
103	Glu_TTC_chr1:16861774-16861845 (-)	TCCCTGGTGGTCTAGTGGCTAGGATTCGGCGCTTTCACCGCCGCGGCCC GGGTTCGATTCCCGGTCAGGGAA
104	Gly_CCC_chr1:16872434-16872504 (-)	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCTCCCACGCGGGAGACCC GGGTTCAATTCCCGGCCAATGCA
105	Gly_CCC_chr2:70476123-70476193 (-)	GCGCCGCTGGTGTAGTGGTATCATGCAAGATTCCCATTCTTGCGACCCG GGTTCGATTCCCGGGCGGCGCA
106	Gly_CCC_chr17:19764175-19764245 (+)	GCATTGGTGGTTCAATGGTAGAATTCTCGCCTCCCACGCAGGAGACCC AGGTTCGATTCCTGGCCAATGCA
107	Gly_GCC_chr1:161413094-161413164 (+)	GCATGGGTGGTTCAGTGGTAGAATTCTCGCCTGCCACGCGGGAGGCCC GGGTTCGATTCCCGGCCCATGCA
108	Gly_GCC_chr1:161493637-161493707 (-)	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCTGCCACGCGGGAGGCCC GGGTTCGATTCCCGGCCAATGCA
109	Gly_GCC_chr16:70812114-70812184 (-)	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCTGCCACGCGGGAGGCCC GGGTTTGATTCCCGGCCAGTGCA

110	Gly_GCC_chr1:161450356-161450426 (+)	GCATAGGTGGTTCAGTGGTAGAATTCTTGCCTGCCACGCAGGAGGCCC AGGTTTGATTCCTGGCCCATGCA
111	Gly_GCC_chr16:70822597-70822667 (+)	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCTGCCATGGCGGGCGGCCG GGCTTCGATTCCTGGCCAATGCA
112	Gly_TCC_chr19:4724082-4724153 (+)	GCGTTGGTGGTATAGTGGTTAGCATAGCTGCCTTCCAAGCAGTTGACC CGGGTTCGATTCCCGGCCAACGCA
113	Gly_TCC_chr1:145397864-145397935 (-)	GCGTTGGTGGTATAGTGGTGAGCATAGCTGCCTTCCAAGCAGTTGACC CGGGTTCGATTCCCGGCCAACGCA
114	Gly_TCC_chr17:8124866-8124937 (+)	GCGTTGGTGGTATAGTGGTAAGCATAGCTGCCTTCCAAGCAGTTGACC CGGGTTCGATTCCCGGCCAACGCA
115	Gly_TCC_chr1:161409961-161410032 (-)	GCGTTGGTGGTATAGTGGTGAGCATAGTTGCCTTCCAAGCAGTTGACC CGGGCTCGATTCCCGCCCCAACGCA
116	His_GTG_chr1:145396881-145396952 (-)	GCCGTGATCGTATAGTGGTTAGTACTCTGCGTTGTGGCCGCAGCAACCT CGGTTCGAATCCGAGTCACGGCA
117	His_GTG_chr1:149155828-149155899 (-)	GCCATGATCGTATAGTGGTTAGTACTCTGCGCTGTGGCCGCAGCAACC TCGGTTCGAATCCGAGTCACGGCA
118	Ile_AAT_chr6:58149254-58149327 (+)	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGCGCTAATAACGCCAAGGT CGCGGGTTCGATCCCCGTACGGGCCA
119	Ile_AAT_chr6:27655967-27656040 (+)	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGGT CGCGGGTTCGATCCCCGTACTGGCCA
120	Ile_AAT_chr6:27242990-27243063 (-)	GGCTGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGGT CGCGGGTTCGATCCCCGTACTGGCCA
121	Ile_AAT_chr17:8130309-8130382 (-)	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGGT CGCGGGTTCGAACCCCGTACGGGCCA
122	Ile_AAT_chr6:26554350-26554423 (+)	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGGT CGCGGGTTCGATCCCCGTACGGGCCA
123	Ile_AAT_chr6:26745255-26745328 (-)	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCTAAGGT CGCGGGTTCGATCCCCGTACTGGCCA
124	Ile_AAT_chr6:26721221-26721294 (-)	GGCCGGTTAGCTCAGTTGGTCAGAGCGTGGTGCTAATAACGCCAAGGT CGCGGGTTCGATCCCCGTACGGGCCA
125	Ile_AAT_chr6:27636362-27636435 (+)	GGCCGGTTAGCTCAGTCGGCTAGAGCGTGGTGCTAATAACGCCAAGGT CGCGGGTTCGATCCCCGTACGGGCCA

126	Ile_AAT_chr6:27241739-27241812 (+)	GGCTGGTTAGTTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGGT CGTGGGTTCGATCCCCATATCGGCCA
127	Ile_GAT_chrX:3756418-3756491 (-)	GGCCGGTTAGCTCAGTTGGTAAGAGCGTGGTGCTGATAACACCAAGGT CGCGGGCTCGACTCCCGCACCGGCCA
128	Ile_TAT_chr19:39902808-39902900 (-)	GCTCCAGTGGCGCAATCGGTTAGCGCGCGGTACTTATATGACAGTGCG AGCGGAGCAATGCCGAGGTTGTGAGTTCGATCCTCACCTGGAGCA
129	Ile_TAT_chr2:43037676-43037768 (+)	GCTCCAGTGGCGCAATCGGTTAGCGCGCGGTACTTATACAGCAGTACA TGCAGAGCAATGCCGAGGTTGTGAGTTCGAGCCTCACCTGGAGCA
130	Ile_TAT_chr6:26988125-26988218 (+)	GCTCCAGTGGCGCAATCGGTTAGCGCGCGGTACTTATATGGCAGTATG TGTGCGAGTGATGCCGAGGTTGTGAGTTCGAGCCTCACCTGGAGCA
131	Ile_TAT_chr6:27599200-27599293 (+)	GCTCCAGTGGCGCAATCGGTTAGCGCGCGGTACTTATACAACAGTATA TGTGCGGGGTGATGCCGAGGTTGTGAGTTCGAGCCTCACCTGGAGCA
132	Ile_TAT_chr6:28505367-28505460 (+)	GCTCCAGTGGCGCAATCGGTTAGCGCGCGGTACTTATAAGACAGTGCA CCTGTGAGCAATGCCGAGGTTGTGAGTTCAAGCCTCACCTGGAGCA
133	Leu_AAG_chr5:180524474-180524555 (-)	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGGATTAAGGCTCCAGTCTC TTCGGAGGCGTGGGTTCGAATCCCACCGCTGCCA
134	Leu_AAG_chr5:180614701-180614782 (+)	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGGATTAAGGCTCCAGTCTC TTCGGGGGCGTGGGTTCGAATCCCACCGCTGCCA
135	Leu_AAG_chr6:28956779-28956860 (+)	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGGATTAAGGCTCCAGTCTC TTCGGGGGCGTGGGTTCAAATCCCACCGCTGCCA
136	Leu_AAG_chr6:28446400-28446481 (-)	GGTAGCGTGGCCGAGTGGTCTAAGACGCTGGATTAAGGCTCCAGTCTC TTCGGGGGCGTGGGTTTGAATCCCACCGCTGCCA
137	Leu_CAA_chr6:28864000-28864105 (-)	GTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGCTAAGCTTCC TCCGCGGTGGGGATTCTGGTCTCCAATGGAGGCGTGGGTTCGAATCCC
138	Leu_CAA_chr6:28908830-28908934 (+)	GTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGCTTGGCTTCC TCGTGTTGAGGATTCTGGTCTCCAATGGAGGCGTGGGTTCGAATCCCA
139	Leu_CAA_chr6:27573417-27573524 (-)	GTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGCTTACTGCTT CCTGTGTTCGGGTCTTCTGGTCTCCGTATGGAGGCGTGGGTTCGAATCC
140	Leu_CAA_chr6:27570348-27570454 (-)	GTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGTTGCTACTTC CCAGGTTTGGGGCTTCTGGTCTCCGCATGGAGGCGTGGGTTCGAATCC
141	Leu_CAA_chr1:249168054-249168159 (+)	GTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGGTAAGCACCT TGCCTGCGGGCTTTCTGGTCTCCGGATGGAGGCGTGGGTTCGAATCCC

142	Leu_CAA_chr11:9296790-9296863 (+)	GCCTCCTTAGTGCAGTAGGTAGCGCATCAGTCTCAAAATCTGAATGGT CCTGAGTTCAAGCCTCAGAGGGGGCA
143	Leu_CAA_chr1:161581736-161581819 (-)	GTCAGGATGGCCGAGCAGTCTTAAGGCGCTGCGTTCAAATCGCACCCT CCGCTGGAGGCGTGGGTTCGAATCCCACTTTTGACA
144	Leu_CAG_chr1:161411323-161411405 (+)	GTCAGGATGGCCGAGCGGTCTAAGGCGCTGCGTTCAGGTCGCAGTCTC CCCTGGAGGCGTGGGTTCGAATCCCACTCCTGACA
145	Leu_CAG_chr16:57333863-57333945 (+)	GTCAGGATGGCCGAGCGGTCTAAGGCGCTGCGTTCAGGTCGCAGTCTC CCCTGGAGGCGTGGGTTCGAATCCCACTTCTGACA
146	Leu_TAA_chr6:144537684-144537766 (+)	ACCAGGATGGCCGAGTGGTTAAGGCGTTGGACTTAAGATCCAATGGAC ATATGTCCGCGTGGGTTCGAACCCCACTCCTGGTA
147	Leu_TAA_chr6:27688898-27688980 (-)	ACCGGGATGGCCGAGTGGTTAAGGCGTTGGACTTAAGATCCAATGGGC TGGTGCCCGCGTGGGTTCGAACCCCACTCTCGGTA
148	Leu_TAA_chr11:59319228-59319310 (+)	ACCAGAATGGCCGAGTGGTTAAGGCGTTGGACTTAAGATCCAATGGAT TCATATCCGCGTGGGTTCGAACCCCACTTCTGGTA
149	Leu_TAA_chr6:27198334-27198416 (-)	ACCGGGATGGCTGAGTGGTTAAGGCGTTGGACTTAAGATCCAATGGAC AGGTGTCCGCGTGGGTTCGAGCCCCACTCCCGGTA
150	Leu_TAG_chr17:8023632-8023713 (-)	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGGATTTAGGCTCCAGTCTC TTCGGAGGCGTGGGTTCGAATCCCACCGCTGCCA
151	Leu_TAG_chr14:21093529-21093610 (+)	GGTAGTGTGGCCGAGCGGTCTAAGGCGCTGGATTTAGGCTCCAGTCTC TTCGGGGGGCGTGGGTTCGAATCCCACCACTGCCA
152	Leu_TAG_chr16:22207032-22207113 (-)	GGTAGCGTGGCCGAGTGGTCTAAGGCGCTGGATTTAGGCTCCAGTCAT TTCGATGGCGTGGGTTCGAATCCCACCGCTGCCA
153	Lys_CTT_chr14:58706613-58706685 (-)	GCCCGGCTAGCTCAGTCGGTAGAGCATGGGACTCTTTAATCCCAGGGTC GTGGGTTCGAGCCCCCACGTTGGGCG
154	Lys_CTT_chr19:36066750-36066822 (+)	GCCCAGCTAGCTCAGTCGGTAGAGCATAAGACTCTTTAATCTCAGGGTT GTGGATTCGTGCCCCATGCTGGGTG
155	Lys_CTT_chr19:52425393-52425466 (-)	GCAGCTAGCTCAGTCGGTAGAGCATGAGACTCTTTAATCTCAGGGTCAT GGGTTCGTGCCCCATGTTGGGTGCCA
156	Lys_CTT_chr1:145395522-145395594 (-)	GCCCGGCTAGCTCAGTCGGTAGAGCATGAGACTCTTTAATCTCAGGGTC GTGGGTTCGAGCCCCCACGTTGGGCG
157	Lys_CTT_chr16:3207406-3207478 (-)	GCCCGGCTAGCTCAGTCGGTAGAGCATGAGACCCCTTAATCTCAGGGTC GTGGGTTCGAGCCCCCACGTTGGGCG

158	Lys_CTT_chr16:3241501-3241573 (+)	GCCCGGCTAGCTCAGTCGGTAGAGCATGGGACTCTTAATCTCAGGGTC GTGGGTTCGAGCCCCACGTTGGGCG
159	Lys_CTT_chr16:3230555-3230627 (-)	GCCCGGCTAGCTCAGTCGATAGAGCATGAGACTCTTAATCTCAGGGTC GTGGGTTCGAGCCGCACGTTGGGCG
160	Lys_CTT_chr1:55423542-55423614 (-)	GCCCAGCTAGCTCAGTCGGTAGAGCATGAGACTCTTAATCTCAGGGTC ATGGGTTTGAGCCCCACGTTTGGTG
161	Lys_CTT_chr16:3214939-3215011 (+)	GCCTGGCTAGCTCAGTCGGCAAAGCATGAGACTCTTAATCTCAGGGTC GTGGGCTCGAGCTCCATGTTGGGCG
162	Lys_CTT_chr5:26198539-26198611 (-)	GCCCGACTACCTCAGTCGGTGGAGCATGGGACTCTTCATCCCAGGGTT GTGGGTTCGAGCCCCACACATTGGGCA
163	Lys_TTT_chr16:73512216-73512288 (-)	GCCTGGATAGCTCAGTTGGTAGAGCATCAGACTTTTAATCTGAGGGTC CAGGGTTCAAGTCCCTGTTCAGGCA
164	Lys_TTT_chr12:27843306-27843378 (+)	ACCCAGATAGCTCAGTCAGTAGAGCATCAGACTTTTAATCTGAGGGTC CAAGGTTCATGTCCCTTTTTGGGTG
165	Lys_TTT_chr11:122430655-122430727 (+)	GCCTGGATAGCTCAGTTGGTAGAGCATCAGACTTTTAATCTGAGGGTC CAGGGTTCAAGTCCCTGTTCAGGCG
166	Lys_TTT_chr1:204475655-204475727 (+)	GCCCGGATAGCTCAGTCGGTAGAGCATCAGACTTTTAATCTGAGGGTC CAGGGTTCAAGTCCCTGTTCGGGCG
167	Lys_TTT_chr6:27559593-27559665 (-)	GCCTGGATAGCTCAGTCGGTAGAGCATCAGACTTTTAATCTGAGGGTC CAGGGTTCAAGTCCCTGTTCAGGCG
168	Lys_TTT_chr11:59323902-59323974 (+)	GCCCGGATAGCTCAGTCGGTAGAGCATCAGACTTTTAATCTGAGGGTC CGGGGTTCAAGTCCCTGTTCGGGCG
169	Lys_TTT_chr6:27302769-27302841 (-)	GCCTGGGTAGCTCAGTCGGTAGAGCATCAGACTTTTAATCTGAGGGTC CAGGGTTCAAGTCCCTGTCCAGGCG
170	Lys_TTT_chr6:28715521-28715593 (+)	GCCTGGATAGCTCAGTTGGTAGAACATCAGACTTTTAATCTGACGGTG CAGGGTTCAAGTCCCTGTTCAGGCG
171	Met_CAT_chr8:124169470-124169542 (-)	GCCTCGTTAGCGCAGTAGGTAGCGCGTCAGTCTCATAATCTGAAGGTC GTGAGTTCGATCCTCACACGGGGCA
172	Met_CAT_chr16:71460396-71460468 (+)	GCCCTCTTAGCGCAGTGGGCAGCGCGTCAGTCTCATAATCTGAAGGTC CTGAGTTCGAGCCTCAGAGAGGGCA
173	Met_CAT_chr6:28912352-28912424 (+)	GCCTCCTTAGCGCAGTAGGCAGCGCGTCAGTCTCATAATCTGAAGGTC CTGAGTTCGAACCTCAGAGGGGGCA

174	Met_CAT_chr6:26735574-26735646 (-)	GCCCTCTTAGCGCAGCGGGCAGCGCGTCAGTCTCATAATCTGAAGGTC CTGAGTTCGAGCCTCAGAGAGGGCA
175	Met_CAT_chr6:26701712-26701784 (+)	GCCCTCTTAGCGCAGCTGGCAGCGCGTCAGTCTCATAATCTGAAGGTC CTGAGTTCAAGCCTCAGAGAGGGCA
176	Met_CAT_chr16:87417628-87417700 (-)	GCCTCGTTAGCGCAGTAGGCAGCGCGTCAGTCTCATAATCTGAAGGTC GTGAGTTCGAGCCTCACACGGGGCA
177	Met_CAT_chr6:58168492-58168564 (-)	GCCCTCTTAGTGCAGCTGGCAGCGCGTCAGTTTCATAATCTGAAAGTCC TGAGTTCAAGCCTCAGAGAGGGCA
178	Phe_GAA_chr6:28758499-28758571 (-)	GCCGAAATAGCTCAGTTGGGAGAGCGTTAGACTGAAGATCTAAAGGTC CCTGGTTCGATCCCGGGTTTCGGCA
179	Phe_GAA_chr11:59333853-59333925 (-)	GCCGAAATAGCTCAGTTGGGAGAGCGTTAGACTGAAGATCTAAAGGTC CCTGGTTCAATCCCGGGTTTCGGCA
180	Phe_GAA_chr6:28775610-28775682 (-)	GCCGAGATAGCTCAGTTGGGAGAGCGTTAGACTGAAGATCTAAAGGTC CCTGGTTCAATCCCGGGTTTCGGCA
181	Phe_GAA_chr6:28791093-28791166 (-)	GCCGAAATAGCTCAGTTGGGAGAGCGTTAGACCGAAGATCTTAAAGGT CCCTGGTTCAATCCCGGGTTTCGGCA
182	Phe_GAA_chr6:28731374-28731447 (-)	GCTGAAATAGCTCAGTTGGGAGAGCGTTAGACTGAAGATCTTAAAGTT CCCTGGTTCAACCCTGGGTTTCAGCC
183	Pro_AGG_chr16:3241989-3242060 (+)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTTAGGATGCGAGAGGTCC CGGGTTCAAATCCCGGACGAGCCC
184	Pro_AGG_chr1:167684725-167684796 (-)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTTAGGGTGCGAGAGGTCC CGGGTTCAAATCCCGGACGAGCCC
185	Pro_CGG_chr1:167683962-167684033 (+)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTTCGGGTGCGAGAGGTCC CGGGTTCAAATCCCGGACGAGCCC
186	Pro_CGG_chr6:27059521-27059592 (+)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTTCGGGTGTGAGAGGTCCC GGGTTCAAATCCCGGACGAGCCC
187	Pro_TGG_chr14:21101165-21101236 (+)	GGCTCGTTGGTCTAGTGGTATGATTCTCGCTTTGGGTGCGAGAGGTCCC GGGTTCAAATCCCGGACGAGCCC
188	Pro_TGG_chr11:75946869-75946940 (-)	GGCTCGTTGGTCTAGGGGTATGATTCTCGGTTTGGGTCCGAGAGGTCCC GGGTTCAAATCCCGGACGAGCCC
189	Pro_TGG_chr5:180615854-180615925 (-)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTTTGGGTGCGAGAGGTCCC GGGTTCAAATCCCGGACGAGCCC

190	SeC_TCA_chr19:45981859-45981945 (-)	GCCCGGATGATCCTCAGTGGTCTGGGGTGCAGGCTTCAAACCTGTAGC
		TGTCTAGCGACAGAGTGGTTCAATTCCACCTTTCGGGCG
191	SeC_TCA_chr22:44546537-44546620 (+)	GCTCGGATGATCCTCAGTGGTCTGGGGTGCAGGCTTCAAACCTGTAGC
		TGTCTAGTGACAGAGTGGTTCAATTCCACCTTTGTA
192	Ser_AGA_chr6:27509554-27509635 (-)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTAGAAATCCATTGGGG
		TTTCCCCCGCGCAGGTTCGAATCCTGCCGACTACG
193	Ser_AGA_chr6:26327817-26327898 (+)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTAGAAATCCATTGGGG
		TCTCCCCCGCGCAGGTTCGAATCCTGCCGACTACG
194	Ser_AGA_chr6:27499987-27500068 (+)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTAGAAATCCATTGGGG
		TTTCCCCCACGCAGGTTCGAATCCTGCCGACTACG
195	Ser_AGA_chr6:27521192-27521273 (-)	GTAGTCGTGGCCGAGTGGTTAAGGTGATGGACTAGAAACCCATTGGGG
		TCTCCCCCGCGCAGGTTCGAATCCTGCCGACTACG
196	Ser_CGA_chr17:8042199-8042280 (-)	GCTGTGATGGCCGAGTGGTTAAGGCGTTGGACTCGAAATCCAATGGGG
		TCTCCCCCGCGCAGGTTCGAATCCTGCTCACAGCG
197	Ser_CGA_chr6:27177628-27177709 (+)	GCTGTGATGGCCGAGTGGTTAAGGCGTTGGACTCGAAATCCAATGGGG
		TCTCCCCCGCGCAGGTTCAAATCCTGCTCACAGCG
198	Ser_CGA_chr6:27640229-27640310 (-)	GCTGTGATGGCCGAGTGGTTAAGGTGTTGGACTCGAAATCCAATGGGG
		GTTCCCCCGCGCAGGTTCAAATCCTGCTCACAGCG
199	Ser_CGA_chr12:56584148-56584229 (+)	GTCACGGTGGCCGAGTGGTTAAGGCGTTGGACTCGAAATCCAATGGGG
		TTTCCCCCGCACAGGTTCGAATCCTGTTCGTGACG
200	Ser_GCT_chr6:27065085-27065166 (+)	GACGAGGTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTGC
		TCTGCACGCGTGGGTTCGAATCCCACCCTCGTCG
201	Ser_GCT_chr6:27265775-27265856 (+)	GACGAGGTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTGC
		TCTGCACGCGTGGGTTCGAATCCCACCTTCGTCG
202	Ser_GCT_chr11:66115591-66115672 (+)	GACGAGGTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTGC
		TTTGCACGCGTGGGTTCGAATCCCATCCTCGTCG
203	Ser_GCT_chr6:28565117-28565198 (-)	GACGAGGTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTGC
		TCTGCACGCGTGGGTTCGAATCCCATCCTCGTCG
204	Ser_GCT_chr6:28180815-28180896 (+)	GACGAGGTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTGC
		TCTGCACACGTGGGTTCGAATCCCATCCTCGTCG
205	Ser_GCT_chr6:26305718-26305801 (-)	GGAGAGGCCTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGT
		GCTCTGCACGCGTGGGTTCGAATCCCATCCTCGTCG

206	Ser_TGA_chr10:69524261-69524342 (+)	GCAGCGATGGCCGAGTGGTTAAGGCGTTGGACTTGAAATCCAATGGGG TCTCCCCCGCGCAGGTTCGAACCCTGCTCGCTGCG
207	Ser_TGA_chr6:27513468-27513549 (+)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTTGAAATCCATTGGGG TTTCCCCCGCGCAGGTTCGAATCCTGCCGACTACG
208	Ser_TGA_chr6:26312824-26312905 (-)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTTGAAATCCATTGGGG TCTCCCCCGCGCAGGTTCGAATCCTGCCGACTACG
209	Ser_TGA_chr6:27473607-27473688 (-)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTTGAAATCCATTGGGG TTTCCCCCGCGCAGGTTCGAATCCTGTCGGCTACG
210	Thr_AGT_chr17:8090478-8090551 (+)	GGCGCCGTGGCTTAGTTGGTTAAAGCGCCTGTCTAGTAAACAGGAGAT CCTGGGTTCGAATCCCAGCGGTGCCT
211	Thr_AGT_chr6:26533145-26533218 (-)	GGCTCCGTGGCTTAGCTGGTTAAAGCGCCTGTCTAGTAAACAGGAGAT CCTGGGTTCGAATCCCAGCGGGGCCT
212	Thr_AGT_chr6:28693795-28693868 (+)	GGCTCCGTAGCTTAGTTGGTTAAAGCGCCTGTCTAGTAAACAGGAGAT CCTGGGTTCGACTCCCAGCGGGGCCT
213	Thr_AGT_chr6:27694473-27694546 (+)	GGCTTCGTGGCTTAGCTGGTTAAAGCGCCTGTCTAGTAAACAGGAGAT CCTGGGTTCGAATCCCAGCGAGGCCT
214	Thr_AGT_chr17:8042770-8042843 (-)	GGCGCCGTGGCTTAGCTGGTTAAAGCGCCTGTCTAGTAAACAGGAGAT CCTGGGTTCGAATCCCAGCGGTGCCT
215	Thr_AGT_chr6:27130050-27130123 (+)	GGCCCTGTGGCTTAGCTGGTCAAAGCGCCTGTCTAGTAAACAGGAGAT CCTGGGTTCGAATCCCAGCGGGGCCT
216	Thr_CGT_chr6:28456770-28456843 (-)	GGCTCTATGGCTTAGTTGGTTAAAGCGCCTGTCTCGTAAACAGGAGAT CCTGGGTTCGACTCCCAGTGGGGCCT
217	Thr_CGT_chr16:14379750-14379821 (+)	GGCGCGGTGGCCAAGTGGTAAGGCGTCGGTCTCGTAAACCGAAGATCA CGGGTTCGAACCCCGTCCGTGCCT
218	Thr_CGT_chr6:28615984-28616057 (-)	GGCTCTGTGGCTTAGTTGGCTAAAGCGCCTGTCTCGTAAACAGGAGAT CCTGGGTTCGAATCCCAGCGGGGCCT
219	Thr_CGT_chr17:29877093-29877164 (+)	GGCGCGGTGGCCAAGTGGTAAGGCGTCGGTCTCGTAAACCGAAGATCG CGGGTTCGAACCCCGTCCGTGCCT
220	Thr_CGT_chr6:27586135-27586208 (+)	GGCCCTGTAGCTCAGCGGTTGGAGCGCTGGTCTCGTAAACCTAGGGGT CGTGAGTTCAAATCTCACCAGGGCCT
221	Thr_TGT_chr6:28442329-28442402 (-)	GGCTCTATGGCTTAGTTGGTTAAAGCGCCTGTCTTGTAAACAGGAGAT CCTGGGTTCGAATCCCAGTAGAGCCT

222	Thr_TGT_chr1:222638347-222638419 (+)	GGCTCCATAGCTCAGTGGTTAGAGCACTGGTCTTGTAAACCAGGGGTC GCGAGTTCGATCCTCGCTGGGGCCT
223	Thr_TGT_chr14:21081949-21082021 (-)	GGCTCCATAGCTCAGGGGTTAGAGGCGCTGGTCTTGTAAACCAGGGGTC GCGAGTTCAATTCTCGCTGGGGCCT
224	Thr_TGT_chr14:21099319-21099391 (-)	GGCTCCATAGCTCAGGGGTTAGAGCACTGGTCTTGTAAACCAGGGGTC GCGAGTTCAAATCTCGCTGGGGCCT
225	Thr_TGT_chr14:21149849-21149921 (+)	GGCCCTATAGCTCAGGGGTTAGAGCACTGGTCTTGTAAACCAGGGGTC GCGAGTTCAAATCTCGCTGGGGCCT
226	Thr_TGT_chr5:180618687-180618758 (-)	GGCTCCATAGCTCAGGGGTTAGAGCACTGGTCTTGTAAACCAGGGTCG CGAGTTCAAATCTCGCTGGGGCCT
227	Trp_CCA_chr17:8124187-8124258 (-)	GGCCTCGTGGCGCAACGGTAGCGCGTCTGACTCCAGATCAGAAGGTTG CGTGTTCAAATCACGTCGGGGGTCA
228	Trp_CCA_chr17:19411494-19411565 (+)	GACCTCGTGGCGCAATGGTAGCGCGTCTGACTCCAGATCAGAAGGTTG CGTGTTCAAGTCACGTCGGGGTCA
229	Trp_CCA_chr6:26319330-26319401 (-)	GACCTCGTGGCGCAACGGTAGCGCGTCTGACTCCAGATCAGAAGGTTG CGTGTTCAAATCACGTCGGGGTCA
230	Trp_CCA_chr12:98898030-98898101 (+)	GACCTCGTGGCGCAACGGTAGCGCGTCTGACTCCAGATCAGAAGGCTG CGTGTTCGAATCACGTCGGGGTCA
231	Trp_CCA_chr7:99067307-99067378 (+)	GACCTCGTGGCGCAACGGCAGCGCGTCTGACTCCAGATCAGAAGGTTG CGTGTTCAAATCACGTCGGGGTCA
232	Tyr_ATA_chr2:219110549-219110641 (+)	CCTTCAATAGTTCAGCTGGTAGAGCAGAGGACTATAGCTACTTCCTCA GTAGGAGACGTCCTTAGGTTGCTGGTTCGATTCCAGCTTGAAGGA
233	Tyr_GTA_chr6:26569086-26569176 (+)	CCTTCGATAGCTCAGTTGGTAGAGCGGAGGACTGTAGTTGGCTGTGTC CTTAGACATCCTTAGGTCGCTGGTTCGAATCCGGCTCGAAGGA
234	Tyr_GTA_chr2:27273650-27273738 (+)	CCTTCGATAGCTCAGTTGGTAGAGCGGAGGACTGTAGTGGATAGGGCG TGGCAATCCTTAGGTCGCTGGTTCGATTCCGGCTCGAAGGA
235	Tyr_GTA_chr6:26577332-26577420 (+)	CCTTCGATAGCTCAGTTGGTAGAGCGGAGGACTGTAGGCTCATTAAGC AAGGTATCCTTAGGTCGCTGGTTCGAATCCGGCTCGGAGGA
236	Tyr_GTA_chr14:21125623-21125716 (-)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGATTGTATAGAC ATTTGCGGACATCCTTAGGTCGCTGGTTCGATTCCAGCTCGAAGGA
237	Tyr_GTA_chr8:67025602-67025694 (+)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGCTACTTCCTCA GCAGGAGACATCCTTAGGTCGCTGGTTCGATTCCGGCTCGAAGGA

238	Tyr_GTA_chr8:67026223-67026311 (+)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGGCGCGCGCCCG TGGCCATCCTTAGGTCGCTGGTTCGATTCCGGCTCGAAGGA
239	Tyr_GTA_chr14:21121258-21121351 (-)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGCCTGTAGAAAC ATTTGTGGACATCCTTAGGTCGCTGGTTCGATTCCGGCTCGAAGGA
240	Tyr_GTA_chr14:21131351-21131444 (-)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGATTGTACAGAC ATTTGCGGACATCCTTAGGTCGCTGGTTCGATTCCGGCTCGAAGGA
241	Tyr_GTA_chr14:21151432-21151520 (+)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGTACTTAATGTG TGGTCATCCTTAGGTCGCTGGTTCGATTCCGGCTCGAAGGA
242	Tyr_GTA_chr6:26595102-26595190 (+)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGGGGTTTGAATG TGGTCATCCTTAGGTCGCTGGTTCGAATCCGGCTCGGAGGA
243	Tyr_GTA_chr14:21128117-21128210 (-)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGACTGCGGAAAC GTTTGTGGACATCCTTAGGTCGCTGGTTCAATTCCGGCTCGAAGGA
244	Tyr_GTA_chr6:26575798-26575887 (+)	CTTTCGATAGCTCAGTTGGTAGAGCGGAGGACTGTAGGTTCATTAAAC TAAGGCATCCTTAGGTCGCTGGTTCGAATCCGGCTCGAAGGA
245	Tyr_GTA_chr8:66609532-66609619 (-)	TCTTCAATAGCTCAGCTGGTAGAGCGGAGGACTGTAGGTGCACGCCCG TGGCCATTCTTAGGTGCTGGTTTGATTCCGACTTGGAGAG
246	Val_AAC_chr3:169490018-169490090 (+)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTAACACGCGAAAGGTCC CCGGTTCGAAACCGGGCGGAAACA
247	Val_AAC_chr5:180615416-180615488 (-)	GTTTCCGTAGTGTAGTGGTCATCACGTTCGCCTAACACGCGAAAGGTC CCCGGTTCGAAACCGGGCGGAAACA
248	Val_AAC_chr6:27618707-27618779 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTAACACGCGAAAGGTCC CTGGATCAAAACCAGGCGGAAACA
249	Val_AAC_chr6:27648885-27648957 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTAACACGCGAAAGGTCC GCGGTTCGAAACCGGGCGGAAACA
250	Val_AAC_chr6:27203288-27203360 (+)	GTTTCCGTAGTGTAGTGGTTATCACGTTTGCCTAACACGCGAAAGGTCC CCGGTTCGAAACCGGGCAGAAACA
251	Val_AAC_chr6:28703206-28703277 (-)	GGGGGTGTAGCTCAGTGGTAGAGCGTATGCTTAACATTCATGAGGCTC TGGGTTCGATCCCCAGCACTTCCA
252	Val_CAC_chr1:161369490-161369562 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTCACACGCGAAAGGTCC CCGGTTCGAAACCGGGCGGAAACA
253	Val_CAC_chr6:27248049-27248121 (-)	GCTTCTGTAGTGTAGTGGTTATCACGTTCGCCTCACACGCGAAAGGTCC CCGGTTCGAAACCGGGCAGAAGCA

254	Val_CAC_chr19:4724647-4724719 (-)	GTTTCCGTAGTGTAGCGGTTATCACATTCGCCTCACACGCGAAAGGTCC CCGGTTCGATCCCGGGCGGAAACA
255	Val_CAC_chr1:149298555-149298627 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTCACACGCGAAAGGTCC CCGGTTCGAAACTGGGCGGAAACA
256	Val_CAC_chr1:149684088-149684161 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTCACACGCGTAAAGGTC CCCGGTTCGAAACCGGGCGGAAACA
257	Val_CAC_chr6:27173867-27173939 (-)	GTTTCCGTAGTGGAGTGGTTATCACGTTCGCCTCACACGCGAAAGGTC CCCGGTTTGAAACCAGGCGGAAACA
258	Val_TAC_chr11:59318102-59318174 (-)	GGTTCCATAGTGTAGTGGTTATCACGTCTGCTTTACACGCAGAAGGTCC TGGGTTCGAGCCCCAGTGGAACCA
259	Val_TAC_chr11:59318460-59318532 (-)	GGTTCCATAGTGTAGCGGTTATCACGTCTGCTTTACACGCAGAAGGTCC TGGGTTCGAGCCCCAGTGGAACCA
260	Val_TAC_chr10:5895674-5895746 (-)	GGTTCCATAGTGTAGTGGTTATCACATCTGCTTTACACGCAGAAGGTCC TGGGTTCAAGCCCCAGTGGAACCA
261	Val_TAC_chr6:27258405-27258477 (+)	GTTTCCGTGGTGTAGTGGTTATCACATTCGCCTTACACGGCGAAAGGTCC TCGGGGTCGAAACCGAGCGGGAAACA
262	iMet_CAT_chr1:153643726-153643797 (+)	AGCAGAGTGGCGCAGCGGAAGCGTGCTGGGCCCATAACCCAGAGGTC GATGGATCGAAACCATCCTCTGCTA
263	iMet_CAT_chr6:27745664-27745735 (+)	AGCAGAGTGGCGCAGCGGAAGCGTGCTGGGCCCATAACCCAGAGGTC GATGGATCTAAACCATCCTCTGCTA
264	Glu_TTC_chr1:16861773-16861845 (-)	TCCCTGGTGGTCTAGTGGCTAGGATTCGGCGCTTTCACCGCCGCGGCCC GGGTTCGATTCCCGGTCAGGGAAT
265	Gly_CCC_chr1:17004765-17004836 (-)	GCGTTGGTGGTTTAGTGGTAGAATTCTCGCCTCCCATGCGGGGAGACCC GGGTTCAATTCCCGGCCACTGCAC
266	Gly_CCC_chr1:17053779-17053850 (+)	GGCCTTGGTGGTGCAGTGGTAGAATTCTCGCCTCCCACGTGGGAGACC CGGGTTCAATTCCCGGCCAATGCA
267	Glu_TTC_chr1:17199077-17199149 (+)	GTCCCTGGTGGTCTAGTGGCTAGGATTCGGCGCTTTCACCGCCGCGGCC CGGGTTCGATTCCCGGCCAGGGAA
268	Asn_GTT_chr1:17216171-17216245 (+)	TGTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGA TTGGTGGTTCGAGCCCACCCAGGGACG
269	Arg_TCT_chr1:94313128-94313213 (+)	TGGCTCCGTGGCGCAATGGATAGCGCATTGGACTTCTAGAGGCTGAAG GCATTCAAAGGTTCCGGGTTCGAGTCCCGGCGGAGTCG

270	Lys_CTT_chr1:145395521-145395594 (-)	GCCCGGCTAGCTCAGTCGGTAGAGCATGAGACTCTTAATCTCAGGGTC GTGGGTTCGAGCCCCACGTTGGGCGC
271	His_GTG_chr1:145396880-145396952 (-)	GCCGTGATCGTATAGTGGTTAGTACTCTGCGTTGTGGCCGCAGCAACCT CGGTTCGAATCCGAGTCACGGCAG
272	Gly_TCC_chr1:145397863-145397935 (-)	GCGTTGGTGGTATAGTGGTGAGCATAGCTGCCTTCCAAGCAGTTGACC CGGGTTCGATTCCCGGCCAACGCAG
273	Glu_CTC_chr1:145399232-145399304 (-)	TCCCTGGTGGTCTAGTGGTTAGGATTCGGCGCTCTCACCGCCGCGGCCC GGGTTCGATTCCCGGTCAGGGAAA
274	Gln_CTG_chr1:145963303-145963375 (+)	AGGTTCCATGGTGTAATGGTGAGCACTCTGGACTCTGAATCCAGCGAT CCGAGTTCGAGTCTCGGTGGAACCT
275	Asn_GTT_chr1:148000804-148000878 (+)	TGTCTCTGTGGCGTAGTCGGTTAGCGCGTTCGGCTGTTAACCGAAAAGT TGGTGGTTCGAGCCCACCCAGGAACG
276	Asn_GTT_chr1:148248114-148248188 (+)	TGTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGG TTGGTGGTTCGAGCCCACCCAGGGACG
277	Asn_GTT_chr1:148598313-148598387 (-)	GTCTCTGTGGCGCAATCGGTTAGCGCATTCGGCTGTTAACCGAAAGGT TGGTGGTTCGAGCCCACCCAGGGACGC
278	Asn_GTT_chr1:149230569-149230643 (-)	GTCTCTGTGGCGCAATGGGTTAGCGCGTTCGGCTGTTAACCGAAAGGT TGGTGGTTCGAGCCCATCCAGGGACGC
279	Val_CAC_chr1:149294665-149294736 (-)	GCACTGGTGGTTCAGTGGTAGAATTCTCGCCTCACACGCGGGACACCC GGGTTCAATTCCCGGTCAAGGCAA
280	Val_CAC_chr1:149298554-149298627 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTCACACGCGAAAGGTCC CCGGTTCGAAACTGGGCGGAAACAG
281	Gly_CCC_chr1:149680209-149680280 (-)	GCACTGGTGGTTCAGTGGTAGAATTCTCGCCTCCCACGCGGGAGACCC GGGTTTAATTCCCGGTCAAGATAA
282	Val_CAC_chr1:149684087-149684161 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTCACACGCGTAAAGGTC CCCGGTTCGAAACCGGGCGGAAACAT
283	Met_CAT_chr1:153643725-153643797 (+)	TAGCAGAGTGGCGCAGCGGAAGCGTGCTGGGCCCATAACCCAGAGGT CGATGGATCGAAACCATCCTCTGCTA
284	Val_CAC_chr1:161369489-161369562 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTCACACGCGAAAGGTCC CCGGTTCGAAACCGGGCGGAAACAA
285	Asp_GTC_chr1:161410614-161410686 (-)	TCCTCGTTAGTATAGTGGTGAGTATCCCCGCCTGTCACGCGGGAGACC GGGGTTCGATTCCCCGACGGGGAGG

286	Gly_GCC_chr1:161413093-161413164 (+)	TGCATGGGTGGTTCAGTGGTAGAATTCTCGCCTGCCACGCGGGAGGCC CGGGTTCGATTCCCGGCCCATGCA
287	Glu_CTC_chr1:161417017-161417089 (-)	TCCCTGGTGGTCTAGTGGTTAGGATTCGGCGCTCTCACCGCCGCGGCCC GGGTTCGATTCCCGGTCAGGGAAG
288	Asp_GTC_chr1:161492934-161493006 (+)	ATCCTTGTTACTATAGTGGTGAGTATCTCTGCCTGTCATGCGTGAGAGA GGGGGTCGATTCCCCGACGGGGAG
289	Gly_GCC_chr1:161493636-161493707 (-)	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCTGCCACGCGGGAGGCCC GGGTTCGATTCCCGGCCAATGCAC
290	Leu_CAG_chr1:161500131-161500214 (-)	GTCAGGATGGCCGAGCGGTCTAAGGCGCTGCGTTCAGGTCGCAGTCTC CCCTGGAGGCGTGGGTTCGAATCCCACTCCTGACAA
291	Gly_TCC_chr1:161500902-161500974 (+)	CGCGTTGGTGGTATAGTGGTGAGCATAGCTGCCTTCCAAGCAGTTGAC CCGGGGTTCGATTCCCGGCCAACGCA
292	Asn_GTT_chr1:161510030-161510104 (+)	CGTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGG TTGGTGGTTCGATCCCACCCAGGGACG
293	Glu_TTC_chr1:161582507-161582579 (+)	CGCGTTGGTGGTGTAGTGGTGAGCACAGCTGCCTTTCAAGCAGTTAAC GCGGGTTCGATTCCCGGGGTAACGAA
294	Pro_CGG_chr1:167683961-167684033 (+)	CGGCTCGTTGGTCTAGGGGTATGATTCTCGCTTCGGGTGCGAGAGGTC CCGGGTTCAAATCCCGGACGAGCCC
295	Pro_AGG_chr1:167684724-167684796 (-)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTTAGGGTGCGAGAGGTCC CGGGTTCAAATCCCGGACGAGCCCT
296	Lys_TTT_chr1:204475654-204475727 (+)	CGCCCGGATAGCTCAGTCGGTAGAGCATCAGACTTTTAATCTGAGGGT CCAGGGTTCAAGTCCCTGTTCGGGCG
297	Lys_TTT_chr1:204476157-204476230 (-)	GCCCGGATAGCTCAGTCGGTAGAGCATCAGACTTTTAATCTGAGGGTC CAGGGTTCAAGTCCCTGTTCGGGCGT
298	Leu_CAA_chr1:249168053-249168159 (+)	TGTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGGTAAGCACC TTGCCTGCGGGCTTTCTGGTCTCCGGATGGAGGCGTGGGTTCGAATCCC
299	Glu_CTC_chr1:249168446-249168518 (+)	TTCCCTGGTGGTCTAGTGGTTAGGATTCGGCGCTCTCACCGCCGCGGCC CGGGTTCGATTCCCGGTCAGGAAA
300	Tyr_GTA_chr2:27273649-27273738 (+)	GCCTTCGATAGCTCAGTTGGTAGAGCGGAGGACTGTAGTGGATAGGGC GTGGCAATCCTTAGGTCGCTGGTTCGATTCCGGCTCGAAGGA
301	Ala_AGC_chr2:27274081-27274154 (+)	CGGGGGATTAGCTCAAATGGTAGAGCGCTCGCTTAGCATGCGAGAGGT AGCGGGATCGATGCCCGCATCCTCCA

302	Ile_TAT_chr2:43037675-43037768 (+)	AGCTCCAGTGGCGCAATCGGTTAGCGCGCGGTACTTATACAGCAGTAC ATGCAGAGCAATGCCGAGGTTGTGAGTTCGAGCCTCACCTGGAGCA
303	Gly_CCC_chr2:70476122-70476193 (-)	GCGCCGCTGGTGTAGTGGTATCATGCAAGATTCCCATTCTTGCGACCCG GGTTCGATTCCCGGGGCGGCGCAT
304	Glu_TTC_chr2:131094700-131094772 (-)	TCCCATATGGTCTAGCGGTTAGGATTCCTGGTTTTCACCCAGGTGGCCC GGGTTCGACTCCCGGTATGGGAAC
305	Ala_CGC_chr2:157257280-157257352 (+)	GGGGGATGTAGCTCAGTGGTAGAGCGCGCGCTTCGCATGTGTGAGGTC CCGGGTTCAATCCCCGGCATCTCCA
306	Gly_GCC_chr2:157257658-157257729 (-)	GCATTGGTGGTTCAGTGGTAGAATTCTCGCCTGCCACGCGGGAGGCCC GGGTTCGATTCCCGGCCAATGCAA
307	Arg_ACG_chr3:45730490-45730563 (-)	GGGCCAGTGGCGCAATGGATAACGCGTCTGACTACGGATCAGAAGATT CTAGGTTCGACTCCTGGCTGGCTCGC
308	Val_AAC_chr3:169490017-169490090 (+)	GGTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTAACACGCGAAAGGT CCCCGGTTCGAAACCGGGCGGAAACA
309	Val_AAC_chr5:180596609-180596682 (+)	AGTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTAACACGCGAAAGGT CCCCGGTTCGAAACCGGGCGGAAACA
310	Leu_AAG_chr5:180614700-180614782 (+)	AGGTAGCGTGGCCGAGCGGTCTAAGGCGCTGGATTAAGGCTCCAGTCT CTTCGGGGGCGTGGGTTCGAATCCCCACCGCTGCCA
311	Val_AAC_chr5:180615415-180615488 (-)	GTTTCCGTAGTGTAGTGGTCATCACGTTCGCCTAACACGCGAAAGGTC CCCGGTTCGAAACCGGGCGGAAACAT
312	Pro_TGG_chr5:180615853-180615925 (-)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTTTGGGTGCGAGAGGTCCC GGGTTCAAATCCCGGACGAGCCCA
313	Thr_TGT_chr5:180618686-180618758 (-)	GGCTCCATAGCTCAGGGGTTAGAGGCACTGGTCTTGTAAACCAGGGTCG CGAGTTCAAATCTCGCTGGGGGCCTG
314	Ala_TGC_chr5:180633867-180633939 (+)	TGGGGATGTAGCTCAGTGGTAGAGCGCATGCTTTGCATGTATGAGGCC CCGGGTTCGATCCCCGGCATCTCCA
315	Lys_CTT_chr5:180634754-180634827 (+)	CGCCCGGCTAGCTCAGTCGGTAGAGCATGAGACTCTTAATCTCAGGGT CGTGGGTTCGAGCCCCCACGTTGGGCG
316	Val_AAC_chr5:180645269-180645342 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTAACACGCGAAAGGTCC CCGGTTCGAAACCGGGCGGAAACAA
317	Lys_CTT_chr5:180648978-180649051 (-)	GCCCGGCTAGCTCAGTCGGTAGAGCATGAGACTCTTAATCTCAGGGTC GTGGGTTCGAGCCCCCACGTTGGGCGT

318	Val_CAC_chr5:180649394-180649467 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTCACACGCGAAAGGTCC CCGGTTCGAAACCGGGCGGAAACAC
319	Met_CAT_chr6:26286753-26286825 (+)	CAGCAGAGTGGCGCAGCGGAAGCGTGCTGGGCCCATAACCCAGAGGT CGATGGATCGAAACCATCCTCTGCTA
320	Ser_GCT_chr6:26305717-26305801 (-)	GGAGAGGCCTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGT GCTCTGCACGCGTGGGTTCGAATCCCATCCTCGTCGC
321	Gln_TTG_chr6:26311423-26311495 (-)	GGCCCCATGGTGTAATGGTTAGCACTCTGGACTTTGAATCCAGCGATC CGAGTTCAAATCTCGGTGGGACCTG
322	Gln_TTG_chr6:26311974-26312046 (-)	GGCCCCATGGTGTAATGGTTAGCACTCTGGACTTTGAATCCAGCGATC CGAGTTCAAATCTCGGTGGGACCTA
323	Ser_TGA_chr6:26312823-26312905 (-)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTTGAAATCCATTGGGG TCTCCCCCGCGCAGGTTCGAATCCTGCCGACTACGG
324	Met_CAT_chr6:26313351-26313423 (-)	AGCAGAGTGGCGCAGCGGAAGCGTGCTGGGCCCATAACCCAGAGGTC GATGGATCGAAACCATCCTCTGCTAT
325	Arg_TCG_chr6:26323045-26323118 (+)	GGACCACGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAGAAGAT TGAGGGTTCGAATCCCCTCCGTGGTTA
326	Ser_AGA_chr6:26327816-26327898 (+)	TGTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTAGAAATCCATTGGG GTCTCCCCCGCGCAGGTTCGAATCCTGCCGACTACG
327	Met_CAT_chr6:26330528-26330600 (-)	AGCAGAGTGGCGCAGCGGAAGCGTGCTGGGCCCATAACCCAGAGGTC GATGGATCGAAACCATCCTCTGCTAG
328	Leu_CAG_chr6:26521435-26521518 (+)	CGTCAGGATGGCCGAGCGGTCTAAGGCGCTGCGTTCAGGTCGCAGTCT CCCCTGGAGGCGTGGGTTCGAATCCCACTCCTGACA
329	Thr_AGT_chr6:26533144-26533218 (-)	GGCTCCGTGGCTTAGCTGGTTAAAGCGCCTGTCTAGTAAACAGGAGAT CCTGGGTTCGAATCCCAGCGGGGCCTG
330	Arg_ACG_chr6:26537725-26537798 (+)	AGGGCCAGTGGCGCAATGGATAACGCGTCTGACTACGGATCAGAAGA TTCCAGGTTCGACTCCTGGCTGGCTCG
331	Val_CAC_chr6:26538281-26538354 (+)	GGTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTCACACGCGAAAGGTC CCCGGTTCGAAACCGGGCGGAAACA
332	Ala_CGC_chr6:26553730-26553802 (+)	AGGGGATGTAGCTCAGTGGTAGAGCGCATGCTTCGCATGTATGAGGTC CCGGGTTCGATCCCCGGGCATCTCCA
333	Ile_AAT_chr6:26554349-26554423 (+)	TGGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGG TCGCGGGGTTCGATCCCCGTACGGGCCA

334	Pro_AGG_chr6:26555497-26555569 (+)	CGGCTCGTTGGTCTAGGGGTATGATTCTCGCTTAGGGTGCGAGAGGTC CCGGGTTCAAATCCCGGACGAGCCC
335	Lys_CTT_chr6:26556773-26556846 (+)	AGCCCGGCTAGCTCAGTCGGTAGAGCATGAGACTCTTAATCTCAGGGT CGTGGGTTCGAGCCCCACGTTGGGCG
336	Tyr_GTA_chr6:26569085-26569176 (+)	TCCTTCGATAGCTCAGTTGGTAGAGCGGAGGACTGTAGTTGGCTGTGT CCTTAGACATCCTTAGGTCGCTGGTTCGAATCCGGCTCGAAGGA
337	Ala_AGC_chr6:26572091-26572164 (-)	GGGGAATTAGCTCAAATGGTAGAGCGCTCGCTTAGCATGCGAGAGGTA GCGGGATCGATGCCCCGCATTCTCCAG
338	Met_CAT_chr6:26766443-26766516 (+)	CGCCCTCTTAGCGCAGCGGGCAGCGCGTCAGTCTCATAATCTGAAGGT CCTGAGTTCGAGCCTCAGAGAGGGCA
339	Ile_TAT_chr6:26988124-26988218 (+)	TGCTCCAGTGGCGCAATCGGTTAGCGCGCGGTACTTATATGGCAGTAT GTGTGCGAGTGATGCCGAGGTTGTGAGTTCGAGCCTCACCTGGAGCA
340	His_GTG_chr6:27125905-27125977 (+)	TGCCGTGATCGTATAGTGGTTAGTACTCTGCGTTGTGGCCGCAGCAACC TCGGTTCGAATCCGAGTCACGGCA
341	Ile_AAT_chr6:27144993-27145067 (-)	GGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGGT CGCGGGTTCGATCCCCGTACGGGCCAC
342	Val_AAC_chr6:27203287-27203360 (+)	AGTTTCCGTAGTGTAGTGGTTATCACGTTTGCCTAACACGCGAAAGGTC CCCGGTTCGAAACCGGGCAGAAACA
343	Val_CAC_chr6:27248048-27248121 (-)	GCTTCTGTAGTGTAGTGGTTATCACGTTCGCCTCACACGCGAAAGGTCC CCGGTTCGAAACCGGGCAGAAGCAA
344	Asp_GTC_chr6:27447452-27447524 (+)	TTCCTCGTTAGTATAGTGGTGAGTATCCCCGCCTGTCACGCGGGAGACC GGGGTTCGATTCCCCGACGGGGAG
345	Ser_TGA_chr6:27473606-27473688 (-)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTTGAAATCCATTGGGG TTTCCCCGCGCAGGTTCGAATCCTGTCGGCTACGG
346	Gln_CTG_chr6:27487307-27487379 (+)	AGGTTCCATGGTGTAATGGTTAGCACTCTGGACTCTGAATCCAGCGAT CCGAGTTCAAATCTCGGTGGAACCT
347	Asp_GTC_chr6:27551235-27551307 (-)	TCCTCGTTAGTATAGTGGTGAGTGTCCCCGTCTGTCACGCGGGAGACC GGGGTTCGATTCCCCGACGGGGAGA
348	Val_AAC_chr6:27618706-27618779 (-)	GTTTCCGTAGTGTAGTGGTTATCACGTTCGCCTAACACGCGAAAGGTCC CTGGATCAAAACCAGGCGGGAAACAA
349	Ile_AAT_chr6:27655966-27656040 (+)	CGGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGGCCAAGG TCGCGGGGTTCGATCCCCGTACTGGCCA

350	Gln_CTG_chr6:27759134-27759206 (-)	GGCCCCATGGTGTAATGGTCAGCACTCTGGACTCTGAATCCAGCGATC CGAGTTCAAATCTCGGTGGGACCCA
351	Gln_TTG_chr6:27763639-27763711 (-)	GGCCCCATGGTGTAATGGTTAGCACTCTGGACTTTGAATCCAGCGATC CGAGTTCAAATCTCGGTGGGACCTT
352	Ala_AGC_chr6:28574932-28575004 (+)	TGGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTAGCATGTACGAGGTC CCGGGTTCAATCCCCGGCACCTCCA
353	Ala_AGC_chr6:28626013-28626085 (-)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTAGCATGCATGAGGTCC CGGGTTCGATCCCCAGCATCTCCAG
354	Ala_CGC_chr6:28697091-28697163 (+)	AGGGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTCGCATGTACGAGGCC CCGGGTTCGACCCCCGGCTCCTCCA
355	Ala_AGC_chr6:28806220-28806292 (-)	GGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTAGCATGCACGAGGCCC CGGGTTCAATCCCCGGCACCTCCAT
356	Ala_AGC_chr6:28831461-28831533 (-)	GGGGGTGTAGCTCAGTGGTAGAGCGCGTGCTTAGCATGCACGAGGCCC CGGGTTCAATCCCCGGCACCTCCAG
357	Leu_CAA_chr6:28863999-28864105 (-)	GTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGCTAAGCTTCC TCCGCGGTGGGGGATTCTGGTCTCCAATGGAGGCGTGGGTTCGAATCCC
358	Leu_CAA_chr6:28908829-28908934 (+)	TGTCAGGATGGCCGAGTGGTCTAAGGCGCCAGACTCAAGCTTGGCTTC CTCGTGTTGAGGATTCTGGTCTCCAATGGAGGCGTGGGTTCGAATCCC
359	Gln_CTG_chr6:28909377-28909449 (-)	GGTTCCATGGTGTAATGGTTAGCACTCTGGACTCTGAATCCAGCGATCC GAGTTCAAATCTCGGTGGAACCTT
360	Leu_AAG_chr6:28911398-28911480 (-)	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGGATTAAGGCTCCAGTCTC TTCGGGGGCGTGGGTTCGAATCCCACCGCTGCCAG
361	Met_CAT_chr6:28912351-28912424 (+)	TGCCTCCTTAGCGCAGTAGGCAGCGCGTCAGTCTCATAATCTGAAGGT CCTGAGTTCGAACCTCAGAGGGGGCA
362	Lys_TTT_chr6:28918805-28918878 (+)	AGCCCGGATAGCTCAGTCGGTAGAGCATCAGACTTTTAATCTGAGGGT CCAGGGTTCAAGTCCCTGTTCGGGCG
363	Met_CAT_chr6:28921041-28921114 (-)	GCCTCCTTAGCGCAGTAGGCAGCGCGTCAGTCTCATAAATCTGAAGGTC CTGAGTTCGAACCTCAGAGGGGGCAG
364	Glu_CTC_chr6:28949975-28950047 (+)	TTCCCTGGTGGTCTAGTGGTTAGGATTCGGCGCTCTCACCGCCGCGGCC CGGGTTCGATTCCCCGGTCAGGGAA
365	Leu_TAA_chr6:144537683-144537766 (+)	CACCAGGATGGCCGAGTGGTTAAGGCGTTGGACTTAAGATCCAATGGA CATATGTCCGCGTGGGTTCGAACCCCACTCCTGGTA

366	Pro_AGG_chr7:128423503-128423575 (+)	TGGCTCGTTGGTCTAGGGGTATGATTCTCGCTTAGGGTGCGAGAGGTC CCGGGTTCAAATCCCGGACGAGCCC
367	Arg_CCT_chr7:139025445-139025518 (+)	AGCCCCAGTGGCCTAATGGATAAGGCATTGGCCTCCTAAGCCAGGGAT TGTGGGTTCGAGTCCCATCTGGGGTG
368	Cys_GCA_chr7:149388271-149388343 (-)	GGGGATATAGCTCAGGGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CCGGTTCAAATCCGGGTGCCCCCCC
369	Tyr_GTA_chr8:67025601-67025694 (+)	CCCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGCTACTTCCTC AGCAGGAGACATCCTTAGGTCGCTGGTTCGATTCCGGCTCGAAGGA
370	Tyr_GTA_chr8:67026222-67026311 (+)	CCCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGGCGCGCGCCC GTGGCCATCCTTAGGTCGCTGGTTCGATTCCGGCTCGAAGGA
371	Ala_AGC_chr8:67026423-67026496 (+)	TGGGGGATTAGCTCAAATGGTAGAGCGCTCGCTTAGCATGCGAGAGGT AGCGGGATCGATGCCCCGCATCCTCCA
372	Ser_AGA_chr8:96281884-96281966 (-)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTAGAAATCCATTGGGG TCTCCCCCGCGCAGGTTCGAATCCTGCCGACTACGG
373	Met_CAT_chr8:124169469-124169542 (-)	GCCTCGTTAGCGCAGTAGGTAGCGCGTCAGTCTCATAATCTGAAGGTC GTGAGTTCGATCCTCACACGGGGCAC
374	Arg_TCT_chr9:131102354-131102445 (-)	GGCTCTGTGGCGCAATGGATAGCGCATTGGACTTCTAGCTGAGCCTAG TGTGGTCATTCAAAGGTTGTGGGTTCGAGTCCCACCAGAGTCGA
375	Asn_GTT_chr10:22518437-22518511 (-)	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGGT TGGTGGTTCGAGCCCACCCAGGGACGC
376	Ser_TGA_chr10:69524260-69524342 (+)	GGCAGCGATGGCCGAGTGGTTAAGGCGTTGGACTTGAAATCCAATGGG GTCTCCCCCGCGCAGGTTCGAACCCTGCTCGCTGCG
377	Val_TAC_chr11:59318101-59318174 (-)	GGTTCCATAGTGTAGTGGTTATCACGTCTGCTTTACACGCAGAAGGTCC TGGGTTCGAGCCCCCAGTGGAACCAT
378	Val_TAC_chr11:59318459-59318532 (-)	GGTTCCATAGTGTAGCGGTTATCACGTCTGCTTTACACGCAGAAGGTCC TGGGTTCGAGCCCCCAGTGGAACCAC
379	Arg_TCT_chr11:59318766-59318852 (+)	TGGCTCTGTGGCGCAATGGATAGCGCATTGGACTTCTAGATAGTTAGA GAAATTCAAAGGTTGTGGGTTCGAGTCCCACCAGAGTCG
380	Leu_TAA_chr11:59319227-59319310 (+)	TACCAGAATGGCCGAGTGGTTAAGGCGTTGGACTTAAGATCCAATGGA TTCATATCCGCGTGGGTTCGAACCCCCACTTCTGGTA
381	Lys_TTT_chr11:59323901-59323974 (+)	GGCCCGGATAGCTCAGTCGGTAGAGCATCAGACTTTTAATCTGAGGGT CCGGGGTTCAAGTCCCTGTTCGGGCG

382	Phe_GAA_chr11:59324969-59325042 (-)	GCCGAAATAGCTCAGTTGGGAGAGCGTTAGACTGAAGATCTAAAGGTC CCTGGTTCGATCCCGGGTTTCGGCAG
383	Lys_TTT_chr11:59327807-59327880 (-)	GCCCGGATAGCTCAGTCGGTAGAGCATCAGACTTTTAATCTGAGGGTC CAGGGTTCAAGTCCCTGTTCGGGCGG
384	Phe_GAA_chr11:59333852-59333925 (-)	GCCGAAATAGCTCAGTTGGGAGAGCGTTAGACTGAAGATCTAAAGGTC CCTGGTTCAATCCCGGGTTTCGGCAG
385	Ser_GCT_chr11:66115590-66115672 (+)	GGACGAGGTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTG CTTTGCACGGCGTGGGTTCGAATCCCATCCTCGTCG
386	Pro_TGG_chr11:75946868-75946940 (-)	GGCTCGTTGGTCTAGGGGTATGATTCTCGGTTTGGGTCCGAGAGGTCCC GGGTTCAAATCCCGGACGAGCCCC
387	Ser_CGA_chr12:56584147-56584229 (+)	AGTCACGGTGGCCGAGTGGTTAAGGCGTTGGACTCGAAATCCAATGGG GTTTCCCCGCACAGGTTCGAATCCTGTTCGTGACG
388	Asp_GTC_chr12:98897280-98897352 (+)	CTCCTCGTTAGTATAGTGGTTAGTATCCCCGCCTGTCACGCGGGAGACC GGGGTTCAATTCCCCGACGGGGAG
389	Trp_CCA_chr12:98898029-98898101 (+)	GGACCTCGTGGCGCAACGGTAGCGCGTCTGACTCCAGATCAGAAGGCT GCGTGTTCGAATCACGTCCGGGGTCA
390	Ala_TGC_chr12:125406300-125406372 (-)	GGGGATGTAGCTCAGTGGTAGAGCGCATGCTTTGCATGTATGAGGCCC CGGGTTCGATCCCCGGGCATCTCCAT
391	Phe_GAA_chr12:125412388-125412461 (-)	GCCGAAATAGCTCAGTTGGGAGAGCGTTAGACTGAAGATCTAAAGGTC CCTGGTTCGATCCCGGGTTTCGGCAC
392	Ala_TGC_chr12:125424511-125424583 (+)	AGGGGATGTAGCTCAGTGGTAGAGCGCATGCTTTGCACGTATGAGGCC CCGGGTTCAATCCCCGGGCATCTCCA
393	Asn_GTT_chr13:31248100-31248174 (-)	GTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGGT TGGTGGTTCGAGCCCACCCAGGGACGG
394	Glu_TTC_chr13:45492061-45492133 (-)	TCCCACATGGTCTAGCGGTTAGGATTCCTGGTTTTCACCCAGGCGGCCC GGGTTCGACTCCCGGTGTGGGAAC
395	Thr_TGT_chr14:21081948-21082021 (-)	GGCTCCATAGCTCAGGGGTTAGAGCGCTGGTCTTGTAAACCAGGGGTC GCGAGTTCAATTCTCGCTGGGGCCTG
396	Leu_TAG_chr14:21093528-21093610 (+)	TGGTAGTGTGGCCGAGCGGTCTAAGGCGCTGGATTTAGGCTCCAGTCT CTTCGGGGGCGTGGGTTCGAATCCCCACCACTGCCA
397	Thr_TGT_chr14:21099318-21099391 (-)	GGCTCCATAGCTCAGGGGTTAGAGCACTGGTCTTGTAAACCAGGGGTC GCGAGTTCAAATCTCGCTGGGGCCTC

398	Pro_TGG_chr14:21101164-21101236 (+)	TGGCTCGTTGGTCTAGTGGTATGATTCTCGCTTTGGGTGCGAGAGGTCC CGGGTTCAAATCCCGGACGAGCCC
399	Tyr_GTA_chr14:21131350-21131444 (-)	CCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGATTGTACAGAC ATTTGCGGACATCCTTAGGTCGCTGGTTCGATTCCGGCTCGAAGGAA
400	Thr_TGT_chr14:21149848-21149921 (+)	AGGCCCTATAGCTCAGGGGTTAGAGCACTGGTCTTGTAAACCAGGGGT CGCGAGTTCAAATCTCGCTGGGGCCT
401	Tyr_GTA_chr14:21151431-21151520 (+)	TCCTTCGATAGCTCAGCTGGTAGAGCGGAGGACTGTAGTACTTAATGT GTGGTCATCCTTAGGTCGCTGGTTCGATTCCGGCTCGAAGGA
402	Pro_TGG_chr14:21152174-21152246 (+)	TGGCTCGTTGGTCTAGGGGTATGATTCTCGCTTTGGGTGCGAGAGGTCC CGGGTTCAAATCCCGGACGAGCCC
403	Lys_CTT_chr14:58706612-58706685 (-)	GCCCGGCTAGCTCAGTCGGTAGAGCATGGGACTCTTAATCCCAGGGTC GTGGGTTCGAGCCCCACGTTGGGCGC
404	Ile_AAT_chr14:102783428-102783502 (+)	CGGCCGGTTAGCTCAGTTGGTTAGAGCGTGGTGCTAATAACGCCAAGG TCGCGGGTTCGATCCCCGTACGGGCCA
405	Glu_TTC_chr15:26327380-26327452 (-)	TCCCACATGGTCTAGCGGTTAGGATTCCTGGTTTTCACCCAGGCGGCCC GGGTTCGACTCCCGGTGTGGGAAT
406	Ser_GCT_chr15:40886022-40886104 (-)	GACGAGGTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTGC TCTGCACGCGTGGGTTCGAATCCCATCCTCGTCGA
407	His_GTG_chr15:45490803-45490875 (-)	GCCGTGATCGTATAGTGGTTAGTACTCTGCGTTGTGGCCGCAGCAACCT CGGTTCGAATCCGAGTCACGGCAT
408	His_GTG_chr15:45493348-45493420 (+)	CGCCGTGATCGTATAGTGGTTAGTACTCTGCGTTGTGGCCGCAGCAAC CTCGGTTCGAATCCGAGTCACGGCA
409	Gln_CTG_chr15:66161399-66161471 (-)	GGTTCCATGGTGTAATGGTTAGCACTCTGGACTCTGAATCCAGCGGATCC GAGTTCAAATCTCGGTGGGAACCTG
410	Lys_CTT_chr15:79152903-79152976 (+)	TGCCCGGCTAGCTCAGTCGGTAGAGCATGGGACTCTTAATCCCAGGGT CGTGGGTTCGAGCCCCACGTTGGGCG
411	Arg_TCG_chr15:89878303-89878376 (+)	GGGCCGCGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAGAAGAT TGCAGGTTCGAGTCCTGCCGCGGTCG
412	Gly_CCC_chr16:686735-686806 (-)	GCGCCGCTGGTGTAGTGGTATCATGCAAGATTCCCATTCTTGCGACCCG GGTTCGATTCCCGGGCGGCGCAC
413	Arg_CCG_chr16:3200674-3200747 (+)	GGGCCGCGTGGCCTAATGGATAAGGCGTCTGATTCCGGATCAGAAGAT TGAGGGTTCGAGTCCCTTCGTGGTCG

414	Arg_CCT_chr16:3202900-3202973 (+)	CGCCCCGGTGGCCTAATGGATAAGGCATTGGCCTCCTAAGCCAGGGAT TGTGGGTTCGAGTCCCACCCGGGGTA
415	Lys_CTT_chr16:3207405-3207478 (-)	GCCCGGCTAGCTCAGTCGGTAGAGCATGAGACCCTTAATCTCAGGGTC GTGGGTTCGAGCCCCACGTTGGGCGT
416	Thr_CGT_chr16:14379749-14379821 (+)	AGGCGCGGTGGCCAAGTGGTAAGGCGTCGGTCTCGTAAACCGAAGATC ACGGGTTCGAACCCCGTCCGTGCCT
417	Leu_TAG_chr16:22207031-22207113 (-)	GGTAGCGTGGCCGAGTGGTCTAAGGCGCTGGATTTAGGCTCCAGTCAT TTCGATGGCGTGGGTTCGAATCCCACCGCTGCCAC
418	Leu_AAG_chr16:22308460-22308542 (+)	GGGTAGCGTGGCCGAGCGGTCTAAGGCGCTGGATTAAGGCTCCAGTCT CTTCGGGGGCGTGGGTTCGAATCCCACCGCTGCCA
419	Leu_CAG_chr16:57333862-57333945 (+)	AGTCAGGATGGCCGAGCGGTCTAAGGCGCTGCGTTCAGGTCGCAGTCT CCCCTGGAGGCGTGGGTTCGAATCCCACTTCTGACA
420	Leu_CAG_chr16:57334391-57334474 (-)	GTCAGGATGGCCGAGCGGTCTAAGGCGCTGCGTTCAGGTCGCAGTCTC CCCTGGAGGCGTGGGTTCGAATCCCACTTCTGACAG
421	Met_CAT_chr16:87417627-87417700 (-)	GCCTCGTTAGCGCAGTAGGCAGCGGCGTCAGTCTCATAATCTGAAGGTC GTGAGTTCGAGCCTCACACGGGGCAG
422	Leu_TAG_chr17:8023631-8023713 (-)	GGTAGCGTGGCCGAGCGGTCTAAGGCGCTGGATTTAGGCTCCAGTCTC TTCGGAGGCGTGGGTTCGAATCCCACCGCTGCCAG
423	Arg_TCT_chr17:8024242-8024330 (+)	TGGCTCTGTGGCGCAATGGATAGCGCATTGGACTTCTAGTGACGAATA GAGCAATTCAAAGGTTGTGGGTTCGAATCCCACCAGAGTCG
424	Gly_GCC_chr17:8029063-8029134 (+)	CGCATTGGTGGTTCAGTGGTAGAATTCTCGCCTGCCACGCGGGAGGCC CGGGTTCGATTCCCGGCCAATGCA
425	Ser_CGA_chr17:8042198-8042280 (-)	GCTGTGATGGCCGAGTGGTTAAGGCGTTGGACTCGAAATCCAATGGGG TCTCCCCGCGCAGGTTCGAATCCTGCTCACAGCGT
426	Thr_AGT_chr17:8042769-8042843 (-)	GGCGCCGTGGCTTAGCTGGTTAAAGCGCCTGTCTAGTAAACAGGAGAT CCTGGGTTCGAATCCCAGCGGTGCCTG
427	Trp_CCA_chr17:8089675-8089747 (+)	CGACCTCGTGGCGCAACGGTAGCGCGTCTGACTCCAGATCAGAAGGTT GCGTGTTCAAATCACGTCCGGGGTCA
428	Ser_GCT_chr17:8090183-8090265 (+)	AGACGAGGTGGCCGAGTGGTTAAGGCGATGGACTGCTAATCCATTGTG CTCTGCACGCGTGGGTTCGAATCCCATCCTCGTCG
429	Thr_AGT_chr17:8090477-8090551 (+)	CGGCGCCGTGGCTTAGTTGGTTAAAGCGCCTGTCTAGTAAACAGGAGA TCCTGGGTTCGAATCCCAGCGGTGCCT

430	Trp_CCA_chr17:8124186-8124258 (-)	GGCCTCGTGGCGCAACGGTAGCGCGTCTGACTCCAGATCAGAAGGTTG CGTGTTCAAATCACGTCGGGGTCAA
431	Gly_TCC_chr17:8124865-8124937 (+)	AGCGTTGGTGGTATAGTGGTAAGCATAGCTGCCTTCCAAGCAGTTGAC CCGGGGTTCGATTCCCGGCCAACGCA
432	Asp_GTC_chr17:8125555-8125627 (-)	TCCTCGTTAGTATAGTGGTGAGTATCCCCGCCTGTCACGCGGGAGACC GGGGTTCGATTCCCCGACGGGGAGA
433	Pro_CGG_chr17:8126150-8126222 (-)	GGCTCGTTGGTCTAGGGGTATGATTCTCGCTTCGGGTGCGAGAGGTCC CGGGTTCAAATCCCGGACGAGCCCT
434	Thr_AGT_chr17:8129552-8129626 (-)	GGCGCCGTGGCTTAGTTGGTTAAAGCGCCTGTCTAGTAAACAGGAGAT CCTGGGTTCGAATCCCAGCGGTGCCTT
435	Ser_AGA_chr17:8129927-8130009 (-)	GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTAGAAATCCATTGGGG TCTCCCCGCGCAGGTTCGAATCCTGCCGACTACGT
436	Trp_CCA_chr17:19411493-19411565 (+)	TGACCTCGTGGCGCAATGGTAGCGCGTCTGACTCCAGATCAGAAGGTT GCGTGTTCAAGTCACGTCGGGGTCA
437	Thr_CGT_chr17:29877092-29877164 (+)	AGGCGCGGTGGCCAAGTGGTAAGGCGTCGGTCTCGTAAACCGAAGATC GCGGGTTCGAACCCCGTCCGTGCCT
438	Cys_GCA_chr17:37023897-37023969 (+)	AGGGGGTATAGCTCAGTGGTAGAGCATTTGACTGCAGATCAAGAGGTC CCCGGTTCAAATCCGGGTGCCCCCT
439	Cys_GCA_chr17:37025544-37025616 (-)	GGGGGTATAGCTCAGTGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CTGGTTCAAATCCGGGTGCCCCCTC
440	Cys_GCA_chr17:37309986-37310058 (-)	GGGGGTATAGCTCAGTGGTAGAGCATTTGACTGCAGATCAAGAGGTCC CCGGTTCAAATCCGGGTGCCCCCTC
441	Gln_TTG_chr17:47269889-47269961 (+)	AGGTCCCATGGTGTAATGGTTAGCACTCTGGACTTTGAATCCAGCGAT CCGAGTTCAAATCTCGGTGGGACCT
442	Arg_CCG_chr17:66016012-66016085 (-)	GACCCAGTGGCCTAATGGATAAGGCATCAGCCTCCGGAGCTGGGGATT GTGGGTTCGAGTCCCATCTGGGTCGC
443	Arg_CCT_chr17:73030000-73030073 (+)	AGCCCCAGTGGCCTAATGGATAAGGCACTGGCCTCCTAAGCCAGGGAT TGTGGGTTCGAGTCCCACCTGGGGTA
444	Arg_CCT_chr17:73030525-73030598 (-)	GCCCCAGTGGCCTAATGGATAAGGCACTGGCCTCCTAAGCCAGGGATT GTGGGTTCGAGTCCCACCTGGGGTGT
445	Arg_TCG_chr17:73031207-73031280 (+)	AGACCGCGTGGCCTAATGGATAAGGCGTCTGACTTCGGATCAGAAGAT TGAGGGTTCGAGTCCCTTCGTGGTCG

446	Asn_GTT_chr19:1383561-1383635 (+)	CGTCTCTGTGGCGCAATCGGTTAGCGCGTTCGGCTGTTAACCGAAAGG TTGGTGGTTCGAGCCCACCCAGGGACG
447	Gly_TCC_chr19:4724081-4724153 (+)	GGCGTTGGTGGTATAGTGGTTAGCATAGCTGCCTTCCAAGCAGTTGAC CCGGGTTCGATTCCCGGCCAACGCA
448	Val_CAC_chr19:4724646-4724719 (-)	GTTTCCGTAGTGTAGCGGTTATCACATTCGCCTCACACGCGAAAGGTCC CCGGTTCGATCCCGGGCGGAAACAG
449	Thr_AGT_chr19:33667962-33668036 (+)	TGGCGCCGTGGCTTAGTTGGTTAAAGCGCCTGTCTAGTAAACAGGAGA TCCTGGGTTCGAATCCCAGCGGTGCCT
450	Ile_TAT_chr19:39902807-39902900 (-)	GCTCCAGTGGCGCAATCGGTTAGCGCGGTACTTATATGACAGTGCG AGCGGAGCAATGCCGAGGTTGTGAGTTCGATCCTCACCTGGAGCAC
451	Gly_GCC_chr21:18827106-18827177 (-)	GCATGGGTGGTTCAGTGGTAGAATTCTCGCCTGCCACGCGGGAGGCCC GGGTTCGATTCCCGGCCCATGCAG

Non-naturally occurring modification

A TREM, a TREM core fragment or a TREM fragment described herein comprises a non-naturally occurring modification, e.g., a modification described in any one of Tables 5-9. A non-naturally occurring modification can be made according to methods known in the art. Exemplary methods of making non-naturally occurring modifications are provided in Examples 4-7.

In an embodiment, a non-naturally occurring modification is a modification that a cell, e.g., a human cell, does not make on an endogenous tRNA.

In an embodiment, a non-naturally occurring modification is a modification that a cell, e.g., a human cell, can make on an endogenous tRNA, but wherein such modification is in a location in which it does not occur on a native tRNA. In an embodiment, the non-naturally occurring modification is in a domain, linker or arm which does not have such modification in nature. In an embodiment, the non-naturally occurring modification is at a position within a domain, linker or arm, which does not have such modification in nature. In an embodiment, the non-naturally occurring modification is on a nucleotide which does not have such modification in nature. In an embodiment, the non-naturally occurring modification is on a nucleotide at a position within a domain, linker or arm, which does not have such modification in nature.

In an embodiment, a TREM, a TREM core fragment or a TREM fragment described herein comprises a non-naturally occurring modification provided in Table 5, or a combination thereof.

Table 5: Exemplary non-naturally occurring modifications

Modification
7-deaza-adenosine
Nl-methyl-adenosine
N6, N6 (dimethyl)adenine
N6-cis-hydroxy-isopentenyl-adenosine
thio-adenosine
2-(amino)adenine
2-(aminopropyl)adenine
2-(methylthio) N6 (isopentenyl)adenine
2-(alkyl)adenine

Modification
2-(aminoalkyl)adenine
2-(aminopropyl)adenine
2-(halo)adenine
2-(propyl)adenine
2'-azido-2'-deoxy-adenosine
2'-Deoxy-2'-alpha-aminoadenosine
2'-Deoxy-2'-alpha-azidoadenosine
6-(alkyl)adenine
6-(methyl)adenine

Modification
6-(alkyl)adenine
6-(methyl)adenine
7-(deaza)adenine
8-(alkenyl)adenine
8-(alkynyl)adenine
8-(amino)adenine
8-(thioalkyl)adenine
8-(alkenyl)adenine
8-(alkyl)adenine
8-(alkynyl)adenine
8-(amino)adenine
8-(halo)adenine
8-(hydroxyl)adenine
8-(thioalkyl)adenine
8-(thiol)adenine
8-azido-adenosine
azaadenine
deazaadenine
N6-(methyl)adenine
N6-(isopentyl)adenine
7-deaza-8-aza-adenosine
7-methyladenine
1-deazaadenosine
2'-Fluoro-N6-Bz-deoxyadenosine
2' -OMe-2-Amino-adenosine
2'O-methyl-N6-Bz-deoxyadenosine
2'-alpha-ethynyladenosine
2-aminoadenine
2-Aminoadenosine
2-Amino-adenosine
2' -alpha-Trifluoromethyladenosine

Modification
2-Azidoadenosine
2' -beta-Ethynyladenosine
2-Bromoadenosine
2'-beta-Trifluoromethyladenosine
2-Chloroadenosine
2' -Deoxy-2',2'-difluoroadenosine
2' -Deoxy-2'-alpha-mercaptoadenosine
2' -Deoxy-2'-alpha-thiomethoxyadenosine
2' -Deoxy-2'-beta-aminoadenosine
2' -Deoxy-2'-beta-azidoadenosine
2' -Deoxy-2'-beta-bromoadenosine
2' -Deoxy-2'-beta-chloroadenosine
2' -Deoxy-2'-beta-fluoroadenosine
2' -Deoxy-2'-beta-iodoadenosine
2' -Deoxy-2'-beta-mercaptoadenosine
2' -Deoxy-2'-beta-thiomethoxyadenosine
2-Fluoroadenosine
2-Iodoadenosine
2-Mercaptoadenosine
2-methoxy-adenine
2-methylthio-adenine
2-Trifluoromethyladenosine
3-Deaza-3-bromoadenosine
3-Deaza-3-chloroadenosine
3-Deaza-3-fluoroadenosine
3-Deaza-3-iodoadenosine
3-Deazaadenosine
4' -Azidoadenosine
4'-Carbocyclic adenosine
4' -Ethynyladenosine

Modification
5'-Homo-adenosine
8-Aza-adenosine
8-bromo-adenosine
8-Trifluoromethyladenosine
9-Deazaadenosine
2-aminopurine
7-deaza-2,6-diaminopurine
7-deaza-8-aza-2,6-diaminopurine
7-deaza-8-aza-2-aminopurine
2,6-diaminopurine
7-deaza-8-aza-adenine, 7-deaza-2-aminopurine
4-methylcytidine
5-aza-cytidine
Pseudo-iso-cytidine
pyrrolo-cytidine
alpha-thio-cytidine
2-(thio)cytosine
2' -Amino-2' -deoxy-cytosine
2' -Azido-2'-deoxy-cytosine
2' -Deoxy-2'-alpha-aminocytidine
2' -Deoxy-2'-alpha-azidocytidine
3 (deaza) 5 (aza)cytosine
3 (methyl)cytosine
3-(alkyl)cytosine
3-(deaza) 5 (aza)cytosine
3-(methyl)cytidine
4,2'-O-dimethylcytidine
5 (halo)cytosine
5 (methyl)cytosine
5 (propynyl)cytosine

Modification
5 (trifluoromethyl)cytosine
5-(alkyl)cytosine
5-(alkynyl)cytosine
5-(halo)cytosine
5-(propynyl)cytosine
5-(trifluoromethyl)cytosine
5-bromo-cytidine
5-iodo-cytidine
5-propynyl cytosine
6-(azo)cytosine
6-aza-cytidine
aza cytosine
deaza cytosine
N4 (acetyl)cytosine
l-methyl-1-deaza-pseudoisocytidine
1-methyl-pseudoisocytidine
2-methoxy-5-methyl-cytidine
2-methoxy-cytidine
2-thio-5-methyl-cytidine
4-methoxy-1-methyl-pseudoisocytidine
4-methoxy-pseudoisocytidine
4-thio- l-methyl-1-deaza-pseudoisocytidine
4-thio-1-methyl-pseudoisocytidine
4-thio-pseudoisocytidine
5-aza-zebularine
5-methyl-zebularine
pyrrolo-pseudoisocytidine
zebularine
(E)-5-(2-Bromo-vinyl)cytidine
2,2'-anhydro-cytidine

Modification
2'-Fluor-N4-Bz-cytidine
2'-Fluoro-N4-Acetyl-cytidine
2'-O-Methyl-N4-Acetyl-cytidine
2'-O-methyl-N4-Bz-cytidine
2' -a-Ethynylcytidine
2' -a-Trifluoromethylcytidine
2' -b-Ethynylcytidine
2'-b-Trifluoromethylcytidine
2' -Deoxy-2',2'-difluorocytidine
2' -Deoxy-2'-alpha-mercaptocytidine
2' -Deoxy-2'-alpha-thiomethoxycytidine
2' -Deoxy-2'-betab-aminocytidine
2' -Deoxy-2'-beta-azidocytidine
2' -Deoxy-2'-beta-bromocytidine
2' -Deoxy-2'-beta-chlorocytidine
2' -Deoxy-2'-beta-fluorocytidine
2' -Deoxy-2'-beta-iodocytidine
2' -Deoxy-2'-beta-mercaptocytidine
2' -Deoxy-2'-beta-thiomethoxycytidine TP
2' -O-Methyl-5-(1-propynyl)cytidine
3'-Ethynylcytidine
4'-Azidocytidine
4'-Carbocyclic cytidine
4' -Ethynylcytidine
5-(1-Propynyl)ara-cytidine
5-(2-Chloro-phenyl)-2-thiocytidine
5-(4-Amino-phenyl)-2-thiocytidine
5-Aminoallyl-cytosine
5-Cyanocytidine
5-Ethynylara-cytidine

Modification
5-Ethynylcytidine
5'-Homo-cytidine
5-Methoxycytidine
5-Trifluoromethyl-Cytidine
N4-Amino-cytidine
N4-Benzoyl-cytidine
pseudoisocytidine
6-thio-guanosine
7-deaza-guanosine
8-oxo-guanosine
Nl-methyl-guanosine
alpha-thio-guanosine
2-(propyl)guanine
2-(alky1)guanine
2'-Amino-2' -deoxy-guanosine
2'-Azido-2'-deoxy-guanosine
2'-Deoxy-2'-alpha-aminoguanosine
2'-Deoxy-2'-alpha-azidoguanosine
6-(methyl)guanine
6-(alky1)guanine
6-(methyl)guanine
6-methyl-guanosine
7-(alkyl)guanine
7-(deaza)guanine
7-(methyl)guanine
7-(alkyl)guanine
7-(deaza)guanine
7-(methyl)guanine
8-(alkyl)guanine
8-(alkynyl)guanine
8-(halo)guanine

Modification
8-(thioalkyl)guanine
8-(alkenyl)guanine
8-(alkyl)guanine
8-(alkynyl)guanine
8-(amino)guanine
8-(halo)guanine
8-(hydroxyl)guanine
8-(thioalkyl)guanine
8-(thiol)guanine
azaguanine
deaza guanine
N (methyl)guanine
N-(methyl)guanine
l-methyl-6-thio-guanosine
6-methoxy-guanosine
6-thio-7-deaza-8-aza-guanosine
6-thio-7-deaza-guanosine
6-thio-7-methyl-guanosine
7-deaza-8-aza-guanosine
7-methyl-8-oxo-guanosine
N2,N2-dimethyl-6-thio-guanosine
N2-methyl-6-thio-guanosine
1-Me-guanosine
2'Fluoro-N2-isobutyl-guanosine
2'O-methyl-N2-isobutyl-guanosine
2' -alpha-Ethynylguanosine
2' -alpha-Trifluoromethylguanosine
2' -beta-Ethynylguanosine
2'-beta-Trifluoromethylguanosine
2' -Deoxy-2',2'-difluoroguanosine
2' -Deoxy-2'-alpha-mercaptoguanosine

Modification
2' -Deoxy-2'-alpha-thiomethoxyguanosine
2' -Deoxy-2'-beta-aminoguanosine
2' -Deoxy-2'-beta-azidoguanosine
2' -Deoxy-2'-beta-bromoguanosine
2' -Deoxy-2'-beta-chloroguanosine
2' -Deoxy-2'-beta-fluoroguanosine
2' -Deoxy-2'-beta-iodoguanosine
2' -Deoxy-2'-beta-mercaptoguanosine
2'-Deoxy-2'-beta-thiomethoxyguanosine
4'-Azidoguanosine
4'-Carbocyclic guanosine
4' -Ethynylguanosine
5'-Homo-guanosine
8-bromo-guanosine
9-Deazaguanosine
N2-isobutyl-guanosine
7-methylinosine
allyamino- thymidine
aza thymidine
deaza thymidine
deoxy-thymidine
5-propynyl uracil
alpha-thio-uridine
1-(aminoalkylamino-carbonylethylenyl)-2(thio)-pseudouracil
1-(aminoalkylaminocarbonylethylenyl)-2,4-(dithio)pseudouracil
1-(aminoalkylaminocarbonylethylenyl)-4(thio)pseudouracil
1-(aminoalkylaminocarbonylethylenyl)-pseudouracil
1-(aminocarbonylethylenyl)-2(thio)-pseudouracil
1-(aminocarbonylethylenyl)-2,4-

Modification
(dithio)pseudouracil
1-(aminocarbonylethylenyl)-4 (thio)pseudouracil
1-(aminocarbonylethylenyl)-pseudouracil
1-substituted 2-(thio)-pseudouracil
1-substituted 2,4-(dithio)pseudouracil
1-substituted 4 (thio)pseudouracil
1-substituted pseudouracil
1-(aminoalkylamino-carbonylethylenyl)-2- (thio)-pseudouracil
l-Methyl-3-(3-amino-3-carboxypropyl) pseudouridine
l-Methyl-3-(3-amino-3-carboxyproovl)pseudo-Uradine
1-Methyl-pseudo-UTP
2 (thio)pseudouracil
2’ deoxy uridine
2’ fluorouridine
2-(thio)uracil
2,4-(dithio)psuedouracil
2’-methyl, 2’-amino, 2’azido, 2’fluro-guanosine
2’-Amino-2’-deoxy-uridine
2’-Azido-2’-deoxy-uridine
2’ -Azido-deoxyuridine
2’-O-methylpseudouridine
2’ deoxyuridine
2’ fluorouridine
2’ -Deoxy-2’-alpha-aminouridine TP
2’ -Deoxy-2’-alpha-azidouridine TP
2-methylpseudouridine
3-(3 amino-3-carboxypropyl)uracil
4-(thio)pseudouracil
4-(thio)pseudouracil

Modification
4-(thio)uracil
4-thiouracil
5-(l ,3-diazole-1-alkyl)uracil
5-(2-aminopropyl)uracil
5-(aminoalkyl)uracil
5-(dimethylaminoalkyl)uracil
5-(guanidiniumalkyl)uracil
5-(methoxycarbonylmethyl)-2-(thio)uracil
5-(methoxycarbonyl-methyl)uracil
5-(methyl)-2-(thio)uracil
5-(methyl)-2,4-(dithio)uracil
5 (methyl) 4 (thio)uracil
5 (methylaminomethyl)-2 (thio)uracil
5 (methylaminomethyl)-2,4 (dithio)uracil
5 (methylaminomethyl)-4 (thio)uracil
5 (propynyl)uracil
5 (trifluoromethyl)uracil
5-(2-aminopropyl)uracil
5-(alky1)-2-(thio)pseudouracil
5-(alkyl)-2,4 (dithio)pseudouracil
5-(alky1)-4 (thio)pseudouracil
5-(alkyl)pseudouracil
5-(alkyl)uracil
5-(alkynyl)uracil
5-(allylamino)uracil
5-(cyanoalkyl)uracil
5-(dialkylaminoalkyl)uracil
5-(dimethylaminoalkyl)uracil
5-(guanidiniumalkyl)uracil
5-(halo)uracil

Modification
5-(1,3-diazole-l-alkyl)uracil
5-(methoxy)uracil
5-(methoxycarbonylmethyl)-2-(thio)uracil
5-(methoxycarbonyl-methyl)uracil
5-(methyl) 2(thio)uracil
5-(methyl) 2,4 (dithio)uracil
5-(methyl) 4 (thio)uracil
5-(methyl)-2-(thio)pseudouracil
5-(methyl)-2,4 (dithio)pseudouracil
5-(methyl)-4 (thio)pseudouracil
5-(methyl)pseudouracil
5-(methylaminomethyl)-2 (thio)uracil
5-(methylaminomethyl)-2,4(dithio)uracil
5-(methylaminomethyl)-4-(thio)uracil
5-(propyny1)uracil
5-(trifluoromethyl)uracil
5-aminoallyl-uridine
5-bromo-uridine
5-iodo-uridine
5-uracil
6 (azo)uracil
6-(azo)uracil
6-aza-uridine
allyamino-uracil
aza uracil
deaza uracil
N3 (methyl)uracil
Pseudo-uridine-1-2-ethanoic acid
pseudouracil
4-Thio-pseudouridine

Modification
1-carboxymethyl-pseudouridine
l-methyl-1-deaza-pseudouridine
1-propynyl-uridine
l-taurinomethyl-1-methyl-uridine
l-taurinomethyl-4-thio-uridine
1-taurinomethyl-pseudouridine
2-methoxy-4-thio-pseudouridine
2-thio- l-methyl-1-deaza-pseudouridine
2-thio-1-methyl-pseudouridine
2-thio-5-aza-uridine
2-thio-dihydropseudouridine
2-thio-dihydrouridine
2-thio-pseudouridine
4-methoxy-2-thio-pseudouridine
4-methoxy-pseudouridine
4-thio-1-methyl-pseudouridine
4-thio-pseudouridine
5-aza-uridine
dihydropseudouridine
(±)1-(2-Hydroxypropyl)pseudouridine
(2R)- 1 -(2-Hydroxypropyl)pseudouridine
(2S)- 1 -(2-Hydroxypropyl)pseudouridine
(E)-5-(2-Bromo-vinyl)ara-uridine
(E)-5-(2-Bromo-vinyl)uridine
(Z)-5-(2-Bromo-vinyl)ara-uridine
(Z)-5-(2-Bromo-vinyl)uridine
1-(2,2,2-Trifluoroethyl)-pseudouridine
1-(2,2,3,3,3-Pentafluoropropyl)pseudouridine
1-(2,2-Diethoxyethy l)pseudouridine
1-(2,4,6-Trimethylbenzyl)pseudouridine

Modification
1-(2,4,6-Trimethyl-benzyl)pseudo-uridine
1-(2,4,6-Trimethyl-phenyl)pseudo-uridine
1-(2-Amino-2-carboxyethyl)pseudo-uridine
1-(2-Amino-ethyl)pseudouridine
1-(2-Hydroxyethyl)pseudouridine
1-(2-Methoxyethyl)pseudouridine
1-(3,4-Bis-trifluoromethoxvbenzvl)pseudouridine
1-(3,4-Dimethoxybenzyl)pseudouridine
1-(3-Amino-3-carboxypropyl)pseudo-uridine
1-(3-Amino-propyl)pseudouridine
1-(3-Cyclopropyl-prop-2-ynyl)pseudouridine TP
1-(4-Amino-4-carboxybutyl)pseudouridine
1-(4-Amino-benzyl)pseudouridine
1-(4-Amino-buty l)pseudouridine
1-(4-Amino-phenyl)pseudouridine
1-(4-Azidobenzyl)pseudouridine
1-(4-Bromobenzyl)pseudouridine
1-(4-Chlorobenzyl)pseudouridine
1-(4-Fluorobenzyl)pseudouridin
1-(4-Iodobenzyl)pseudouridine
1-(4-Methanesulfonvlbenzvl)pseudouridine
1-(4-Methoxybenzy l)pseudouridine
1-(4-Methoxy-benzyl)pseudouridine
1-(4-Methoxy-phenyl)pseudouridine
1-(4-Methylbenzyl)pseudouridine
1-(4-Methyl-benzyl)pseudouridine
1-(4-Nitrobenzyl)pseudouridine
1-(4-Nitro-benzy!)pseudouridine

Modification
1(4-Nitro-phenyl)pseudouridine
1-(4-Thiomethoxybenzyl)pseudouridine
1-(4-Trifluoromethoxybenzvl)pseudouridine
1-(4-Trifluoromethylbenzyl)pseudouridine
1-(5-Amino-pentyl)pseudouridine
1-(6-Amino-hexyl)pseudouridine
1,6-Dimethyl-pseudouridine
l-[3-(2-{2-[2-(2-Aminoethoxy)-ethoxy]-ethoxy}-ethoxy)-propionyl]pseudouridine
1-{3-[2-(2-Aminoethoxy)-ethoxy]-propionvl } pseudouridine
1-Acetylpseudouridine
l-Alkyl-6-(1-propynyl)-pseudo-uridine
l-Alkyl-6-(2-propynyl)-pseudo-uridine
l-Alkyl-6-allyl-pseudo-uridine
l-Alkyl-6-ethynyl-pseudo-uridine
l -Alkyl-6-homoallyl-pseudo-uridine
l-Alkyl-6-vinyl-pseudo-uridine
1-Allylpseudouridine
1-Aminomethyl-pseudo-uridine
1-Benzoylpseudouridine
1-Benzyloxymethylpseudouridine
1-Benzyl-pseudo-uridine
l-Biotinyl-PEG2-pseudouridine
1-Biotinylpseudouridine
1-Butyl-pseudo-uridine
1-Cyanomethylpseudouridine
1-Cyclobutylmethyl-pseudo-uridine
1-Cyclobutyl-pseudo-uridine
1-Cycloheptylmethyl-pseudo-uridine
1-Cycloheptyl-pseudo-uridine

Modification
1-Cyclohexylmethyl-pseudo-uridine
1-Cyclohexyl-pseudo-uridine
1-Cyclooctylmethyl-pseudo-uridine
1-Cyclooctyl-pseudo-uridine
1-Cyclopentylmethyl-pseudo-uridine
1-Cyclopentyl-pseudo-uridine
1-Cyclopropylmethyl-pseudo-uridine
1-Cyclopropyl-pseudo-uridine
1-Ethyl-pseudo-uridine
1-Hexyl-pseudo-uridine
1-Homoallylpseudouridine
1-Hydroxymethylpseudouridine
1-iso-propyl-pseudo-uridine
1-Me-2-thio-pseudo-uridine
1-Me-4-thio-pseudo-uridine
1-Me-alpha-thio-pseudo-uridine
1-Methanesulfonylmethylpseudouridine
1-Methoxymethylpseudouridine uridine
l -Methyl-6-(2,2,2-Trifluoroethyl)pseudo-uridine
l-Methyl-6-(4-morpholino)-pseudo-uridine
l -Methyl-6-(4-thiomorpholino)-pseudo-uridine
l-Methyl-6-(substituted phenyl)pseudo-uridine
1-Methyl-6-amino-pseudo-uridine
l -Methyl-6-azido-pseudo-uridine
1-Methyl-6-bromo-pseudo-uridine
l-Methyl-6-butyl-pseudo-uridine
l -Methyl-6-chloro-pseudo-uridine
1-Methyl-6-cyano-pseudo-uridine
l -Methyl-6-dimethylamino-pseudo-uridine

Modification
l -Methyl-6-ethoxy-pseudo-uridine
l -Methyl-6-ethylcarboxylate-pseudo-uridine
l-Methyl-6-ethyl-pseudo-uridine
l -Methyl-6-fluoro-pseudo-uridine
l-Methyl-6-formyl-pseudo-uridine
1-Methyl-6-hydroxyamino-pseudo-uridine
l -Methyl-6-hydroxy-pseudo-uridine
l -Methyl-6-iodo-pseudo-uridine
l-Methyl-6-iso-propyl-pseudo-uridine
l-Methyl-6-methoxy-pseudo-uridine
l -Methyl-6-methylamino-pseudo-uridine
l-Methyl-6-phenyl-pseudo-uridine
l-Methyl-6-propyl-pseudo-uridine
l-Methyl-6-tert-butyl-pseudo-uridine
1-Methyl-6-trifluoromethoxy-pseudo-uridine
l-Methyl-6-trifluoromethyl-pseudo-uridine
1-Morpholinomethylpseudouridine
1-Pentyl-pseudo-uridineuridine
1-Phenyl-pseudo-uridine
1-Pivaloylpseudouridine
1-Propargylpseudouridine
1-Propyl-pseudo-uridine
1-propynyl-pseudouridine
1-p-tolyl-pseudo-uridine
1-tert-Butyl-pseudo-uridine
1-Thiomethoxymethylpseudouridine
1-Thiomorpholinomethylpseudouridine
1-Trifluoroacetylpseudouridine
1-Trifluoromethyl-pseudouridine

Modification
1-Vinylpseudouridine
2,2'-anhydro-uridine
2' -bromo-deoxyuridine
2' -F-5-Methyl-2'-deoxy-uridine
2' -OMe-5-Me-uridine
2' -OMe-pseudouridine
2' -alpha-Ethynyluridine
2' -alpha-Trifluoromethyluridine
2' -beta-Ethynyluridine
2' -beta-Trifluoromethyluridiner
2' -Deoxy-2',2'-difluorouridine
2' -Deoxy-2'-a-mercaptouridin
2' -Deoxy-2'-alpha-thiomethoxyuridine
2' -Deoxy-2'-beta-aminouridine
2' -Deoxy-2'-beta-azidouridine
2' -Deoxy-2'-beta-bromouridine
2' -Deoxy-2'-beta-chlorouridine
2' -Deoxy-2'-beta-fluorouridine
2' -Deoxy-2'-beta-iodouridine
2' -Deoxy-2'-beta-mercaptouridine
2' -Deoxy-2'-beta-thiomethoxyuridine
2-methoxy-4-thio-uridine
2-methoxyuridine
2' -O-Methyl-5-(1-propynyl)uridine
3-Alkyl-pseudo-uridine
4' -Azidouridine
4'-Carbocyclic uridine
4' -Ethynyluridine
5-(1-Propynyl)ara-uridine
5-(2-Furanyl)uridine
5-Cyanouridine

Modification
5-Dimethylaminouridine
5'-Homo-uridine
5-iodo-2'-fluoro-deoxyuridine
5-Phenylethynyluridine
5-Trideuteromethyl-6-deuterouridine
5-Trifluoromethyl-Uridine
5-Vinylarauridine
6-(2,2,2-Trifluoroethyl)-pseudo-uridine
6-(4-Morpholino)-pseudo-uridine
6-(4-Thiomorpholino)-pseudo-uridine
6-(Substituted-Phenyl)-pseudo-uridine
6-Amino-pseudo-uridine
6-Azido-pseudo-uridine
6-Bromo-pseudo-uridine
6-Butyl-pseudo-uridine
6-Chloro-pseudo-uridine
6-Cyano-pseudo-uridine
6-Dimethylamino-pseudo-uridine
6-Ethoxy-pseudo-uridine
6-Ethylcarboxylate-pseudo-uridine
6-Ethyl-pseudo-uridine
6-Fluoro-pseudo-uridine
6-Formyl-pseudo-uridine
6-Hydroxyamino-pseudo-uridine
6-Hydroxy-pseudo-uridine
6-Iodo-pseudo-uridine
6-iso-Propyl-pseudo-uridine
6-Methoxy-pseudo-uridine
6-Methylamino-pseudo-uridine
6-Methyl-pseudo-uridine
6-Phenyl-pseudo-uridine

Modification
6-Phenyl-pseudo-uridine
6-Propyl-pseudo-uridine
6-tert-Butyl-pseudo- uridine
6-Trifluoromethoxy-pseudo-uridine
6-Trifluoromethyl-pseudo-uridine
alpha-thio-pseudo-uridine
Pseudouridine 1-(4-methylbenzenesulfonic acid)
Pseudouridine 1-(4-methylbenzoic acid) TP
Pseudouridine l-[3-(2-ethoxy)]propionic acid
Pseudouridine l-[3-{2-(2-[2-(2-ethoxy)-ethoxy]-ethoxy)-ethoxy}]propionic acid
Pseudouridine l-[3-{2-(2-[2-{2(2-ethoxy)-ethoxy}-ethoxy]-ethoxy)-

Modification
ethoxy}]propionic acid
Pseudouridine l-[3-{2-(2-[2-ethoxy]-ethoxy)-ethoxv}]propionic acid
Pseudouridine l-[3-{2-(2-ethoxy)-ethoxv}] propionic acid
Pseudouridine 1-methylphosphonic acid
Pseudouridine TP 1-methylphosphonic acid diethyl ester
Pseudo-uridine-N1-3-propionic acid
Pseudo-uridine-N1-4-butanoic acid
Pseudo-uridine-N 1-5-pentanoic acid
Pseudo-uridine-N1-6-hexanoic acid
Pseudo-uridine-Nl-7-heptanoic acid
Pseudo-uridine-N1-methy1-p-benzoic acid
Pseudo-uridine-N1-p-benzoic acid

In an embodiment, a TREM, a TREM core fragment or a TREM fragment described herein comprises a modification provided in Table 6, or a combination thereof. The modifications provided in Table 6 occur naturally in RNAs, and are used herein on a synthetic TREM, a TREM core fragment or a TREM fragment at a position that does not occur in nature.

Table 6: Additional exemplary modifications

Modification
2-methylthio-N6-(cis-hvdroxvisopentenvl)adenosine
2-methylthio-N6-methyladenosine
2-methylthio-N6-threonyl carbamoyladenosine
N6-glycinylcarbamoyladenosine
N6-isopentenyladenosine
N6-methyladenosine
N6-threonylcarbamoyladenosine

Modification
1,2'-O-dimethyladenosine
1-methyladenosine
2'-O-methyladenosine
2'-O-ribosyladenosine (phosphate)
2-methyladenosine
2-methylthio-N6 isopentenyladenosine
2-methylthio-N6-hydroxynorvalyl carbamoyladenosine
2' -O-methyladenosine

Modification
2’ -O-ribosyladenosine (phosphate)
isopenteny ladenosine
N6-(cis-hydroxyisopentenyl)adenosine
N6,2’-O-dimethyladenosine
N6,2’-O-dimethyladenosine
N6,N6,2’-O-trimethyladenosine
N6,N6-dimethyladenosine
N6-acetyladenosine
N6-hydroxynorvalylcarbamoyladenosine
N6-methyl-N6-threonylcarbamoyladenosine
2-methyladenosine
2-methylthio-N^6-isopentenyladenosine
2-thiocytidine
3-methylcytidine
5-formylcytidine
5-hydroxymethylcytidine
5-methylcytidine
N4-acetylcytidine
2’-O-methylcytidine
2’ -O-methylcytidine
5,2’-O-dimethylcytidine
5-formyl-2’-O-methylcytidine
lysidine
N4,2’-O-dimethy lcytidine
N4-acetyl-2’-O-methylcytidine
N4-methylcytidine
N4,N4-Dimethyl-2’-OMe-Cytidine
7-methylguanosine
N2,2’-O-dimethylguanosine
N2-methylguanosine
wyosme
1,2’-O-dimethylguanosine
1-methylguanosine

Modification
2’-O-methylguanosine
2’-O-ribosylguanosine (phosphate)
2’ -O-methylguanosine
2’-O-ribosylguanosine (phosphate)
7-aminomethyl-7-deazaguanosine
7-cyano-7-deazaguanosine
archaeosine
methylwyosine
N2,7-dimethylguanosine
N2,N2,2’-O-trimethylguanosine
N2,N2,7-trimethylguanosine
N2,N2-dimethylguanosine
N2, 7,2 ‘-O-trimethylguanosine
1-methylinosine
mosme
1,2’-O-dimethylinosine
2’-O-methylinosine
2’ -O-methylinosine
epoxyqueuosine
galactosyl-queuosine
mannosyl-queuosine
2’ -O-methyluridine
2-thiouridine
3-methyluridine
5-carboxymethyluridine
5-hydroxyuridine
5-methyluridine
5-taurinomethyl-2-thiouridine
5-taurinomethyluridine
dihydrouridine
pseudouridine

Modification
(3-(3-amino-3-carboxypropyl)uridine
l-methyl-3-(3-amino-5-carboxypropyl)pseudouridine
1-methylpseduouridine
1-methyl-pseudouridine
2'-O-methyluridine
2'-O-methylpseudouridine
2' -O-methyluridine
2-thio-2'-O-methyluridine
3-(3-amino-3-carboxypropyl)uridine
3,2'-0-dimethyluridine
3-Methyl-pseudo-Uridine
4-thiouridine
5-(carboxyhydroxymethyl)uridine
5-(carboxyhydroxymethyl)uridine methyl ester
5,2'-O-dimethyluridine
5,6-dihydro-uridine
5-aminomethy1-2-thiouridine
5-carbamoylmethyl-2'-0-methyluridine
5-carbamoylmethyluridine
5-carboxyhydroxymethyluridine
5-carboxyhydroxymethyluridine methyl ester
5-carboxymethylaminomethyl-2'-O-methyluridine
5-carboxymethylaminomethyl-2-thiouridine
5-carboxymethylaminomethyl-2-thiouridine
5-carboxymethylaminomethyluridine

Modification
5-carboxymethylaminomethyluridine
5-Carbamoylmethyluridine
5-methoxycarbonylmethyl-2'-O-methyluridine
5-methoxycarbonylmethy1-2-thiouridine
5-methoxycarbonylmethyluridine
5-methoxyuridine
5-methyl-2-thiouridine
5-methylaminomethyl-2-selenouridine
5-methylaminomethyl-2-thiouridine
5-methylaminomethyluridine
5-Methyldihydrouridine
5-Oxyacetic acid- Uridine
5-Oxyacetic acid-methyl ester-Uridin Nl-methyl-pseudo-uridine
uridine 5-oxyacetic acid
uridine 5-oxyacetic acid methyl ester
3-(3-Amino-3-carboxypropyl)-Uridine
5-(iso-Pentenylaminomethyl)- 2-thiouridine
5-(iso-Pentenylaminomethyl)-2 '-O-methyluridine
5-(iso-Pentenylaminomethyl)uridine
wybutosine
hydroxywybutosine
isowyosme
peroxywybutosine
undermodified hydroxywybutosine
4-demethylwyosine
altriol

In an embodiment, a TREM, a TREM core fragment or a TREM fragment described herein comprises a non-naturally occurring modification provided in Table 7, or a combination thereof.

Table 7: Additional exemplary non-naturally occurring modifications

Modification
2,6-(diamino)purine
1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl
1,3-(diaza)-2-(oxo)-phenthiazin-1-yl
1,3-(diaza)-2-(oxo)-phenoxazin-1-yl
1,3,5-(triaza)-2,6-(dioxa)-naphthalene
2 (amino)purine
2,4,5-(trimethyl)phenyl
2' methyl, 2'amino, 2'azido, 2'fluro-cytidine
2' methyl, 2'amino, 2'azido, 2'fluro-adenine
2'methyl, 2'amino, 2'azido, 2'fluro-uridine
2' -amino-2' -deoxyribose
2-amino-6-Chloro-purine
2-aza-inosinyl
2' -azido-2'-deoxyribose
2'fluoro-2 '-deoxyribose
2' -fluoro-modified bases
2' -O-methyl-ribose
2-oxo-7-aminopyridopyrimidin-3-yl
2-oxo-pyridopyrimidine-3-yl
2-pyridinone
3 nitropyrrole
3-(methyl)-7-(propynyl)isocarbostyrilyl
3-(methyl)isocarbostyrilyl
4-(fluoro)-6-(methyl)benzimidazole
4-(methyl)benzimidazole
4-(methyl)indolyl
4,6-(dimethyl)indolyl
5 nitroindole
5 substituted pyrimidines
5-(methyl)isocarbostyrilyl
5-nitroindole
6-(aza)pyrimidine

Modification
6-(azo)thymine
6-(methyl)-7-(aza)indolyl
6-chloro-purine
6-phenyl-pyrrolo-pyrimidin-2-on-3-yl
7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)- phenthiazin-1-yl
7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl
7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl
7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin- 1-yl
7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-l- yl
7-(aza)indolyl
7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)- phenoxazinl-yl
7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl
7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)- phenoxazin-1-yl
7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)- phenoxazin-1-yl
7-(guanidiniumalkyl-hydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin-1-yl
7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)- phenoxazin-1-yl
7-(propynyl)isocarbostyrilyl
7-(propynyl)isocarbostyrilyl, propynyl-7-(aza)indolyl
7-deaza-inosinyl
7-substituted 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl
7-substituted 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl

Modification
9-(methyl)-imidizopyridinyl
aminoindolyl
anthracenyl
bis-ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo- nvrimidin-2-on-3-yl
bis-ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl
difluorotolyl
hypoxanthine
imidizopyridinyl
inosinyl
isocarbostyrilyl
isoguanosine
N2-substituted purines
N6-methyl-2-amino-purine
N6-substituted purines
N-alkylated derivative
napthalenyl
nitrobenzimidazolyl
nitroimidazolyl
nitroindazolyl
nitropyrazolyl
nubularine
O6-substituted purines
O-alkylated derivative
ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2- on-3-yl
ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl
Oxoformycin TP
para-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2- on-3-yl
para-substituted-6-phenyl-pyrrolo-

Modification
pyrimidin-2-on-3-yl
pentacenyl
phenanthracenyl
phenyl
propynyl-7-(aza)indolyl
pyrenyl
pyridopyrimidin-3-yl
pyridopyrimidin-3-yl, 2-oxo-7-amino-pyridopyrimidin-3- yl
pyrrolo-pyrimidin-2-on-3-yl
pyrrolopyrimidinyl
pyrrolopyrizinyl
stilbenzyl
substituted 1,2,4-triazoles
tetracenyl
tubercidine
xanthine
Xanthosine
2-thio-zebularine
5-aza-2-thio-zebularine
7-deaza-2-amino-purine
pyridin-4-one ribonucleoside
2-Amino-riboside
Formycin A
Formycin B
Pyrrolosine
2’ -OH-ara-adenosine
2’ -OH-ara-cytidine
2’ -OH-ara-uridine
2’ -OH-ara-guanosine
5-(2-carbomethoxyvinyl)uridine
N6-(19-Amino-pentaoxanonadecyl)adenosine

In an embodiment, a TREM, a TREM core fragment or a TREM fragment described herein comprises a non-naturally occurring modification provided in Table 8, or a combination thereof.

Table 8: Exemplary backbone modifications

Modification
3'-alkylene phosphonates
3'-amino phosphoramidate
alkene containing backbones
aminoalkylphosphoramidates
aminoalkylphosphotriesters
boranophosphates
-CH2-O-N(CH3)-CH2-
-CH2-N(CH3)-N(CH3)-CH2-
-CH2-NH-CH2-
chiral phosphonates
chiral phosphorothioates
formacetyl and thioformacetyl backbones
methylene (methylimino)
methylene formacetyl and thioformacetyl backbones
methyleneimino and methylenehydrazino backbones
morpholino linkages
-N(CH3)-CH2-CH2-
oligonucleosides with heteroatom intenucleoside linkage
phosphinates
phosphoramidates
phosphorodithioates
phosphorothioate intenucleoside linkages
phosphorothioates
phosphotriesters
Peptide nucleic acid (PNA)
siloxane backbones
sulfamate backbones
Sulfide, sulfoxide, and sulfone backbones
sulfonate and sulfonamide backbones
thionoalkylphosphonates
thionoalkylphosphotriesters
thionophosphoramidates

Modification
methylphosphonates
phosphonoacetates
Phosphorothioate
Constrained nucleic acid (CNA)
2'-O-methyl
2'-O-methoxyethyl (MOE)
2' Fluoro
Locked nucleic acid (LNA)
(*S*)-constrained ethyl (*cEt*)
Fluoro hexitol nucleic acid (FHNA)
5'-phosphorothioate
Phosphorodiamidate Morpholino Oligomer (PMO)
Tricyclo-DNA (tcDNA)
(*S*) 5'-C-methyl
(*E*)-vinylphosphonate
Methyl phosphonate
(*S*) 5'-C-methyl with phosphate
(R) 5'-C-methyl with phosphate
DNA
(R) 5'-C-methyl
GNA (glycol nucleic acid)
alkyl phosphonates
Phosphorothioate
Constrained nucleic acid (CNA)
2'-O-methyl
2'-O-methoxyethyl (MOE)
2' Fluoro
Locked nucleic acid (LNA)
(*S*)-constrained ethyl (*cEt*)
Fluoro hexitol nucleic acid (FHNA)
5'-phosphorothioate
Phosphorodiamidate Morpholino Oligomer (PMO)
Tricyclo-DNA (tcDNA)
(*S*) 5'-C-methyl
(*E*)-vinylphosphonate
Methyl phosphonate

Modification
(*S*) 5'-C-methyl with phosphate
(R) 5'-C-methyl with phosphate
DNA
(R) 5'-C-methyl

Modification
GNA (glycol nucleic acid)
alkyl phosphonates

In an embodiment, a TREM, a TREM core fragment or a TREM fragment described herein comprises a non-naturally occurring modification provided in Table 9, or a combination thereof.

Table 9: Exemplary non-naturally occurring backbone modificiations

Name of synthetic backbone modifications
Phosphorothioate
Constrained nucleic acid (CNA)
2' O'methylation
2'-O-methoxyethylribose (MOE)
2' Fluoro
Locked nucleic acid (LNA)
(*S*)-constrained ethyl (*cEt*)
Fluoro hexitol nucleic acid (FHNA)
5'phosphorothioate
Phosphorodiamidate Morpholino Oligomer (PMO)
Tricyclo-DNA (tcDNA)
(*S*) 5'-C-methyl
(*E*)-vinylphosphonate
Methyl phosphonate
(*S*) 5'-C-methyl with phosphate

TREM, TREM core fragment and TREM fragment fusions

In an embodiment, a TREM, a TREM core fragment or a TREM fragment disclosed herein comprises an additional moiety, *e.g.*, a fusion moiety. In an embodiment, the fusion moiety can be used for purification, to alter folding of the TREM, TREM core fragment or TREM fragment, or as a targeting moiety. In an embodiment, the fusion moiety can comprise a tag, a linker, can be cleavable or can include a binding site for an enzyme. In an embodiment, the fusion moiety can be disposed at the N terminal of the TREM or at the C terminal of the TREM, TREM core fragment or TREM fragment. In an embodiment, the fusion moiety can be encoded by the same or different nucleic acid molecule that encodes the TREM, TREM core fragment or TREM fragment.

TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises a consensus sequence provided herein.

In an embodiment, a TREM disclosed herein comprises a consensus sequence of Formula I ZZZ, wherein ZZZ indicates any of the twenty amino acids and Formula I corresponds to all species.

In an embodiment, a TREM disclosed herein comprises a consensus sequence of Formula II ZZZ, wherein ZZZ indicates any of the twenty amino acids and Formula II corresponds to mammals.

In an embodiment, a TREM disclosed herein comprises a consensus sequence of Formula III ZZZ, wherein ZZZ indicates any of the twenty amino acids and Formula III corresponds to humans.

In an embodiment, ZZZ indicates any of the twenty amino acids: alanine, arginine, asparagine, aspartate, cysteine, glutamine, glutamate, glycine, histidine, isoleucine, methionine, leucine, lysine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine.

In an embodiment, a TREM disclosed herein comprises a property selected from the following:

a) under physiological conditions residue R_0 forms a linker region, *e.g.*, a Linker 1 region;

b) under physiological conditions residues R_1-R_2-R_3-R_4 -R_5-R_6-R_7 and residues R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71} form a stem region, *e.g.*, an AStD stem region;

c) under physiological conditions residues R_8-R_9 forms a linker region, *e.g.*, a Linker 2 region;

d) under physiological conditions residues -R_{10}-R_{11}-R_{12}-R_{13}-R_{14} R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28} form a stem-loop region, *e.g.*, a D arm Region;

e) under physiological conditions residue -R_{29} forms a linker region, *e.g.*, a Linker 3 Region;

f) under physiological conditions residues -R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}-R_{43}-R_{44}-R_{45}-R_{46} form a stem-loop region, *e.g.*, an AC arm region;

g) under physiological conditions residue -$[R_{47}]_x$ comprises a variable region, *e.g.*, as described herein;

h) under physiological conditions residues -R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64} form a stem-loop region, *e.g.*, a T arm Region; or

i) under physiological conditions residue R_{72} forms a linker region, *e.g.*, a Linker 4 region.

Alanine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{ALA} (SEQ ID NO: 562),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ala is:

R_0= absent;

R_{14}, R_{57}=are independently A or absent;

R_{26}= A, C, G or absent;

R_5, R_6, R_{15}, R_{16}, R_{21}, R_{30}, R_{31}, R_{32}, R_{34}, R_{37}, R_{41}, R_{42}, R_{43}, R_{44}, R_{45}, R_{48}, R_{49}, R_{50}, R_{58}, R_{59}, R_{63}, R_{64}, R_{66}, R_{67}= are independently N or absent;

R_{11}, R_{35}, R_{65}= are independently A, C, U or absent;

R_1, R_9, R_{20}, R_{38}, R_{40}, R_{51}, R_{52}, R_{56}= are independently A, G or absent;

R_7, R_{22}, R_{25}, R_{27}, R_{29}, R_{46}, R_{53}, R_{72}= are independently A, G, U or absent;

R_{24}, R_{69}= are independently A, U or absent;

R_{70}, R_{71}=are independently C or absent;

R_3, R_4= are independently C, G or absent;

R_{12}, R_{33}, R_{36}, R_{62}, R_{68}= are independently C, G, U or absent;

R_{13}, R_{17}, R_{28}, R_{39}, R_{55}, R_{60}, R_{61}= are independently C, U or absent;

R_{10}, R_{19}, R_{23}= are independently G or absent;

R_2= G, U or absent;

R_8, R_{18}, R_{54}= are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II_{ALA} (SEQ ID NO: 563),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ala is:

R_0, R_{18}= are absent;

R_{14}, R_{24}, R_{57}=are independently A or absent;

R_{15}, R_{26}, R_{64}= are independently A, C, G or absent;

R_{16}, R_{31}, R_{50}, R_{59}= are independently N or absent;

R_{11}, R_{32}, R_{37}, R_{41}, R_{43}, R_{45}, R_{49}, R_{65}, R_{66}= are independently A, C, U or absent;

R_1, R_5, R_9, R_{25}, R_{27}, R_{38}, R_{40}, R_{46}, R_{51}, R_{56}= are independently A, G or absent;

R_7, R_{22}, R_{29}, R_{42}, R_{44}, R_{53}, R_{63}, R_{72}= are independently A, G, U or absent;

R_6, R_{35}, R_{69}= are independently A, U or absent;

R_{55}, R_{60}, R_{70}, R_{71}= are independently C or absent;

R_3= C, G or absent;

R_{12}, R_{36}, R_{48}= are independently C, G, U or absent;

R_{13}, R_{17}, R_{28}, R_{30}, R_{34}, R_{39}, R_{58}, R_{61}, R_{62}, R_{67}, R_{68}= are independently C, U or absent;

R_4, R_{10}, R_{19}, R_{20}, R_{23}, R_{52}= are independently G or absent;

R_2, R_8, R_{33}= are independently G, U or absent;

R_{21}, R_{54}= are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III_{ALA} (SEQ ID NO: 564),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-

R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ala is:

R_0, R_{18}= are absent;

R_{14}, R_{24}, R_{57}, R_{72}=are independently A or absent;

R_{15}, R_{26}, R_{64}= are independently A, C, G or absent;

R_{16}, R_{31}, R_{50}= are independently N or absent;

R_{11}, R_{32}, R_{37}, R_{41}, R_{43}, R_{45}, R_{49}, R_{65}, R_{66}= are independently A, C, U or absent;

R_5, R_9, R_{25}, R_{27}, R_{38}, R_{40}, R_{46}, R_{51}, R_{56}= are independently A, G or absent;

R_7, R_{22}, R_{29}, R_{42}, R_{44}, R_{53}, R_{63}= are independently A, G, U or absent;

R_6, R_{35}= are independently A, U or absent;

R_{55}, R_{60}, R_{61}, R_{70}, R_{71}= are independently C or absent;

R_{12}, R_{48}, R_{59}= are independently C, G, U or absent;

R_{13}, R_{17}, R_{28}, R_{30}, R_{34}, R_{39}, R_{58}, R_{62}, R_{67}, R_{68}= are independently C, U or absent;

R_1, R_2, R_3, R_4, R_{10}, R_{19}, R_{20}, R_{23}, R_{52}= are independently G or absent;

R_{33}, R_{36}= are independently G, U or absent;

R_8, R_{21}, R_{54}, R_{69}= are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Arginine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I $_{ARG}$ (SEQ ID NO: 565),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Arg is:

R_{57}=A or absent;

R_9,R_{27}=are independently A,C,G or absent;

R_1,R_2,R_3,R_4,R_5,R_6,R_7,R_{11},R_{12},R_{16},R_{21},R_{22},R_{23},R_{25},R_{26},R_{29},R_{30},R_{31},R_{32},R_{33},R_{34},R_{37},R_{42},R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{51},R_{58},R_{62},R_{63},R_{64},R_{65},R_{66},R_{67},R_{68},R_{69},R_{70},R_{71}=are independently N or absent;

R_{13},R_{17},R_{41}=are independently A,C,U or absent;

R_{19},R_{20},R_{24},R_{40},R_{56}=are independently A,G or absent;

R_{14},R_{15},R_{72}=are independently A,G,U or absent;

R_{18}= A,U or absent;

R_{38}= C or absent;

R_{35},R_{43},R_{61}=are independently C,G,U or absent;

R_{28},R_{55},R_{59},R_{60}=are independently C,U or absent;

R_0,R_{10},R_{52}=are independently G or absent;

R_8,R_{39}=are independently G,U or absent;

R_{36},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17,

x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{ARG}$ (SEQ ID NO: 566),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Arg is:

R_{18}= absent;

R_{24},R_{57}=are independently A or absent;

R_{41}= A,C or absent;

R_3,R_7,R_{34},R_{50}=are independently A,C,G or absent;

R_2,R_5,R_6,R_{12},R_{26},R_{32},R_{37},R_{44},R_{58},R_{66},R_{67},R_{68},R_{70}=are independently N or absent;

R_{49},R_{71}=are independently A,C,U or absent;

R_1,R_{15},R_{19},R_{25},R_{27},R_{40},R_{45},R_{46},R_{56},R_{72}=are independently A,G or absent;

R_{14},R_{29},R_{63}=are independently A,G,U or absent;

R_{16},R_{21}=are independently A,U or absent;

R_{38},R_{61}=are independently C or absent;

R_{33},R_{48}=are independently C,G or absent;

R_4,R_9,R_{11},R_{43},R_{62},R_{64},R_{69}=are independently C,G,U or absent;

R_{13},R_{22},R_{28},R_{30},R_{31},R_{35},R_{55},R_{60},R_{65}=are independently C,U or absent;

R_0,R_{10},R_{20},R_{23},R_{51},R_{52}=are independently G or absent;

R_8,R_{39},R_{42}=are independently G,U or absent;

R_{17},R_{36},R_{53},R_{54},R_{59}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{ARG}$ (SEQ ID NO: 567),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Arg is:

R_{18}=is absent;

R_{15},R_{21},R_{24},R_{41},R_{57}=are independently A or absent;

R_{34},R_{44}=are independently A,C or absent;

R_3,R_5,R_{58}=are independently A,C,G or absent;

R_2,R_6,R_{66},R_{70}=are independently N or absent;

R_{37},R_{49}=are independently A,C,U or absent;

R_1,R_{25},R_{29},R_{40},R_{45},R_{46},R_{50}=are independently A,G or absent;

R_{14},R_{63},R_{68}=are independently A,G,U or absent;

R_{16}= A,U or absent;

R_{38},R_{61}=are independently C or absent;

R_7,R_{11},R_{12},R_{26},R_{48}=are independently C,G or absent;

R_{64},R_{67},R_{69}=are independently C,G,U or absent;

R_4,R_{13},R_{22},R_{28},R_{30},R_{31},R_{35},R_{43},R_{55},R_{60},R_{62},R_{65},R_{71}=are independently C,U or absent;

R_0,R_{10},R_{19},R_{20},R_{23},R_{27},R_{33},R_{51},R_{52},R_{56},R_{72}=are independently G or absent;

R_8,R_9,R_{32},R_{39},R_{42}=are independently G,U or absent;

R_{17},R_{36},R_{53},R_{54},R_{59}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Asparagine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{ASN} (SEQ ID NO: 568),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asn is:

R_0,R_{18}=are absent;

R_{41}= A or absent;

R_{14},R_{48},R_{56}=are independently A,C,G or absent;

R_2,R_4,R_5,R_6,R_{12},R_{17},R_{26},R_{29},R_{30},R_{31},R_{44},R_{45},R_{46},R_{49},R_{50},R_{58},R_{62},R_{63},R_{65},R_{66},R_{67},R_{68},R_{70},R_{71}= are independently N or absent;

R_{11},R_{13},R_{22},R_{42},R_{55},R_{59}=are independently A,C,U or absent;

R_9,R_{15},R_{24},R_{27},R_{34},R_{37},R_{51},R_{72}=are independently A,G or absent;

R_1,R_7,R_{25},R_{69}=are independently A,G,U or absent;

R_{40},R_{57}=are independently A,U or absent;

R_{60}= C or absent;

R_{33}= C,G or absent;

R_{21},R_{32},R_{43},R_{64}=are independently C,G,U or absent;

R_3,R_{16},R_{28},R_{35},R_{36},R_{61}=are independently C,U or absent;

R_{10},R_{19},R_{20},R_{52}=are independently G or absent;

R_{54}= G,U or absent;

R_8,R_{23},R_{38},R_{39},R_{53}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{ASN}$ (SEQ ID NO: 569),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asn is:

R_0,R_{18}=are absent

R_{24},R_{41},R_{46},R_{62}=are independently A or absent;

R_{59}= A,C or absent;

R_{14},R_{56},R_{66}=are independently A,C,G or absent;

R_{17},R_{29}=are independently N or absent;

R_{11},R_{26},R_{42},R_{55}=are independently A,C,U or absent;

R_{1},R_{9},R_{12},R_{15},R_{25},R_{34},R_{37},R_{48},R_{51},R_{67},R_{68},R_{69},R_{70},R_{72}=are independently A,G or absent;

R_{44},R_{45},R_{58}=are independently A,G,U or absent;

R_{40},R_{57}=are independently A,U or absent;

R_{5},R_{28},R_{60}=are independently C or absent;

R_{33},R_{65}=are independently C,G or absent;

R_{21},R_{43},R_{71}=are independently C,G,U or absent;

R_{3},R_{6},R_{13},R_{22},R_{32},R_{35},R_{36},R_{61},R_{63},R_{64}=are independently C,U or absent;

R_{7},R_{10},R_{19},R_{20},R_{27},R_{49},R_{52}=are independently G or absent;

R_{54}= G,U or absent;

R_{2},R_{4},R_{8},R_{16},R_{23},R_{30},R_{31},R_{38},R_{39},R_{50},R_{53}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{ASN}$ (SEQ ID NO: 570),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asn is:

$R_{0,}R_{18}$=are absent

R_{24},R_{40},R_{41},R_{46},R_{62}=are independently A or absent;

R_{59}= A,C or absent;

R_{14},R_{56},R_{66}=are independently A,C,G or absent;

R_{11},R_{26},R_{42},R_{55}=are independently A,C,U or absent;

R_1,R_9,R_{12},R_{15},R_{34},R_{37},R_{48},R_{51},R_{67},R_{68},R_{69},R_{70}=are independently A,G or absent;

R_{44},R_{45},R_{58}=are independently A,G,U or absent;

R_{57}= A,U or absent;

R_5,R_{28},R_{60}=are independently C or absent;

R_{33},R_{65}=are independently C,G or absent;

R_{17},R_{21},R_{29}=are independently C,G,U or absent;

R_3,R_6,R_{13},R_{22},R_{32},R_{35},R_{36},R_{43},R_{61},R_{63},R_{64},R_{71}=are independently C,U or absent;

R_7,R_{10},R_{19},R_{20},R_{25},R_{27},R_{49},R_{52},R_{72}=are independently G or absent;

R_{54}= G,U or absent;

R_2,R_4,R_8,R_{16},R_{23},R_{30},R_{31},R_{38},R_{39},R_{50},R_{53}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271),

provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Aspartate TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{ASP} (SEQ ID NO: 571),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asp is:

R_0=absent

R_{24},R_{71}=are independently A,C or absent;

R_{33},R_{46}=are independently A,C,G or absent;

R_2,R_3,R_4,R_5,R_6,R_{12},R_{16},R_{22},R_{26},R_{29},R_{31},R_{32},R_{44},R_{48},R_{49},R_{58},R_{63},R_{64},R_{66},R_{67},R_{68},R_{69}=are independently N or absent;

R_{13},R_{21},R_{34},R_{41},R_{57},R_{65}=are independently A,C,U or absent;

R_9,R_{10},R_{14},R_{15},R_{20},R_{27},R_{37},R_{40},R_{51},R_{56},R_{72}=are independently A,G or absent;

R_7,R_{25},R_{42}=are independently A,G,U or absent;

R_{39}= C or absent;

R_{50},R_{62}=are independently C,G or absent;

R_{30},R_{43},R_{45},R_{55},R_{70}=are independently C,G,U or absent;

R_8,R_{11},R_{17},R_{18},R_{28},R_{35},R_{53},R_{59},R_{60},R_{61}=are independently C,U or absent;

R_{19},R_{52}=are independently G or absent;

R_1= G,U or absent;

R_{23},R_{36},R_{38},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24,

x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{ASP}$ (SEQ ID NO: 572),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asp is:

R_0,R_{17},R_{18},R_{23}=are independently absent;

R_9,R_{40}=are independently A or absent;

R_{24},R_{71}=are independently A,C or absent;

R_{67},R_{68}=are independently A,C,G or absent;

R_2,R_6,R_{66}=are independently N or absent;

R_{57},R_{63}=are independently A,C,U or absent;

R_{10},R_{14},R_{27},R_{33},R_{37},R_{44},R_{46},R_{51},R_{56},R_{64},R_{72}=are independently A,G or absent;

R_7,R_{12},R_{26},R_{65}=are independently A,U or absent;

R_{39},R_{61},R_{62}=are independently C or absent;

R_3,R_{31},R_{45},R_{70}=are independently C,G or absent;

R_4,R_5,R_{29},R_{43},R_{55}=are independently C,G,U or absent;

R_8,R_{11},R_{13},R_{30},R_{32},R_{34},R_{35},R_{41},R_{48},R_{53},R_{59},R_{60}=are independently C,U or absent;

R_{15},R_{19},R_{20},R_{25},R_{42},R_{50},R_{52}=are independently G or absent;

R_1,R_{22},R_{49},R_{58},R_{69}=are independently G,U or absent;

R_{16},R_{21},R_{28},R_{36},R_{38},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{ASP}$ (SEQ ID NO: 573),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Asp is:

R_0,R_{17},R_{18},R_{23}=are absent

R_9,R_{12},R_{40},R_{65},R_{71}=are independently A or absent;

R_2,R_{24},R_{57}=are independently A,C or absent;

R_6,R_{14},R_{27},R_{46},R_{51},R_{56},R_{64},R_{67},R_{68}=are independently A,G or absent;

R_3,R_{31},R_{35},R_{39},R_{61},R_{62}=are independently C or absent;

R_{66}= C,G or absent;

R_5,R_8,R_{29},R_{30},R_{32},R_{34},R_{41},R_{43},R_{48},R_{55},R_{59},R_{60},R_{63}=are independently C,U or absent;

R_{10},R_{15},R_{19},R_{20},R_{25},R_{33},R_{37},R_{42},R_{44},R_{45},R_{49},R_{50},R_{52},R_{69},R_{70},R_{72}=are independently G or absent;

R_{22},R_{58}=are independently G,U or absent;

R_1,R_4,R_7,R_{11},R_{13},R_{16},R_{21},R_{26},R_{28},R_{36},R_{38},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Cysteine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{CYS} (SEQ ID NO: 574),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Cys is:

R_0 =absent

R_{14},R_{39},R_{57}=are independently A or absent;

R_{41}= A,C or absent;

R_{10},R_{15},R_{27},R_{33},R_{62}=are independently A,C,G or absent;

R_3,R_4,R_5,R_6,R_{12},R_{13},R_{16},R_{24},R_{26},R_{29},R_{30},R_{31},R_{32},R_{34},R_{42},R_{44},R_{45},R_{46},R_{48},R_{49},R_{58},R_{63},R_{64},R_{66}, R_{67},R_{68},R_{69},R_{70}=are independently N or absent;

R_{65}= A,C,U or absent;

R_9,R_{25},R_{37},R_{40},R_{52},R_{56}=are independently A,G or absent;

R_7,R_{20},R_{51}=are independently A,G,U or absent;

R_{18},R_{38},R_{55}=are independently C or absent;

R_2= C, G or absent;

R_{21},R_{28},R_{43},R_{50}=are independently C,G,U or absent;

R_{11},R_{22},R_{23},R_{35},R_{36},R_{59},R_{60},R_{61},R_{71},R_{72}=are independently C,U or absent;

R_1,R_{19}=are independently G or absent;

R_{17}= G,U or absent;

R_8,R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{CYS}$ (SEQ ID NO: 575),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Cys is:

R_0,R_{18},R_{23}=are absent;

R_{14},R_{24},R_{26},R_{29},R_{39},R_{41},R_{45},R_{57}=are independently A or absent;

R_{44}= A,C or absent;

R_{27},R_{62}=are independently A,C,G or absent;

R_{16}= A,C,G,U or absent;

R_{30},R_{70}=are independently A,C,U or absent;

R_5,R_7,R_9,R_{25},R_{34},R_{37},R_{40},R_{46},R_{52},R_{56},R_{58},R_{66}=are independently A,G or absent;

R_{20},R_{51}=are independently A,G,U or absent;

R_{35},R_{38},R_{43},R_{55},R_{69}=are independently C or absent;

R_2,R_4,R_{15}=are independently C,G or absent;

R_{13}= C,G,U or absent;

R_6,R_{11},R_{28},R_{36},R_{48},R_{49},R_{50},R_{60},R_{61},R_{67},R_{68},R_{71},R_{72}=are independently C,U or absent;

R_1,R_3,R_{10},R_{19},R_{33},R_{63}=are independently G or absent;

R_8,R_{17},R_{21},R_{64}=are independently G,U or absent;

R_{12},R_{22},R_{31},R_{32},R_{42},R_{53},R_{54},R_{65}=are independently U or absent;

R_{59}= U, or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{CYS}$ (SEQ ID NO: 576),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Cys is:

$R_{0,}R_{18,}R_{23}$=are absent

$R_{14},R_{24},R_{26},R_{29},R_{34},R_{39},R_{41},R_{45},R_{57},R_{58}$=are independently A or absent;

R_{44},R_{70}=are independently A,C or absent;

R_{62}= A,C,G or absent;

R_{16}= N or absent;

$R_{5},R_{7},R_{9},R_{20},R_{40},R_{46},R_{51},R_{52},R_{56},R_{66}$=are independently A,G or absent;

$R_{28},R_{35},R_{38},R_{43},R_{55},R_{67},R_{69}$=are independently C or absent;

R_{4},R_{15}=are independently C,G or absent;

$R_{6},R_{11},R_{13},R_{30},R_{48},R_{49},R_{50},R_{60},R_{61},R_{68},R_{71},R_{72}$=are independently C,U or absent;

$R_{1},R_{2},R_{3},R_{10},R_{19},R_{25},R_{27},R_{33},R_{37},R_{63}$=are independently G or absent;

R_{8},R_{21},R_{64}=are independently G,U or absent;

$R_{12},R_{17},R_{22},R_{31},R_{32},R_{36},R_{42},R_{53},R_{54}$, R_{59},R_{65}=are independently U or absent;

$[R_{47}]_{x}$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Glutamine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{GLN} (SEQ ID NO: 577),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Gln is:

R_0,R_{18}=are absent;

R_{14},R_{24},R_{57}=are independently A or absent;

R_9,R_{26},R_{27},R_{33},R_{56}=are independently A,C,G or absent;

R_2,R_4,R_5,R_6,R_{12},R_{13},R_{16},R_{21},R_{22},R_{25},R_{29},R_{30},R_{31},R_{32},R_{34},R_{41},R_{42},R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{58},R_{62},R_{63},R_{66},R_{67},R_{68},R_{69},R_{70}=are independently N or absent;

R_{17},R_{23},R_{43},R_{65},R_{71}=are independently A,C,U or absent;

R_{15},R_{40},R_{51},R_{52}=are independently A,G or absent;

R_1,R_7,R_{72}=are independently A,G,U or absent;

R_3,R_{11},R_{37},R_{60},R_{64}=are independently C,G,U or absent;

R_{28},R_{35},R_{55},R_{59},R_{61}=are independently C,U or absent;

R_{10},R_{19},R_{20}=are independently G or absent;

R_{39}= G,U or absent;

R_8,R_{36},R_{38},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{GLN}$ (SEQ ID NO: 578),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Gln is:

$R_{0,}R_{18,}R_{23}$=are absent

R_{14},R_{24},R_{57}=are independently A or absent;

R_{17},R_{71}=are independently A,C or absent;

$R_{25},R_{26},R_{33},R_{44},R_{46},R_{56},R_{69}$=are independently A,C,G or absent;

$R_4,R_5,R_{12},R_{22},R_{29},R_{30},R_{48},R_{49},R_{63},R_{67},R_{68}$=are independently N or absent;

$R_{31},R_{43},R_{62},R_{65},R_{70}$=are independently A,C,U or absent;

$R_{15},R_{27},R_{34},R_{40},R_{41},R_{51},R_{52}$=are independently A,G or absent;

$R_2,R_7,R_{21},R_{45},R_{50},R_{58},R_{66},R_{72}$=are independently A,G,U or absent;

$R_3,R_{13},R_{32},R_{37},R_{42},R_{60},R_{64}$=are independently C,G,U or absent;

$R_6,R_{11},R_{28},R_{35},R_{55},R_{59},R_{61}$=are independently C,U or absent;

R_9,R_{10},R_{19},R_{20}=are independently G or absent;

R_1,R_{16},R_{39}=are independently G,U or absent;

$R_8,R_{36},R_{38},R_{53},R_{54}$=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271),

provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{GLN}$ (SEQ ID NO: 579),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Gln is:

$R_{0,}R_{18,}R_{23}$=are absent

R_{14},R_{24},R_{41},R_{57}=are independently A or absent;

R_{17},R_{71}=are independently A,C or absent;

R_5,R_{25},R_{26},R_{46},R_{56},R_{69}=are independently A,C,G or absent;

R_4,R_{22},R_{29},R_{30},R_{48},R_{49},R_{63},R_{68}=are independently N or absent;

R_{43},R_{62},R_{65},R_{70}=are independently A,C,U or absent;

R_{15},R_{27},R_{33},R_{34},R_{40},R_{51},R_{52}=are independently A,G or absent;

R_2,R_7,R_{12},R_{45},R_{50},R_{58},R_{66}=are independently A,G,U or absent;

R_{31}= A,U or absent;

R_{32},R_{44},R_{60}=are independently C,G or absent;

R_3,R_{13},R_{37},R_{42},R_{64},R_{67}=are independently C,G,U or absent;

R_6,R_{11},R_{28},R_{35},R_{55},R_{59},R_{61}=are independently C,U or absent;

R_9,R_{10},R_{19},R_{20}=are independently G or absent;

R_1,R_{21},R_{39},R_{72}=are independently G,U or absent;

R_8,R_{16},R_{36},R_{38},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-

271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Glutamate TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I $_{GLU}$ (SEQ ID NO: 580),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Glu is:

R_0=absent;

R_{34},R_{43},R_{68},R_{69}=are independently A,C,G or absent;

R_1,R_2,R_5,R_6,R_9,R_{12},R_{16},R_{20},R_{21},R_{26},R_{27},R_{29},R_{30},R_{31},R_{32},R_{33},R_{41},R_{44},R_{45},R_{46},R_{48},R_{50},R_{51},R_{58},R_{63},R_{64},R_{65},R_{66},R_{70},R_{71}=are independently N or absent;

R_{13},R_{17},R_{23},R_{61}=are independently A,C,U or absent;

R_{10},R_{14},R_{24},R_{40},R_{52},R_{56}=are independently A,G or absent;

R_7,R_{15},R_{25},R_{67},R_{72}=are independently A,G,U or absent;

R_{11},R_{57}=are independently A,U or absent;

R_{39}= C,G or absent;

R_3,R_4,R_{22},R_{42},R_{49},R_{55},R_{62}=are independently C,G,U or absent;

R_{18},R_{28},R_{35},R_{37},R_{53},R_{59},R_{60}=are independently C,U or absent;

R_{19}= G or absent;

R_8,R_{36},R_{38},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{GLU}$ (SEQ ID NO: 581),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Glu is:

$R_{0,}R_{18,}R_{23}$=are absent

$R_{17,}R_{40}$=are independently A or absent;

$R_{26,}R_{27,}R_{34,}R_{43,}R_{68,}R_{69,}R_{71}$=are independently A,C,G or absent;

$R_{1,}R_{2,}R_{5,}R_{12,}R_{21,}R_{31,}R_{33,}R_{41,}R_{45,}R_{48,}R_{51,}R_{58,}R_{66,}R_{70}$=are independently N or absent;

$R_{44,}R_{61}$=are independently A,C,U or absent;

$R_{9,}R_{14,}R_{24,}R_{25,}R_{52,}R_{56,}R_{63}$=are independently A,G or absent;

$R_{7,}R_{15,}R_{46,}R_{50,}R_{67,}R_{72}$=are independently A,G,U or absent;

$R_{29,}R_{57}$=are independently A,U or absent;

R_{60}= C or absent;

R_{39}= C,G or absent;

$R_{3,}R_{6,}R_{20,}R_{30,}R_{32,}R_{42,}R_{55,}R_{62,}R_{65}$=are independently C,G,U or absent;

$R_{4,}R_{8,}R_{16,}R_{28,}R_{35,}R_{37,}R_{49,}R_{53,}R_{59}$=are independently C,U or absent;

R_{10},R_{19}=are independently G or absent;

R_{22},R_{64}=are independently G,U or absent;

R_{11},R_{13},R_{36},R_{38},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{GLU}$ (SEQ ID NO: 582),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Glu is:

R_0,R_{17},R_{18},R_{23}=are absent

R_{14},R_{27},R_{40},R_{71}=are independently A or absent;

R_{44}= A,C or absent;

R_{43}= A,C,G or absent;

R_1,R_{31},R_{33},R_{45},R_{51},R_{66}=are independently N or absent;

R_{21},R_{41}=are independently A,C,U or absent;

R_7,R_{24},R_{25},R_{50},R_{52},R_{56},R_{63},R_{68},R_{70}=are independently A,G or absent;

R_5,R_{46}=are independently A,G,U or absent;

R_{29},R_{57},R_{67},R_{72}=are independently A,U or absent;

R_2,R_{39},R_{60}=are independently C or absent;

R_3,R_{12},R_{20},R_{26},R_{34},R_{69}=are independently C,G or absent;

R_6,R_{30},R_{42},R_{48},R_{65}=are independently C,G,U o rabsent;

R_4,R_{16},R_{28},R_{35},R_{37},R_{49},R_{53},R_{55},R_{58},R_{61},R_{62}=are independently C,U or absent;

R_9,R_{10},R_{19},R_{64}=are independently G or absent;

R_{15},R_{22},R_{32}=are independently G,U or absent;

R_8,R_{11},R_{13},R_{36},R_{38},R_{54},R_{59}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Glycine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{GLY} (SEQ ID NO: 583),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Gly is:

R_0=absent;

R_{24}= A or absent;

R_3,R_9,R_{40},R_{50},R_{51}=are independently A,C,G or absent;

R_4,R_5,R_6,R_7,R_{12},R_{16},R_{21},R_{22},R_{26},R_{29},R_{30},R_{31},R_{32},R_{33},R_{34},R_{41},R_{42},R_{43},R_{44},R_{45},R_{46},R_{48},R_{49},R_{58},R_{63},R_{64},R_{65},R_{66},R_{67},R_{68}=are independently N or absent;

R_{59}= A,C,U or absent;

R_1,R_{10},R_{14},R_{15},R_{27},R_{56}=are independently A,G or absent;

R_{20},R_{25}=are independently A,G,U or absent;

R_{57},R_{72}=are independently A,U or absent;

R_{38},R_{39},R_{60}=are independently C or absent;

R_{52}= C,G or absent;

R_2,R_{19},R_{37},R_{54},R_{55},R_{61},R_{62},R_{69},R_{70}=are independently C,G,U or absent;

R_{11},R_{13},R_{17},R_{28},R_{35},R_{36},R_{71}=are independently C,U or absent;

R_8,R_{18},R_{23},R_{53}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{GLY}$ (SEQ ID NO: 584),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-

R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Gly is:

$R_{0,}R_{18,}R_{23}$=are absent

$R_{24},R_{27},R_{40},R_{72}$=are independently A or absent;

R_{26}= A,C or absent;

R_3,R_7,R_{68}=are independently A,C,G or absent;

$R_5,R_{30},R_{41},R_{42},R_{44},R_{49},R_{67}$=are independently A,C,G,U or absent;

R_{31},R_{32},R_{34}=are independently A,C,U or absent;

$R_9,R_{10},R_{14},R_{15},R_{33},R_{50},R_{56}$=are independently A,G or absent;

$R_{12},R_{16},R_{22},R_{25},R_{29},R_{46}$=are independently A,G,U or absent;

R_{57}= A,U or absent;

$R_{17},R_{38},R_{39},R_{60},R_{61},R_{71}$=are independently C or absent;

R_6,R_{52},R_{64},R_{66}=are independently C,G or absent;

$R_2,R_4,R_{37},R_{48},R_{55},R_{65}$=are independently C,G,U or absent;

$R_{13},R_{35},R_{43},R_{62},R_{69}$=are independently C,U or absent;

$R_1,R_{19},R_{20},R_{51},R_{70}$=are independently G or absent;

R_{21},R_{45},R_{63}=are independently G,U or absent;

$R_8,R_{11},R_{28},R_{36},R_{53},R_{54},R_{58},R_{59}$=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271),

provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{GLY}$ (SEQ ID NO: 585),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Gly is:

$R_{0,}R_{18,}R_{23}$=are absent

$R_{24},R_{27},R_{40},R_{72}$=are independently A or absent;

R_{26}= A,C or absent;

R_3,R_7,R_{49},R_{68}=are independently A,C,G or absent;

$R_5,R_{30},R_{41},R_{44},R_{67}$=are independently N or absent;

R_{31},R_{32},R_{34}=are independently A,C,U or absent;

$R_9,R_{10},R_{14},R_{15},R_{33},R_{50},R_{56}$=are independently A,G or absent;

$R_{12},R_{25},R_{29},R_{42},R_{46}$=are independently A,G,U or absent;

R_{16},R_{57}=are independently A,U or absent;

$R_{17},R_{38},R_{39},R_{60},R_{61},R_{71}$=are independently C or absent;

R_6,R_{52},R_{64},R_{66}=are independently C,G or absent;

R_{37},R_{48},R_{65}=are independently C,G,U or absent;

$R_2,R_4,R_{13},R_{35},R_{43},R_{55},R_{62},R_{69}$=are independently C,U or absent;

$R_1,R_{19},R_{20},R_{51},R_{70}$=are independently G or absent;

$R_{21},R_{22},R_{45},R_{63}$=are independently G,U or absent;

$R_8,R_{11},R_{28},R_{36},R_{53},R_{54},R_{58},R_{59}$=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24,

x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Histidine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{HIS} (SEQ ID NO: 586),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for His is:

R_{23}=absent;

R_{14},R_{24},R_{57}=are independently A or absent;

R_{72}= A,C or absent;

R_9,R_{27},R_{43},R_{48},R_{69}=are independently A,C,G or absent;

R_3,R_4,R_5,R_6,R_{12},R_{25},R_{26},R_{29},R_{30},R_{31},R_{34},R_{42},R_{45},R_{46},R_{49},R_{50},R_{58},R_{62},R_{63},R_{66},R_{67},R_{68}=are independently N or absent;

R_{13},R_{21},R_{41},R_{44},R_{65}=are independently A,C,U or absent;

R_{40},R_{51},R_{56},R_{70}=are independently A,G or absent;

R_7,R_{32}=are independently A,G,U or absent;

R_{55},R_{60}=are independently C or absent;

R_{11},R_{16},R_{33},R_{64}=are independently C,G,U or absent;

R_2,R_{17},R_{22},R_{28},R_{35},R_{53},R_{59},R_{61},R_{71}=are independently C,U or absent;

R_1,R_{10},R_{15},R_{19},R_{20},R_{37},R_{39},R_{52}=are independently G or absent;

R_0= G,U or absent;

R_8,R_{18},R_{36},R_{38},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{HIS}$ (SEQ ID NO: 587),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for His is:

R_0,R_{17},R_{18},R_{23}=are absent;

R_7,R_{12},R_{14},R_{24},R_{27},R_{45},R_{57},R_{58},R_{63},R_{67},R_{72}=are independently A or absent;

R_3= A,C,U or absent;

R_4,R_{43},R_{56},R_{70}=are independently A,G or absent;

R_{49}= A,U or absent;

R_2,R_{28},R_{30},R_{41},R_{42},R_{44},R_{48},R_{55},R_{60},R_{66},R_{71}=are independently C or absent;

R_{25}= C,G or absent;

R_9= C,G,U or absent;

R_8,R_{13},R_{26},R_{33},R_{35},R_{50},R_{53},R_{61},R_{68}=are independently C,U or absent;

R_1,R_6,R_{10},R_{15},R_{19},R_{20},R_{32},R_{34},R_{37},R_{39},R_{40},R_{46},R_{51},R_{52},R_{62},R_{64},R_{69}=are independently G or absent;

R_{16}= G,U or absent;

R_5,R_{11},R_{21},R_{22},R_{29},R_{31},R_{36},R_{38},R_{54},R_{59},R_{65}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{HIS}$ (SEQ ID NO: 588),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for His is:

R_0,R_{17},R_{18},R_{23}=are absent

R_7,R_{12},R_{14},R_{24},R_{27},R_{45},R_{57},R_{58},R_{63},R_{67},R_{72}=are independently A or absent;

R_3= A,C or absent;

R_4,R_{43},R_{56},R_{70}=are independently A,G or absent;

R_{49}= A,U or absent;

R_2,R_{28},R_{30},R_{41},R_{42},R_{44},R_{48},R_{55},R_{60},R_{66},R_{71}=are independently C or absent;

R_8,R_9,R_{26},R_{33},R_{35},R_{50},R_{61},R_{68}=are independently C,U or absent;

R_1,R_6,R_{10},R_{15},R_{19},R_{20},R_{25},R_{32},R_{34},R_{37},R_{39},R_{40},R_{46},R_{51},R_{52},R_{62},R_{64},R_{69}=are independently G or absent;

R_5,R_{11},R_{13},R_{16},R_{21},R_{22},R_{29},R_{31},R_{36},R_{38},R_{53},R_{54},R_{59},R_{65}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Isoleucine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{ILE} (SEQ ID NO: 589),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ile is:

R_{23}=absent;

R_{38},R_{41},R_{57},R_{72}=are independently A or absent;

R_1,R_{26}=are independently A,C,G or absent;

R_0,R_3,R_4,R_6,R_{16},R_{31},R_{32},R_{34},R_{37},R_{42},R_{43},R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{58},R_{59},R_{62},R_{63},R_{64},R_{66},R_{67},R_{68},R_{69}=are independently N or absent;

R_{22},R_{61},R_{65}=are independently A,C,U or absent;

R_9,R_{14},R_{15},R_{24},R_{27},R_{40}=are independently A,G or absent;

R_7,R_{25},R_{29},R_{51},R_{56}=are independently A,G,U or absent;

R_{18},R_{54}=are independently A,U or absent;

R_{60}= C or absent;

R_2,R_{52},R_{70}=are independently C,G or absent;

R_5,R_{12},R_{21},R_{30},R_{33},R_{71}=are independently C,G,U or absent;

R_{11},R_{13},R_{17},R_{28},R_{35},R_{53},R_{55}=are independently C,U or absent;

R_{10},R_{19},R_{20}=are independently G or absent;

R_8,R_{36},R_{39}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{ILE}$ (SEQ ID NO: 590),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ile is:

R_0,R_{18},R_{23}=are absent

R_{24},R_{38},R_{40},R_{41},R_{57},R_{72}=are independently A or absent;

R_{26},R_{65}=are independently A,C or absent;

R_{58},R_{59},R_{67}=are independently N or absent;

R_{22}= A,C,U or absent;

R_6,R_9,R_{14},R_{15},R_{29},R_{34},R_{43},R_{46},R_{48},R_{50},R_{51},R_{63},R_{69}=are independently A,G or absent;

R_{37},R_{56}=are independently A,G,U or absent;

R_{54}= A,U or absent;

R_{28},R_{35},R_{60},R_{62},R_{71}=are independently C or absent;

R_2,R_{52},R_{70}=are independently C,G or absent;

R_5= C,G,U or absent;

R_3,R_4,R_{11},R_{13},R_{17},R_{21},R_{30},R_{42},R_{44},R_{45},R_{49},R_{53},R_{55},R_{61},R_{64},R_{66}=are independently C,U or absent;

R_1,R_{10},R_{19},R_{20},R_{25},R_{27},R_{31},R_{68}=are independently G or absent;

R_7,R_{12},R_{32}=are independently G,U or absent;

R_8,R_{16},R_{33},R_{36},R_{39}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{ILE}$ (SEQ ID NO: 591),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-

R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ile is:

$R_{0,}R_{18,}R_{23}$=are absent

$R_{14},R_{24},R_{38},R_{40},R_{41},R_{57},R_{72}$=are independently A or absent;

R_{26},R_{65}=are independently A,C or absent;

R_{22},R_{59}=are independently A,C,U or absent;

$R_{6},R_{9},R_{15},R_{34},R_{43},R_{46},R_{51},R_{56},R_{63},R_{69}$=are independently A,G or absent;

R_{37}= A,G,U or absent;

$R_{13},R_{28},R_{35},R_{44},R_{55},R_{60},R_{62},R_{71}$=are independently C or absent;

R_{2},R_{5},R_{70}=are independently C,G or absent;

R_{58},R_{67}=are independently C,G,U or absent;

$R_{3},R_{4},R_{11},R_{17},R_{21},R_{30},R_{42},R_{45},R_{49},R_{53},R_{61},R_{64},R_{66}$=are independently C,U or absent;

$R_{1},R_{10},R_{19},R_{20},R_{25},R_{27},R_{29},R_{31},R_{32},R_{48},R_{50},R_{52},R_{68}$=are independently G or absent;

R_{7},R_{12}=are independently G,U or absent;

$R_{8},R_{16},R_{33},R_{36},R_{39},R_{54}$=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Methionine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I $_{MET}$ (SEQ ID NO: 592),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Met is:

R_0,R_{23}=are absent;

R_{14},R_{38},R_{40},R_{57}=are independently A or absent;

R_{60}= A,C or absent;

R_{33},R_{48},R_{70}=are independently A,C,G or absent;

R_1,R_3,R_4,R_5,R_6,R_{11},R_{12},R_{16},R_{17},R_{21},R_{22},R_{26},R_{27},R_{29},R_{30},R_{31},R_{32},R_{42},R_{44},R_{45},R_{46},R_{49},R_{50},R_{58},R_{62},R_{63},R_{66},R_{67},R_{68},R_{69},R_{71}=are independently N or absent;

R_{18},R_{35},R_{41},R_{59},R_{65}=are independently A,C,U or absent;

R_9,R_{15},R_{51}=are independently A,G or absent;

R_7,R_{24},R_{25},R_{34},R_{53},R_{56}=are independently A,G,U or absent;

R_{72}= A,U or absent;

R_{37}= C or absent;

R_{10},R_{55}=are independently C,G or absent;

R_2,R_{13},R_{28},R_{43},R_{64}=are independently C,G,U or absent;

R_{36},R_{61}=are independently C,U or absent;

R_{19},R_{20},R_{52}=are independently G or absent;

R_8,R_{39},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17,

x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{MET}$ (SEQ ID NO: 593),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Met is:

$R_{0,}R_{18,}R_{22,}R_{23}$=are absent

$R_{14},R_{24},R_{38},R_{40},R_{41},R_{57},R_{72}$=are independently A or absent;

$R_{59},R_{60},R_{62},R_{65}$=are independently A,C or absent;

R_6,R_{45},R_{67}=are independently A,C,G or absent;

R_4= N or absent;

R_{21},R_{42}=are independently A,C,U or absent;

$R_1,R_9,R_{27},R_{29},R_{32},R_{46},R_{51}$=are independently A,G or absent;

$R_{17},R_{49},R_{53},R_{56},R_{58}$=are independently A,G,U or absent;

R_{63}=A,U or absent;

R_3,R_{13},R_{37}=are independently C or absent;

$R_{48},R_{55},R_{64},R_{70}$=are independently C,G or absent;

R_2,R_5,R_{66},R_{68}=are independently C,G,U or absent;

$R_{11},R_{16},R_{26},R_{28},R_{30},R_{31},R_{35},R_{36},R_{43},R_{44},R_{61},R_{71}$=are independently C,U or absent;

$R_{10},R_{12},R_{15},R_{19},R_{20},R_{25},R_{33},R_{52},R_{69}$=are independently G or absent;

R_7,R_{34},R_{50}=are independently G,U or absent;

R_8,R_{39},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{MET}$ (SEQ ID NO: 594),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Met is:

R_0,R_{18},R_{22},R_{23}=are absent

R_{14},R_{24},R_{38},R_{40},R_{41},R_{57},R_{72}=are independently A or absent;

R_{59},R_{62},R_{65}=are independently A,C or absent;

R_6,R_{67}=are independently A,C,G or absent;

R_4,R_{21}=are independently A,C,U or absent;

R_1,R_9,R_{27},R_{29},R_{32},R_{45},R_{46},R_{51}=are independently A,G or absent;

R_{17},R_{56},R_{58}=are independently A,G,U or absent;

R_{49},R_{53},R_{63}=are independently A,U or absent;

R_3,R_{13},R_{26},R_{37},R_{43},R_{60}=are independently C or absent;

R_2,R_{48},R_{55},R_{64},R_{70}=are independently C,G or absent;

R_5,R_{66}=are independently C,G,U or absent;

R_{11},R_{16},R_{28},R_{30},R_{31},R_{35},R_{36},R_{42},R_{44},R_{61},R_{71}=are independently C,U or absent;

R_{10},R_{12},R_{15},R_{19},R_{20},R_{25},R_{33},R_{52},R_{69}=are independently G or absent;

R_7,R_{34},R_{50},R_{68}=are independently G,U or absent;

R_8,R_{39},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Leucine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{LEU} (SEQ ID NO: 595),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Leu is:

R_0=absent;

R_{38},R_{57}=are independently A or absent;

R_{60}= A,C or absent;

R_1,R_{13},R_{27},R_{48},R_{51},R_{56}=are independently A,C,G or absent;

R_2,R_3,R_4,R_5,R_6,R_7,R_9,R_{10},R_{11},R_{12},R_{16},R_{23},R_{26},R_{28},R_{29},R_{30},R_{31},R_{32},R_{33},R_{34},R_{37},R_{41},R_{42},R_{43},R_{44}, R_{45},R_{46},R_{49},R_{50},R_{58},R_{62},R_{63},R_{65},R_{66},R_{67},R_{68},R_{69},R_{70}=are independently N or absent;

R_{17},R_{18},R_{21},R_{22},R_{25},R_{35},R_{55}=are independently A,C,U or absent;

R_{14},R_{15},R_{39},R_{72}=are independently A,G or absent;

R_{24},R_{40}=are independently A,G,U or absent;

R_{52},R_{61},R_{64},R_{71}=are independently C,G,U or absent;

R_{36},R_{53},R_{59}=are independently C,U or absent;

R_{19}= G or absent;

R_{20}= G,U or absent;

R_8,R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{LEU}$ (SEQ ID NO: 596),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Leu is:

R_0 =absent

R_{38},R_{57},R_{72}=are independently A or absent;

R_{60}= A,C or absent;

R_4,R_5,R_{48},R_{50},R_{56},R_{69}=are independently A,C,G or absent;

R_6,R_{33},R_{41},R_{43},R_{46},R_{49},R_{58},R_{63},R_{66},R_{70}=are independently N or absent;

R_{11},R_{12},R_{17},R_{21},R_{22},R_{28},R_{31},R_{37},R_{44},R_{55}=are independently A,C,U or absent;

R_1,R_9,R_{14},R_{15},R_{24},R_{27},R_{34},R_{39}=are independently A,G or absent;

R_7,R_{29},R_{32},R_{40},R_{45}=are independently A,G,U or absent;

R_{25}= A,U or absent;

R_{13}= C,G or absent;

R_2,R_3,R_{16},R_{26},R_{30},R_{52},R_{62},R_{64},R_{65},R_{67},R_{68}=are independently C,G,U or absent;

R_{18},R_{35},R_{42},R_{53},R_{59},R_{61},R_{71}=are independently C,U or absent;

R_{19},R_{51}=are independently G or absent;

R_{10},R_{20}=are independently G,U or absent;

R_8,R_{23},R_{36},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{LEU}$ (SEQ ID NO: 597),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Leu is:

R_0 =absent

R_{38},R_{57},R_{72}=are independently A or absent;

R_{60}= A,C or absent;

R_4,R_5,R_{48},R_{50},R_{56},R_{58},R_{69}=are independently A,C,G or absent;

R_6,R_{33},R_{43},R_{46},R_{49},R_{63},R_{66},R_{70}=are independently N or absent;

R_{11},R_{12},R_{17},R_{21},R_{22},R_{28},R_{31},R_{37},R_{41},R_{44},R_{55}=are independently A,C,U or absent;

R_1,R_9,R_{14},R_{15},R_{24},R_{27},R_{34},R_{39}=are independently A,G or absent;

R_7,R_{29},R_{32},R_{40},R_{45}=are independently A,G,U or absent;

R_{25}= A,U or absent;

R_{13}= C,G or absent;

R_2,R_3,R_{16},R_{30},R_{52},R_{62},R_{64},R_{67},R_{68}=are independently C,G,U or absent;

R_{18},R_{35},R_{42},R_{53},R_{59},R_{61},R_{65},R_{71}=are independently C,U or absent;

R_{19},R_{51}=are independently G or absent;

R_{10},R_{20},R_{26}=are independently G,U or absent;

R_8,R_{23},R_{36},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Lysine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I $_{LYS}$ (SEQ ID NO: 598),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Lys is:

R_0 =absent

R_{14}= A or absent;

R_{40},R_{41}=are independently A,C or absent;

R_{34},R_{43},R_{51}=are independently A,C,G or absent;

R_1,R_2,R_3,R_4,R_5,R_6,R_7,R_{11},R_{12},R_{16},R_{21},R_{26},R_{30},R_{31},R_{32},R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{58},R_{62},R_{63},R_{65}, R_{66},R_{67},R_{68},R_{69},R_{70}=are independently N or absent;

R_{13},R_{17},R_{59},R_{71}=are independently A,C,U or absent;

R_9,R_{15},R_{19},R_{20},R_{25},R_{27},R_{52},R_{56}=are independently A,G or absent;

R_{24},R_{29},R_{72}=are independently A,G,U or absent;

R_{18},R_{57}=are independently A,U or absent;

R_{10},R_{33}=are independently C,G or absent;

R_{42},R_{61},R_{64}=are independently C,G,U or absent;

R_{28},R_{35},R_{36},R_{37},R_{53},R_{55},R_{60}=are independently C,U or absent;

R_8,R_{22},R_{23},R_{38},R_{39},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17,

x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{LYS}$ (SEQ ID NO: 599),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Lys is:

$R_{0,}R_{18,}R_{23}$=are absent

R_{14}= A or absent;

R_{40},R_{41},R_{43}=are independently A,C or absent;

R_3,R_7=are independently A,C,G or absent;

R_1,R_6,R_{11},R_{31},R_{45},R_{48},R_{49},R_{63},R_{65},R_{66},R_{68}=are independently N or absent;

R_2,R_{12},R_{13},R_{17},R_{44},R_{67},R_{71}=are independently A,C,U or absent;

R_9,R_{15},R_{19},R_{20},R_{25},R_{27},R_{34},R_{50},R_{52},R_{56},R_{70},R_{72}=are independently A,G or absent;

R_5,R_{24},R_{26},R_{29},R_{32},R_{46},R_{69}=are independently A,G,U or absent;

R_{57}= A,U or absent;

R_{10},R_{61}=are independently C,G or absent;

R_4,R_{16},R_{21},R_{30},R_{58},R_{64}=are independently C,G,U or absent;

R_{28},R_{35},R_{36},R_{37},R_{42},R_{53},R_{55},R_{59},R_{60},R_{62}=are independently C,U or absent;

R_{33},R_{51}=are independently G or absent;

R_8=G,U or absent;

R_{22},R_{38},R_{39},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24,

x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{LYS}$ (SEQ ID NO: 600),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Lys is:

$R_{0,}R_{18,}R_{23}$=absent

R_9,R_{14},R_{34},R_{41}=are independently A or absent;

R_{40}= A,C or absent;

R_1,R_3,R_7,R_{31}=are independently A,C,G or absent;

R_{48},R_{65},R_{68}=are independently N or absent;

R_2,R_{13},R_{17},R_{44},R_{63},R_{66}=are independently A,C,U or absent;

R_5,R_{15},R_{19},R_{20},R_{25},R_{27},R_{29},R_{50},R_{52},R_{56},R_{70},R_{72}=are independently A,G or absent;

R_6,R_{24},R_{32},R_{49}=are independently A,G,U or absent;

R_{12},R_{26},R_{46},R_{57}=are independently A,U or absent;

R_{11},R_{28},R_{35},R_{43}=are independently C or absent;

R_{10},R_{45},R_{61}=are independently C,G or absent;

R_4,R_{21},R_{64}=are independently C,G,U or absent;

R_{37},R_{53},R_{55},R_{59},R_{60},R_{62},R_{67},R_{71}=are independently C,U or absent;

R_{33},R_{51}=are independently G or absent;

R_8,R_{30},R_{58},R_{69}=are independently G,U or absent;

R_{16},R_{22},R_{36},R_{38},R_{39},R_{42},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Phenylalanine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{PHE} (SEQ ID NO: 601),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Phe is:

R_0,R_{23}=are absent

R_9,R_{14},R_{38},R_{39},R_{57},R_{72}=are independently A or absent;

R_{71}= A,C or absent;

R_{41},R_{70}=are independently A,C,G or absent;

R_4,R_5,R_6,R_{30},R_{31},R_{32},R_{34},R_{42},R_{44},R_{45},R_{46},R_{48},R_{49},R_{58},R_{62},R_{63},R_{66},R_{67},R_{68},R_{69}=are independently N or absent;

R_{16},R_{61},R_{65}=are independently A,C,U or absent;

R_{15},R_{26},R_{27},R_{29},R_{40},R_{56}=are independently A,G or absent;

R_7,R_{51}=are independently A,G,U or absent;

R_{22},R_{24}=are independently A,U or absent;

R_{55},R_{60}=are independently C or absent;

R_2,R_3,R_{21},R_{33},R_{43},R_{50},R_{64}=are independently C,G,U or absent;

R_{11},R_{12},R_{13},R_{17},R_{28},R_{35},R_{36},R_{59}=are independently C,U or absent;

R_{10},R_{19},R_{20},R_{25},R_{37},R_{52}=are independently G or absent;

R_1= G,U or absent;

R_8,R_{18},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{PHE}$ (SEQ ID NO: 602),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Phe is:

R_0,R_{18},R_{23}=absent

R_{14},R_{24},R_{38},R_{39},R_{57},R_{72}=are independently A or absent;

R_{46},R_{71}=are independently A,C or absent;

R_4,R_{70}=are independently A,C,G or absent;

R_{45}= A,C,U or absent;

R_6,R_7,R_{15},R_{26},R_{27},R_{32},R_{34},R_{40},R_{41},R_{56},R_{69}=are independently A,G or absent;

R_{29}= A,G,U or absent;

R_5,R_9,R_{67}=are independently A,U or absent;

R_{35},R_{49},R_{55},R_{60}=are independently C or absent;

R_{21},R_{43},R_{62}=are independently C,G or absent;

R_2,R_{33},R_{68}=are independently C,G,U or absent;

R_3,R_{11},R_{12},R_{13},R_{28},R_{30},R_{36},R_{42},R_{44},R_{48},R_{58},R_{59},R_{61},R_{66}=are independently C,U or absent;

R_{10},R_{19},R_{20},R_{25},R_{37},R_{51},R_{52},R_{63},R_{64}=are independently G or absent;

R_1,R_{31},R_{50}=are independently G,U or absent;

R_8,R_{16},R_{17},R_{22},R_{53},R_{54},R_{65}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{PHE}$ (SEQ ID NO: 603),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Phe is:

$R_{0,}R_{18,}R_{22,}R_{23}$=absent

$R_5,R_7,R_{14},R_{24},R_{26},R_{32},R_{34},R_{38},R_{39},R_{41},R_{57},R_{72}$=are independently A or absent;

R_{46}= A,C or absent;

R_{70}= A,C,G or absent;

$R_4,R_6,R_{15},R_{56},R_{69}$=are independently A,G or absent;

R_9,R_{45}=are independently A,U or absent;

$R_2,R_{11},R_{13},R_{35},R_{43},R_{49},R_{55},R_{60},R_{68},R_{71}$=are independently C or absent;

R_{33}= C,G or absent;

$R_3,R_{28},R_{36},R_{48},R_{58},R_{59},R_{61}$=are independently C,U or absent;

$R_1,R_{10},R_{19},R_{20},R_{21},R_{25},R_{27},R_{29},R_{37},R_{40},R_{51},R_{52},R_{62},R_{63},R_{64}$=are independently G or absent;

$R_8,R_{12},R_{16},R_{17},R_{30},R_{31},R_{42},R_{44},R_{50},R_{53},R_{54},R_{65},R_{66},R_{67}$=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Proline TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{PRO} (SEQ ID NO: 604),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-

R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Pro is:

R_0 =absent

R_{14},R_{57}=are independently A or absent;

R_{70},R_{72}=are independently A,C or absent;

R_9,R_{26},R_{27}=are independently A,C,G or absent;

R_4,R_5,R_6,R_{16},R_{21},R_{29},R_{30},R_{31},R_{32},R_{33},R_{34},R_{37},R_{41},R_{42},R_{43},R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{58},R_{61},R_{62}, R_{63},R_{64},R_{66},R_{67},R_{68}=are independently N or absent;

R_{35},R_{65}=are independently A,C,U or absent;

R_{24},R_{40},R_{56}=are independently A,G or absent;

R_7,R_{25},R_{51}=are independently A,G,U or absent;

R_{55},R_{60}=are independently C or absent;

R_1,R_3,R_{71}=are independently C,G or absent;

R_{11},R_{12},R_{20},R_{69}=are independently C,G,U or absent;

R_{13},R_{17},R_{18},R_{22},R_{23},R_{28},R_{59}=are independently C,U or absent;

R_{10},R_{15},R_{19},R_{38},R_{39},R_{52}=are independently G or absent;

R_2= are independently G,U or absent;

R_8,R_{36},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{PRO}$ (SEQ ID NO: 605),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Pro is:

$R_{0,}R_{17,}R_{18,}R_{22,}R_{23}$=absent;

$R_{14,}R_{45,}R_{56,}R_{57,}R_{58,}R_{65,}R_{68}$=are independently A or absent;

R_{61}= A,C,G or absent;

R_{43}=N or absent;

R_{37}= A, C,U or absent;

$R_{24,}R_{27,}R_{33,}R_{40,}R_{44,}R_{63}$=are independently A,G or absent;

$R_{3,}R_{12,}R_{30,}R_{32,}R_{48,}R_{55,}R_{60,}R_{70,}R_{71,}R_{72}$=are independently C or absent;

$R_{5,}R_{34,}R_{42,}R_{66}$=are independently C,G or absent;

R_{20}= C,G,U or absent;

$R_{35,}R_{41,}R_{49,}R_{62}$=are independently C,U or absent;

$R_{1,}R_{2,}R_{6,}R_{9,}R_{10,}R_{15,}R_{19,}R_{26,}R_{38,}R_{39,}R_{46,}R_{50,}R_{51,}R_{52,}R_{64,}R_{67,}R_{69}$=are independently G or absent;

$R_{11,}R_{16}$=are independently G,U or absent;

$R_{4,}R_{7,}R_{8,}R_{13,}R_{21,}R_{25,}R_{28,}R_{29,}R_{31,}R_{36,}R_{53,}R_{54,}R_{59}$=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17,

x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{PRO}$ (SEQ ID NO: 606),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Pro is:

$R_{0,}R_{17,}R_{18,}R_{22,}R_{23}$=absent

$R_{14,}R_{45,}R_{56,}R_{57,}R_{58,}R_{65,}R_{68}$=are independently A or absent;

R_{37}= A,C,U or absent;

$R_{24,}R_{27,}R_{40}$=are independently A,G or absent;

$R_{3,}R_{5,}R_{12,}R_{30,}R_{32,}R_{48,}R_{49,}R_{55,}R_{60,}R_{61,}R_{62,}R_{66,}R_{70,}R_{71,}R_{72}$=are independently C or absent;

$R_{34,}R_{42}$=are independently C,G or absent;

R_{43}= C,G,U or absent;

R_{41}= C,U or absent;

$R_{1,}R_{2,}R_{6,}R_{9,}R_{10,}R_{15,}R_{19,}R_{20,}R_{26,}R_{33,}R_{38,}R_{39,}R_{44,}R_{46,}R_{50,}R_{51,}R_{52,}R_{63,}R_{64,}R_{67,}R_{69}$=are independently G or absent;

R_{16}= G,U or absent;

$R_{4,}R_{7,}R_{8,}R_{11,}R_{13,}R_{21,}R_{25,}R_{28,}R_{29,}R_{31,}R_{35,}R_{36,}R_{53,}R_{54,}R_{59}$=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1,

x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Serine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I $_{SER}$ (SEQ ID NO: 607),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ser is:

R_0=absent;

R_{14},R_{24},R_{57}=are independently A or absent;

R_{41}= A,C or absent;

R_2,R_3,R_4,R_5,R_6,R_7,R_9,R_{10},R_{11},R_{12},R_{13},R_{16},R_{21},R_{25},R_{26},R_{27},R_{28},R_{30},R_{31},R_{32},R_{33},R_{34},R_{37},R_{42},R_{43}, R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{62},R_{63},R_{64},R_{65},R_{66},R_{67},R_{68},R_{69},R_{70}=are independently N or absent;

R_{18}= A,C,U or absent;

R_{15},R_{40},R_{51},R_{56}=are independently A,G or absent;

R_1,R_{29},R_{58},R_{72}=are independently A,G,U or absent;

R_{39}= A,U or absent;

R_{60}= C or absent;

R_{38}= C,G or absent;

R_{17},R_{22},R_{23},R_{71}=are independently C,G,U or absent;

R_8,R_{35},R_{36},R_{55},R_{59},R_{61}=are independently C,U or absent;

R_{19},R_{20}=are independently G or absent;

R_{52}= G,U or absent;

R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{SER}$ (SEQ ID NO: 608),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ser is:

$R_{0,}R_{23}$=absent

R_{14},R_{24},R_{41},R_{57}=are independently A or absent;

R_{44}= A,C or absent;

R_{25},R_{45},R_{48}=are independently A,C,G or absent;

R_2,R_3,R_4,R_5,R_{37},R_{50},R_{62},R_{66},R_{67},R_{69},R_{70}=are independently N or absent;

R_{12},R_{28},R_{65}=are independently A,C,U or absent;

R_9,R_{15},R_{29},R_{34},R_{40},R_{56},R_{63}=are independently A,G or absent;

R_7,R_{26},R_{30},R_{33},R_{46},R_{58},R_{72}=are independently A,G,U or absent;

R_{39}= A,U or absent;

R_{11},R_{35},R_{60},R_{61}=are independently C or absent;

R_{13},R_{38}=are independently C,G or absent;

R_6,R_{17},R_{31},R_{43},R_{64},R_{68}=are independently C,G,U or absent;

R_{36},R_{42},R_{49},R_{55},R_{59},R_{71}=are independently C,U or absent;

R_{10},R_{19},R_{20},R_{27},R_{51}=are independently G or absent;

R_1,R_{16},R_{32},R_{52}=are independently G,U or absent;

R_8,R_{18},R_{21},R_{22},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{SER}$ (SEQ ID NO: 609),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Ser is:

R_0,R_{23}=absent

R_{14},R_{24},R_{41},R_{57},R_{58}=are independently A or absent;

R_{44}= A,C or absent;

R_{25},R_{48}=are independently A,C,G or absent;

R_2,R_3,R_5,R_{37},R_{66},R_{67},R_{69},R_{70}=are independently N or absent;

R_{12},R_{28},R_{62}=are independently A,C,U or absent;

R_7,R_9,R_{15},R_{29},R_{33},R_{34},R_{40},R_{45},R_{56},R_{63}=are independently A,G or absent;

R_4,R_{26},R_{46},R_{50}=are independently A,G,U or absent;

R_{30},R_{39}=are independently A,U or absent;

R_{11},R_{17},R_{35},R_{60},R_{61}=are independently C or absent;

R_{13},R_{38}=are independently C,G or absent;

R_6,R_{64}=are independently C,G,U or absent;

R_{31},R_{42},R_{43},R_{49},R_{55},R_{59},R_{65},R_{68},R_{71}=are independently C,U or absent;

R_{10},R_{19},R_{20},R_{27},R_{51},R_{52}=are independently G or absent;

R_1,R_{16},R_{32},R_{72}=are independently G,U or absent;

R_8,R_{18},R_{21},R_{22},R_{36},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Threonine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{THR} (SEQ ID NO: 610),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-

R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Thr is:

$R_{0,}R_{23}$=absent

R_{14},R_{41},R_{57}=are independently A or absent;

R_{56},R_{70}=are independently A,C,G or absent;

R_4,R_5,R_6,R_7,R_{12},R_{16},R_{26},R_{30},R_{31},R_{32},R_{34},R_{37},R_{42},R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{58},R_{62},R_{63},R_{64},R_{65},R_{66},R_{67},R_{68},R_{72}=are independently N or absent;

R_{13},R_{17},R_{21},R_{35},R_{61}=are independently A,C,U or absent;

R_1,R_9,R_{24},R_{27},R_{29},R_{69}=are independently A,G or absent;

R_{15},R_{25},R_{51}=are independently A,G,U or absent;

R_{40},R_{53}=are independently A,U or absent;

R_{33},R_{43}=are independently C,G or absent;

R_2,R_3,R_{59}=are independently C,G,U or absent;

R_{11},R_{18},R_{22},R_{28},R_{36},R_{54},R_{55},R_{60},R_{71}=are independently C,U or absent;

R_{10},R_{20},R_{38},R_{52}=are independently G or absent;

R_{19}= G,U or absent;

R_8,R_{39}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{THR}$ (SEQ ID NO: 611),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Thr is:

R_0,R_{18},R_{23}=absent

R_{14},R_{41},R_{57}=are independently A or absent;

R_9,R_{42},R_{44},R_{48},R_{56},R_{70}=are independently A,C,G or absent;

R_4,R_6,R_{12},R_{26},R_{49},R_{58},R_{63},R_{64},R_{66},R_{68}=are independently N or absent;

R_{13},R_{21},R_{31},R_{37},R_{62}=are independently A,C,U or absent;

R_1,R_{15},R_{24},R_{27},R_{29},R_{46},R_{51},R_{69}=are independently A,G or absent;

R_7,R_{25},R_{45},R_{50},R_{67}=are independently A,G,U or absent;

R_{40},R_{53}=are independently A,U or absent;

R_{35}= C or absent;

R_{33},R_{43}=are independently C,G or absent;

R_2,R_3,R_5,R_{16},R_{32},R_{34},R_{59},R_{65},R_{72}=are independently C,G,U or absent;

R_{11},R_{17},R_{22},R_{28},R_{30},R_{36},R_{55},R_{60},R_{61},R_{71}=are independently C,U or absent;

R_{10},R_{19},R_{20},R_{38},R_{52}=are independently G or absent;

R_8,R_{39},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271),

provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{THR}$ (SEQ ID NO: 612),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Thr is:

$R_{0,}R_{18,}R_{23}$=absent

R_{14},R_{40},R_{41},R_{57}=are independently A or absent;

R_{44}= A,C or absent;

R_9,R_{42},R_{48},R_{56}=are independently A,C,G or absent;

R_4,R_6,R_{12},R_{26},R_{58},R_{64},R_{66},R_{68}=are independently N or absent;

R_{13},R_{21},R_{31},R_{37},R_{49},R_{62}=are independently A,C,U or absent;

R_1,R_{15},R_{24},R_{27},R_{29},R_{46},R_{51},R_{69}=are independently A,G or absent;

R_7,R_{25},R_{45},R_{50},R_{63},R_{67}=are independently A,G,U or absent;

R_{53}= A,U or absent;

R_{35}= C or absent;

R_2,R_{33},R_{43},R_{70}=are independently C,G or absent;

R_5,R_{16},R_{34},R_{59},R_{65}=are independently C,G,U or absent;

R_3,R_{11},R_{22},R_{28},R_{30},R_{36},R_{55},R_{60},R_{61},R_{71}=are independently C,U or absent;

R_{10},R_{19},R_{20},R_{38},R_{52}=are independently G or absent;

R_{32}= G,U or absent;

R_8,R_{17},R_{39},R_{54},R_{72}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24,

x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Tryptophan TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I $_{TRP}$ (SEQ ID NO: 613),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Trp is:

R_0= absent;

R_{24},R_{39},R_{41},R_{57}=are independently A or absent;

R_2,R_3,R_{26},R_{27},R_{40},R_{48}=are independently A,C,G or absent;

R_4,R_5,R_6,R_{29},R_{30},R_{31},R_{32},R_{34},R_{42},R_{44},R_{45},R_{46},R_{49},R_{51},R_{58},R_{63},R_{66},R_{67},R_{68}=are independently N or absent;

R_{13},R_{14},R_{16},R_{18},R_{21},R_{61},R_{65},R_{71}=are independently A,C,U or absent;

R_1,R_9,R_{10},R_{15},R_{33},R_{50},R_{56}=are independently A,G or absent;

R_7,R_{25},R_{72}=are independently A,G,U or absent;

R_{37},R_{38},R_{55},R_{60}=are independently C or absent;

R_{12},R_{35},R_{43},R_{64},R_{69},R_{70}=are independently C,G,U or absent;

R_{11},R_{17},R_{22},R_{28},R_{59},R_{62}=are independently C,U or absent;

R_{19},R_{20},R_{52}=are independently G or absent;

R_8,R_{23},R_{36},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{TRP}$ (SEQ ID NO: 614),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Trp is:

$R_{0,}R_{18,}R_{22,}R_{23}$=absent

R_{14},R_{24},R_{39},R_{41},R_{57},R_{72}=are independently A or absent;

R_3,R_4,R_{13},R_{61},R_{71}=are independently A,C or absent;

R_6,R_{44}=are independently A,C,G or absent;

R_{21}= A,C,U or absent;

R_2,R_7,R_{15},R_{25},R_{33},R_{34},R_{45},R_{56},R_{63}=are independently A,G or absent;

R_{58}= A,G,U or absent;

R_{46}= A,U or absent;

R_{37},R_{38},R_{55},R_{60},R_{62}=are independently C or absent;

R_{12},R_{26},R_{27},R_{35},R_{40},R_{48},R_{67}=are independently C,G or absent;

R_{32},R_{43},R_{68}=are independently C,G,U or absent;

R_{11},R_{16},R_{28},R_{31},R_{49},R_{59},R_{65},R_{70}=are independently C,U or absent;

R_{1},R_{9},R_{10},R_{19},R_{20},R_{50},R_{52},R_{69}=are independently G or absent;

R_{5},R_{8},R_{29},R_{30},R_{42},R_{51},R_{64},R_{66}=are independently G,U or absent;

R_{17},R_{36},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{TRP}$ (SEQ ID NO: 615),

R_{0}- R_{1}-R_{2}- R_{3}-R_{4} -R_{5}-R_{6}-R_{7}-R_{8}-R_{9}-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Trp is:

R_{0},R_{18},R_{22},R_{23}=absent

R_{14},R_{24},R_{39},R_{41},R_{57},R_{72}=are independently A or absent;

R_{3},R_{4},R_{13},R_{61},R_{71}=are independently A,C or absent;

R_{6},R_{44}=are independently A,C,G or absent;

R_{21}= A,C,U or absent;

R_{2},R_{7},R_{15},R_{25},R_{33},R_{34},R_{45},R_{56},R_{63}=are independently A,G or absent;

R_{58}= A,G,U or absent;

R_{46}= A,U or absent;

R_{37},R_{38},R_{55},R_{60},R_{62}=are independently C or absent;

R_{12},R_{26},R_{27},R_{35},R_{40},R_{48},R_{67}=are independently C,G or absent;

R_{32},R_{43},R_{68}=are independently C,G,U or absent;

R_{11},R_{16},R_{28},R_{31},R_{49},R_{59},R_{65},R_{70}=are independently C,U or absent;

R_{1},R_{9},R_{10},R_{19},R_{20},R_{50},R_{52},R_{69}=are independently G or absent;

R_{5},R_{8},R_{29},R_{30},R_{42},R_{51},R_{64},R_{66}=are independently G,U or absent;

R_{17},R_{36},R_{53},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Tyrosine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I_{TYR} (SEQ ID NO: 616),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Tyr is:

R_0 =absent

R_{14},R_{39},R_{57}=are independently A or absent;

R_{41},R_{48},R_{51},R_{71}=are independently A,C,G or absent;

R_3,R_4,R_5,R_6,R_9,R_{10},R_{12},R_{13},R_{16},R_{25},R_{26},R_{30},R_{31},R_{32},R_{42},R_{44},R_{45},R_{46},R_{49},R_{50},R_{58},R_{62},R_{63},R_{66}, R_{67},R_{68},R_{69},R_{70}=are independently N or absent;

R_{22},R_{65}=are independently A,C,U or absent;

R_{15},R_{24},R_{27},R_{33},R_{37},R_{40},R_{56}=are independently A,G or absent;

R_7,R_{29},R_{34},R_{72}=are independently A,G,U or absent;

R_{23},R_{53}=are independently A,U or absent;

R_{35},R_{60}=are independently C or absent;

R_{20}= C,G or absent;

R_1,R_2,R_{28},R_{61},R_{64}=are independently C,G,U or absent;

R_{11},R_{17},R_{21},R_{43},R_{55}=are independently C,U or absent;

R_{19},R_{52}=are independently G or absent;

R_8,R_{18},R_{36},R_{38},R_{54},R_{59}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{TYR}$ (SEQ ID NO: 617),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Tyr is:

R_0,R_{18},R_{23}=absent

R_7,R_9,R_{14},R_{24},R_{26},R_{34},R_{39},R_{57}=are independently A or absent;

R_{44},R_{69}=are independently A,C or absent;

R_{71}= A,C,G or absent;

R_{68}= N or absent;

R_{58}= A,C,U or absent;

R_{33},R_{37},R_{41},R_{56},R_{62},R_{63}=are independently A,G or absent;

R_6,R_{29},R_{72}=are independently A,G,U or absent;

R_{31},R_{45},R_{53}=are independently A,U or absent;

R_{13},R_{35},R_{49},R_{60}=are independently C or absent;

R_{20},R_{48},R_{64},R_{67},R_{70}=are independently C,G or absent;

R_1,R_2,R_5,R_{16},R_{66}=are independently C,G,U or absent;

R_{11},R_{21},R_{28},R_{43},R_{55},R_{61}=are independently C,U or absent;

R_{10},R_{15},R_{19},R_{25},R_{27},R_{40},R_{51},R_{52}=are independently G or absent;

R_3,R_4,R_{30},R_{32},R_{42},R_{46}=are independently G,U or absent;

R_8,R_{12},R_{17},R_{22},R_{36},R_{38},R_{50},R_{54},R_{59},R_{65}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17,

x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{TYR}$ (SEQ ID NO: 618),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Tyr is:

$R_{0,}R_{18,}R_{23}$=absent

R_7,R_9,R_{14},R_{24},R_{26},R_{34},R_{39},R_{57},R_{72}=are independently A or absent;

R_{44},R_{69}=are independently A,C or absent;

R_{71}= A,C,G or absent;

R_{37},R_{41},R_{56},R_{62},R_{63}=are independently A,G or absent;

R_6,R_{29},R_{68}=are independently A,G,U or absent;

R_{31},R_{45},R_{58}=are independently A,U or absent;

R_{13},R_{28},R_{35},R_{49},R_{60},R_{61}=are independently C or absent;

R_5,R_{48},R_{64},R_{67},R_{70}=are independently C,G or absent;

R_1,R_2=are independently C,G,U or absent;

R_{11},R_{16},R_{21},R_{43},R_{55},R_{66}=are independently C,U or absent;

R_{10},R_{15},R_{19},R_{20},R_{25},R_{27},R_{33},R_{40},R_{51},R_{52}=are independently G or absent;

R_3,R_4,R_{30},R_{32},R_{42},R_{46}=are independently G,U or absent;

R_8,R_{12},R_{17},R_{22},R_{36},R_{38},R_{50},R_{53},R_{54},R_{59},R_{65}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13,

x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Valine TREM Consensus sequence

In an embodiment, a TREM disclosed herein comprises the sequence of Formula I $_{VAL}$ (SEQ ID NO: 619),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Val is:

R_0,R_{23}=absent;

R_{24},R_{38},R_{57}=are independently A or absent;

R_9,R_{72}=are independently A,C,G or absent;

R_2,R_4,R_5,R_6,R_7,R_{12},R_{15},R_{16},R_{21},R_{25},R_{26},R_{29},R_{31},R_{32},R_{33},R_{34},R_{37},R_{41},R_{42},R_{43},R_{44},R_{45},R_{46},R_{48},R_{49},R_{50},R_{58},R_{61},R_{62},R_{63},R_{64},R_{65},R_{66},R_{67},R_{68},R_{69},R_{70}=are independently N or absent;

R_{17},R_{35},R_{59}=are independently A,C,U or absent;

R_{10},R_{14},R_{27},R_{40},R_{52},R_{56}=are independently A,G or absent;

R_1,R_3,R_{51},R_{53}=are independently A,G,U or absent;

R_{39}= C or absent;

R_{13},R_{30},R_{55}=are independently C,G,U or absent;

R_{11},R_{22},R_{28},R_{60},R_{71}=are independently C,U or absent;

R_{19}= G or absent;

R_{20}= G ,U or absent;

R_8,R_{18},R_{36},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula II $_{VAL}$ (SEQ ID NO: 620),

R_0- R_1- R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Val is:

$R_{0,}R_{18,}R_{23}$=absent;

R_{24},R_{38},R_{57}=are independently A or absent;

R_{64},R_{70},R_{72}=are independently A,C,G or absent;

R_{15},R_{16},R_{26},R_{29},R_{31},R_{32},R_{43},R_{44},R_{45},R_{49},R_{50},R_{58},R_{62},R_{65}=are independently N or absent;

R_6,R_{17},R_{34},R_{37},R_{41},R_{59}=are independently A,C,U or absent;

R_9,R_{10},R_{14},R_{27},R_{40},R_{46},R_{51},R_{52},R_{56}=are independently A,G or absent;

R_7,R_{12},R_{25},R_{33},R_{53},R_{63},R_{66},R_{68}=are independently A,G,U or absent;

R_{69}= A,U or absent;

R_{39}= C or absent;

R_5,R_{67}=are independently C,G or absent;

R_2,R_4,R_{13},R_{48},R_{55},R_{61}=are independently C,G,U or absent;

R_{11},R_{22},R_{28},R_{30},R_{35},R_{60},R_{71}=are independently C,U or absent;

R_{19}= G or absent;

R_1,R_3,R_{20},R_{42}=are independently G,U or absent;

R_8,R_{21},R_{36},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

In an embodiment, a TREM disclosed herein comprises the sequence of Formula III $_{VAL}$ (SEQ ID NO: 621),

R_0- R_1-R_2- R_3-R_4 -R_5-R_6-R_7-R_8-R_9-R_{10}-R_{11}-R_{12}-R_{13}-R_{14}-R_{15}-R_{16}-R_{17}-R_{18}-R_{19}-R_{20}-R_{21}-R_{22}-R_{23}-R_{24}-R_{25}-R_{26}-R_{27}-R_{28}-R_{29}-R_{30}-R_{31}-R_{32}-R_{33}-R_{34}-R_{35}-R_{36}-R_{37}-R_{38}-R_{39}-R_{40}-R_{41}-R_{42}- R_{43}- R_{44}-R_{45}-R_{46}- $[R_{47}]_x$-R_{48}-R_{49}-R_{50}-R_{51}-R_{52}-R_{53}-R_{54}-R_{55}-R_{56}-R_{57}-R_{58}-R_{59}-R_{60}-R_{61}-R_{62}-R_{63}-R_{64}-R_{65}-R_{66}-R_{67}-R_{68}-R_{69}-R_{70}-R_{71}-R_{72}

wherein R is a ribonucleotide residue and the consensus for Val is:

R_0,R_{18},R_{23}=absent

R_{24},R_{38},R_{40},R_{57},R_{72}=are independently A or absent;

R_{29},R_{64},R_{70}=are independently A,C,G or absent;

R_{49},R_{50},R_{62}=are independently N or absent;

R_{16},R_{26},R_{31},R_{32},R_{37},R_{41},R_{43},R_{59},R_{65}=are independently A,C,U or absent;

R_9,R_{14},R_{27},R_{46},R_{52},R_{56},R_{66}=are independently A,G or absent;

R_7,R_{12},R_{25},R_{33},R_{44},R_{45},R_{53},R_{58},R_{63},R_{68}=are independently A,G,U or absent;

R_{69}= A,U or absent;

R_{39}= C or absent;

R_5,R_{67}=are independently C,G or absent;

R_2,R_4,R_{13},R_{15},R_{48},R_{55}=are independently C,G,U or absent;

R_6,R_{11},R_{22},R_{28},R_{30},R_{34},R_{35},R_{60},R_{61},R_{71}=are independently C,U or absent;

R_{10},R_{19},R_{51}=are independently G or absent;

R_1,R_3,R_{20},R_{42}=are independently G,U or absent;

R_8,R_{17},R_{21},R_{36},R_{54}=are independently U or absent;

$[R_{47}]_x$ = N or absent;

wherein, *e.g.*, x=1-271 (*e.g.*, x=1-250, x=1-225, x=1-200, x=1-175, x=1-150, x=1-125, x=1-100, x=1-75, x=1-50, x=1-40, x=1-30, x=1-29, x=1-28, x=1-27, x=1-26, x=1-25, x=1-24, x=1-23, x=1-22, x=1-21, x=1-20, x=1-19, x=1-18, x=1-17, x=1-16, x=1-15, x=1-14, x=1-13, x=1-12, x=1-11, x=1-10, x=10-271, x=20-271, x=30-271, x=40-271, x=50-271, x=60-271, x=70-271, x=80-271, x=100-271, x=125-271, x=150-271, x=175-271, x=200-271, x=225-271, x=1, x=2, x=3, x=4, x=5, x=6, x=7, x=8, x=9, x=10, x=11, x=12, x=13, x=14, x=15, x=16, x=17, x=18, x=19, x=20, x=21, x=22, x=23, x=24, x=25, x=26, x=27, x=28, x=29, x=30, x=40, x=50, x=60, x=70, x=80, x=90, x=100, x=110, x=125, x=150, x=175, x=200, x=225, x=250, or x=271), provided that the TREM has one or both of the following properties: no more than 15% of the residues are N; or no more than 20 residues are absent.

Variable region consensus sequence

In an embodiment, a TREM disclosed herein comprises a variable region at position R_{47}. In an embodiment, the variable region is 1-271 ribonucleotides in length (*e.g.* 1-250, 1-225, 1-200, 1-175, 1-150, 1-125, 1-100, 1-75, 1-50, 1-40, 1-30, 1-29, 1-28, 1-27, 1-26, 1-25, 1-24, 1-23, 1-22, 1-21, 1-20, 1-19, 1-18, 1-17, 1-16, 1-15, 1-14, 1-13, 1-12, 1-11, 1-10, 10-271, 20-271, 30-271, 40-271, 50-271, 60-271, 70-271, 80-271, 100-271, 125-271, 150-271, 175-271, 200-271, 225-271, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 50, 60, 70, 80, 90, 100, 110, 125, 150, 175, 200, 225, 250, or 271

ribonucleotides). In an embodiment, the variable region comprises any one, all or a combination of Adenine, Cytosine, Guanine or Uracil.

In an embodiment, the variable region comprises a ribonucleic acid (RNA) sequence encoded by a deoxyribonucleic acid (DNA) sequence disclosed in Table 10, *e.g.*, any one of SEQ ID NOs: 452-561 disclosed in Table 10.

Table 10: Exemplary variable region sequences.

	SEQ ID NO	**SEQUENCE**
1	452	AAAATATAAATATATTTC
2	453	AAGCT
3	454	AAGTT
4	455	AATTCTTCGGAATGT
5	456	AGA
6	457	AGTCC
7	458	CAACC
8	459	CAATC
9	460	CAGC
10	461	CAGGCGGGTTCTGCCCGCGC
11	462	CATACCTGCAAGGGTATC
12	463	CGACCGCAAGGTTGT
13	464	CGACCTTGCGGTCAT
14	465	CGATGCTAATCACATCGT
15	466	CGATGGTGACATCAT
16	467	CGATGGTTTACATCGT
17	468	CGCCGTAAGGTGT
18	469	CGCCTTAGGTGT
19	470	CGCCTTTCGACGCGT
20	471	CGCTTCACGGCGT
21	472	CGGCAGCAATGCTGT
22	473	CGGCTCCGCCTTC
23	474	CGGGTATCACAGGGTC
24	475	CGGTGCGCAAGCGCTGT
25	476	CGTACGGGTGACCGTACC
26	477	CGTCAAAGACTTC
27	478	CGTCGTAAGACTT
28	479	CGTTGAATAAACGT
29	480	CTGTC
30	481	GGCC
31	482	GGGGATT
32	483	GGTC

33	484	GGTTT
34	485	GTAG
35	486	TAACTAGATACTTTCAGAT
36	487	TACTCGTATGGGTGC
37	488	TACTTTGCGGTGT
38	489	TAGGCGAGTAACATCGTGC
39	490	TAGGCGTGAATAGCGCCTC
40	491	TAGGTCGCGAGAGCGGCGC
41	492	TAGGTCGCGTAAGCGGCGC
42	493	TAGGTGGTTATCCACGC
43	494	TAGTC
44	495	TAGTT
45	496	TATACGTGAAAGCGTATC
46	497	TATAGGGTCAAAAACTCTATC
47	498	TATGCAGAAATACCTGCATC
48	499	TCCCCATACGGGGGC
49	500	TCCCGAAGGGGTTC
50	501	TCTACGTATGTGGGC
51	502	TCTCATAGGAGTTC
52	503	TCTCCTCTGGAGGC
53	504	TCTTAGCAATAAGGT
54	505	TCTTGTAGGAGTTC
55	506	TGAACGTAAGTTCGC
56	507	TGAACTGCGAGGTTCC
57	508	TGAC
58	509	TGACCGAAAGGTCGT
59	510	TGACCGCAAGGTCGT
60	511	TGAGCTCTGCTCTC
61	512	TGAGGCCTCACGGCCTAC
62	513	TGAGGGCAACTTCGT
63	514	TGAGGGTCATACCTCC
64	515	TGAGGGTGCAAATCCTCC
65	516	TGCCGAAAGGCGT
66	517	TGCCGTAAGGCGT
67	518	TGCGGTCTCCGCGC
68	519	TGCTAGAGCAT
69	520	TGCTCGTATAGAGCTC
70	521	TGGACAATTGTCTGC
71	522	TGGACAGATGTCCGT
72	523	TGGACAGGTGTCCGC
73	524	TGGACGGTTGTCCGC
74	525	TGGACTTGTGGTC
75	526	TGGAGATTCTCTCCGC

76	527	TGGCATAGGCCTGC
77	528	TGGCTTATGTCTAC
78	529	TGGGAGTTAATCCCGT
79	530	TGGGATCTTCCCGC
80	531	TGGGCAGAAATGTCTC
81	532	TGGGCGTTCGCCCGC
82	533	TGGGCTTCGCCCGC
83	534	TGGGGGATAACCCCGT
84	535	TGGGGGTTTCCCCGT
85	536	TGGT
86	537	TGGTGGCAACACCGT
87	538	TGGTTTATAGCCGT
88	539	TGTACGGTAATACCGTACC
89	540	TGTCCGCAAGGACGT
90	541	TGTCCTAACGGACGT
91	542	TGTCCTATTAACGGACGT
92	543	TGTCCTTCACGGGCGT
93	544	TGTCTTAGGACGT
94	545	TGTGCGTTAACGCGTACC
95	546	TGTGTCGCAAGGCACC
96	547	TGTTCGTAAGGACTT
97	548	TTCACAGAAATGTGTC
98	549	TTCCCTCGTGGAGT
99	550	TTCCCTCTGGGAGC
100	551	TTCCCTTGTGGATC
101	552	TTCCTTCGGGAGC
102	553	TTCTAGCAATAGAGT
103	554	TTCTCCACTGGGGAGC
104	555	TTCTCGAGAGGGAGC
105	556	TTCTCGTATGAGAGC
106	557	TTTAAGGTTTTCCCTTAAC
107	558	TTTCATTGTGGAGT
108	559	TTTCGAAGGAATCC
109	560	TTTCTTCGGAAGC
110	561	TTTGGGGCAACTCAAC

Method of making TREMs, TREM core fragments, and TREM fragments

In vitro methods for synthesizing oligonucleotides are known in the art and can be used to make a TREM, a TREM core fragment or a TREM fragment disclosed herein. For example, a TREM, TREM core fragment or TREM fragment can be synthesized using solid state synthesis or liquid phase synthesis.

In an embodiment, a TREM, a TREM core fragment or a TREM fragment made according to an in vitro synthesis method disclosed herein has a different modification profile compared to a TREM expressed and isolated from a cell, or compared to a naturally occurring tRNA.

An exemplary method for making a synthetic TREM via 5'-Silyl-2'-Orthoester (2'- ACE) Chemistry is provided in Example 3. The method provided in Example 3 can also be used to make a synthetic TREM core fragment or synthetic TREM fragment. Additional synthetic methods are disclosed in Hartsel SA et al., (2005) *Oligonucleotide Synthesis*, 033–050, the entire contents of which are hereby incorporated by reference.

TREM composition

In an embodiment, a TREM composition, *e.g.*, a TREM pharmaceutical composition, comprises a pharmaceutically acceptable excipient. Exemplary excipients include those provided in the FDA Inactive Ingredient Database (https://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm).

In an embodiment, a TREM composition, *e.g.*, a TREM pharmaceutical composition, comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, 80, 90, 100 or 150 grams of TREM, TREM core fragment or TREM fragment. In an embodiment, a TREM composition, *e.g.*, a TREM pharmaceutical composition, comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50 or 100 milligrams of TREM, TREM core fragment or TREM fragment.

In an embodiment, a TREM composition, *e.g.*, a TREM pharmaceutical composition, is at least 10, 20, 30, 40, 50, 60, 70, 80, 90, 95 or 99% dry weight TREMs, TREM core fragments or TREM fragments.

In an embodiment, a TREM composition comprises at least 1 x 10^6 TREM molecules, at least 1 x 10^7 TREM molecules, at least 1 x 10^8 TREM molecules or at least 1 x 10^9 TREM molecules.

In an embodiment, a TREM composition comprises at least 1 x 10^6 TREM core fragment molecules, at least 1 x 10^7 TREM core fragment molecules, at least 1 x 10^8 TREM core fragment molecules or at least 1 x 10^9 TREM core fragment molecules.

In an embodiment, a TREM composition comprises at least 1 x 10^6 TREM fragment molecules, at least 1 x 10^7 TREM fragment molecules, at least 1 x 10^8 TREM fragment molecules or at least 1 x 10^9 TREM fragment molecules.

In an embodiment, a TREM composition produced by any of the methods of making disclosed herein can be charged with an amino acid using an in vitro charging reaction as known in the art.

In an embodiment, a TREM composition comprise one or more species of TREMs, TREM core fragments, or TREM fragments. In an embodiment, a TREM composition comprises a single species of TREM, TREM core fragment, or TREM fragment. In an embodiment, a TREM composition comprises a first TREM, TREM core fragment, or TREM fragment species and a second TREM, TREM core fragment, or TREM fragment species. In an embodiment, the TREM composition comprises X TREM, TREM core fragment, or TREM fragment species, wherein X=2, 3, 4, 5, 6, 7, 8, 9, or 10.

In an embodiment, the TREM, TREM core fragment, or TREM fragment has at least 70, 75, 80, 85, 90, or 95, or has 100%, identity with a sequence encoded by a nucleic acid in Table 4.

In an embodiment, the TREM comprises a consensus sequence provided herein.

A TREM composition can be formulated as a liquid composition, as a lyophilized composition or as a frozen composition.

In some embodiments, a TREM composition can be formulated to be suitable for pharmaceutical use, e.g., a pharmaceutical TREM composition. In an embodiment, a pharmaceutical TREM composition is substantially free of materials and/or reagents used to separate and/or purify a TREM, TREM core fragment, or TREM fragment.

In some embodiments, a TREM composition can be formulated with water for injection. In some embodiments, a TREM composition formulated with water for injection is suitable for pharmaceutical use, e.g., comprises a pharmaceutical TREM composition.

TREM characterization

A TREM, TREM core fragment, or TREM fragment, or a TREM composition, *e.g.*, a pharmaceutical TREM composition, produced by any of the methods disclosed herein can be assessed for a characteristic associated with the TREM, TREM core fragment, or TREM fragment or the TREM composition, such as purity, sterility, concentration, structure, or

functional activity of the TREM, TREM core fragment, or TREM fragment. Any of the above-mentioned characteristics can be evaluated by providing a value for the characteristic, *e.g.*, by evaluating or testing the TREM, TREM core fragment, or TREM fragment, or the TREM composition, or an intermediate in the production of the TREM composition. The value can also be compared with a standard or a reference value. Responsive to the evaluation, the TREM composition can be classified, *e.g.*, as ready for release, meets production standard for human trials, complies with ISO standards, complies with cGMP standards, or complies with other pharmaceutical standards. Responsive to the evaluation, the TREM composition can be subjected to further processing, *e.g.*, it can be divided into aliquots, *e.g.*, into single or multi-dosage amounts, disposed in a container, *e.g.*, an end-use vial, packaged, shipped, or put into commerce. In embodiments, in response to the evaluation, one or more of the characteristics can be modulated, processed or re-processed to optimize the TREM composition. For example, the TREM composition can be modulated, processed or re-processed to (i) increase the purity of the TREM composition; (ii) decrease the amount of fragments in the composition; (iii) decrease the amount of endotoxins in the composition; (iv) increase the in vitro translation activity of the composition; (v) increase the TREM concentration of the composition; or (vi) inactivate or remove any viral contaminants present in the composition, *e.g.*, by reducing the pH of the composition or by filtration.

In an embodiment, the TREM, TREM core fragment, or TREM fragment (*e.g.*, TREM composition or an intermediate in the production of the TREM composition) has a purity of at least 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99%, i.e., by mass.

In an embodiment, the TREM (*e.g.*, TREM composition or an intermediate in the production of the TREM composition) has less than 0.1%, 0,5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25% TREM fragments relative to full length TREMs.

In an embodiment, the TREM, TREM core fragment, or TREM fragment (*e.g.*, TREM composition or an intermediate in the production of the TREM composition) has low levels or absence of endotoxins, *e.g.*, a negative result as measured by the Limulus amebocyte lysate (LAL) test.

In an embodiment, the TREM, TREM core fragment, or TREM fragment (*e.g.*, TREM composition or an intermediate in the production of the TREM composition) has in-vitro translation activity, *e.g.*, as measured by an assay described in Examples 12-13.

In an embodiment, the TREM, TREM core fragment, or TREM fragment (*e.g.*, TREM composition or an intermediate in the production of the TREM composition) has a TREM concentration of at least 0.1 ng/mL, 0.5 ng/mL, 1 ng/mL, 5 ng/mL, 10 ng/mL, 50 ng/mL, 0.1 ug/mL, 0.5 ug/mL,1 ug/mL, 2 ug/mL, 5 ug/mL, 10 ug/mL, 20 ug/mL, 30 ug/mL, 40 ug/mL, 50 ug/mL, 60 ug/mL, 70 ug/mL, 80 ug/mL, 100 ug/mL, 200 ug/mL, 300 ug/mL, 500 ug/mL, 1000 ug/mL, 5000 ug/mL, 10,000 ug/mL, or 100,000 ug/mL.

In an embodiment, the TREM, TREM core fragment, or TREM fragment (*e.g.*, TREM composition or an intermediate in the production of the TREM composition) is sterile, *e.g.*, the composition or preparation supports the growth of fewer than 100 viable microorganisms as tested under aseptic conditions, the composition or preparation meets the standard of USP <71>, and/or the composition or preparation meets the standard of USP <85>.

In an embodiment, the TREM, TREM core fragment, or TREM fragment (*e.g.*, TREM composition or an intermediate in the production of the TREM composition) has an undetectable level of viral contaminants, *e.g.*, no viral contaminants. In an embodiment, any viral contaminant, *e.g.*, residual virus, present in the composition is inactivated or removed. In an embodiment, any viral contaminant, *e.g.*, residual virus, is inactivated, *e.g.*, by reducing the pH of the composition. In an embodiment, any viral contaminant, *e.g.*, residual virus, is removed, *e.g.*, by filtration or other methods known in the field.

TREM administration

Any TREM composition or pharmaceutical composition described herein can be administered to a cell, tissue or subject, *e.g.*, by direct administration to a cell, tissue and/or an organ in vitro, ex-vivo or in vivo. In-vivo administration may be via, *e.g.*, by local, systemic and/or parenteral routes, for example intravenous, subcutaneous, intraperitoneal, intrathecal, intramuscular, ocular, nasal, urogenital, intradermal, dermal, enteral, intravitreal, intracerebral, intrathecal, or epidural.

Vectors and Carriers

In some embodiments the TREM, TREM core fragment, or TREM fragment or TREM composition described herein, is delivered to cells, *e.g.* mammalian cells or human cells, using a vector. The vector may be, *e.g.*, a plasmid or a virus. In some embodiments, delivery is *in vivo, in vitro*, *ex vivo*, or *in situ*. In some embodiments, the virus is an adeno associated virus (AAV), a lentivirus, or an adenovirus. In some embodiments, the system or components of the system are delivered to cells with a viral-like particle or a virosome. In some embodiments, the delivery uses more than one virus, viral-like particle or virosome.

Carriers

A TREM, a TREM composition or a pharmaceutical TREM composition described herein may comprise, may be formulated with, or may be delivered in, a carrier.

Viral vectors

The carrier may be a viral vector (*e.g.*, a viral vector comprising a sequence encoding a TREM, a TREM core fragment or a TREM fragment). The viral vector may be administered to a cell or to a subject (*e.g.*, a human subject or animal model) to deliver a TREM, a TREM core fragment or a TREM fragment, a TREM composition or a pharmaceutical TREM composition.

A viral vector may be systemically or locally administered (*e.g.*, injected). Viral genomes provide a rich source of vectors that can be used for the efficient delivery of exogenous genes into a mammalian cell. Viral genomes are known in the art as useful vectors for delivery because the polynucleotides contained within such genomes are typically incorporated into the nuclear genome of a mammalian cell by generalized or specialized transduction. These processes occur as part of the natural viral replication cycle, and do not require added proteins or reagents in order to induce gene integration. Examples of viral vectors include a retrovirus (*e.g.*, Retroviridae family viral vector), adenovirus (*e.g.*, Ad5, Ad26, Ad34, Ad35, and Ad48), parvovirus (*e.g.*, adeno-associated viruses), coronavirus, negative strand RNA viruses such as orthomyxovirus (*e.g.*, influenza virus), rhabdovirus (*e.g.*, rabies and vesicular stomatitis virus), paramyxovirus (*e.g.*, measles and Sendai), positive strand RNA viruses, such as picornavirus and alphavirus, and double stranded DNA viruses including adenovirus, herpesvirus (*e.g.*, Herpes Simplex virus types 1 and 2, Epstein-Barr virus, cytomegalovirus, replication deficient herpes

virus), and poxvirus (*e.g.*, vaccinia, modified vaccinia Ankara (MVA), fowlpox and canarypox). Other viruses include Norwalk virus, togavirus, flavivirus, reoviruses, papovavirus, hepadnavirus, human papilloma virus, human foamy virus, and hepatitis virus, for example. Examples of retroviruses include: avian leukosis-sarcoma, avian C-type viruses, mammalian C-type, B-type viruses, D-type viruses, oncoretroviruses, HTLV-BLV group, lentivirus, alpharetrovirus, gammaretrovirus, spumavirus (Coffin, J. M., Retroviridae: The viruses and their replication, Virology (Third Edition) Lippincott-Raven, Philadelphia, 1996). Other examples include murine leukemia viruses, murine sarcoma viruses, mouse mammary tumor virus, bovine leukemia virus, feline leukemia virus, feline sarcoma virus, avian leukemia virus, human T-cell leukemia virus, baboon endogenous virus, Gibbon ape leukemia virus, Mason Pfizer monkey virus, simian immunodeficiency virus, simian sarcoma virus, Rous sarcoma virus and lentiviruses. Other examples of vectors are described, for example, in US Patent No. 5,801,030, the teachings of which are incorporated herein by reference. In some embodiments the system or components of the system are delivered to cells with a viral-like particle or a virosome.

Cell and vesicle-based carriers

A TREM, a TREM core fragment or a TREM fragment, a TREM composition or a pharmaceutical TREM composition described herein can be administered to a cell in a vesicle or other membrane-based carrier.

In embodiments, a TREM, a TREM core fragment or a TREM fragment, or TREM composition, or pharmaceutical TREM composition described herein is administered in or via a cell, vesicle or other membrane-based carrier. In one embodiment, the TREM, TREM core fragment, TREM fragment, or TREM composition or pharmaceutical TREM composition can be formulated in liposomes or other similar vesicles. Liposomes are spherical vesicle structures composed of a uni- or multilamellar lipid bilayer surrounding internal aqueous compartments and a relatively impermeable outer lipophilic phospholipid bilayer. Liposomes may be anionic, neutral or cationic. Liposomes are biocompatible, nontoxic, can deliver both hydrophilic and lipophilic drug molecules, protect their cargo from degradation by plasma enzymes, and transport their load across biological membranes and the blood brain barrier (BBB) (see, *e.g.*, Spuch and Navarro, Journal of Drug Delivery, vol. 2011, Article ID 469679, 12 pages, 2011. doi:10.1155/2011/469679 for review).

Vesicles can be made from several different types of lipids; however, phospholipids are most commonly used to generate liposomes as drug carriers. Methods for preparation of multilamellar vesicle lipids are known in the art (see for example U.S. Pat. No. 6,693,086, the teachings of which relating to multilamellar vesicle lipid preparation are incorporated herein by reference). Although vesicle formation can be spontaneous when a lipid film is mixed with an aqueous solution, it can also be expedited by applying force in the form of shaking by using a homogenizer, sonicator, or an extrusion apparatus (see, *e.g.*, Spuch and Navarro, Journal of Drug Delivery, vol. 2011, Article ID 469679, 12 pages, 2011. doi:10.1155/2011/469679 for review). Extruded lipids can be prepared by extruding through filters of decreasing size, as described in Templeton et al., Nature Biotech, 15:647-652, 1997, the teachings of which relating to extruded lipid preparation are incorporated herein by reference.

Lipid nanoparticles are another example of a carrier that provides a biocompatible and biodegradable delivery system for the TREM, TREM core fragment, TREM fragment, or TREM composition or pharmaceutical TREM composition described herein. Nanostructured lipid carriers (NLCs) are modified solid lipid nanoparticles (SLNs) that retain the characteristics of the SLN, improve drug stability and loading capacity, and prevent drug leakage. Polymer nanoparticles (PNPs) are an important component of drug delivery. These nanoparticles can effectively direct drug delivery to specific targets and improve drug stability and controlled drug release. Lipid–polymer nanoparticles (PLNs), a new type of carrier that combines liposomes and polymers, may also be employed. These nanoparticles possess the complementary advantages of PNPs and liposomes. A PLN is composed of a core–shell structure; the polymer core provides a stable structure, and the phospholipid shell offers good biocompatibility. As such, the two components increase the drug encapsulation efficiency rate, facilitate surface modification, and prevent leakage of water-soluble drugs. For a review, see, *e.g.*, Li et al. 2017, Nanomaterials 7, 122; doi:10.3390/nano7060122.

Exemplary lipid nanoparticles are disclosed in International Application PCT/US2014/053907, the entire contents of which are hereby incorporated by reference. For example, an LNP described in paragraphs [403-406] or [410-413] of PCT/US2014/053907 can be used as a carrier for the TREM, TREM core fragment, TREM fragment, or TREM composition or pharmaceutical TREM composition described herein.

Additional exemplary lipid nanoparticles are disclosed in U.S. Patent 10,562,849 the entire contents of which are hereby incorporated by reference. For example, an LNP of formula (I) as described in columns 1-3 of U.S. Patent 10,562,849 can be used as a carrier for the TREM, TREM core fragment, TREM fragment, or TREM composition or pharmaceutical TREM composition described herein.

Lipids that can be used in nanoparticle formations (e.g., lipid nanoparticles) include, for example those described in Table 4 of WO2019217941, which is incorporated by reference, e.g., a lipid-containing nanoparticle can comprise one or more of the lipids in Table 4 of WO2019217941. Lipid nanoparticles can include additional elements, such as polymers, such as the polymers described in Table 5 of WO2019217941, incorporated by reference.

In some embodiments, conjugated lipids, when present, can include one or more of PEG-diacylglycerol (DAG) (such as l-(monomethoxy-polyethyleneglycol)-2,3- dimyristoylglycerol (PEG-DMG)), PEG-dialkyloxypropyl (DAA), PEG-phospholipid, PEG- ceramide (Cer), a pegylated phosphatidylethanoloamine (PEG-PE), PEG succinate diacylglycerol (PEGS-DAG) (such as 4-0-(2',3'-di(tetradecanoyloxy)propyl-l-0-(w- methoxy(polyethoxy)ethyl) butanedioate (PEG-S-DMG)), PEG dialkoxypropylcarbam, N- (carbonyl-methoxypoly ethylene glycol 2000)-1 ,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt, and those described in Table 2 of WO2019051289 (incorporated by reference), and combinations of the foregoing.

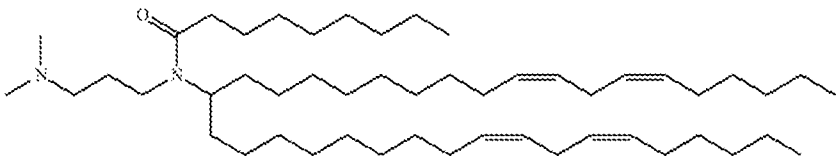
In some embodiments, sterols that can be incorporated into lipid nanoparticles include one or more of cholesterol or cholesterol derivatives, such as those in W02009/127060 or US2010/0130588, which are incorporated by reference. Additional exemplary sterols include phytosterols, including those described in Eygeris et al (2020), incorporated herein by reference.

In some embodiments, the lipid particle comprises an ionizable lipid, a non-cationic lipid, a conjugated lipid that inhibits aggregation of particles, and a sterol. The amounts of these components can be varied independently and to achieve desired properties. For example, in some embodiments, the lipid nanoparticle comprises an ionizable lipid is in an amount from about 20 mol % to about 90 mol % of the total lipids (in other embodiments it may be 20-70% (mol), 30-60% (mol) or 40-50% (mol); about 50 mol % to about 90 mol % of the total lipid present in the lipid nanoparticle), a non-cationic lipid in an amount from about 5 mol % to about 30 mol % of the total lipids, a conjugated lipid in an amount from about 0.5 mol % to about 20 mol % of the total lipids, and a sterol in an amount from about 20 mol % to about 50 mol % of

the total lipids. The ratio of total lipid to nucleic acid can be varied as desired. For example, the total lipid to nucleic acid (mass or weight) ratio can be from about 10: 1 to about 30: 1.

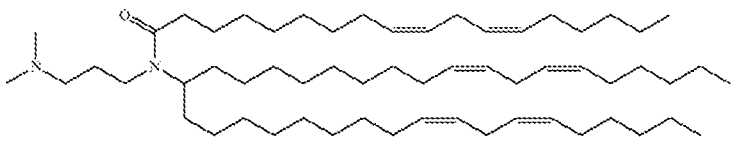
In some embodiments, the lipid to nucleic acid ratio (mass/mass ratio; w/w ratio) can be in the range of from about 1 : 1 to about 25: 1, from about 10: 1 to about 14: 1, from about 3 : 1 to about 15: 1, from about 4: 1 to about 10: 1, from about 5: 1 to about 9: 1, or about 6: 1 to about 9: 1. The amounts of lipids and nucleic acid can be adjusted to provide a desired N/P ratio, for example, N/P ratio of 3, 4, 5, 6, 7, 8, 9, 10 or higher. Generally, the lipid nanoparticle formulation's overall lipid content can range from about 5 mg/ml to about 30 mg/mL.

Some non-limiting example of lipid compounds that may be used (e.g., in combination with other lipid components) to form lipid nanoparticles for the delivery of compositions described herein, e.g., nucleic acid (e.g., RNA) described herein includes,



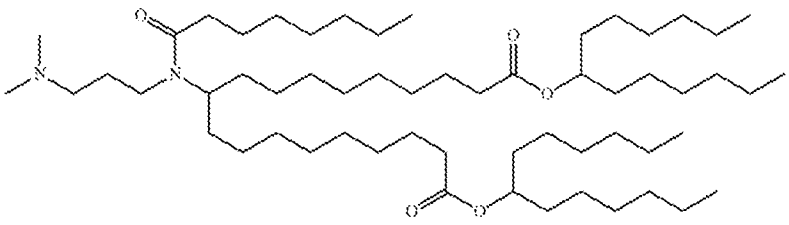
(i)

In some embodiments an LNP comprising Formula (i) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.



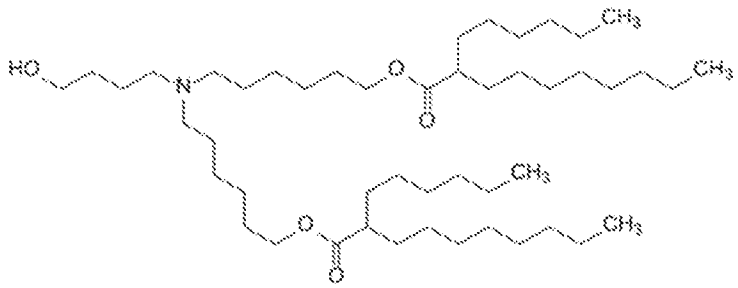
(ii)

In some embodiments an LNP comprising Formula (ii) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.

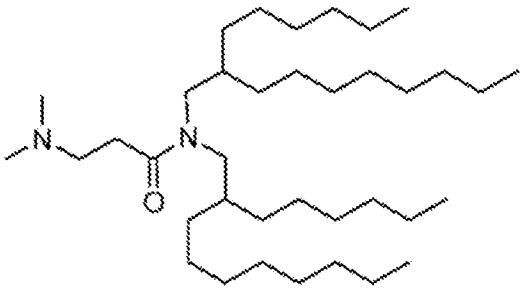


(iii)

In some embodiments an LNP comprising Formula (iii) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.

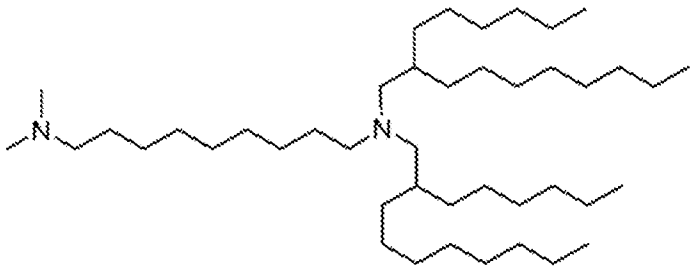


(iv)



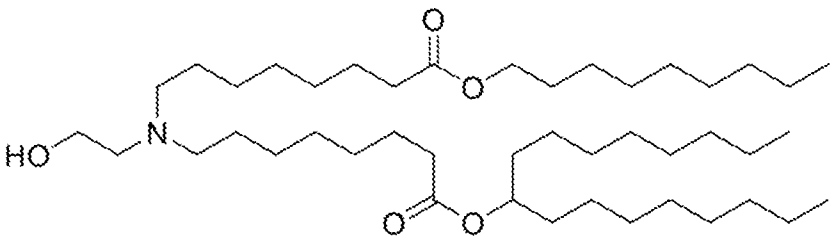
(v)

In some embodiments an LNP comprising Formula (v) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.

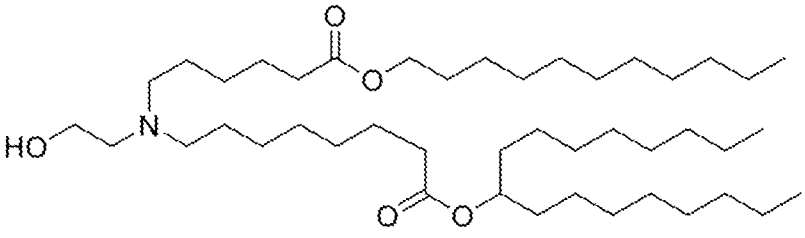


(vi)

In some embodiments an LNP comprising Formula (vi) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.

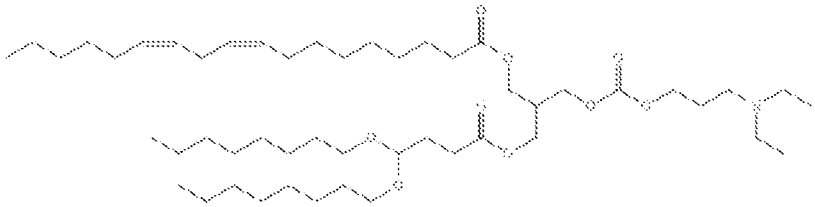


(vii)



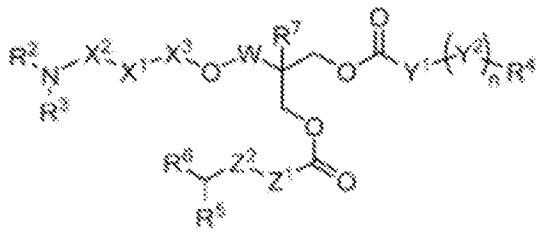
(viii)

In some embodiments an LNP comprising Formula (viii) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.



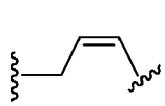
(ix)

In some embodiments an LNP comprising Formula (ix) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.

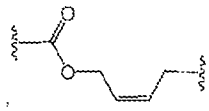


(x)

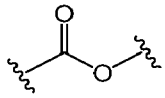
wherein X^1 is O, NR^1, or a direct bond, X^2 is C2-5 alkylene, X^3 is C(=O) or a direct bond, R^1 is H or Me, R^3 is Ci-3 alkyl, R^2 is Ci-3 alkyl, or R^2 taken together with the nitrogen atom to which it is attached and 1-3 carbon atoms of X^2 form a 4-, 5-, or 6-membered ring, or X^1 is NR^1, R^1 and R^2 taken together with the nitrogen atoms to which they are attached form a 5- or 6-membered ring, or R^2 taken together with R^3 and the nitrogen atom to which they are attached form a 5-, 6-, or 7-membered ring, Y^1 is C2-12 alkylene, Y^2 is selected from



(in either orientation),

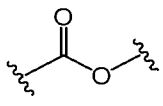


(in either orientation),

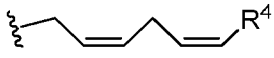


(in either orientation),

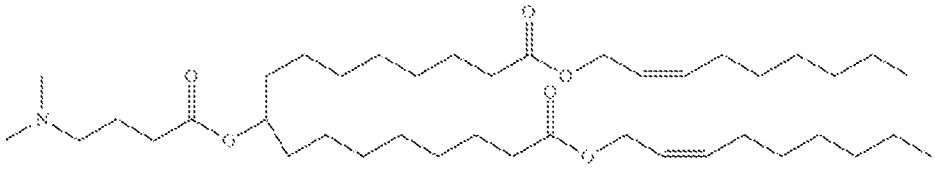
n is 0 to 3, R^4 is Ci-15 alkyl, Z^1 is Ci-6 alkylene or a direct bond, Z^2 is



, (in either orientation) or absent, provided that if Z^1 is a direct bond, Z^2 is absent; R^5 is C5-9 alkyl or C6-10 alkoxy, R^6 is C5-9 alkyl or C6-10 alkoxy, W is methylene or a direct bond, and R^7 is H or Me, or a salt thereof, provided that if R^3 and R^2 are C2 alkyls, X^1 is O, X^2 is linear C3 alkylene, X^3 is

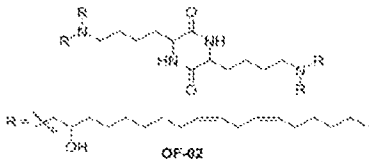
C(=O), Y^1 is linear Ce alkylene, (Y^2)n-R^4 is  , R^4 is linear C5 alkyl, Z^1 is C2 alkylene, Z^2 is absent, W is methylene, and R^7 is H, then R^5 and R^6 are not Cx alkoxy.

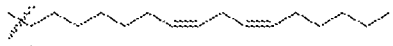
In some embodiments an LNP comprising Formula (xii) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.



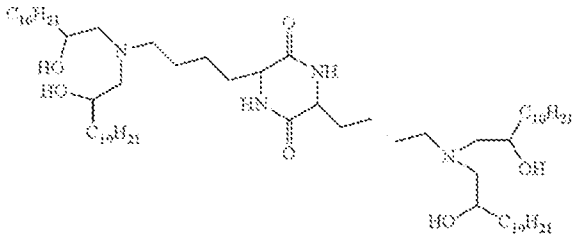
(xi)

In some embodiments an LNP comprising Formula (xi) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.

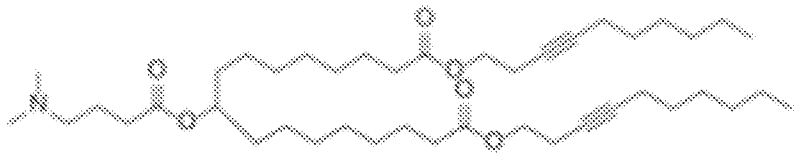


where R= 

(xii)

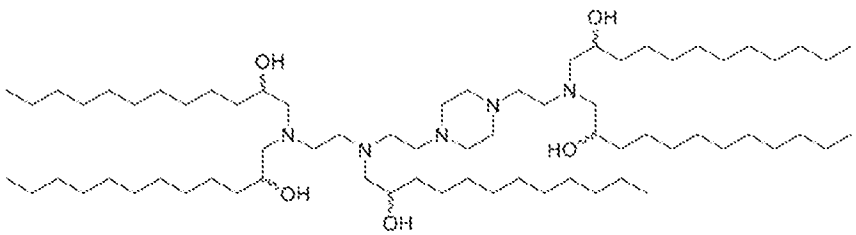


(xiii)



(xiv)

In some embodiments an LNP comprises a compound of Formula (xiii) and a compound of Formula (xiv).



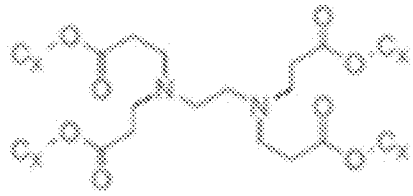
(xv)

In some embodiments, an LNP comprising Formula (xv) is used to deliver a TREM composition described herein to the liver and/or hepatocyte cells.

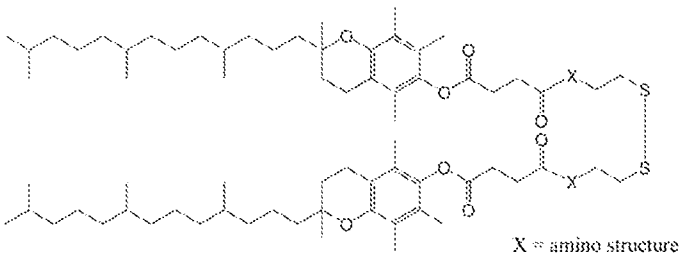


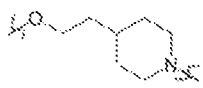
(xvi)

In some embodiments an LNP comprising a formulation of Formula (xvi) is used to deliver a TREM composition described herein to the lung endothelial cells.

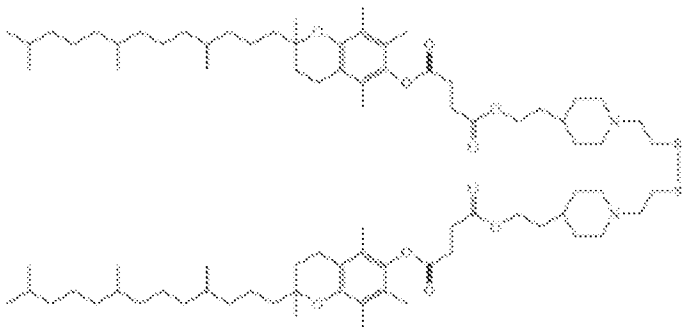


(xvii)

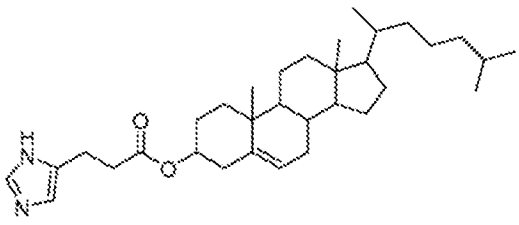


where X=  (xviii)

(a)

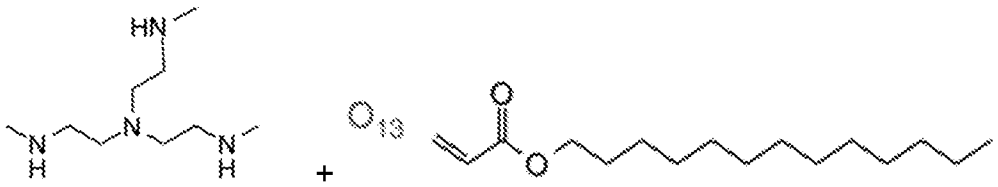


(xviii)(b)

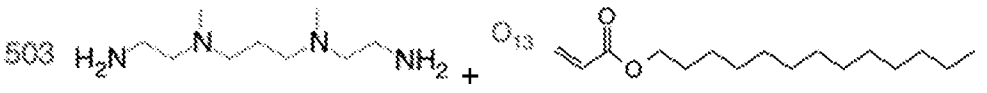


(xix)

In some embodiments, a lipid compound used to form lipid nanoparticles for the delivery of compositions described herein, e.g., a TREM described herein is made by one of the following reactions:



(xx) (a)



(xx)(b)

In some embodiments, a composition described herein (e.g., TREM composition) is provided in an LNP that comprises an ionizable lipid. In some embodiments, the ionizable lipid is heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate (SM-102); e.g., as described in Example 1 of US9,867,888 (incorporated by reference herein in its entirety). In some embodiments, the ionizable lipid is 9Z,12Z)-3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9,12-dienoate (LP01), e.g., as synthesized in Example 13 of WO2015/095340 (incorporated by reference herein in its entirety). In some embodiments, the ionizable lipid is Di((Z)-non-2-en-1-yl) 9-((4-dimethylamino)-butanoyl)oxy)heptadecanedioate (L319), e.g. as synthesized in Example 7, 8, or 9 of US2012/0027803 (incorporated by reference herein in its entirety). In some embodiments, the ionizable lipid is 1,1'-((2-(4-(2-((2-(Bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl) amino)ethyl)piperazin-1-yl)ethyl)azanediyl)bis(dodecan-2-ol) (C12-200), e.g., as synthesized in Examples 14 and 16 of WO2010/053572 (incorporated by reference herein in its entirety). In some embodiments, the ionizable lipid is Imidazole cholesterol ester (ICE) lipid (3S, 10R, 13R, 17R)-10, 13-dimethyl-17- ((R)-6-methylheptan-2-yl)-2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17-tetradecahydro-lH- cyclopenta[a]phenanthren-3-yl 3-(1H-imidazol-4-yl)propanoate, e.g., Structure (I) from WO2020/106946 (incorporated by reference herein in its entirety).

In some embodiments, an ionizable lipid may be a cationic lipid, an ionizable cationic lipid, e.g., a cationic lipid that can exist in a positively charged or neutral form depending on pH, or an amine-containing lipid that can be readily protonated. In some embodiments, the cationic lipid is a lipid capable of being positively charged, e.g., under physiological conditions. Exemplary cationic lipids include one or more amine group(s) which bear the positive charge. In

some embodiments, the lipid particle comprises a cationic lipid in formulation with one or more of neutral lipids, ionizable amine-containing lipids, biodegradable alkyne lipids, steroids, phospholipids including polyunsaturated lipids, structural lipids (e.g., sterols), PEG, cholesterol and polymer conjugated lipids. In some embodiments, the cationic lipid may be an ionizable cationic lipid. An exemplary cationic lipid as disclosed herein may have an effective pKa over 6.0. In embodiments, a lipid nanoparticle may comprise a second cationic lipid having a different effective pKa (e.g., greater than the first effective pKa), than the first cationic lipid. A lipid nanoparticle may comprise between 40 and 60 mol percent of a cationic lipid, a neutral lipid, a steroid, a polymer conjugated lipid, and a therapeutic agent, e.g., a TREM described herein, encapsulated within or associated with the lipid nanoparticle. In some embodiments, the TREM is co-formulated with the cationic lipid. The TREM may be adsorbed to the surface of an LNP, e.g., an LNP comprising a cationic lipid. In some embodiments, the TREM may be encapsulated in an LNP, e.g., an LNP comprising a cationic lipid. In some embodiments, the lipid nanoparticle may comprise a targeting moiety, e.g., coated with a targeting agent. In embodiments, the LNP formulation is biodegradable. In some embodiments, a lipid nanoparticle comprising one or more lipid described herein, e.g., Formula (i), (ii), (ii), (vii) and/or (ix) encapsulates at least 1%, at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 92%, at least 95%, at least 97%, at least 98% or 100% of a TREM.

Exemplary ionizable lipids that can be used in lipid nanoparticle formulations include, without limitation, those listed in Table 1 of WO2019051289, incorporated herein by reference. Additional exemplary lipids include, without limitation, one or more of the following formulae: X of US2016/0311759; I of US20150376115 or in US2016/0376224; I, II or III of US20160151284; I, IA, II, or IIA of US20170210967; I-c of US20150140070; A of US2013/0178541; I of US2013/0303587 or US2013/0123338; I of US2015/0141678; II, III, IV, or V of US2015/0239926; I of US2017/0119904; I or II of WO2017/117528; A of US2012/0149894; A of US2015/0057373; A of WO2013/116126; A of US2013/0090372; A of US2013/0274523; A of US2013/0274504; A of US2013/0053572; A of W02013/016058; A of W02012/162210; I of US2008/042973; I, II, III, or IV of US2012/01287670; I or II of US2014/0200257; I, II, or III of US2015/0203446; I or III of US2015/0005363; I, IA, IB, IC, ID, II, IIA, IIB, IIC, IID, or III-XXIV of US2014/0308304; of US2013/0338210; I, II, III, or IV of

W02009/132131; A of US2012/01011478; I or XXXV of US2012/0027796; XIV or XVII of US2012/0058144; of US2013/0323269; I of US2011/0117125; I, II, or III of US2011/0256175; I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII of US2012/0202871; I, II, III, IV, V, VI, VII, VIII, X, XII, XIII, XIV, XV, or XVI of US2011/0076335; I or II of US2006/008378; I of US2013/0123338; I or X-A-Y-Z of US2015/0064242; XVI, XVII, or XVIII of US2013/0022649; I, II, or III of US2013/0116307; I, II, or III of US2013/0116307; I or II of US2010/0062967; I-X of US2013/0189351; I of US2014/0039032; V of US2018/0028664; I of US2016/0317458; I of US2013/0195920; 5, 6, or 10 of US10,221,127; III-3 of WO2018/081480; I-5 or I-8 of WO2020/081938; 18 or 25 of US9,867,888; A of US2019/0136231; II of WO2020/219876; 1 of US2012/0027803; OF-02 of US2019/0240349; 23 of US10,086,013; cKK-E12/A6 of Miao et al (2020); C12-200 of WO2010/053572; 7C1 of Dahlman et al (2017); 304-O13 or 503-O13 of Whitehead et al; TS-P4C2 of US9,708,628; I of WO2020/106946; I of WO2020/106946.

In some embodiments, the ionizable lipid is MC3 (6Z,9Z,28Z,3 lZ)-heptatriaconta-6,9,28,3 l-tetraen-l9-yl-4-(dimethylamino) butanoate (DLin-MC3-DMA or MC3), e.g., as described in Example 9 of WO2019051289A9 (incorporated by reference herein in its entirety). In some embodiments, the ionizable lipid is the lipid ATX-002, e.g., as described in Example 10 of WO2019051289A9 (incorporated by reference herein in its entirety). In some embodiments, the ionizable lipid is (l3Z,l6Z)-A,A-dimethyl-3- nonyldocosa-l3, l6-dien-l-amine (Compound 32), e.g., as described in Example 11 of WO2019051289A9 (incorporated by reference herein in its entirety). In some embodiments, the ionizable lipid is Compound 6 or Compound 22, e.g., as described in Example 12 of WO2019051289A9 (incorporated by reference herein in its entirety).

Exemplary non-cationic lipids include, but are not limited to, distearoyl-sn-glycero-phosphoethanolamine, distearoylphosphatidylcholine (DSPC), dioleoylphosphatidylcholine (DOPC), dipalmitoylphosphatidylcholine (DPPC), dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoyl-phosphatidylethanolamine (DOPE), palmitoyloleoylphosphatidylcholine (POPC), palmitoyloleoylphosphatidylethanolamine (POPE), dioleoyl-phosphatidylethanolamine 4-(N-maleimidomethyl)-cyclohexane- 1 - carboxylate (DOPE-mal), dipalmitoyl phosphatidyl ethanolamine (DPPE), dimyristoylphosphoethanolamine (DMPE), distearoyl-phosphatidyl-ethanolamine (DSPE), monomethyl-phosphatidylethanolamine (such as 16-O-monomethyl PE), dimethyl- phosphatidylethanolamine (such as 16-O-dimethyl

PE), 18-1-trans PE, 1-stearoyl-2-oleoyl- phosphatidyethanolamine (SOPE), hydrogenated soy phosphatidylcholine (HSPC), egg phosphatidylcholine (EPC), dioleoylphosphatidylserine (DOPS), sphingomyelin (SM), dimyristoyl phosphatidylcholine (DMPC), dimyristoyl phosphatidylglycerol (DMPG), distearoylphosphatidylglycerol (DSPG), dierucoylphosphatidylcholine (DEPC), palmitoyloleyolphosphatidylglycerol (POPG), dielaidoyl-phosphatidylethanolamine (DEPE), lecithin, phosphatidylethanolamine, lysolecithin, lysophosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, sphingomyelin, egg sphingomyelin (ESM), cephalin, cardiolipin, phosphatidicacid,cerebrosides, dicetylphosphate, lysophosphatidylcholine, dilinoleoylphosphatidylcholine, or mixtures thereof. It is understood that other diacylphosphatidylcholine and diacylphosphatidylethanolamine phospholipids can also be used. The acyl groups in these lipids are preferably acyl groups derived from fatty acids having C10-C24 carbon chains, e.g., lauroyl, myristoyl, paimitoyl, stearoyl, or oleoyl. Additional exemplary lipids, in certain embodiments, include, without limitation, those described in Kim et al. (2020) dx.doi.org/10.1021/acs.nanolett.0c01386, incorporated herein by reference. Such lipids include, in some embodiments, plant lipids found to improve liver transfection with mRNA (e.g., DGTS).

Other examples of non-cationic lipids suitable for use in the lipid nanoparticles include, without limitation, nonphosphorous lipids such as, e.g., stearylamine, dodeeylamine, hexadecylamine, acetyl palmitate, glycerol ricinoleate, hexadecyl stereate, isopropyl myristate, amphoteric acrylic polymers, triethanolamine-lauryl sulfate, alkyl-aryl sulfate polyethyloxylated fatty acid amides, dioctadecyl dimethyl ammonium bromide, ceramide, sphingomyelin, and the like. Other non-cationic lipids are described in WO2017/099823 or US patent publication US2018/0028664, the contents of which is incorporated herein by reference in their entirety.

In some embodiments, the non-cationic lipid is oleic acid or a compound of Formula I, II, or IV of US2018/0028664, incorporated herein by reference in its entirety. The non-cationic lipid can comprise, for example, 0-30% (mol) of the total lipid present in the lipid nanoparticle. In some embodiments, the non-cationic lipid content is 5-20% (mol) or 10-15% (mol) of the total lipid present in the lipid nanoparticle. In embodiments, the molar ratio of ionizable lipid to the neutral lipid ranges from about 2:1 to about 8:1 (e.g., about 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, or 8:1).

In some embodiments, the lipid nanoparticles do not comprise any phospholipids.

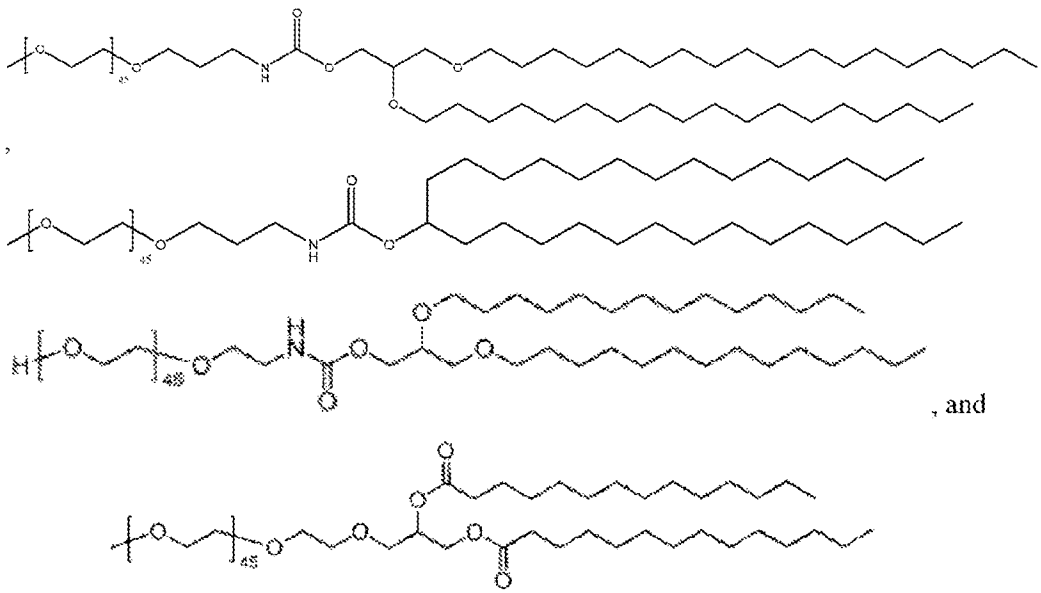
In some aspects, the lipid nanoparticle can further comprise a component, such as a sterol, to provide membrane integrity. One exemplary sterol that can be used in the lipid nanoparticle is cholesterol and derivatives thereof. Non-limiting examples of cholesterol derivatives include polar analogues such as 5a-choiestanol, 53-coprostanol, choiesteryl-(2'-hydroxy)-ethyl ether, choiesteryl-(4'- hydroxy)-butyl ether, and 6-ketocholestanol; non-polar analogues such as 5a-cholestane, cholestenone, 5a-cholestanone, 5p-cholestanone, and cholesteryl decanoate; and mixtures thereof. In some embodiments, the cholesterol derivative is a polar analogue, e.g., choiesteryl-(4 '-hydroxy)-buty1 ether. Exemplary cholesterol derivatives are described in PCT publication W02009/127060 and US patent publication US2010/0130588, each of which is incorporated herein by reference in its entirety.

In some embodiments, the component providing membrane integrity, such as a sterol, can comprise 0-50% (mol) (e.g., 0-10%, 10-20%, 20-30%, 30-40%, or 40-50%) of the total lipid present in the lipid nanoparticle. In some embodiments, such a component is 20-50% (mol) 30-40% (mol) of the total lipid content of the lipid nanoparticle.

In some embodiments, the lipid nanoparticle can comprise a polyethylene glycol (PEG) or a conjugated lipid molecule. Generally, these are used to inhibit aggregation of lipid nanoparticles and/or provide steric stabilization. Exemplary conjugated lipids include, but are not limited to, PEG-lipid conjugates, polyoxazoline (POZ)-lipid conjugates, polyamide-lipid conjugates (such as ATTA-lipid conjugates), cationic-polymer lipid (CPL) conjugates, and mixtures thereof. In some embodiments, the conjugated lipid molecule is a PEG-lipid conjugate, for example, a (methoxy polyethylene glycol)-conjugated lipid.

Exemplary PEG-lipid conjugates include, but are not limited to, PEG-diacylglycerol (DAG) (such as l-(monomethoxy-polyethyleneglycol)-2,3-dimyristoylglycerol (PEG-DMG)), PEG-dialkyloxypropyl (DAA), PEG-phospholipid, PEG-ceramide (Cer), a pegylated phosphatidylethanoloamine (PEG-PE), PEG succinate diacylglycerol (PEGS-DAG) (such as 4-0-(2',3'-di(tetradecanoyloxy)propyl-l-0-(w-methoxy(polyethoxy)ethyl) butanedioate (PEG-S-DMG)), PEG dialkoxypropylcarbam, N-(carbonyl-methoxypolyethylene glycol 2000)-l,2-distearoyl-sn-glycero-3-phosphoethanolamine sodium salt, or a mixture thereof. Additional exemplary PEG-lipid conjugates are described, for example, in US5,885,613, US6,287,591, US2003/0077829, US2003/0077829, US2005/0175682, US2008/0020058, US2011/0117125, US2010/0130588, US2016/0376224, US2017/0119904, and US/099823, the contents of all of

which are incorporated herein by reference in their entirety. In some embodiments, a PEG-lipid is a compound of Formula III, III-a-I, III-a-2, III-b-1, III-b-2, or V of US2018/0028664, the content of which is incorporated herein by reference in its entirety. In some embodiments, a PEG-lipid is of Formula II of US20150376115 or US2016/0376224, the content of both of which is incorporated herein by reference in its entirety. In some embodiments, the PEG-DAA conjugate can be, for example, PEG-dilauryloxypropyl, PEG- dimyristyloxypropyl, PEG-dipalmityloxypropyl, or PEG-distearyloxypropyl. The PEG-lipid can be one or more of PEG-DMG, PEG-dilaurylglycerol, PEG-dipalmitoylglycerol, PEG- disterylglycerol, PEG-dilaurylglycamide, PEG-dimyristylglycamide, PEG- dipalmitoylglycamide, PEG-disterylglycamide, PEG-cholesterol (l-[8'-(Cholest-5-en-3[beta]- oxy)carboxamido-3',6'-dioxaoctanyl] carbamoyl-[omega]-methyl-poly(ethylene glycol), PEG- DMB (3,4-Ditetradecoxylbenzyl- [omega]-methyl-poly(ethylene glycol) ether), and 1,2- dimyristoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]. In some embodiments, the PEG-lipid comprises PEG-DMG, 1,2- dimyristoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]. In some embodiments, the PEG-lipid comprises a structure selected from:



, and

In some embodiments, lipids conjugated with a molecule other than a PEG can also be used in place of PEG-lipid. For example, polyoxazoline (POZ)-lipid conjugates, polyamide-lipid conjugates (such as ATTA-lipid conjugates), and cationic-polymer lipid (GPL) conjugates can be used in place of or in addition to the PEG-lipid.

Exemplary conjugated lipids, i.e., PEG-lipids, (POZ)-lipid conjugates, ATTA-lipid conjugates and cationic polymer-lipids are described in the PCT and LIS patent applications listed in Table 2 of WO2019051289A9, the contents of all of which are incorporated herein by reference in their entirety.

In some embodiments, the PEG or the conjugated lipid can comprise 0-20% (mol) of the total lipid present in the lipid nanoparticle. In some embodiments, PEG or the conjugated lipid content is 0.5- 10% or 2-5% (mol) of the total lipid present in the lipid nanoparticle. Molar ratios of the ionizable lipid, non-cationic-lipid, sterol, and PEG/conjugated lipid can be varied as needed. For example, the lipid particle can comprise 30-70% ionizable lipid by mole or by total weight of the composition, 0-60% cholesterol by mole or by total weight of the composition, 0-30% non-cationic-lipid by mole or by total weight of the composition and 1-10% conjugated lipid by mole or by total weight of the composition. Preferably, the composition comprises 30-40% ionizable lipid by mole or by total weight of the composition, 40-50% cholesterol by mole or by total weight of the composition, and 10- 20% non-cationic-lipid by mole or by total weight of the composition. In some other embodiments, the composition is 50-75% ionizable lipid by mole or by total weight of the composition, 20-40% cholesterol by mole or by total weight of the composition, and 5 to 10% non-cationic-lipid, by mole or by total weight of the composition and 1-10% conjugated lipid by mole or by total weight of the composition. The composition may contain 60-70% ionizable lipid by mole or by total weight of the composition, 25-35% cholesterol by mole or by total weight of the composition, and 5-10% non-cationic-lipid by mole or by total weight of the composition. The composition may also contain up to 90% ionizable lipid by mole or by total weight of the composition and 2 to 15% non-cationic lipid by mole or by total weight of the composition. The formulation may also be a lipid nanoparticle formulation, for example comprising 8-30% ionizable lipid by mole or by total weight of the composition, 5-30% non- cationic lipid by mole or by total weight of the composition, and 0-20% cholesterol by mole or by total weight of the composition; 4-25% ionizable lipid by mole or by total weight of the composition, 4-25% non-cationic lipid by mole or by total weight of the composition, 2 to 25% cholesterol by mole or by total weight of the composition, 10 to 35% conjugate lipid by mole or by total weight of the composition, and 5% cholesterol by mole or by total weight of the composition; or 2-30% ionizable lipid by mole or by total weight of the composition, 2-30% non-cationic lipid by mole or by total weight of the composition, 1 to 15% cholesterol by mole or

by total weight of the composition, 2 to 35% conjugate lipid by mole or by total weight of the composition, and 1-20% cholesterol by mole or by total weight of the composition; or even up to 90% ionizable lipid by mole or by total weight of the composition and 2-10% non-cationic lipids by mole or by total weight of the composition, or even 100% cationic lipid by mole or by total weight of the composition. In some embodiments, the lipid particle formulation comprises ionizable lipid, phospholipid, cholesterol and a PEG-ylated lipid in a molar ratio of 50: 10:38.5: 1.5. In some other embodiments, the lipid particle formulation comprises ionizable lipid, cholesterol and a PEG-ylated lipid in a molar ratio of 60:38.5: 1.5.

In some embodiments, the lipid particle comprises ionizable lipid, non-cationic lipid (e.g. phospholipid), a sterol (e.g., cholesterol) and a PEG-ylated lipid, where the molar ratio of lipids ranges from 20 to 70 mole percent for the ionizable lipid, with a target of 40-60, the mole percent of non-cationic lipid ranges from 0 to 30, with a target of 0 to 15, the mole percent of sterol ranges from 20 to 70, with a target of 30 to 50, and the mole percent of PEG-ylated lipid ranges from 1 to 6, with a target of 2 to 5.

In some embodiments, the lipid particle comprises ionizable lipid / non-cationic- lipid / sterol / conjugated lipid at a molar ratio of 50: 10:38.5: 1.5.

In an aspect, the disclosure provides a lipid nanoparticle formulation comprising phospholipids, lecithin, phosphatidylcholine and phosphatidylethanolamine.

In some embodiments, one or more additional compounds can also be included. Those compounds can be administered separately, or the additional compounds can be included in the lipid nanoparticles of the invention. In other words, the lipid nanoparticles can contain other compounds in addition to the nucleic acid or at least a second nucleic acid, different than the first. Without limitations, other additional compounds can be selected from the group consisting of small or large organic or inorganic molecules, monosaccharides, disaccharides, trisaccharides, oligosaccharides, polysaccharides, peptides, proteins, peptide analogs and derivatives thereof, peptidomimetics, nucleic acids, nucleic acid analogs and derivatives, an extract made from biological materials, or any combinations thereof.

In some embodiments, LNPs are directed to specific tissues by the addition of targeting domains. For example, biological ligands may be displayed on the surface of LNPs to enhance interaction with cells displaying cognate receptors, thus driving association with and cargo delivery to tissues wherein cells express the receptor. In some embodiments, the biological

ligand may be a ligand that drives delivery to the liver, e.g., LNPs that display GalNAc result in delivery of nucleic acid cargo to hepatocytes that display asialoglycoprotein receptor (ASGPR). The work of Akinc et al. *Mol Ther* 18(7):1357-1364 (2010) teaches the conjugation of a trivalent GalNAc ligand to a PEG-lipid (GalNAc-PEG-DSG) to yield LNPs dependent on ASGPR for observable LNP cargo effect (see, e.g., FIG. 6 of Akinc et al. 2010, *supra*). Other ligand-displaying LNP formulations, e.g., incorporating folate, transferrin, or antibodies, are discussed in WO2017223135, which is incorporated herein by reference in its entirety, in addition to the references used therein, namely Kolhatkar et al., Curr Drug Discov Technol. 2011 8:197-206; Musacchio and Torchilin, Front Biosci. 2011 16:1388-1412; Yu et al., Mol Membr Biol. 2010 27:286-298; Patil et al., Crit Rev Ther Drug Carrier Syst. 2008 25:1-61 ; Benoit et al., Biomacromolecules. 2011 12:2708-2714; Zhao et al., Expert Opin Drug Deliv. 2008 5:309-319; Akinc et al., Mol Ther. 2010 18:1357-1364; Srinivasan et al., Methods Mol Biol. 2012 820:105-116; Ben-Arie et al., Methods Mol Biol. 2012 757:497-507; Peer 2010 J Control Release. 20:63-68; Peer et al., Proc Natl Acad Sci U S A. 2007 104:4095-4100; Kim et al., Methods Mol Biol. 2011 721:339-353; Subramanya et al., Mol Ther. 2010 18:2028-2037; Song et al., Nat Biotechnol. 2005 23:709-717; Peer et al., Science. 2008 319:627-630; and Peer and Lieberman, Gene Ther. 2011 18:1127-1133.

In some embodiments, LNPs are selected for tissue-specific activity by the addition of a Selective ORgan Targeting (SORT) molecule to a formulation comprising traditional components, such as ionizable cationic lipids, amphipathic phospholipids, cholesterol and poly(ethylene glycol) (PEG) lipids. The teachings of Cheng et al. Nat Nanotechnol 15(4):313-320 (2020) demonstrate that the addition of a supplemental "SORT" component precisely alters the in vivo RNA delivery profile and mediates tissue-specific (e.g., lungs, liver, spleen) gene delivery and editing as a function of the percentage and biophysical property of the SORT molecule.

In some embodiments, the LNPs comprise biodegradable, ionizable lipids. In some embodiments, the LNPs comprise (9Z,l2Z)-3-((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl octadeca-9,l2-dienoate, also called 3- ((4,4-bis(octyloxy)butanoyl)oxy)-2-((((3-(diethylamino)propoxy)carbonyl)oxy)methyl)propyl (9Z,l2Z)-octadeca-9,l2-dienoate) or another ionizable lipid. See, e.g, lipids of WO2019/067992, WO/2017/173054, WO2015/095340, and WO2014/136086, as well as references provided

therein. In some embodiments, the term cationic and ionizable in the context of LNP lipids is interchangeable, e.g., wherein ionizable lipids are cationic depending on the pH.

In some embodiments, the average LNP diameter of the LNP formulation may be between 10s of nm and 100s of nm, e.g., measured by dynamic light scattering (DLS). In some embodiments, the average LNP diameter of the LNP formulation may be from about 40 nm to about 150 nm, such as about 40 nm, 45 nm, 50 nm, 55 nm, 60 nm, 65 nm, 70 nm, 75 nm, 80 nm, 85 nm, 90 nm, 95 nm, 100 nm, 105 nm, 110 nm, 115 nm, 120 nm, 125 nm, 130 nm, 135 nm, 140 nm, 145 nm, or 150 nm. In some embodiments, the average LNP diameter of the LNP formulation may be from about 50 nm to about 100 nm, from about 50 nm to about 90 nm, from about 50 nm to about 80 nm, from about 50 nm to about 70 nm, from about 50 nm to about 60 nm, from about 60 nm to about 100 nm, from about 60 nm to about 90 nm, from about 60 nm to about 80 nm, from about 60 nm to about 70 nm, from about 70 nm to about 100 nm, from about 70 nm to about 90 nm, from about 70 nm to about 80 nm, from about 80 nm to about 100 nm, from about 80 nm to about 90 nm, or from about 90 nm to about 100 nm. In some embodiments, the average LNP diameter of the LNP formulation may be from about 70 nm to about 100 nm. In a particular embodiment, the average LNP diameter of the LNP formulation may be about 80 nm. In some embodiments, the average LNP diameter of the LNP formulation may be about 100 nm. In some embodiments, the average LNP diameter of the LNP formulation ranges from about 1 mm to about 500 mm, from about 5 mm to about 200 mm, from about 10 mm to about 100 mm, from about 20 mm to about 80 mm, from about 25 mm to about 60 mm, from about 30 mm to about 55 mm, from about 35 mm to about 50 mm, or from about 38 mm to about 42 mm.

A LNP may, in some instances, be relatively homogenous. A polydispersity index may be used to indicate the homogeneity of a LNP, e.g., the particle size distribution of the lipid nanoparticles. A small (e.g., less than 0.3) polydispersity index generally indicates a narrow particle size distribution. A LNP may have a polydispersity index from about 0 to about 0.25, such as 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19, 0.20, 0.21, 0.22, 0.23, 0.24, or 0.25. In some embodiments, the polydispersity index of a LNP may be from about 0.10 to about 0.20.

The zeta potential of a LNP may be used to indicate the electrokinetic potential of the composition. In some embodiments, the zeta potential may describe the surface charge of an LNP. Lipid nanoparticles with relatively low charges, positive or negative, are generally

desirable, as more highly charged species may interact undesirably with cells, tissues, and other elements in the body. In some embodiments, the zeta potential of a LNP may be from about -10 mV to about +20 mV, from about -10 mV to about +15 mV, from about -10 mV to about +10 mV, from about -10 mV to about +5 mV, from about -10 mV to about 0 mV, from about -10 mV to about -5 mV, from about -5 mV to about +20 mV, from about -5 mV to about +15 mV, from about -5 mV to about +10 mV, from about -5 mV to about +5 mV, from about -5 mV to about 0 mV, from about 0 mV to about +20 mV, from about 0 mV to about +15 mV, from about 0 mV to about +10 mV, from about 0 mV to about +5 mV, from about +5 mV to about +20 mV, from about +5 mV to about +15 mV, or from about +5 mV to about +10 mV.

The efficiency of encapsulation of a TREM describes the amount of TREM that is encapsulated or otherwise associated with a LNP after preparation, relative to the initial amount provided. The encapsulation efficiency is desirably high (e.g., close to 100%). The encapsulation efficiency may be measured, for example, by comparing the amount of TREM in a solution containing the lipid nanoparticle before and after breaking up the lipid nanoparticle with one or more organic solvents or detergents. An anion exchange resin may be used to measure the amount of free protein or nucleic acid (e.g., RNA) in a solution. Fluorescence may be used to measure the amount of free TREM in a solution. For the lipid nanoparticles described herein, the encapsulation efficiency of a TREM may be at least 50%, for example 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100%. In some embodiments, the encapsulation efficiency may be at least 80%. In some embodiments, the encapsulation efficiency may be at least 90%. In some embodiments, the encapsulation efficiency may be at least 95%.

A LNP may optionally comprise one or more coatings. In some embodiments, a LNP may be formulated in a capsule, film, or table having a coating. A capsule, film, or tablet including a composition described herein may have any useful size, tensile strength, hardness or density.

Additional exemplary lipids, formulations, methods, and characterization of LNPs are taught by WO2020061457, which is incorporated herein by reference in its entirety.

In some embodiments, in vitro or ex vivo cell lipofections are performed using Lipofectamine MessengerMax (Thermo Fisher) or TransIT-mRNA Transfection Reagent (Mirus Bio). In certain embodiments, LNPs are formulated using the GenVoy_ILM ionizable lipid mix

(Precision NanoSystems). In certain embodiments, LNPs are formulated using 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA) or dilinoleylmethyl-4-dimethylaminobutyrate (DLin-MC3-DMA or MC3), the formulation and in vivo use of which are taught in Jayaraman et al. Angew Chem Int Ed Engl 51(34):8529-8533 (2012), incorporated herein by reference in its entirety.

LNP formulations optimized for the delivery of CRISPR-Cas systems, e.g., Cas9-gRNA RNP, gRNA, Cas9 mRNA, are described in WO2019067992 and WO2019067910, both incorporated by reference.

Additional specific LNP formulations useful for delivery of nucleic acids are described in US8158601 and US8168775, both incorporated by reference, which include formulations used in patisiran, sold under the name ONPATTRO.

Exosomes can also be used as drug delivery vehicles for the TREM, TREM core fragment, TREM fragment, or TREM compositions or pharmaceutical TREM composition described herein. For a review, see Ha et al. July 2016. Acta Pharmaceutica Sinica B. Volume 6, Issue 4, Pages 287-296; https://doi.org/10.1016/j.apsb.2016.02.001.

Ex vivo differentiated red blood cells can also be used as a carrier for a TREM, TREM core fragment, TREM fragment, or TREM composition, or pharmaceutical TREM composition described herein. See, *e.g.*, WO2015073587; WO2017123646; WO2017123644; WO2018102740; wO2016183482; WO2015153102; WO2018151829; WO2018009838; Shi et al. 2014. Proc Natl Acad Sci USA. 111(28): 10131–10136; US Patent 9,644,180; Huang et al. 2017. Nature Communications 8: 423; Shi et al. 2014. Proc Natl Acad Sci USA. 111(28): 10131–10136.

Fusosome compositions, *e.g.*, as described in WO2018208728, can also be used as carriers to deliver the TREM, TREM core fragment, TREM fragment, or TREM composition, or pharmaceutical TREM composition described herein.

Virosomes and virus-like particles (VLPs) can also be used as carriers to deliver a TREM, TREM core fragment, TREM fragment, or TREM composition, or pharmaceutical TREM composition described herein to targeted cells.

Plant nanovesicles, e.g., as described in WO2011097480A1, WO2013070324A1, or WO2017004526A1 can also be used as carriers to deliver the TREM, TREM core fragment,

TREM fragment, or TREM composition, or pharmaceutical TREM composition described herein.

Delivery without a carrier

A TREM, a TREM core fragment or a TREM fragment, a TREM composition or a pharmaceutical TREM composition described herein can be administered to a cell without a carrier, e.g., via naked delivery of the TREM, a TREM core fragment or a TREM fragment, a TREM composition or a pharmaceutical TREM composition.

In some embodiments, naked delivery as used herein refers to delivery without a carrier. In some embodiments, delivery without a carrier, e.g., naked delivery, comprises delivery with a moiety, e.g., a targeting peptide.

In some embodiments, a TREM, a TREM core fragment or a TREM fragment, or TREM composition, or pharmaceutical TREM composition described herein is delivered to a cell without a carrier, e.g., via naked delivery. In some embodiments, the delivery without a carrier, e.g., naked delivery, comprises delivery with a moiety, e.g., a targeting peptide.

All references and publications cited herein are hereby incorporated by reference.

ENUMERATED EMBODIMENTS

1. A TREM comprising a sequence of Formula A:

[L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2],

wherein:

independently, [L1] and [VL Domain], are optional;

one of [L1], [ASt Domain1], [L2]-[DH Domain], [L3], [ACH Domain], [VL Domain], [TH Domain], [L4], and [ASt Domain2] comprises a nucleotide having a non-naturally occurring modification; and

wherein:

(a) the TREM retains the ability to: support protein synthesis, be charged by a synthetase, be bound by an elongation factor, introduce an amino acid into a peptide chain, support elongation, or support initiation;

(b) the TREM comprises at least X contiguous nucleotides without a non-naturally occurring modification, wherein X is greater than 10;

(c) at least 3, but less than all of the nucleotides of a type (e.g., A, T, C, G or U) comprise the same non-naturally occurring modification;

(d) at least X nucleotides of a type (e.g., A, T, C, G or U) do not comprise a non-naturally occurring modification, wherein X=1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50;

(e) no more than 5, 10, or 15 nucleotides of a type (e.g., A, T, C, G or U) comprise a non-naturally occurring modification; and/or

(f) no more than 5, 10, or 15 nucleotides of a type (e.g., A, T, C, G or U) do not comprise a non-naturally occurring modification.

2. The TREM of embodiment 1, comprising the feature provided in embodiment 1(a).

3. The TREM of embodiment 1, comprising the feature provided in embodiment 1(b).

4. The TREM of embodiment 1, comprising the feature provided in embodiment 1(c).

5. The TREM of embodiment 1, comprising the feature provided in embodiment 1(d).

6. The TREM of embodiment 1, comprising the feature provided in embodiment 1(e).

7. The TREM of embodiment 1, comprising the feature provided in embodiment 1(f).

8. The TREM of embodiment 1, comprising all of the features provided in embodiments 1(a)-(f).

9. The TREM of any one of embodiments 1-8, wherein the Domain comprising the non-naturally occurring modification retains a function, e.g., a domain function described herein.

10. The TREM of any one of embodiments 1-8, comprising an [L1].

11. The TREM of any one of embodiments 1-8, comprising a [VL Domain].

12. The TREM of any one of embodiments 1-8, wherein: [L1] is a linker comprising a nucleotide having a non-naturally occurring modification.

13. The TREM of any one of embodiments 1-8, wherein [ASt Domain1 (AstD1)] comprises a nucleotide having a non-naturally occurring modification.

14. The TREM of any one of embodiments 1-8, wherein [L2] is a linker comprising a nucleotide having a non-naturally occurring modification.

15. The TREM of any one of embodiments 1-8, wherein [DH Domain (DHD)] comprises a nucleotide having a non-naturally occurring modification.

16. The TREM of any one of embodiments 1-8, wherein [L3] is a linker comprising a nucleotide having a non-naturally occurring modification.

17. The TREM of any one of embodiments 1-8, wherein [ACH Domain (ACHD)] comprises a nucleotide having a non-naturally occurring modification.

18. The TREM of any one of embodiments 1-8, wherein [VL Domain (VLD)] comprises a nucleotide having a non-naturally occurring modification.

19. The TREM of any one of embodiments 1-8, wherein [TH Domain (THD)] comprises a nucleotide having a non-naturally occurring modification.

20. The TREM of any one of embodiments 1-8, wherein [L4] is a linker comprises a nucleotide having a non-naturally occurring modification.

21. The TREM of any one of embodiments 1-8, wherein: [ASt Domain2 (AStD2)] comprises a nucleotide having a non-naturally occurring modification.

22. A TREM core fragment comprising a sequence of Formula B:

$[L1]_y$-[ASt Domain1]$_x$-$[L2]_y$-[DH Domain]$_y$-$[L3]_y$-[ACH Domain]$_x$-[VL Domain]$_y$-[TH Domain]$_y$-$[L4]_y$-[ASt Domain2]$_x$,

wherein:

x=1 and y=0 or 1;

one of [ASt Domain1], [ACH Domain], and [ASt Domain2] comprises a nucleotide having a non-naturally occurring modification; and

the TREM retains the ability to: support protein synthesis; be able to be charged by a synthetase, be bound by an elongation factor, introduce an amino acid into a peptide chain, support elongation, or support initiation.

23. The TREM core fragment of embodiment 22, wherein AStD1 and AStD2 comprise an ASt Domain (AStD).

24. The TREM core fragment of embodiment 22, wherein the [ASt Domain 1], and/or [ASt Domain 2] comprising the non-naturally occurring modification retains the ability to initiate or elongate a polypeptide chain.

25. The TREM core fragment of embodiment 22, wherein the [ACH Domain] comprising the non-naturally occurring modification retains the ability to mediate pairing with a codon.

26. The TREM core fragment of embodiment 22, wherein y=1 for any one, two, three, four, five, six, all or a combination of [L1], [L2], [DH Domain], [L3], [VL Domain], [TH Domain], [L4].

27. The TREM core fragment of embodiment 22, wherein y=0 for any one, two, three, four, five, six, all or a combination of [L1], [L2], [DH Domain], [L3], [VL Domain], [TH Domain], [L4].

28. The TREM core fragment of embodiment 22, wherein y=1 for linker [L1], and L1 comprises a nucleotide having a non-naturally occurring modification.

29. The TREM core fragment of embodiment 22, wherein y=1 for linker [L2], and L2 comprises a nucleotide having a non-naturally occurring modification.

30. The TREM core fragment of embodiment 22, wherein y=1 for [DH Domain (DHD)], and DHD comprises a nucleotide having a non-naturally occurring modification.

31. The TREM core fragment of embodiment 30, wherein the DHD comprising the non-naturally occurring modification retains the ability to mediate recognition of aminoacyl-tRNA synthetase.

32. The TREM core fragment of embodiment 22, wherein y=1 for linker [L3], and L3 comprises a nucleotide having a non-naturally occurring modification.

33. The TREM core fragment of embodiment 22, wherein y=1 for [VL Domain (VLD)], and VLD comprises a nucleotide having a non-naturally occurring modification.

34. The TREM core fragment of embodiment 22, wherein y=1 for [TH Domain (THD)], and THD comprises a nucleotide having a non-naturally occurring modification.

35. The TREM core fragment of embodiment 34, wherein the THD comprising the non-naturally occurring modification retains the ability to mediate recognition of the ribosome.

36. The TREM core fragment of embodiment 22, wherein y=1 for linker [L4], and L4 comprises a nucleotide having a non-naturally occurring modification.

37. A TREM fragment comprising a portion of a TREM, wherein the TREM comprises a sequence of Formula A:

[L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2], and wherein:

the TREM fragment comprises:

a non-naturally occurring modification; and

one, two, three or all or any combination of the following:

(a) a TREM half (*e.g.*, from a cleavage in the ACH Domain, *e.g.*, in the anticodon sequence, *e.g.*, a 5'half or a 3' half);

(b) a 5' fragment (*e.g.*, a fragment comprising the 5' end, *e.g.*, from a cleavage in a DH Domain or the ACH Domain);

(c) a 3' fragment (*e.g.*, a fragment comprising the 3' end, *e.g.*, from a cleavage in the TH Domain); or

(d) an internal fragment (*e.g.*, from a cleavage in any one of the ACH Domain, DH Domain or TH Domain).

38. The TREM of embodiment 37, wherein the TREM fragment comprise (a) a TREM half which comprises a nucleotide having a non-naturally occurring modification.

39. The TREM of embodiment 37, wherein the TREM fragment comprise (b) a 5' fragment which comprises a nucleotide having a non-naturally occurring modification.

40. The TREM of embodiment 37, wherein the TREM fragment comprise (c) a 3' fragment which comprises a nucleotide having a non-naturally occurring modification.

41. The TREM of embodiment 37, wherein the TREM fragment comprise (d) an internal fragment which comprises a nucleotide having a non-naturally occurring modification.

42. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM Domain comprises a plurality of nucleotides each having a non-naturally occurring modification.

43. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X of the nucleotides of AStD1 have a non-naturally occurring modification, wherein X is equal to or greater than 1, 2, 3, 4, 5, 6 or 7.

44. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein no more than X of the nucleotides of AStD1 have a non-naturally occurring modification, wherein X is equal to or greater than 1, 2, 3, 4, 5, 6 or 7.

45. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X of the nucleotides of AStD2 have a non-naturally occurring modification, wherein X is equal to or greater than 1, 2, 3, 4, 5, 6 or 7.

46. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein no more than X of the nucleotides of AStD2 have a non-naturally occurring modification, wherein X is equal to or greater than 1, 2, 3, 4, 5, 6 or 7.

47. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X of the nucleotides of ACHD have a non-naturally occurring modification, wherein X is equal to or greater than 1, 2, 3, 4, 5, 6,7, 8, 9, or 10.

48. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X of the nucleotides of ACHD have a non-naturally occurring modification, wherein X is equal to or greater than 11, 12, 13, 14, 15, 16, or 17.

49. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein no more than X of the nucleotides of ACHD have a non-naturally occurring modification, wherein X is equal to or greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

50. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein no more than X of the nucleotides of ACHD have a non-naturally occurring modification, wherein X is equal to or greater than 11, 12, 13, 14, 15, or 16.

51. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X of the nucleotides of THD have a non-naturally occurring modification, wherein X is equal to or greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

52. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X of the nucleotides of THD have a non-naturally occurring modification, wherein X is equal to or greater than 11, 12, 13, 14, 15, 16, or 17.

53. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein no more than X of the nucleotides of THD have a non-naturally occurring modification, wherein X is equal to or greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

54. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein no more than X of the nucleotides of THD have a non-naturally occurring modification, wherein X is equal to or greater than 11, 12, 13, 14, 15, or 16.

55. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X of the nucleotides of DHD have a non-naturally occurring modification, wherein X is equal to or greater than 2, 3, 4, 5, 6,7, 8, 9 or 10.

56. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X of the nucleotides of DHD have a non-naturally occurring modification, wherein X is equal to or greater than 11, 12, 13, 14, 15, 16, 17, 18 or 19.

57. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein no more than X of the nucleotides of DHD have a non-naturally occurring modification, wherein X is equal to or greater than 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

58. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein no more than X of the nucleotides of DHD have a non-naturally occurring modification, wherein X is equal to or greater than 11, 12, 13, 14, 15, 16, 17, or 18.

59. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X of the nucleotides of the VLD have a non-naturally occurring modification, wherein X is equal to or greater than 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 50, 100, 150, 200 or 271.

60. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein all of the nucleotides of the AStD1, AStD2, ACHD, DHD, and/or THD have a non-naturally occurring modification.

61. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X of the nucleotides of AStD1 and/or AStD2 do not have a non-naturally occurring modification, wherein X is equal to or greater than 1, 2, 3, 4, 5, 6 or 7.

62. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X of the nucleotides of ACHD do not

have a non-naturally occurring modification, wherein X is equal to or greater than 1, 2, 3, 4, 5, 6,7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17.

63. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X of the nucleotides of THD do not have a non-naturally occurring modification, wherein X is equal to or greater than 1, 2, 3, 4, 5, 6,7, 8, 9, 10, 11, 12, 13, 14, 15, 16, or 17.

64. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X of the nucleotides of DHD do not have a non-naturally occurring modification, wherein X is equal to or greater than 1, 2, 3, 4, 5, 6,7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or 19.

65. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X of the nucleotides of VLD do not have a non-naturally occurring modification, wherein X is equal to or greater than 1, 2, 3, 4, 5, 6,7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 50, 100, 150, 200 or 271.

66. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM Linker L2 comprises two nucleotides each having a non-naturally occurring modification.

67. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X of the nucleotides of the TREM Linker do not have a non-naturally occurring modification, wherein X is equal to 1 or 2.

68. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein:

each of a plurality of TREM Domains and Linkers comprises a nucleotide having a non-naturally occurring modification.

69. The TREM, TREM core fragment or TREM fragment of embodiment 68, wherein one of the TREM Domains and Linkers of the plurality comprises a plurality of nucleotides each having a non-naturally occurring modification.

70. The TREM, TREM core fragment or TREM fragment of any of the preceding embodiments, wherein the non-naturally occurring modification is a modification in a base or a backbone of a nucleotide, e.g., a modification chosen from any one of Tables 5-9.

71. The TREM, TREM core fragment or TREM fragment of any of the preceding embodiments, wherein the non-naturally occurring modification is a base modification chosen from a modification listed in Table 5.

72. The TREM, TREM core fragment or TREM fragment of any of the preceding embodiments, wherein the non-naturally occurring modification is a base modification chosen from a modification listed in Table 6.

73. The TREM, TREM core fragment or TREM fragment of any of the preceding embodiments, wherein the non-naturally occurring modification is a base modification chosen from a modification listed in Table 7.

74. The TREM, TREM core fragment or TREM fragment of any of the preceding embodiments, wherein the non-naturally occurring modification is a backbone base modification chosen from a modification listed in Table 8.

75. The TREM, TREM core fragment or TREM fragment of any of the preceding embodiments, wherein the non-naturally occurring modification is a backbone modification chosen from a modification listed in Table 9.

76. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, comprising a nucleotide of a first type comprising a non-naturally occurring modification.

77. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, comprising a nucleotide of a first type and a nucleotide of a second type comprising a non-naturally occurring modification.

78. The TREM, TREM core fragment or TREM fragment of embodiment 77, wherein the non-naturally occurring modification on the nucleotide of the first type and the non-naturally occurring modification on the nucleotide of the second type are the same non-naturally occurring modification.

79. The TREM, TREM core fragment or TREM fragment of embodiment 77, wherein the non-naturally occurring modification on the nucleotide of the first type and the non-naturally occurring modification on the nucleotide of the second type are different non-naturally occurring modifications.

80. The TREM, TREM core fragment or TREM fragment of embodiments 76 or 77, wherein the nucleotide of the first type is chosen from: A, T, C, G or U.

81. The TREM, TREM core fragment or TREM fragment of embodiments 76 or 77, wherein the nucleotide of the second type is chosen from: A, T, C, G or U.

82. The TREM, TREM core fragment or TREM fragment of embodiments 76 or 77, wherein the nucleotide of the first type is an A.

83. The TREM, TREM core fragment or TREM fragment of embodiments 76 or 77, wherein the nucleotide of the first type is a G.

84. The TREM, TREM core fragment or TREM fragment of embodiments 76 or 77, wherein the nucleotide of the first type is a C.

85. The TREM core fragment or TREM fragment of embodiments 76 or 77, wherein the nucleotide of the first type is a T.

86. The TREM, TREM core fragment or TREM fragment of embodiments 76 or 77, wherein the nucleotide of the first type is a U.

87. The TREM, TREM core fragment or TREM fragment of embodiment 77, wherein when the nucleotide of the first type is an A, the nucleotide of the second type is chosen from: T, C, G or U.

88. The TREM, TREM core fragment or TREM fragment of embodiment 77, wherein when the nucleotide of the first type is a G, the nucleotide of the second type is chosen from: T, C, A or U.

89. The TREM, TREM core fragment or TREM fragment of embodiment 77, wherein when the nucleotide of the first type is a C, the nucleotide of the second type is chosen from: T, A, G or U.

90. The TREM, TREM core fragment or TREM fragment of embodiment 77, wherein when the nucleotide of the first type is a T, the nucleotide of the second type is chosen from: A, C, G or U.

91. The TREM, TREM core fragment or TREM fragment of embodiment 77, wherein when the nucleotide of the first type is a U, the nucleotide of the second type is chosen from: T, C, G or A.

92. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the non-naturally modification is in a purine (A or G).

93. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the non-naturally modification is not in a purine (A or G).

94. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the non-naturally modification is in a pyrimidine (U, T or C).

95. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the non-naturally modification is not in a pyrimidine (U, T or C).

96. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the DHD has a first sequence, a second sequence and a third sequence, optionally wherein the first sequence and the third sequence form a stem and the second sequence forms a loop, e.g., under physiological conditions.

97. The TREM, TREM core fragment or TREM fragment of embodiment 96, wherein the DHD comprises a non-naturally occurring modification in the first sequence or the third sequence, e.g., in the stem.

98. The TREM, TREM core fragment or TREM fragment of embodiment 96, wherein the DHD comprises a non-naturally occurring modification in the second sequence, e.g., in the loop.

100. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the ACHD has a first sequence, a second sequence and a third sequence, optionally wherein the first sequence and the third sequence form a stem and the second sequence forms a loop, e.g., under physiological conditions.

101. The TREM, TREM core fragment or TREM fragment of embodiment 100, wherein the ACHD comprises a non-naturally occurring modification in the first sequence or the third sequence, e.g., in the stem.

102. The TREM, TREM core fragment or TREM fragment of embodiment 100, wherein the ACHD comprises a non-naturally occurring modification in the second sequence, e.g., in the loop.

103. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the THD has a first sequence, a second sequence and a third sequence, optionally wherein the first sequence and the third sequence form a stem and the second sequence forms a loop, e.g., under physiological conditions.

104. The TREM, TREM core fragment or TREM fragment of embodiment 103, wherein the THD comprises a non-naturally occurring modification in the first sequence or the third sequence, e.g., in the stem.

105. The TREM, TREM core fragment or TREM fragment of embodiment 103, wherein the THD comprises a non-naturally occurring modification in the second sequence, e.g., in the loop.

106. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the VLD comprises a variable region having 1-271 nucleotides.

107. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM comprises at least X contiguous nucleotides without a non-naturally occurring modification, wherein X is greater than 10.

108. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least 3, but less than all of the nucleotides of a type (e.g., A, T, C, G or U) comprise the same non-naturally occurring modification.

109. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein at least X nucleotides of a type (e.g., A, T, C, G or U) do not comprise a non-naturally occurring modification, wherein X=1, 2, 3, 4, 5, 6, 7, 8, 9,

10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50.

110. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein no more than 5, 10, or 15 of a type (e.g., A, T, C, G or U) comprise a non-naturally occurring modification.

111. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein no more than 5, 10, or 15 of a type (e.g., A, T, C, G or U) do not comprise a non-naturally occurring modification.

112. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, which specifies X, wherein X is an amino acid selected from alanine, arginine, asparagine, aspartate, cysteine, glutamine, glutamate, glycine, histidine, isoleucine, methionine, leucine, lysine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, or valine.

113. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, which recognizes a codon provided in Table 2 or Table 3.

114. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM is a cognate TREM.

115. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM is a non-cognate TREM.

116. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM, TREM core fragment, or TREM fragment is encoded by a sequence provided in Table 4, e.g., any one of SEQ ID NOs 1-451.

117. The TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM, TREM core fragment, or TREM fragment is encoded by a consensus sequence chosen from any one of SEQ ID NOs: 562-621.

118. A pharmaceutical composition comprising a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37.

119. The pharmaceutical composition of embodiment 118, comprising a pharmaceutically acceptable component, *e.g.*, an excipient.

120. A method of making a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, comprising linking a first nucleotide to a second nucleotide to form the TREM.

121. The method of embodiment 120, wherein the TREM, TREM core fragment or TREM fragment is synthetic.

122. The method of embodiment 120 or 121, wherein the synthesis is performed in vitro.

123. The method of embodiment 120, wherein the TREM, TREM core fragment or TREM fragment is made by cell-free solid phase synthesis.

124. A cell comprising a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37.

125. A cell comprising a TREM, TREM core fragment or TREM fragment made according to the method of embodiment 120.

126. A method of evaluating a tRNA pool in a cell comprising an endogenous open reading frame (ORF), which ORF comprises a codon having a first sequence, comprising acquiring, e.g., directly or indirectly acquiring, knowledge of the abundance of one or both of (i) and (ii), e.g.,

acquiring knowledge of the relative amounts of (i) and (ii) in the cell wherein (i) is a tRNA moiety having an anticodon that pairs with the codon of the ORF having a first sequence (the first tRNA moiety) and (ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the codon having the first sequence (the second tRNA moiety) in the cell, thereby evaluating the tRNA pool in the cell.

127. A method of evaluating a tRNA pool in a subject comprising an endogenous open reading frame (ORF), which ORF comprises a codon having a first sequence, comprising acquiring, e.g., directly or indirectly acquiring, knowledge of the abundance of one or both of (i) and (ii), e.g., acquiring knowledge of the relative amounts of (i) and (ii) in the subject wherein (i) is a tRNA moiety having an anticodon that pairs with the codon of the ORF having a first sequence (the first tRNA moiety) and (ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the codon having the first sequence (the second tRNA moiety) in the cell, thereby evaluating the tRNA pool in the subject.

128. The method of embodiment 126 or 127, comprising acquiring knowledge of (i).

129. The method of embodiment 126 or 127, comprising acquiring knowledge of (ii).

130. The method of embodiment 126 or 127, comprising acquiring knowledge of (i) and (ii).

131. The method of any one of embodiments 126-130, wherein:

acquiring knowledge of (i) comprises acquiring a value for the abundance, e.g., relative amount, of (i); and/or

acquiring knowledge of (ii) comprises acquiring a value for the abundance, e.g., relative amount, of (ii).

132. The method of embodiment 131, wherein responsive to said value, the method comprises administering a TREM composition comprising a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM has an anticodon that pairs with: (a) the codon having the first sequence; or (b) the codon

other than the codon having the first sequence, in an amount and for a time sufficient to modulate the relative amounts of the first tRNA moiety and the second tRNA moiety.

133. A method of modulating a tRNA pool in a cell comprising an endogenous open reading frame (ORF), which ORF comprises a codon having a first sequence, comprising:

optionally, acquiring knowledge of the abundance of one or both of (i) and (ii), e.g., acquiring knowledge of the relative amounts of: (i) and (ii) in the cell, wherein (i) is a tRNA moiety having an anticodon that pairs with the codon of the ORF having a first sequence (the first tRNA moiety) and (ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the codon having the first sequence (the second tRNA moiety) in the cell;

contacting the cell with a TREM composition comprising a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM, TREM core fragment or TREM fragment has an anticodon that pairs with: (a) the codon having the first sequence; or (b) the codon other than the codon having the first sequence, in an amount and/or for a time sufficient to modulate the relative amounts of the first tRNA moiety and the second tRNA moiety in the cell,

thereby modulating the tRNA pool in the cell.

134. The method of embodiment 133, wherein the TREM comprises an anticodon that pairs with (a).

135. The method of embodiment134, wherein the TREM comprises an anticodon that pairs with (b).

136. A method of modulating a tRNA pool in a subject having an endogenous open reading frame (ORF), which ORF comprises a codon having a first sequence, comprising:

optionally, acquiring knowledge of the abundance of one or both of (i) and (ii), e.g., acquiring knowledge of the relative amounts of: (i) and (ii) in the subject, wherein (i) is a tRNA moiety having an anticodon that pairs with the codon of the ORF having a first sequence (the first tRNA moiety) and (ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the codon having the first sequence (the second tRNA moiety) in the subject;

contacting the subject with a TREM composition comprising a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM, TREM core fragment or TREM fragment has an anticodon that pairs with: (a) the codon having the first sequence; or (b) the codon other than the codon having the first sequence, in an amount and/or for a time sufficient to modulate the relative amounts of the first tRNA moiety and the second tRNA moiety in the subject,

thereby modulating the tRNA pool in the subject.

137. The method of embodiment 136, wherein the TREM comprises an anticodon that pairs with (a).

138 The method of embodiment 136, wherein the TREM comprises an anticodon that pairs with (b).

139. The method of any one of embodiments 136-138, comprising acquiring knowledge of (i).

140. The method of any one of embodiments 136-138, comprising acquiring knowledge of (ii).

141. The method of any one of embodiments 136-138, comprising acquiring knowledge of (i) and (ii).

142. The method of any one of embodiments 136-139 or 141, wherein acquiring knowledge of (i) comprises acquiring a value for the abundance, e.g., relative amounts, of (i).

143. The method of any one of embodiments 136-138 or 140-141, wherein acquiring knowledge of (ii) comprises acquiring a value for the abundance, e.g., relative amounts, of (ii).

144. The method of embodiment 18 or 19, wherein responsive to said value, the cell or subject is contacted with the TREM composition having an anticodon that pairs with (a) or (b).

145. A method of modulating a tRNA pool in a subject having an endogenous open reading frame (ORF) comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

providing a TREM composition comprising a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM, TREM core fragment or TREM fragment comprises an isoacceptor tRNA moiety comprising an anticodon sequence that pairs with the SMC (the TREM);

contacting the subject with the TREM composition in an amount and/or for a time sufficient to modulate the tRNA pool in the subject,

thereby modulating the tRNA pool in the subject.

146. A method of modulating a tRNA pool in a cell comprising an endogenous open reading frame (ORF) comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

providing a TREM composition comprising a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM, TREM core fragment or TREM fragment comprises an isoacceptor tRNA moiety comprising an anticodon sequence that pairs with the SMC (the TREM);

contacting the cell with the TREM composition in an amount and/or for a time sufficient to modulate the tRNA pool in the cell,

thereby modulating the tRNA pool in the cell.

147. The method of embodiment 145 or 146, comprising acquiring knowledge of the abundance of one or both of (i) and (ii) e.g., acquiring knowledge of the relative amounts of (i) and (ii) wherein (i) is a tRNA moiety having an anticodon that pairs with the SMC (the first tRNA moiety) and (ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the SMC (the second tRNA moiety), in the subject or cell.

148. The method of embodiment 147, comprising acquiring knowledge of (i).

149. The method of embodiment 147, comprising acquiring knowledge of (ii).

150. The method of embodiment 147, comprising acquiring knowledge of (i) and (ii).

151. The method of embodiment 147, wherein acquiring knowledge of (i) comprises acquiring a value for the abundance, e.g., relative amounts, of (i).

152. The method of embodiment 147, wherein acquiring knowledge of (ii) comprises acquiring a value for the abundance, e.g., relative amounts, of (ii).

153. The method of embodiment 151 or 152, wherein responsive to said value, the cell or subject is contacted with the TREM composition.

154. A method of treating a subject having an endogenous open reading frame (ORF) which comprises a codon having a first sequence, comprising:

providing a TREM composition comprising a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM, TREM core fragment or TREM fragment comprises an isoacceptor tRNA moiety having: an anticodon that pairs with the codon of the ORF having the first sequence; or an anticodon that pairs with a codon other than the codon having the first sequence,

contacting the subject with the TREM composition in an amount and/or for a time sufficient to treat the subject,

thereby treating the subject.

155. A method of treating a subject having an endogenous open reading frame (ORF) comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

providing a TREM composition comprising a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM, TREM core fragment or TREM fragment comprises an isoacceptor tRNA moiety having an anticodon that pairs with the SMC (the TREM);

contacting the subject with the TREM composition in an amount and/or for a time sufficient to treat the subject,

thereby treating the subject.

156. The method of embodiment 154 or 155, comprising acquiring knowledge of the abundance of one or both (i) and (ii), e.g., acquiring knowledge of the relative amounts of:

(i) a tRNA moiety having an anticodon that pairs with the codon having a first sequence or the SMC (the first tRNA moiety); and/or

(ii) an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than a codon having the first sequence, or pairs with a codon other than the SMC (the second tRNA moiety).

157. The method of embodiment 156, comprising acquiring knowledge of (i).

158. The method of embodiment 156, comprising acquiring knowledge of (ii).

159. The method of embodiment 156, comprising acquiring knowledge of (i) and (ii).

160. The method of embodiment 156, wherein acquiring knowledge of (i) comprises acquiring a value for the abundance, e.g., relative amounts, of (i).

161. The method of embodiment 156, wherein acquiring knowledge of (ii) comprises acquiring a value for the abundance, e.g., relative amounts, of (ii).

162. The method of embodiment 160 or 161, wherein responsive to said value, the subject is contacted with the TREM composition.

163. A method of treating a subject having an endogenous open reading frame (ORF) comprising a codon having a first sequence, comprising:

(i) acquiring, e.g., directly or indirectly acquiring, a value for the status of the codon having the first sequence in the subject, wherein said value comprises a measure of the presence

or absence of the codon having the first sequence in a sample from the subject; and identifying the subject as having the codon having the first sequence; and

(ii) responsive to said value, administering a TREM composition comprising a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM, TREM core fragment or TREM fragment comprises an isoacceptor tRNA moiety having an anticodon that pairs with the codon having the first sequence, to the subject,

thereby treating the subject.

164. A method of treating a subject having an endogenous open reading frame (ORF) comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

(i) acquiring, e.g., directly or indirectly acquiring, a value for the SMC status of the subject, wherein said value comprises a measure of the presence or absence of SMC in a sample from the subject, and identifying the subject as having a SMC; and

(ii) responsive to said value, administering a TREM composition comprising a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, wherein the TREM, TREM core fragment or TREM fragment comprises comprising an isoacceptor tRNA moiety having an anticodon that pairs with the SMC, to the subject,

thereby treating the subject.

165. A method of selecting a therapy for a subject having an endogenous open reading frame (ORF) which comprises a codon having a first sequence, comprising:

acquiring, e.g., directly or indirectly acquiring, a value for the status of the codon having the first sequence in the subject, wherein said value comprises a measure of the presence or absence of the codon having the first sequence in a sample from the subject; and

wherein the presence of the codon having the first sequence is indicative that said subject is likely to be a responder to the therapy, or said subject will respond, or will likely respond, to the therapy,

thereby selecting the therapy.

166. A method of selecting a therapy for a subject having an endogenous open reading frame (ORF) comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

acquiring, e.g., directly or indirectly acquiring, a value for the SMC status of the subject, wherein said value comprises a measure of the presence or absence of SMC in a sample from the subject, and

wherein the presence of SMC is indicative that said subject is likely to be a responder to the therapy, or said subject will respond, or will likely respond, to the therapy,

thereby selecting the therapy.

167. A method of evaluating a subject having an endogenous open reading frame (ORF) comprising a codon having a first sequence, comprising:

acquiring, e.g., directly or indirectly acquiring, a value for the status of the codon having the first sequence in the subject, wherein said value comprises a measure of the presence or absence of the codon having the first sequence in a sample from the subject; and

identifying the subject as having a codon having the first sequence,

thereby evaluating the subject.

168. A method of evaluating a subject having an endogenous open reading frame (ORF) comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

acquiring, e.g., directly or indirectly acquiring, a value for the SMC status of the subject, wherein said value comprises a measure of the presence or absence of SMC in a sample from the subject; and

identifying the subject as having a SMC,

thereby evaluating the subject.

169. The method of any one of embodiments 126-168, wherein the TREM, TREM core fragment or TREM fragment does not comprise an anticodon that pairs with a stop codon.

170. The method of any one of embodiments 126-169, wherein: (a) the ORF codon having the first sequence; or (b) the SMC; is other than a stop codon, e.g., TAA, TGA or TAG.

171. The method of any one of embodiments 126-170, wherein the TREM, TREM core fragment or TREM fragment comprises a canonical anti-codon/charging site combination.

172. The method of any one of embodiments 126-171, wherein: (a) the ORF codon having the first sequence; or (b) the SMC; has a mutation, e.g., a SNP, in the first position of said codon.

173. The method of any one of embodiments 126-171, wherein: (a) the ORF codon having the first sequence; or (b) the SMC; has a mutation, e.g., a SNP, in the second position of said codon.

174. The method of any one of embodiments 126-171, wherein: (a) the ORF codon having the first sequence; or (b) the SMC; has a mutation, e.g., a SNP, in the third position of said codon.

175. The method of any one of embodiments 126-174, wherein the first tRNA moiety comprises an endogenous tRNA, and the second tRNA moiety comprises an endogenous tRNA, e.g., wherein the cell or subject has not been contacted with a composition comprising a TREM.

176. The method of any one of embodiments 126-174, wherein one of the first tRNA moiety and the second tRNA moiety comprises an endogenous tRNA and a TREM.

177. The method of any one of embodiments 126-176, wherein: (a) the ORF codon having the first sequence; or (b) the SMC; in the absence of contact with the composition comprising a TREM, is associated with a phenotype, e.g., an unwanted phenotype, e.g., a disorder or symptom, e.g., a disorder or symptom chosen from Table 1.

178. The method of embodiment 177, wherein the disorder or symptom is chosen from a disease group provided in Table 1, e.g., cardiovascular, dermatology, endocrine, immunology, neurology, oncology, ophthalmology, or respiratory.

179. A method of modulating a production parameter of an RNA, or a protein encoded by an RNA, in a target cell or tissue, comprising:

providing, *e.g.*, administering, to the target cell or tissue, or contacting the target cell or tissue with, an effective amount of a TREM composition comprising a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, which TREM, TREM core fragment or TREM fragment corresponds to a contextually-rare codon ("con-rare codon") of the RNA,

thereby modulating the production parameter of the RNA, or protein encoded by the RNA in the target cell or tissue.

180. The method of embodiment 179, wherein the target cell or tissue is obtained from a subject.

181. The method of embodiment 179, comprising administering the TREM composition to a subject.

182. The method of embodiment 181, comprising contacting the TREM composition with the target tissue or cell ex vivo.

183. The method of embodiment 182, comprising introducing the ex vivo-contacted target tissue or cell into a subject, *e.g.*, an allogeneic or autologous subject.

184. The method of any one of embodiments 179-183, wherein the target cell or tissue is a specific or selected target cell or tissue, *e.g.*, a cell or tissue type in a particular developmental stage; a cell or tissue type in a particular disease state; or a cell present in a particular extracellular milieu.

185. The method of any one of embodiments 179-184, wherein the production parameter comprises an expression parameter or a signaling parameter, *e.g.*, as described herein.

186. The method of any one of embodiments 179-185, wherein the production parameter of the RNA is modulated, *e.g.*, an RNA that can be translated into a polypeptide, *e.g.*, a messenger RNA.

187. The method of embodiment 186, wherein the production parameter of the RNA is increased or decreased.

188. The method of any one of embodiments 179-187, wherein the production parameter of the protein encoded by the RNA is modulated.

189. The method of embodiment 188, wherein the production parameter of the protein is increased.

190. The method of embodiment 188, wherein the production parameter of the protein is decreased.

191. A method of determining the presence of a nucleic acid sequence, *e.g.*, a DNA or RNA, having a contextually-rare codon ("con-rare codon nucleic acid sequence"), comprising:

acquiring knowledge of the presence of the con-rare codon nucleic acid sequence in a sample from a subject, *e.g.*, a target cell or tissue sample,

wherein responsive to the acquisition of knowledge of the presence of the con-rare codon nucleic acid sequence:

(1) the subject is classified as being a candidate to receive administration of an effective amount of a TREM composition comprising a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, which TREM, TREM core fragment or TREM fragment corresponds to a contextually-rare codon ("con-rare codon") of the nucleic acid sequence; or

(2) the subject is identified as likely to respond to a treatment comprising the TREM composition.

192. A method of treating a subject having a disease associated with a contextually-rare codon ("con-rare codon"), comprising:

acquiring knowledge of the presence of a nucleic acid sequence, *e.g.*, a DNA or RNA, having the con-rare codon ("con-rare codon nucleic acid sequence") in a target cell or tissue sample from the subject; and

administering to the subject an effective amount of a TREM composition comprising a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, which TREM, TREM core fragment or TREM fragment corresponds to the con-rare codon of the nucleic acid sequence,

thereby treating the disease in the subject.

193. A method of providing a tRNA effector molecule (TREM) to a subject, comprising:

providing, *e.g.*, administering, to the subject, an effective amount of a TREM composition comprising a TREM of any one of embodiments 1-8, the TREM core fragment of embodiment 22, or the TREM fragment of embodiment 37, which TREM, TREM core fragment or TREM fragment corresponds to a contextually-rare codon ("con-rare codon") for a nucleic acid sequence in a target cell or tissue in the subject,

thereby providing a TREM composition to the subject.

194. A method of manufacturing a tRNA effector molecule (TREM) composition comprising:

identifying a TREM corresponding to a contextually-rare (con-rare) codon;

combining the TREM with a component, *e.g.*, a carrier or excipient.

thereby manufacturing a TREM composition.

195. The method of any one of embodiments 179-194, wherein the method comprises acquiring a value for a con-rare codon in the nucleic acid sequence, *e.g.*, DNA or RNA, wherein the value is a function of one or more of the following factors, *e.g.*, by evaluating or determining one or more of the following factors:

(1) the sequence of the codon;

(2) the availability of a corresponding tRNA, *e.g.*, charged tRNA, for that con-rare codon in a target cell or tissue, *e.g.*, one or more iso-acceptor tRNA molecules;

(3) the expression profile (or proteomic properties) of the target cell or tissue (*e.g.*, the abundance of expression of other proteins which include the con-rare codon);

(4) the proportion of the tRNAs corresponding to the con-rare codon which are charged; and

(5) the iso-decoder isotype of the tRNA corresponding to the con-rare codon;

196. The method of embodiment 195, wherein (1) comprises determining the presence or absence of a con-rare codon.

197. The method of embodiment 196, wherein a determination of the availability of a tRNA comprises acquiring a measure of one, two, three or all of the following parameters:

(a) level of a tRNA corresponding to the con-rare codon ("con-rare codon tRNA") compared to a tRNA corresponding to a different codon;

(b) function, *e.g.*, polypeptide chain elongation function, of a con-rare codon tRNA compared to a tRNA corresponding to a different codon;

(c) modification, *e.g.*, aminoacylation or post-transcriptional modification, of a con-rare codon tRNA compared to a tRNA corresponding to a different codon; and/or

(d) sequence of a con-rare codon tRNA.

198. The method of embodiment 197, wherein a measure of availability (*e.g.*, level) of a con-rare codon tRNA comprises a measure of the con-rare codon tRNA that is charged, *e.g.*, aminoacylated, compared to: (1) the proportion of the con-rare codon tRNA that is not charged; or (2) the proportion of charged tRNA corresponding to a different codon.

199. The method of any one of embodiments 195-198, wherein responsive to said value, the target cell, or tissue, is identified as having a nucleic acid sequence having a con-rare codon ("con-rare codon nucleic acid sequence") or an RNA having a con-rare codon ("con-rare codon RNA").

200. The method of any one of embodiments 195-198, wherein responsive to said value, the RNA is identified as, an RNA having a con-rare codon.

201. The method of any one of embodiments 179-200, wherein the target cell or tissue is identified as having an RNA having a con-rare codon.

202. The method of any one of embodiments 179-201, wherein the nucleic acid sequence, *e.g.*, DNA or RNA, is identified as, a nucleic acid sequence having a con-rare codon ("con-rare codon nucleic acid sequence") or an RNA having a con-rare codon ("con-rare codon RNA").

203. The method of any one of embodiments 179-202, wherein the nucleic acid sequence (*e.g.*, DNA or RNA) is, or is identified as, a nucleic acid sequence (*e.g.*, DNA or RNA) having a plurality of con-rare codons.

204. The method of any one of embodiments 179-203, wherein the nucleic acid sequence (*e.g.*, DNA or RNA) is, or is identified as, a nucleic acid sequence (*e.g.*, DNA or RNA) having a plurality of occurrences of a con-rare codon.

205. The method of any one of embodiments 179-204, wherein the nucleic acid, *e.g.*, RNA is, or is identified as, a nucleic acid, *e.g.*, RNA, having a first tRNA which corresponds to a first con-rare codon; and an additional tRNA, *e.g.*, a second tRNA, which corresponds to a different, *e.g.*, a second, con-rare codon.

206. The method of any one of embodiments 179-205, wherein the nucleic acid sequence (*e.g.*, DNA or RNA) is, or is identified as, a nucleic acid sequence (*e.g.*, DNA or RNA), having multiple occurrences of the first tRNA which corresponds to a first con-rare codon.

207. The method of embodiment 205 or 206, wherein the nucleic acid sequence (*e.g.*, DNA or RNA) is, or is identified as, a nucleic acid sequence (*e.g.*, DNA or RNA) having multiple occurrences of the additional tRNA, *e.g.*, a second tRNA, which corresponds to a different, *e.g.*, a second, con-rare codon.

208. The method of any one of embodiments 179-207, wherein modulation of a production parameter of the con-rare codon RNA comprises increasing a production parameter, *e.g.*, an expression parameter or signaling parameter of the protein encoded by the con-rare codon RNA, *e.g.*, increasing the expression level of the protein encoded by the con-rare codon RNA.

209. The method of any one of embodiments 179-208, wherein modulation of a production parameter of the con-rare codon RNA comprises decreasing a production parameter, *e.g.*, an expression parameter or signaling parameter, of the protein encoded by the con-rare codon RNA, *e.g.*, decreasing the expression level of the protein encoded by the con-rare codon RNA.

210. The method of any one of embodiments 195-198, wherein a determination of the expression profile (or proteome codon count) of the target cell or tissue, comprises a measure of:

(a) the abundance (*e.g.*, expression) of proteins in a target cell or tissue; and

(b) a protein codon count for expressed proteins in a target cell or tissue.

211. The method of any one of embodiments 179-210, wherein the target cell or tissue is identified as comprising a con-rare-codon nucleic acid, *e.g.*, RNA.

212. The method of any one of embodiments 179-211, wherein, the con-rare codon meets a reference value for one or more of the following:

(1) the sequence of the codon;

(2) the availability of a corresponding tRNA, *e.g.*, charged tRNA, for that con-rare codon in a target cell or tissue, *e.g.*, one or more iso-acceptor tRNA molecules;

(3) the expression profile (or proteomic properties) of the target cell or tissue (*e.g.*, the abundance of expression of other proteins which include the con-rare codon);

(4) the proportion of the tRNAs corresponding to the con-rare codon which are charged; and

(5) the iso-decoder isotype of the tRNA corresponding to the con-rare codon;

213. The method of embodiment 212, wherein the con-rare-codon meets a reference value for two of (1)-(5).

214. The method of embodiment 212, wherein the con-rare-codon meets a reference value for three of (1)-(5).

215. The method of embodiment 212, wherein the con-rare-codon meets a reference value for four of (1)-(5).

216. The method of embodiment 212, wherein the con-rare-codon meets a reference value for all of (1)-(5).

217. The method of embodiment 212, wherein the con-rare-codon meets a reference value for (1).

218. The method of embodiment 212, wherein the con-rare-codon meets a reference value for (2).

219. The method of embodiment 212, wherein the con-rare-codon meets a reference value for (3).

220. The method of embodiment 212, wherein the con-rare-codon meets a reference value for (4).

221. The method of embodiment 212, wherein the con-rare-codon meets a reference value for (5).

222. The method of embodiment 212, wherein the reference value is a pre-determined or pre-selected reference value.

223. The method of embodiment 212, wherein the reference value is determined according to a method described herein.

224. The method of any of embodiments 179-223, wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the TREMs, TREM core fragments or TREM fragments in the TREM composition correspond to a con-rare codon.

225. The method of any one of embodiments 179-224, wherein the TREM composition comprises TREMs, TREM core fragments or TREM fragments that correspond to a plurality of con-rare codons.

226. The method of any of embodiments 179-225, wherein the TREM composition comprises: a first TREM which corresponds to a first con-rare codon; and an additional TREM which corresponds to a different con-rare codon.

227. The method of any of embodiments 179-226, wherein the TREM composition comprises: a first TREM which corresponds to a first con-rare codon; and a second TREM which corresponds to a second con-rare codon.

228. The method of any of embodiments 179-227, wherein the TREM composition comprises: a first TREM which corresponds to a first con-rare codon; a second TREM which corresponds to a second con-rare codon; and a third TREM which corresponds to a third con-rare codon.

229. The method of any of embodiments 179-228, wherein the TREM composition comprises: a first TREM which corresponds to a first con-rare codon; a second TREM which corresponds to a second con-rare codon; a third TREM which corresponds to a third con-rare codon; and a fourth TREM which corresponds to a fourth con-rare codon.

230. The method of any of embodiments 179-229, wherein the TREM composition comprises: a first TREM which corresponds to a first con-rare codon; a second TREM which corresponds to a second con-rare codon; a third TREM which corresponds to a third con-rare codon; a fourth TREM which corresponds to a fourth con-rare codon; and a fifth TREM which corresponds to a fifth con-rare codon.

231. The method of any one of embodiments 226-230, wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the TREMs in the TREM composition correspond to the first con-rare codon.

232. The method of any one of embodiments 226-231, wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the TREMs in the TREM composition correspond to the additional, *e.g.*, second, third, fourth or fifth, con-rare codon.

233. The method of any of embodiments 179-232, wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the TREMs in the composition are charged.

234. The method of any of embodiments 179-233, wherein the TREM composition comprises a first TREM which corresponds to a first con-rare codon and an additional TREM, *e.g.*, a second, third, fourth, or fifth TREM, which corresponds to a different, *e.g.*, second, third, fourth, or fifth, con-rare codon, and wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the first TREM in the composition is charged.

235. The method of embodiment 234, wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the additional TREM *e.g.*, second, third, fourth, or fifth TREM, in the composition is charged.

236. The method of any of embodiments 179-235, wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the TREMs in the preparation are of the same iso-decoder isotype.

237. The method of any one of embodiments 179-236, wherein the TREM composition comprises: a first TREM which corresponds to a first con-rare codon; and an additional TREM which corresponds to the first con-rare codon, *e.g.*, the first TREM and the additional TREM are of the same iso-decoder isotype.

238. The method of any one of embodiments 179-237, wherein the TREM composition comprises: a first TREM which corresponds to a first con-rare codon; and a second TREM which corresponds to the first con-rare codon, *e.g.*, the first TREM and the second TREM are of the same iso-decoder isotype.

239. The method of any one of embodiments 179-238, wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the TREMs in the TREM composition correspond to the first con-rare codon.

240. The method of any one of embodiments embodiments 179-239, wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the TREMs in the TREM composition correspond to the additional, *e.g.*, second or third, con-rare codon, *e.g.*, the first TREM and the additional TREM are of the same iso-decoder isotype.

241. The method of any one of embodiments 179-240, wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the TREMs in the composition are charged.

242. The method of any one of embodiments 179-241, wherein the TREM composition comprises a first TREM which corresponds to a first con-rare codon, and an additional TREM, *e.g.*, a second or third TREM, which corresponds to the first con-rare codon, and wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the first TREM in the composition is charged.

243. The method of embodiment 242, wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the additional TREM *e.g.*, second or third TREM, in the composition is charged.

244. The method of any one of embodiments embodiments 179-243, wherein the cell is a host cell.

245. The method of any one of embodiments embodiments 179-244, wherein the cell is a mammalian cell, *e.g.*, a human cell, a murine cell, or a rodent cell.

246. The method of any one of embodiments embodiments 179-245, wherein the cell is a non-mammalian cell, *e.g.*, a bacterial cell, an insect cell or a yeast cell.

247. The method of any one of embodiments embodiments 179-246, wherein the cell is a host cell chosen from: a HeLa cell, a HEK293T cell (*e.g.*, a Freestyle 293-F cell), a HT-1080 cell, a PER.C6 cell, a HKB-11 cell, a CAP cell, a HuH-7 cell, a BHK 21 cell, an MRC-S cell, a MDCK cell, a VERO cell, a WI-38 cell, or a Chinese Hamster Ovary (CHO) cell.

248. The method of any one of embodiments embodiments 179-247, wherein the cell comprises an exogenous nucleic acid sequence.

249. The method of any one of embodiments embodiments 179-248, wherein the cell is autologous to the exogenous nucleic acid sequence.

250. The method of any one of embodiments embodiments 179-249, wherein the cell is allogeneic to the exogenous nucleic acid sequence.

251. The method of any one of embodiments 248-250, wherein the exogenous nucleic acid sequence (*e.g.*, DNA or RNA) comprises a con-rare codon.

252. The method of any one of embodiments 248-251, wherein administration of a TREM composition corresponding to the con-rare codon to the cell, modulates a production parameter, *e.g.*, expression parameter or signaling parameter, of a product, *e.g.*, RNA or polypeptide, of the exogenous nucleic sequence.

253. The method of any one of embodiments 248-251, wherein administration of a TREM composition corresponding to the con-rare codon to the cell, increases a production parameter,

e.g., expression parameter or signaling parameter, of a product, *e.g.*, RNA or polypeptide, of the exogenous nucleic sequence.

254. The method of any one of embodiments 248-251, wherein administration of a TREM composition corresponding to the con-rare codon, to the cell decreases a production parameter, *e.g.*, expression parameter or signaling parameter, of a product, *e.g.*, RNA or polypeptide, of the exogenous nucleic sequence.

255. The method of any one of embodiments 179-254, wherein the modulation, increase or decrease in production parameter, is compared to an otherwise similar cell, which: (1) is not contacted with the TREM composition; (2) does not comprise an exogenous nucleic acid sequence; or (3) comprises an exogenous nucleic acid sequence which does not comprise a con-rare codon.

256. A method of modulating a production parameter of an RNA, or a protein encoded by the RNA, in a cell, comprising:

optionally, acquiring knowledge of the presence of an RNA having a contextually-rare codon ("con-rare codon RNA") in the cell,

providing to the cell an effective amount of a tRNA corresponding to the con-rare codon RNA,

thereby modulating the production parameter of the RNA, or the protein encoded by the RNA in the cell.

257. A method of modulating a production parameter of an RNA, or a protein encoded by an RNA, in a cell, comprising:

optionally, acquiring knowledge of the presence of an RNA having a contextually-rare codon ("con-rare codon RNA") in the cell,

modulating a culture parameter such that a production parameter of the RNA or protein encoded by the RNA is modulated.

258. The method of embodiment 256 or 257, wherein acquiring knowledge of the con-rare codon RNA comprises acquiring a value for a con-rare codon in the RNA, wherein the value is a function of one or more of the following factors, *e.g.*, by evaluating or determining one or more of the following factors:

(1) the sequence of the codon;

(2) the availability of a corresponding tRNA, *e.g.*, charged tRNA, for that con-rare codon in a target cell or tissue, *e.g.*, one or more iso-acceptor tRNA molecules;

(3) the expression profile (or proteomic properties) of the target cell or tissue (*e.g.*, the abundance of expression of other proteins which include the con-rare codon);

(4) the proportion of the tRNAs corresponding to the con-rare codon which are charged;

(5) the iso-decoder isotype of the tRNA corresponding to the con-rare codon;

259. The method of embodiment 257 or 258, wherein modulating a culture parameter comprises any one or all of the following:

(i) changing the amount of time a cell is cultured, *e.g.*, increasing or decreasing the time;

(ii) changing the density of cells in the culture, *e.g.*, increasing or decreasing the cell density;

(iii) changing a component of the culture, *e.g.*, adding or removing or changing the concentration of a media component, a nutrient, a supplement, a pH modulator;

(iv) culturing the cell with one or more additional components, *e.g.*, a cell or a purified cell component (*e.g.*, a tRNA), a cell lysate;

(v) changing the temperature at which the cell is cultured, *e.g.*, increasing or decreasing the temperature; or

(vi) changing the size of the vessel in which the cell is cultured in, *e.g.*, increasing or decreasing the size of the vessel.

260. The method of any of embodiments 256-259, wherein the cell is a host cell.

261. The method of any one of embodiments 256-260, wherein the cell is a mammalian cell, *e.g.*, a human cell, a murine cell, or a rodent cell.

262. The method of any one of embodiments 256-260, wherein the cell is a non-mammalian cell, *e.g.*, a bacterial cell, an insect cell or a yeast cell.

263. The method of any one of embodiments 256-261, wherein the cell is a host cell chosen from: a HeLa cell, a HEK293T cell (*e.g.*, a Freestyle 293-F cell), a HT-1080 cell, a PER.C6 cell, a HKB-11 cell, a CAP cell, a HuH-7 cell, a BHK 21 cell, an MRC-S cell, a MDCK cell, a VERO cell, a WI-38 cell, or a Chinese Hamster Ovary (CHO) cell.

264. The method of any one of embodiments 256-263, wherein the cell comprises an exogenous nucleic acid sequence.

265. The method of any one of embodiments 256-264, wherein the cell is autologous to the exogenous nucleic acid sequence.

266. The method of any one of embodiments 256-265, wherein the cell is allogeneic to the exogenous nucleic acid sequence.

267. The method of any one of embodiments 256-266, wherein the exogenous nucleic acid sequence comprises a con-rare codon.

EXAMPLES

The following examples are provided to further illustrate some embodiments of the present invention, but are not intended to limit the scope of the invention; it will be understood by their exemplary nature that other procedures, methodologies, or techniques known to those skilled in the art may alternatively be used.

Table of Contents for Examples

Example 1	Method of synthesizing guanosine 2'-O-MOE phosphoramidite
Example 2	Method of synthesizing 5,6 dihydrouridine

Example 3	Method of synthesizing a TREM via 5'-Silyl-2'-Orthoester (2'- ACE) Chemistry
Example 4	Method of synthesizing an arginine TREM having a 2'-*O*-MOE modification
Example 5	Method of synthesizing an arginine TREM having a pseudouridine and a 2'-*O*-MOE modification
Example 6	Method of synthesizing a glutamine TREM having a 5,6 dihydrouridine modification
Example 7	Method of synthesizing a glutamine TREM having a pseudouridine modification
Example 8	Quality control of synthesized TREM via Mass Spectrometry Analysis
Example 9	Quality control of synthesized TREM via anion-exchange HPLC
Example 10	Quality control of synthesized TREM via PAGE Purification and Analysis
Example 11	Deprotection of synthesized TREM

Con-rare codon identification	
Example 12	Quantitative tRNA profiling
Example 13	Quantification of protein expression levels across cell lines or tissue types
Example 14	Evaluation of contextual rarity and identification of contextually rare codons
Example 15	Identification of a nucleic acid sequence having con-rare codons (A)
Example 16	Identification of a nucleic acid sequence having con-rare codons (B)
Example 17	Exemplary nucleic acid sequence having con-rare codons
Example 18	Exemplary computational pipeline for codon modifying a nucleic acid sequence
Determining the effect of TREM administration on protein expression	
Example 19	Determining that administration of a TREM affects expression of a protein encoded by a nucleic acid sequence having a con-rare codon
Manufacturing and preparation of TREMs	
Example20	Manufacture of TREM in a mammalian production host cell, and use thereof to modulate a cellular function
Example 21	Manufacture of TREM in a mammalian production host cell, and use thereof to modulate a cellular function
Example 22	Manufacture of TREMs in modified mammalian production host cell expressing an oncogene
Example 23	Preparation of a TREM production host cell modified to inhibit a repressor of tRNA synthesis
Example 24	Manufacture of TREMs in modified mammalian production host cell overexpressing an oncogene and a tRNA modifying enzyme
Assays to analyze TREM activity	
Example 25	TREM translational activity assay
Production of TREMs	
Example 26	Production of a candidate TREM complementary to the con-rare codon through mammalian cell purification

Example 27	Production of a candidate TREM complementary to the con-rare codon through bacterial cell purification
Example 28	Production of a candidate TREM complementary to the con-rare codon through chemical synthesis
Example 29	Production of a candidate TREM complementary to the con-rare codon through in vitro transcription
Assays to analyze TREM activity	
Example 30	Assay for the activity of an uncharged TREM to modulate autophagy
Example 31	Assay for activity of a mischarged TREM (mTREM)
Identifying SMC-containing proteins that would benefit from TREM administration	
Example 32	Identification of disease-associated SMC that could be ameliorated by TREM modulation
Example 33	PNPL3A SMC
Example 34	TERT SMC
Example 35	ACHE SMC
Example 36	CFTR SMC
Example 37	MAP3K1 SMC
Production of TREMs	
Example 38	Production of a candidate TREM complementary to the SMC through mammalian cell purification
Example 39	Production of a candidate TREM complementary to the SMC through bacterial cell purification
Example 40	Production of a candidate TREM complementary to the SMC through chemical synthesis
Example 41	Production of a candidate TREM complementary to the SMC through in vitro transcription
Modulation of tRNA pool	
Example 42	Modulation of a tRNA pool through TREM administration to a cell
Example 43	Modulation of a tRNA pool through TREM administration to a cell using liposome

Example 44	Modulation of a tRNA pool through delivery of TREM-encoding plasmid to a cell
Example 45	Modulation of a tRNA pool through delivery of a TREM-encoding viral vector to a cell
Method of making a cell line with an SMC of interest to test effects of TREM administration	
Example 46	System to test the effects of TREM administration on an SMC containing ORF
Assays to test TREM administration effects on characteristics of SMC-containing protein	
Example 47	Evaluation of protein expression levels of SMC-containing ORF with administration of a TREM
Example 48	Modulation of translation rate of SMC-containing ORF with TREM administration
Example 49	Determining that modulation of a TREM complementary to the SMC changes the function of the protein derived from the SMC-containing ORF
Example 50	Determining that modulation of a TREM complementary to an SMC changes the localization of the protein derived from the SMC-containing ORF
Example 51	Determining that modulation of a TREM complementary to an SMC changes folding of the protein translated from the SMC-containing ORF
Example 52	Determining that modulation of a TREM complementary to an SMC alters the cellular phenotype resulting from translation of the SMC-containing ORF
Example 53	Modulation of TREM to ameliorate a disease state resulting from translation of the SMC-containing ORF

Example 1: Method of synthesizing guanosine 2'-O-MOE phosphoramidite

This example describes the synthesis of guanosine 2'-O-MOE phosphoramidite. Guanosine 2'-O-MOE phosphoramidite is prepared and purified according to previously published procedures (Wen K. et al. (2002) *The Journal of Organic Chemistry*, 67(22), 7887–7889).

Briefly, guanosine and imidazole are dried by co-evaporation with pyridine, dissolved in dry DMF, and treated with bis(diisopropylchlorosilyl) methane added dropwise at 0 °C. The temperature is gradually increased to 25 °C and then held for 5 h. The reaction mixture is poured into ice water, and the precipitated white solid filtered to afford compound 1.

To a solution of compound 1, BrCH2CH2OCH3, and TBAI in DMF at -20 °C is added with sodium bis (trimethylsilyl)amide, and the mixture is stirred for 4 hours under argon. After the reaction is quenched with methanol, the THF is evaporated and the residue is precipitated in ice to furnish compound 2.

TBAF is added to a solution of compound 2 at 25 °C and then the mixture is stirred at 35 °C for 5 hours. The solvent is then evaporated under reduced pressure, and the residue is filtered in a short pad of silica gel using 10% methanol in dichloromethane to afford guanosine 2'-O-MOE phosphoramidite.

Example 2: Method of synthesizing a 5,6 dihydrouridine

This example describes the synthesis of 5,6 dihydrouridine. 5,6 dihydrouridine phosphoramidite is prepared and purified according to previously published procedures (Hanze AR et al., (1967) *Journal of the American Chemical Society*, 89(25), 6720–6725).

Briefly, oxygen is bubbled through a solution uridine in the presence of platinum black. The reaction is followed by spotting the reaction mixture on silica gel thin layer chromatographic plates and developing in methanol-chloroform (1:1). After 1 hour, the mixture is cooled and centrifuged and the clear liquid lyophilized to yield the 5,6 dihydrouridine product.

Example 3: Method of synthesizing a TREM via 5'-Silyl-2'-Orthoester (2'- ACE) Chemistry

This example describes the synthesis of a TREM via 5'-Silyl-2'-Orthoester (2'- ACE) Chemistry summarized from (Hartsel SA et al., (2005) *Oligonucleotide Synthesis*, 033–050).

Protected Ribonucleoside Monomers

5'-O-silyl-2'-O-ACE protected phosphoramidites are prepared and purified according to previously published procedures (Hartsel SA et al., (2005) *Oligonucleotide Synthesis*, 033–050). Briefly, monomer synthesis begins from standard base-protected ribonucleosides [rA(ibu),

rC(acetyl), rG(ibu) and U]. Orthogonal, 5'-silyl-2'-ACE protection and amidite preparation is then accomplished in five general steps:

1. Simultaneous transient protection of the 5'- and 3'-hydroxyl groups with 1,1,3,3tetraispropyldisiloxane (TIPS).
2. Regiospecific conversion of the 2'-hydroxyl to the 2'-O-orthoester using tris(acetoxyethyl)orthoformate (ACE orthoformate).
3. Removal of the 5',3'-TIPS protection.
4. Introduction of the 5'-O-silyl ether protecting group using benzhydryloxybis-(trimethylsilyloxy)-chlorosilane (BzH-Cl).
5. Phosphitylation of the 3'-OH with bis(N,N'-diisopropylamino)methoxyphosphine.

The fully protected, phosphitylated monomer is an oil. For ease of handling and dissolution, the phosphoramidite solution is evaporated to dryness in a tared flask to enable quantitation of yields. The phosphoramidite oil is then dissolved in anhydrous acetonitrile, distributed into synthesis vials in 1.0-mmol aliquots, and evaporated to dryness under vacuum in the presence of potassium hydroxide (KOH) and P2O5.

Synthesis of Oligoribonucleosides

Table 11

Synthesis Step	**Reagent**	**Delivery Time**	**Reaction Time**
Deblock	3% DCA in DCM	35	
Activator	0.5M S-ethyl-tetrazole	6	
Coupling	0.1M amidite8.0	30	
	0.5M S-ethyl-tetrazole	8	30
Repeat Coupling			
Oxidation	t-Butyl hydroperoxide	20	10
Repeat Oxidation Delivery			
Capping	1-methylimidazole and acetic anhydride	12	10
Desilylation	TEAHF	35	

5'-silyl-2'-ACE oligoribonucleotide synthesis begins with the appropriately modified 3'-terminal nucleoside attached through the 3'-hydroxyl to a polystyrene support. The solid support contained in an appropriate reaction cartridge is then placed on the appropriate column position on the instrument. A synthesis cycle is created using the delivery times and wait steps outlined in Table 11.

1. Initial detritylation: The first step in the synthesis cycle is the removal of the 5' O-DMT from the nucleoside-bound polystyrene support using 3% DCA in DCM.
2. Coupling: The 5-ethylthio-1H-tetrazole solution is delivered to the solid support, followed by simultaneous delivery of an equal quantity of activator and phosphoramidite solution. Depending on the desired sequence and synthesis scale, excess activator and activator plus amidite are alternately delivered repeatedly to increase coupling efficiency, which is typically in excess of 99% per coupling reaction. The 5-ethylthio-1H-tetrazole activates coupling by protonating the diisopropyl amine attached to the trivalent phosphorous. Nucleophilic attack of the 5-ethylthio-1H-tetrazole leads to the formation of the tetrazolide intermediate that reacts with the free 5'-OH of the support-bound nucleoside forming the internucleotide phosphite linkage.
3. Oxidation: In the next step of chain elongation, the phosphorous(III) linkage is oxidized for 10-20s to the more stable and ultimately desired P(V) linkage using t-butylhydroperoxide.
4. Capping: Although delivery of excess activator and phosphoramidite increases coupling efficiency, a small percentage of unreacted nucleoside may remain support-bound. To prevent the introduction of mixed sequences, the unreacted 5'-OH are "capped" or blocked by acetylating the primary hydroxyl. This acetylation is achieved through simultaneous delivery of 1-methylimidazole and acetic anhydride.
5. 5'-Desilylation: Before the next nucleoside in the sequence can be added to the growing oligonucleotide chain, the 5'-silyl group is removed with fluoride ion. This requires the delivery of triethylamine trihydrogenfluoride for 45 s. The desilylation is rapid and quantitative and no wait step is required.

Steps 2-5 are repeated for each subsequent nucleotide until the desired sequence is constructed.

Oligonucleotide Deprotection

A two-stage rapid deprotection strategy is employed to remove phosphate backbone protection, release the oligonucleotide from the solid support, and remove the exocyclic amine protecting groups on A, G, and C. The treatment also removes the acetyl moiety from the acetoxyethyl orthoester, resulting in the 2'-bis-hydroxyethyl protected intermediate that is now 10 times more labile to final acid deprotection. In the first deprotection step, S2Na2 is used to selectively remove the methyl protection from the internucleotide phosphate, leaving the oligoribonucleotide attached to the polystyrene support. This configuration allows any residual reagent to be thoroughly washed away before proceeding. Alternatively, a multicolumn, manifold approach can also be used.

1. A syringe barrel is attached to one of the two luer fittings on the synthesis column. 2 mL of the S2Na2 reagent is drawn into a second syringe and attached to the opposite side of the synthesis column. The S2Na2 reagent is gently pushed through the column and into the empty syringe barrel continuing back and forth several times. The column, filled with reagent is allowed to sit at room temperature for 10 min.
2. S2Na2 reagent is removed from the column. Using a clean syringe, the column is washed thoroughly with water. In the second deprotection step, 40% 1-methylamine in water is used to free the oligoribonucleotide from the solid support, deprotect the exocyclic base amines, and deacylate the 2'-orthoester leaving the deprotected species.

N-Methylamine Deprotection

1. The solid support resin is transferred from the column into a 4-mL vial
2. 2 mL 40% methylamine is added and heated for 12 min at 60°C.
3. The methylamine is removed and is transferred into a fresh vial.
4. The oligonucleotide solution is evaporated to dryness in a SpeedVac or similar device.

Oligonucleotide yields are measured using an ultraviolet (UV) spectrophotometer (absorbance at 260 nm).

Example 4: Method of synthesizing an arginine TREM having a 2'-*O*-MOE modification

This example describes the synthesis of an Arg TREM having one 2'-*O*-MOE modification. The 2'-*O*-MOE modification can be placed on a nucleotide on any domain or linker of the Arg TREM, or at any position in said domain or linker.

A 2'-ACE RNA oligoribonucleotide synthesis is performed on a modified Applied Biosystems 394 DNA/RNA synthesizer or similar instrument. 2'-*O*-MOE amidites are synthesized as in example 1. An oligonucleotide sequence: GGCUCCGUGGCGCAAUGGAUAGCGCAUUGGACUUCUAAUUCAAAGGUUCCGGGUU CG(A-MOE)GUCCCGGCGGAGUCG is synthesized following the protocol described in example 3. A similar method can be used to add a 2'-*O*-MOE modification on a TREM specifying any one of the other 19 amino acids.

Example 5: Method of synthesizing an arginine TREM having a pseudouridine and a 2'-*O*-MOE modification

This example describes the synthesis of an Arg TREM having a pseudouridine and 2'-*O*-MOE modification. The modification can be placed on a nucleotide on any domain or linker of the Arg TREM, or at any position in said domain or linker.

A 2'-ACE RNA oligoribonucleotide synthesis is performed on a modified Applied Biosystems 394 DNA/RNA synthesizer or similar instrument. 2'-*O*-MOE amidites are synthesized as in example 1. Pseudouridine (P) amidites are obtained from Glen Research or similar provider. An oligonucleotide sequence: GGCUCCGUGGCGCAAUGGAUAGCGCA**P**UGGACUUCUAAUUCAAAGGUUCCGGGUU CG(**A-MOE**)GUCCCGGCGGAGUCG is synthesized following the protocol described in example 3. A similar method can be used to add a pseudouridine and 2'-*O*-MOE modification on a TREM specifying any one of the other 19 amino acids.

Example 6: Method of synthesizing a glutamine TREM having a dihydrouridine modification

This example describes the synthesis of a Gln TREM having a dihydrouridine modification. The modification can be placed on a nucleotide on any domain or linker of the Gln TREM, or at any position in said domain or linker.

A 2'-ACE RNA oligoribonucleotide synthesis is performed on a modified Applied Biosystems 394 DNA/RNA synthesizer or similar instrument. Dihydrouridine (D) is synthesized as in example 2. An oligonucleotide sequence: GGUUCCAUGGUGUAAUGG**D**AAGCACUCUGGACUCTGAAUCCAGCGAUCCGAGUUC GAGUCUCGGUGGAACCUCCA is synthesized following the protocol described in example 3. A similar method can be used to add a dihydrouridine modification on a TREM specifying any one of the other 19 amino acids.

Example 7: Method of synthesizing a glutamine TREM having a pseudouridine modification

This example describes the synthesis of a Gln TREM having a pseudouridine modification. The modification can be placed on a nucleotide on any domain or linker of the Gln TREM, or at any position in said domain or linker.

A 2'-ACE RNA oligoribonucleotide synthesis is performed on a modified Applied Biosystems 394 DNA/RNA synthesizer or similar instrument. Pseudouridine (P) amidites are obtained from Glen Research or similar provider. An oligonucleotide sequence: GGUUCCAUGGUG**P**AAUGGUAAGCACUCUGGACUCTGAAUCCAGCGAUCCGAGUUC GAGUCUCGGUGGAACCUCCA is synthesized following the protocol described in example 3.

A similar method can be used to add a pseudouridine modification on a TREM specifying any one of the other 19 amino acids.

Example 8: Quality control of synthesized TREM via Mass Spectrometry Analysis

This example describes the quality control of a synthesized TREM via Mass Spectrometry Analysis.

Using the Perseptive Biosystems Voyager-DE BioSpectrometry Workstation, the referenced protocol for mass spectrometry analysis (4- Van Ausdall) is followed. Briefly, a 3-hydroxy picolinic acid matrix is used for sample crystallization. It is prepared by mixing (10:1:1) 3-HPA:picolinic acid:ammonium hydrogen citrate where each component is dissolved in 30% aqueous acetonitrile at a concentration of 50 mg/mL. One optical density unit (ODU) of oligonucleotide is dissolved in the matrix and heated at 55°C for 10 min. The sample is spotted on a MALDI plate, allowed to dry, and analyzed accordingly. This method allows confirmation

of oligonucleotide identity and detection of low-level impurities present in synthetic oligonucleotide samples.

Example 9: Quality control of synthesized TREM via anion-exchange HPLC

This example describes the quality control of a synthesized TREM via anion-exchange HPLC.

Using the Dionex DNA-Pac–PA-100 column, a gradient is employed using HPLC buffer A and HPLC buffer B. 0.5 ODUs of a sample that has been dissolved in H2O or Tris buffer, pH 7.5 is injected onto the gradient. The gradient employed is based on oligonucleotide length and can be applied according to Table 12. The parameters provided in Table 13 can be used to program a linear gradient on the HPLC analyzer.

Table 12: Oligonucleotide length and gradient percentages

Length (bases)	**Gradient (%B)**
0–5	0–30
6–10	10–40
11–16	20–50
17–32	30–60
33–50	40–70
>50	50–80

Table 13: Parameters for a linear gradient on HPLC analyzer

Time (min)	**Flow (mL/min)**	**% Buffer A**	**% Buffer B**
0	1.5	100	0
1	1.5	100	0
3	1.5	70a	30a
15	1.5	40a	60a
15.5	2.5	0	100
17	2.5	0	100

17.25	2.5	100	0
23	2.5	100	0
s23.1	1.5	100	0
24	1.5	100	0
25	0.1	100	0

Example 10: Quality control of synthesized TREM via PAGE Purification and Analysis

This example describes the quality control of a synthesized TREM via PAGE Purification and Analysis. Gel purification and analysis of 2'-ACE protected RNA follows standard protocols for denaturing PAGE (Ellington and Pollard (1998) *In Current Protocols in Molecular Biology*, Chanda, V). Briefly, the 2'-ACE protected oligo is resuspended in 200 mL of gel loading buffer. Invitrogen™ NuPAGE™ 4-12% Bis-Tris Gels or similar gel is prepared in gel apparatus. Samples are loaded and gel ran at 50-120 W, maintaining the apparatus at 40°C. When complete, the gel is exposed to ultraviolet (UV) light at 254 nm to visualize the purity of the RNA using UV shadowing. If necessary, the desired gel band is excised with a clean razor blade. The gel slice is crushed and 0.3M NaOAc elution buffer is added to the gel particles, and soaked overnight. The mixture is decanted and filtered through a Sephadex column such as Nap-10 or Nap-25.

Example 11: Deprotection of synthesized TREM

This example describes the deprotection of a TREM made according to an in vitro synthesis method, e.g., as described in Example 3. The 2'-protecting groups are removed using 100 mM acetic acid, pH 3.8. The formic acid and ethylene glycol byproducts are removed by incubating at 60°C for 30 min followed by lyophilization or SpeedVac-ing to dryness. After this final deprotection step, the oligonucleotides are ready for use.

Example 12: Quantitative tRNA Profiling

This Example describes the quantification of tRNA levels in a cell line or tissue type. Transfer RNA levels are determined using Oxford Nanopore direct RNA sequencing, as previously described in Sadaoka et al., *Nature Communications* (2019) 10, 754.

Briefly, cells transfected with a tRNA molecule are lysed and total RNA is purified using a method such as phenol chloroform. RNAs smaller than 200 nucleotides are separated from the lysate using a small RNA isolation kit per manufacturer's instructions, to generate a small RNA (sRNA) fraction.

The sRNA fraction is de-acylated using 100mM Tris-HCl (pH 9.0) at 37°C for 30 minutes. The solution is neutralized by the addition of an equal volume of 100mM Na-acetate/acetic acid (pH 4.8) and 100mM NaCl, followed by ethanol precipitation. Deacylated sRNA is dissolved in water, and its integrity verified by agarose gel electrophoresis. Deacylated sRNA is then polyadenylated using yeast poly(A) tailing kit per manufacturer's instructions to generate a sRNA polyadenylated pool. Following polyadenylation, a reverse transcription reaction is performed to generate cDNA using SuperScript III Reverse Transcriptase (Thermo Fisher Scientific) or a thermostable group II intron RT (TGIRT, InGex LLC) that is less sensitive to RNA structure and modifications. A sequencing adapter is ligated onto the cDNA mixture by incubating the cDNA mixture with RNA adapter, T4 ligase and ligation buffer following the standard protocol for Oxford Nanopore resulting in a cDNA library. Nanopore sequencing is then performed on the libraries and the sequences are mapped to a genomic database, in this example to the genomic tRNA database, GtRNAdb. The methods described in this example can be adopted for use to evaluate the tRNA pool across cell lines or tissue types.

Example 13: Quantification of protein expression levels across cell lines or tissue types

This Example describes the quantification of protein expression levels across cell lines or tissue types.

Cell culture/sample preparation

The protein expression levels are monitored using SILAC based mass-spectrometry proteomics, as previously described in Geiger et al., *Molecular and Cellular Proteomics* (2012) 10, 754.

Briefly, populations of cells are cultured either in media containing isotope-labeled amino acids, such as Lys8 (*e.g.*, 13C615N2-lysine) and Arg10 (*e.g.*, 13C615N4-arginine); or in media containing natural amino acids. The media is further supplemented with 10% dialyzed serum. Cell cultured in media containing isotope-labeled amino acids incorporate the isotope-labeled

amino acids into all of the proteins translated after incubation with said isotope-labeled amino acids. For example, all peptides containing a single arginine will be 6 Da heavier in cells cultured in the presence of instead of isotope-labeled amino acid compared to cells cultured with natural amino acids. Cultured are lysed and sonicated. Cell lysates (*e.g.*, about100 g) are diluted in 8 M urea in 0.1 M Tris-HCl followed by protein digestion with trypsin according to the FASP protocol (Wisniewski, J. R., et al. (2009) Universal sample preparation method for proteome analysis. *Nat. Methods* 6, 359 –362). After an overnight digestion, peptides are eluted from the filters with 25 mM ammonium bicarbonate buffer. From each sample, about 40 ug of peptides are separated into six fractions by strong anion exchange as described previously (Wisniewski, J. R., et al. (2009) Combination of FASP and StageTip-based fractionation allows in-depth analysis of the hippocampal membrane proteome. J. Proteome Res. 8, 5674 –5678).

Eluted peptides are concentrated and purified on C18 StageTips, *e.g.*, as described in Rappsilber *et al., Nature Protocols* (2007).

LC-MS/MS Analysis

Peptides are separated by reverse-phase chromatography using a nano-flow HPLC (Easy nanoLC, Thermo Fisher Scientific). The high performance liquid chromatography (HPLC) is coupled to an LTQ-Orbitrap Velos mass spectrometer (Thermo Fisher Scientific). Peptides are loaded onto the column with buffer A (0.5% acetic acid) and eluted with a 200 min linear gradient from 2 to 30% buffer B (80% acetonitrile, 0.5% acetic acid). After the gradient the column is washed with 90% buffer B and re-equilibrated with buffer A.

Mass spectra are acquired in a data-dependent manner, with an automatic switch between MS and MS/MS scans using a top 10 method. MS spectra are acquired in the Orbitrap analyzer, with a mass range of 300–1650 Th and a target value of 106 ions. Peptide fragmentation is performed with the HCD method and MS/MS spectra is acquired in the Orbitrap analyzer and with a target value of 40,000 ions. Ion selection threshold is set to 5000 counts. Two of the data sets are acquired with a high field Orbitrap cell in which the resolution is 60,000 instead of 30,000 (at 400 m/z) for the MS scans. In the first of the two replicates with the high field Orbitrap MS/MS scans are acquired with 15,000 resolution, and in the second with 7500 resolution, which is the same as in the standard Orbitrap, but with shorter transients.

Data Analysis

Raw MS files are analyzed by MaxQuant using standard metrics, *e.g.*, as described in Table 2 of Tyanova S et al. (2016) *Nat. Protocols* 11(12) pp.2301-19. Categorical annotation is supplied in the form of Gene Ontology (GO) biological process, molecular function, and cellular component, the TRANSFAC database as well as participation in a KEGG pathway and membership in a protein complex as defined by CORUM.

The methods described in this example can be adopted for use to evaluate the protein expression levels across cell lines or tissue types.

Example 14: Evaluation of contextual rarity and identification of contextually rare codons

This example describes the method used to determine components of contextual rarity (con-rarity). This method utilizes the cell line or tissue protein expression level determined by proteomics described in Example 13 or taken from literature. This method also utilizes the tRNA profile determined by Nanopore or other tRNA sequencing platform described in the Example 1 or taken from literature.

Codon count per nucleic acid sequence

Using the coding DNA sequence (CDS) defined using National Center for Biotechnology Information (NCBI https://www.ncbi.nlm.nih.gov/) or other database, the protein-coding sequence is segmented into codons and summed per codon to give a codon count per nucleic acid sequence for each codon encoded in the protein-coding sequence.

Normalized proteome codon count

The codon count per nucleic acid sequence is then multiplied by the corresponding cell line or tissue protein expression level determined by proteomics to give a cell type normalized proteome codon count across the cell line or tissue.

Con-rarity

Con-rarity is a function of normalized proteome codon count and the tRNA expression level. In an embodiment, the con-rarity is determined by dividing the normalized proteome codon count by the tRNA expression level determined by Nanopore or other tRNA sequencing

experiment. This provides a measure of codon usage that is contextually dependent on the tRNA profile, *e.g.*, tRNA abundance levels. A codon is determined to be contextually rare (con-rare) if the con-rarity meets a reference value, *e.g.*, a pre-determined or pre-selected reference value, *e.g.*, a threshold. In an embodiment, a codon is con-rare if the value of a normalized proteome codon count divided by the tRNA expression level for a particular tRNA meets a pre-determined reference. In an embodiment, the reference value is a value under *e.g.*, 1.5X sigma of the normally fit distribution to that codon frequency.

Example 15: Identification of a nucleic acid sequence having con-rare codons (A)

This Example describes the identification of a nucleic acid sequence having con-rare codons. Con-rare codons are identified as described in Example 14.

Codon count per nucleic acid sequence

Using the coding DNA sequences (CDS) defined using National Center for Biotechnology Information (NCBI https://www.ncbi.nlm.nih.gov/) or other database, all human gene sequences are segmented into codons and summed per codon to give a codon count per nucleic acid sequence, *e.g.*, gene.

Con-rare count per nucleic acid sequence

Each codon, per nucleic acid sequence, is classified as a con-rare codon or a con-abundant codon. The counts for all con-rare codons, for each nucleic acid sequence, are summed and normalized to the sequence length.

Determining a nucleic acid sequence having con-rare codons

The con-rare codon count is fit to a normalized distribution. A nucleic acid sequence that meets a reference value, *e.g.*, a pre-determined reference value, is classified as a nucleic acid sequence having con-rare codons. In an embodiment, a nucleic acid sequence is classified as having con-rare codons if it falls above a reference value, *e.g.*, in the upper 3sigma of the normalized distribution. In an embodiment, a nucleic acid sequence having con-rare codons can have one, two, or more (*e.g.*, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 50, 100, 200, 500) of the same con-rare codon or different con-rare codons.

Example 16: Identification of a nucleic acid sequence having con-rare codons (B)

This Example describes the identification of a nucleic acid sequence having con-rare codons. Con-rare codons are identified as described in the Example 14.

Codon count per nucleic acid sequence

Using the coding DNA sequences (CDS) defined using National Center for Biotechnology Information (NCBI https://www.ncbi.nlm.nih.gov/) or other database, all human gene sequences are segmented into codons and summed per codon to give a codon count per nucleic acid sequence, *e.g.*, gene.

Determining a nucleic acid sequence having con-rare codons

Each codon, per nucleic acid sequence, is classified as a con-rare codon or a con-abundant codon. For each con-rare codon, the counts per nucleic acid sequence is fit to a normalized distribution. A nucleic acid sequence that meets a reference value, *e.g.*, a pre-determined reference value, is classified as a nucleic acid sequence having con-rare codons. In an embodiment, a nucleic acid sequence is classified as having con-rare codons, *e.g.*, specified con-rare codons, if it falls *e.g.*, in the upper 3sigma of the normalized distribution. In an embodiment, a nucleic acid sequence having con-rare codons can have one, two, or more (*e.g.*, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 50, 100, 200, 500) of the same con-rare codon or different con-rare codons.

Example 17: Exemplary nucleic acid sequence having con-rare codons

This Example describes an exemplary nucleic acid sequence having con-rare codons.

The GRK2 nucleic acid sequence encodes the GRK2 protein (G-protein coupled receptor kinase 2). The method of Examples 4 or 5 was used to identify the GRK2 nucleic acid sequence as having con-rare codons. The GRK2 nucleic acid sequence has a coding sequence that has con-rare codons AAG and CTG. The AAG codon codes for lysine and the CTG codon codes for leucine. In an embodiment, under certain cellular conditions, the expression of the GRK2 protein can be affected by the frequency of tRNAs corresponding to one or more con-rare codons in the GRK2 nucleic acid sequence, *e.g.*, CUU-tRNA which corresponds to con-rare codon AAG, and/or CAG-tRNA which corresponds to con-rare codon CTG.

Example 18: Exemplary computational pipeline for codon modifying a nucleic acid sequence

This Example describes the computational pipeline that can be utilized to codon modify a nucleic acid sequence.

Mapping con-rare codons

Con-rarity (determined using the method described in Example 14) is read into the algorithm. Con-rare codons are identified as described in Example 14. For example, a codon is determined to be contextually rare (con-rare) if the con-rarity meets a reference value, *e.g.*, a pre-determined or pre-selected reference value, *e.g.*, a threshold. A corresponding contextually abundant (con-abundant) codon is identified as the most contextually frequent codon that encodes the same amino acid as the con-rare codon (*e.g.*, an isoacceptor or an isodecoder). In an embodiment, a con-rare codon can have more than one corresponding con-abundant codon. In an embodiment, the corresponding con-abundant codon can be utilized to replace a con-rare codon.

Con-rare codon modification

Each sequence to be modified is read in and segmented into codons. Each codon is then evaluated to determine if it is a con-rare codon. If the codon is identified as a con-rare codon, the codon is replaced, *e.g.*, with a corresponding con-abundant codon. A con-abundant codon is a codon other than a con-rare codon. This process can be repeated for two, three, four, or a portion of, or all of the con-rare codons found in the sequence. The resultant con-rare modified sequence (*e.g.*, also referred to as contextually modified nucleic acid sequence) is then outputted.

Example 19: Determining that administration of a TREM affects expression of a protein encoded by a nucleic acid sequence having a con-rare codon

This Example describes administration of a TREM to modulate expression levels of a protein encoded by a nucleic acid sequence having a con-rare codon in its coding sequence (CDS).

To create a system in which to study the effects of TREM administration on protein expression levels of a protein encoded by a nucleic acid sequence having a con-rare codon in its

CDS, the sequence for the GRK2 gene (GRK2- CCDS8156.1 sequence) is inserted into a plasmid. The plasmid is transfected in the normal human hepatocyte cell line THLE-3. A TREM is delivered to the CCDS8156.1 containing cells. As a control, a population of cells prior to the delivery of the TREM is set aside. In this example, the tRNA-Lys^{CUU} containing an CUU anticodon, that base pairs to the AAG codon, i.e. with the sequence GCCCGGCUAGCUCAGUCGGUAGAGCAUGGGACUCUUAAUCCCAGGGUCGUGGGUU CGAGCCCCACGUUGGGCG is used. A time course is performed ranging from 30 minutes to 6 hours with hour-long interval time points. At each time point, a population of cells that have been delivered the TREM, and a population of cells that have not been exposed to the TREM are trypsinized, washed and lysed. Cell lysates are analyzed by Western blotting and blots are probed with antibodies against the GRK2 protein. A total protein loading control, such as GAPDH, actin or tubulin, is also used.

The methods described in this example can be adopted to evaluate the expression levels of the GRK2 protein in cells endogenously expressing CCDS8156.1.

Example 20: Manufacture of TREM in a mammalian production host cell, and use thereof to modulate a cellular function

This example describes the manufacturing of a TREM produced in mammalian host cells.

Plasmid generation

To generate a plasmid comprising a TREM which comprises a tRNA gene, in this example, tRNAiMet, a DNA fragment containing the tRNA gene (chr6.tRNA-iMet(CAT) with genomic location 6p22.2 and sequence AGCAGAGTGGCGCAGCGGAAGCGTGCTGGGCCCATAACCCAGAGGTCGATGGATCG AAACCATCCTCTGCTA) is PCR-amplified from human genomic DNA using the following primer pairs: 5′-TGAGTTGGCAACCTGTGGTA and 5′-TTGGGTGTCCATGAAAATCA. This fragment is cloned into the pLKO.1 puro backbone plasmid with a U6 promoter (or any other RNA polymerase III recruiting promoter) following the manufacturer's instructions.

Transfection

1 mg of plasmid described above is used to transfect a 1L culture of suspension-adapted HEK293T cells (Freestyle 293-F cells) at 1 X 10^5 cells/mL. Cells are harvested at 24, 48, 72, or 96 hours post-transfection to determine the optimized timepoint for TREM expression as determined by Northern blot, or by quantitative PCR (q-PCR).

Purification

At the optimized harvest cell density point, the TREM is purified as previously described in Cayama et al., *Nucleic Acids Research.* 28 (12), e64 (2000). Briefly, short RNAs (*e.g.*, tRNAs) are recovered from cells by phenol extraction and concentrated by ethanol precipitation. The total tRNA in the precipitate is then separated from larger nucleic acids (including rRNA and DNA) under high salt conditions by a stepwise isopropanol precipitation. The elution fraction containing the TREM is further purified through probe binding. The TREM fraction is incubated with annealing buffer and the biotinylated capture probe corresponding to a DNA probe or a 2′-OMe nucleic acid that is complementary to a unique region of the TREM being purified, in this example, a probe conjugated to biotin at the 3′ end with the sequence UAGCAGAGGAUGGUUUCGAUCCAUCA, is used to purify the TREM comprising tRNA-Lys-UUU. The mixture is incubated at 90°C for 2-3 minutes and quickly cooled down to 45°C and incubated overnight at 45°C. The admixture is then incubated with binding buffer previously heated to 45°C and streptavidin-conjugated RNase-free magnetic beads for 3 hours to allow binding of the DNA-tRNA complexes to the beads. The mixture is then added to a pre-equilibrated column in a magnetic field separator rack and washed 4 times. The TREM retained on the beads are eluted three times by adding elution buffer pre-heated to 80°C and then admixed with a pharmaceutically acceptable excipient to make a test TREM product.

Use

One microgram of the test TREM preparation and a control agent are contacted by transfection, electroporation or liposomal delivery, with a cultured cell line, such as a HEP-3B or HEK293T, a tissue or a subject, for a time sufficient for the TREM preparation to modulate a translation level or activity of the cell, relative to the control agent.

Example 21: Manufacture of TREM in a mammalian production host cell, and use thereof to modulate a cellular function

This example describes the manufacturing of a TREM produced in mammalian host cells.

Plasmid generation

To generate a plasmid comprising a TREM which comprises a tRNA gene, in this example, tRNA-iMet-CAT, a DNA fragment containing at least one copy of the tRNA gene with the sequence AGCAGAGTGGCGCAGCGGAAGCGTGCTGGGCCCATAACCCAGAGGTCGATGGATCG AAACCATCCTCTGCTA is synthesized and cloned into the pLKO.1 puro backbone plasmid with a U6 promoter (or any other RNA polymerase III recruiting promoter) following the manufacturer's instructions and standard molecular cloning techniques.

Transfection

1 mg of plasmid described above is used to transfect a 1L culture of suspension-adapted HEK293T cells (Freestyle 293-F cells) at 1 X 10^5 cells/mL. Cells are harvested at 24, 48, 72, or 96 hours post-transfection to determine the optimized timepoint for TREM expression as determined by Northern blot, or by quantitative PCR (q-PCR) or Nanopore sequencing.

Purification

At the optimized harvest timepoint, the cells are lysed and separation from the lysate of RNAs smaller than 200 nucleotides is performed using a small RNA isolation kit per manufacturer's instructions, to generate a small RNA (sRNA) fraction.

To prepare the affinity purification reagents, streptavidin-conjugated RNase-free magnetic beads are incubated at room temperature for 30 min with 200 mM of biotinylated oligonucleotides corresponding to a DNA probe or a 2′-OMe nucleic acid that is complementary to a unique region of the TREM being purified. In this example, a probe with the sequence 5'biotin-TAGCAGAGGATGGTTTCGATCCATCA is used to purify the TREM comprising tRNA-iMet (CAT). The beads are washed and heated for 10 min at 75°C.

The sRNA fraction is heated for 10 min at 75°C and then mixed with the affinity purification reagent described above. The admixture is incubated at room temperature for 3 hours to allow binding of the TREMs to the bead-bound DNA probe in a sequence specific manner.

The beads are then washed until the absorbance of the wash solution at 260 nm is close to zero. Alternatively, the beads are washed three times and the final wash is examined by UV spectroscopy to measure the amount of nucleic acid present in the final wash. The TREM retained on the beads are eluted three times using RNase-free water which can be pre-heated to 80°C, and then admixed with a pharmaceutically acceptable excipient to make a test TREM product.

Use

One microgram of the test TREM preparation and a control agent are contacted by transfection, electroporation or liposomal delivery, with a cultured cell line, such as HeLa, HEP-3B or HEK293T, a tissue or a subject, for a time sufficient for the TREM preparation to modulate a translation level or activity of the cell, relative to the control agent.

Example 22: Manufacture of TREMs in modified mammalian production host cell expressing an oncogene

This example describes the manufacturing of a TREM in mammalian host cells modified to overexpress myc.

Plasmid generation and host cell modification

To make the production host cells for this example, HeLa cells (ATCC® CCL-2™) or HEP-3B cells (ATCC® HB-8064™) are transfected with a plasmid containing the gene sequence coding for the c-myc oncogene protein (*e.g.*, pcDNA3-cmyc (Addgene plasmid # 16011)) using routine molecular biology techniques. The resulting cell line is referred to herein as HeLamyc+ host cells or HEP-3Bmyc+ host cells.

Preparation of TREM expressing lentivirus

To prepare a TREM expressing lentivirus, HEK293T cells are co-transfected with 3 μg of each packaging vector (pRSV-Rev, pCMV-VSVG-G and pCgpV) and 9 μg of the plasmid comprising a TREM as described in Example 9, using Lipofectamine 2000 according to manufacturer's instructions. After 24 hours, the media is replaced with fresh antibiotic-free media and after 48 hours, virus-containing supernatant is collected and centrifuged for 10 min at 2000 rpm before being filtered through a 0.45 μm filter.

Transduction of host cells with TREM expressing lentivirus

2 mL of virus prepared as described above is used to transduce 100,000 HeLamyc+ host cells or HEP-3Bmyc+ host cells, in the presence of 8 μg/mL polybrene. Forty-eight hours after transduction, puromycin (at 2 μg/mL) antibiotic selection is performed for 2–7 days alongside a population of untransduced control cells.

The TREMs are isolated, purified, and formulated as described in Example 20 or 21 to result in a composition comprising a TREM or preparation comprising a TREM.

Example 23: Preparation of a TREM production host cell modified to inhibit a repressor of tRNA synthesis

This example describes the preparation of Hek293Maf-/TRM1 cells for the production of a TREM.

Maf1 is a repressor of tRNA synthesis. A Maf1 knockout HEK293T cell line is generated using standard CRISPR/Cas knockout techniques, *e.g.*, a CRISPR/Cas system can be designed to introduce a frameshift mutation in a coding exon of Maf1 to reduce the expression of Maf1 or knockout Maf1 expression, to generate a Hek293Maf- cell line that has reduced expression level and/or activity of Maf1. This cell line is then transfected with an expression plasmid for modifying enzyme Trm1 (tRNA (guanine26-N2)-dimethyltransferase) such as pCMV6-XL4-Trm1, and selected with a selection marker, *e.g.*, neomycin, to generate a stable cell line overexpressing Trm1 (Hek293Maf-/TRM1 cells).

Hek293Maf-/TRM1 cells can be used as production host cells for the preparation of a TREM as described in any of Examples 20-22.

Example 24: Manufacture of TREM in modified mammalian production host cell overexpressing an oncogene and a tRNA modifying enzyme

This Example describes the manufacturing of a TREM in mammalian host cells modified to overexpress Myc and Trm1.

Plasmid generation

In this example, a plasmid comprising a TREM is generated as described in Example 20 or 21.

Host cell modification, transduction and purification

A human cell line, such as HEK293T, stably overexpressing Myc oncogene is generated by transduction of retrovirus expressing the myc oncogene from the pBABEpuro-c-myc^{T58A} plasmid into HEK293T cells. To generate myc-expressing retrovirus, HEK293T cells are transfected using the calcium phosphate method with the human c-myc retroviral vector, pBABEpuro-c-myc^{T58A} and the packaging vector, ψ2 vector. After 6 hours, transfection media is removed and replaced with fresh media. After a 24-hour incubation, media is collected and filtered through a 0.45um filter. For the retroviral infection, HEK293T cells are infected with retrovirus and polybrene (8ug/ml) using spin infection at 18ºC for 1 hour at 2500 rpm. After 24 hours, the cell culture medium is replaced with fresh medium and 24 hours later, the cells are selected with 2 μg/mL puromycin. Once cells stably overexpressing the oncogene myc are established, they are transfected with a Trm1 plasmid, such as the pCMV6-XL4-Trm1 plasmid, and selected with a selection marker, in this case with neomycin, to generate a stable cell line overexpressing Trm1, in addition to Myc. In parallel, lentivirus to overexpress TREM is generated as described in Example 3 with HEK293T cells and PLKO.1-tRNA vectors.

1 x 10^5 cells overexpressing Myc and Trm1 are transduced with the TREM virus in the presence of 8 μg/mL polybrene. Media is replaced 24 hours later. Forty-eight hours after transduction, antibiotic selection is performed with 2 μg/mL puromycin for 2–7 days alongside a population of untransduced control cells. The TREMs are isolated, purified and formulated using the method described in Example 20 or 21 to produce a TREM preparation.

Example 25: TREM translational activity assays

This example describes assays to evaluate the ability of a TREM to be incorporated into a nascent polypeptide chain.

Translation of the FLAG-AA-His peptide sequence

A test TREM is assayed in an in-vitro translation reaction with an mRNA encoding the peptide FLAG-XXX-His6x, where XXX are 3 consecutive codons corresponding to the test TREM anticodon.

A tRNA-depleted rabbit reticulocyte lysate or human cell lysate (Jackson et al. 2001. RNA 7:765-773) is incubated 1 hour at 30°C with 10-25ug/mL of the test TREM in addition to 10-25ug/mL of the tRNAs required for the FLAG and His tag translation. A different mammalian lysate such as a HEK293T human cell-derived lysate can also be used in this assay. In this example, the TREM used is tRNA-Ile-GAT, therefore the peptide used is FLAG-LLL-His6x and the tRNAs added are tRNA-Ile-GAT, in addition to the following, which are added for translate the peptide FLAG and HIS tags: tRNA-Asp-GAC, tRNA-Tyr-TAC, tRNA-Lys-AAA, tRNA-Lys-AAAG, tRNA-Asp-GAT, tRNA-His-CAT. To determine if the test TREM is functionally able to be incorporated into a nascent peptide, an ELISA capture assay is performed. Briefly, an immobilized anti-His6X antibody is used to capture the FLAG-LLL-His6x peptide from the reaction mixture. The reaction mixture is then washed off and the peptide is detected with an enzyme-conjugated anti-FLAG antibody, which reacts to a substrate in the ELISA detection step. If the TREM produced is functional, the FLAG-LLL-His6 peptide is produced and detection occurs by the ELISA capture assay. The methods described in this example can be adopted for use to evaluate the functionality of the TREM.

Translational suppression assay

This assay describes a test TREM having translational adaptor molecule function by rescuing a suppression mutation and allowing the full protein to be translated. The test TREM, in this example tRNA-Ile-GAT, is produced such that it contains the sequence of the tRNA-Ile-GAT body but with the anticodon sequence corresponding to CUA instead of GAT. HeLa cells are co-transfected with 50 ng of TREM and with 200 ng of a DNA plasmid encoding a mutant GFP containing a UAG stop codon at the S29 position as described in Geslain et al. 2010. *J Mol Biol.* 396:821–831. HeLa cells transfected with the GFP plasmid alone serve as a negative control. After 24 hours, cells are collected and analyzed for fluorescence recovery by flow cytometry. The fluorescence is read out with an emission peak at 509nm (excitation at 395nm). The methods described in this example can be adopted for use to evaluate the functionality of the

TREM, or if the TREM can rescue the stop mutation in the GFP molecule and can produce the full-length fluorescent protein.

In vitro translational assay

This assay describes a test TREM having translational adaptor molecule function by successfully being incorporated into a nascent polypeptide chain in an *in vitro* translation reaction. First, a rabbit reticulocyte lysate that is depleted of the endogenous tRNA using an antisense or complimentary oligonucleotide which (i) targets the sequence between the anticodon and variable loop; or (ii) binds the region between the anticodon and variable loop is generated (see, *e.g.*, Cui et al. 2018. *Nucleic Acids Res.* 46(12):6387–6400). 10-25 ug/mL of the test TREM is added in addition to 2 ug/uL of a GFP-encoding mRNA to the depleted lysate. A non-depleted lysate with the GFP mRNA and with or without test TREM added are used as a positive control. A depleted lysate with the GFP mRNA but without the test TREM added is used as a negative control. The progress of GFP mRNA translation is monitored by fluorescence increase on a microplate reader at 37 °C for 3–5 h using $\lambda_{ex}485/\lambda_{em}528$. The methods described in this example can be adopted for use to evaluate if the test TREM can complement the depleted lysate and is thus likely functional.

Example 26: Production of a candidate TREM complementary to the con-rare codon through mammalian cell purification

This example describes the production of a TREM in mammalian host cells.

Plasmid generation

To generate a plasmid comprising a TREM which comprises a tRNA gene, in this example, tRNA-Ser-AGA, a DNA fragment containing at least one copy of the tRNA gene with the sequence GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTAGAAATCCATTGGGGTTTCCCCGCGCAGGTTCGAATCCTGCCGACTACG is synthesized and cloned into the pLKO.1 puro backbone plasmid with a U6 promoter (or any other RNA polymerase III recruiting promoter) following the manufacturer's instructions and standard molecular cloning techniques.

Transfection

One (1) mg of plasmid described above is used to transfect a 1L culture of suspension-adapted HEK293T cells (Freestyle 293-F cells) at 1 X 10^5 cells/mL. Cells are harvested at 24, 48, 72, or 96 hours post-transfection to determine the optimized timepoint for TREM expression as determined by a quantitative method such as Northern blot, quantitative PCR (q-PCR) or Nanopore sequencing.

Purification

At the optimized harvest timepoint, the cells are lysed, and total RNA is purified using a method such as phenol chloroform. RNAs smaller than 200 nucleotides are separated from the lysate using a small RNA isolation kit per manufacturer's instructions, to generate a small RNA (sRNA) fraction.

The sRNA fraction is incubated with annealing buffer and the biotinylated capture probe corresponding to a DNA probe that is complementary to a unique region of the TREM being purified, in this example, a probe with the sequence 3′ biotin-CCAATGGATTTCTATCCATCGCCTTAACCACTCGGCCACGACTACAAAA is used to purify the TREM comprising tRNA-Ser-AGA. The mixture is incubated at 90°C for 2-3 minutes and quickly cooled down to 45°C and incubated overnight at 45°C. The admixture is then incubated with binding buffer previously heated to 45°C and streptavidin-conjugated RNase-free magnetic beads for 3 hours to allow binding of the DNA-tRNA complexes to the beads. The mixture is then added to a pre-equilibrated column in a magnetic field separator rack and washed 4 times. The TREM retained on the beads are eluted three times by adding elution buffer pre-heated to 80°C and then admixed with a pharmaceutically acceptable excipient to make a test TREM product.

Example 27: Production of a candidate TREM complementary to a con-rare codon through bacterial cell purification

This example describes the production of a TREM in bacterial host cells.

Plasmid generation

To generate a plasmid to produce a TREM in bacteria, a tRNA gene, in this example, a DNA fragment containing at least one copy of the tRNA-Lys-UUU gene with the sequence GCCCGGATAGCTCAGTCGGTAGAGCATCAGACTTTTAATCTGAGGGTCCAGGGTTCA AGTCCCTGTTCGGGCG is synthesized and cloned into a bacterial tRNA expression vector as previously described in Ponchon et al., *Nat Protoc* 4, 947-959 (2009).

Transformation

1 X 10^9 bacteria grown from TREM expression plasmid transformed competent bacteria will be harvested at different cell density points, in this example OD(600)=0.5, OD(600)=0.7, OD(600)=0.9 to determine the optimal point of TREM expression as determined by a quantitative method such as Northern blot, quantitative PCR (q-PCR) or Nanopore sequencing.

Purification

At the optimized harvest cell density point, the TREM is purified as previously described in Cayama et al., *Nucleic Acids Research.* 28 (12), e64 (2000). Briefly, short RNAs (*e.g.*, tRNAs) are recovered from cells by phenol extraction and concentrated by ethanol precipitation. The total tRNA in the precipitate is then separated from larger nucleic acids (including rRNA and DNA) under high salt conditions by a stepwise isopropanol precipitation. The elution fraction containing the TREM is further purified through probe binding. The TREM fraction is incubated with annealing buffer and the biotinylated capture probe corresponding to a DNA probe that is complementary to a unique region of the TREM being purified, in this example, a probe conjugated to biotin at the 3′ end with the sequence CAGAUUAAAAGUCUG, is used to purify the TREM comprising tRNA-Lys-UUU. The mixture is incubated at 90°C for 2-3 minutes and quickly cooled down to 45°C and incubated overnight at 45°C. The admixture is then incubated with binding buffer previously heated to 45°C and streptavidin-conjugated RNase-free magnetic beads for 3 hours to allow binding of the DNA-tRNA complexes to the beads. The mixture is then added to a pre-equilibrated column in a magnetic field separator rack and washed 4 times. The TREM retained on the beads are eluted three times by adding elution buffer pre-heated to 80°C and then admixed with a pharmaceutically acceptable excipient to make a test TREM product.

Example 28: Production of a candidate TREM complementary to a con-rare codon through chemical synthesis

This example describes production of a TREM using chemical synthesis.

The TREM, in this example, tRNA-Thr-CGT, is chemically synthesized with the sequence GGCUCUAUGGCUUAGUUGGUUAAAGCGCCUGUCUCGUAAACAGGAGAUCCUGGGUUCGACUCCCAGUGGGGCCUCAA. This TREM is produced by solid-phase chemical synthesis using phosphoroamedite chemistry as previously described, for example as in Zlatev et. al. (2012) *Current Protocols,* 50 (1), 1.28.1–1.28.16. Briefly, protected RNA phorphoroamedites are sequentially added in a desired order to a growing chain immobilized on a solid support (*e.g.* controlled pore glass). Each cycle of addition has multiple steps, including: (i) deblocking the DMT group protecting the 5′-hydroxyl of the growing chain, (ii) coupling the growing chain to an incoming phosphoramidite building block, (iii) capping any chain molecules still featuring a 5′-hydroxyl, i.e. those that failed to couple with the desired incoming building block, and (iv) oxidation of the newly formed tricoordinated phosphite triester linkage. After the final building block has been coupled and oxidized, the chain is cleaved from the solid support and all protecting groups except for the DMT group protecting the 5′-hydroxyl are removed. The chain is then purified by RP-HPLC (*e.g.*, DMT-on purification) and the fraction containing the chain is subjected to deprotection of the DMT group under acidic conditions, affording the final TREM. The TREM will feature a 5′-phosphate and a 3′-OH. The TREM is then admixed with a pharmaceutically acceptable excipient to make a test TREM product.

If the TREM needs to be charged, the TREM produced by the chemical synthesis reaction is then aminoacylated in vitro using aminoacyl tRNA synthetase, as previously described in Stanley, *Methods Enzymol* 29:530–547 (1974). Briefly, the TREM is incubated for 30 min at 37 °C with its synthetase and its cognate amino, in this example, with threonyl-tRNA synthetase and threonine, respectively, and then phenol extracted, filtered using a Nuc-trap column, and ethanol precipitated. The TREM is then admixed with a pharmaceutically acceptable excipient to make a test TREM product.

Example 29: Production of a candidate TREM complementary to a con-rare codon through in vitro transcription

This example describes production of a TREM using in vitro transcription (IVT).

The TREM, in this example, tRNA-Leu-CAA, is produced using in vitro transcription with the sequence GUCAGGAUGGCCGAGUGGUCUAAGGCGCCAGACUCAAGUUCUGGUCUCCGUAUG GAGGCGUGGGUUCGAAUCCCACUUCUGACA as previously described in Pestova et al., *RNA* 7(10):1496-505 (2001). Briefly, a DNA plasmid containing a bacteriophage T7 promoter followed by the tRNA-Leu-CAA gene sequence is linearized and transcribed in vitro with T7 RNA polymerase at 37 °C for 45 min and then phenol extracted, filtered using a Nuc-trap column, and ethanol precipitated. The TREM is then admixed with a pharmaceutically acceptable excipient to make a test TREM product. Optionally, before admixing with a pharmaceutically acceptable excipient, the TREM is heated and cooled to refold the TREM.

If the TREM needs to be charged, the TREM produced by the IVT reaction is then aminoacylated in vitro using aminoacyl tRNA synthetase, as previously described in Stanley, *Methods Enzymol* 29:530–547 (1974). Briefly, the TREM is incubated for 30 min at 37 °C with its synthetase and its cognate amino, in this example, with leucyl-tRNA synthetase and leucine, respectively, and then phenol extracted, filtered using a Nuc-trap column, and ethanol precipitated. The TREM is then admixed with a pharmaceutically acceptable excipient to make a test TREM product.

Example 30: Assay for the activity of an uncharged TREM to modulate autophagy

This example describes an assay to test an uncharged TREM for ability to modulate, *e.g.*, induce, autophagy, *e.g.*, the ability to activate GCN2-dependent stress response (starvation) pathway signaling, inhibit mTOR or activate autophagy.

A test uncharged TREM (uTREM) preparation is delivered to HEK293T or HeLa cells through transfection or liposomal delivery. Once the uTREM is delivered, a time course is performed ranging from 30 minutes to 6 hours with hour-long interval time points. Cells are then trypsinized, washed and lysed. The same procedure is executed with a charged control TREM as well as random RNA oligos as controls. Cell lysates are analyzed by Western blotting and blots are probed with antibodies against known readouts of GCN2 pathway activation, mTOR

pathway inhibition or autophagy induction, including but not limited to phospho-eIF2a, ATF4, phospho-ULK1, phospho-4EBP1, phospho-eIF2a, phospho-Akt and phospho-p70S6K. A total protein loading control, such as GAPDH, actin or tubulin, as well as the non-modified (i.e. non-phosphorylated) signaling protein, i.e. using eIF2a as a control for phospho-eIF2a, are probed as loading controls. The methods described in this example can be adopted for use to evaluate activation of GCN2 starvation signaling pathway, autophagy pathway and/or inhibition of the mTOR pathway upon TREM delivery.

Example 31: Assay for activity of a mischarged TREM (mTREM)

This example describes an assay to test the functionality of a mTREM produced in a cell system using plasmid transfection followed by *in vitro* mischarging.

In this example, an mTREM can translate a mutant mRNA into a wild type (WT) protein by incorporation of the WT amino acid in the protein despite an mRNA containing a mutated codon. GFP mRNA molecules with either a T203I or E222G mutation, which prevent GFP excitation at the 470 nm and 390 nm wavelengths, respectively, are used for this example. GFP mutants which prevent GFP fluorescence could also be used as reporter proteins in this assay. Briefly, an *in vitro* translation assay is used, using a rabbit reticulocyte lysate containing the GFP E222G mutated mRNA (GAG→GGG mutation) and an excess of the mTREM, in this case tRNA-Glu-CCC. As a negative control, no mischarged TREM is added to the reaction. The methods described in this example can be adopted for use to evaluate the functionality of the mTREM.

Example 32: Identification of disease-associated SMC that could be ameliorated by TREM modulation

This example describes SMC-containing protein target selection for TREM-based therapy. SMCs can be understood as mutations that are informationally silent, they change the codon sequence to a synonymous codon but may have an effect on a translational or post-translational property. The selection method was segmented into three progressive selection steps (1) SMC identification, (2) examination of tRNA frequency and (3) annotation of disease relevance. These steps are described in further detail below.

SMC identification

A curated inclusive list of all known SNPs was utilized as a starting point for SMC selection. In this example, the dbSNP NCBI mutation database (https://www.ncbi.nlm.nih.gov/ and FTP site ftp://ftp.ncbi.nih.gov/snp/organisms/) was filtered to select for a SMC, also known as synonymous SNPs (i.e. single nucleotide changes in the coding sequence not causing a change in the amino acid). Briefly, the mutated sequences were aligned to the human genome (here GRCh38p7) and the SNPS were classified into variant and mutation types, such as: non-coding-variant or coding-variant; and synonymous or non-synonymous mutations. Those classified as coding variants with synonymous mutations were designated as SMCs and taken forward into the next selection.

Examination of tRNA frequency

For each SMC, the corresponding tRNA to each wildtype and mutated codon (SMC) was identified. The abundance of the tRNA for each of the wildtype and mutated codon (SMC) was determined from tRNA-sequencing data. In this example, the tRNA-seq previously determined from HEK293T cells (Zheng et al., N*ature Methods* 12, 835-837 (2015)) was utilized. SNPs that have differences, e.g., large differences, such as >10X change, in the tRNA abundance are prioritized into the next selection.

Determining disease relevance

SNP IDs were mapped to a collection of known disease associated SNPs to determine which SNPs have disease correlation. In this example we utilize the GWAS (Genome Wide Associate Studies) (https://www.ebi.ac.uk/gwas/) or a similar resource to determine which SNPs have known disease correlations. Those with therapeutically relevant disease correlations (e.g., oncogenic, or relevant to a neurological disorder) were taken forward to the next step.

Final selection

The filtered list of SMCs contains SMCs in coding regions that: (1) do not alter the coding sequence of an amino acid; (2) have difference, e.g., large difference, in tRNA population; and (3) have disease relevancy. In this example, the final selection is done based upon a disease of interest, e.g., pancreatic cancer. The BCAR1 gene is, e.g., known to be

associated with pancreatic cancer, and has a SNP (rs7190458) that causes a change from codon CUC to CUU. This coding sequence change results in a corresponding change in incorporated TREMs. In some embodiments, the mutated incorporated TREMs has, e.g., about a 100X fold decrease in abundance making it a potential target for upregulation and/or amelioration of the disease phenotype.

Example 33: PNPL3A SMC

The method of Example 32 was used to identify an SMC in the PNPL3A gene. The PNPL3A gene has a rs738408 polymorphism that was identified as a predisposing factor for nonalcoholic fatty liver disease, fibrosis and elevation of serum alanine transaminase in the human. The rs738408 polymorphism is a SMC as it is located in an ORF and changes the codon from CCC to CCU. Both the CCC and CCU codons code for the proline amino acid, resulting in an identical polypeptide sequence at that position of the chain as that of the wildtype PNPL3A ORF. This polypeptide chain is the adiponutrin protein.

Example 34: TERT SMC

The method of Example 32 was used to identify an SMC in the TERT gene. The TERT gene has a rs2736098 polymorphism that was identified as a susceptibility factor for pancreatic cancer and non-small cell lung carcinoma in the human. The rs2736098 polymorphism is a SMC as it is located in an ORF and changes the codon from GCG to GCA. Both the GCG and GCA codons code for the alanine amino acid, resulting in an identical polypeptide sequence at that position of the chain as that of the wildtype TERT ORF. This polypeptide chain is the telomerase reverse transcriptase protein.

Example 35: ACHE SMC

The method of Example 32 was used to identify an SMC in the ACHE gene. The ACHE gene has a rs7636 polymorphism that was identified as a susceptibility factor for Type 2 Diabetes in Asian populations. The rs7636 polymorphism is a SMC as it is located in an ORF and changes the codon from CCC to CCT. Both the CCC and CCT codons code for the proline amino acid, resulting in an identical polypeptide sequence at that position of the chain as that of the wildtype ACHE ORF. This polypeptide chain is the acetylcholinesterase (AChE) protein,

which is the primary enzyme responsible for the hydrolytic metabolism of the neurotransmitter acetylcholine (ACh) into choline and acetate.

Example 36: CFTR SMC

The method of Example 32 was used to identify an SMC in the CFTR gene. The CFTR gene has a rs1042077 polymorphism that is present in patients with CFTR-related disorders. The rs1042077 polymorphism is a SMC as it is located in an ORF and changes the codon from ACT to ACG. Both the ACT and ACG codons code for the threonine amino acid, resulting in an identical polypeptide sequence at that position of the chain as that of the wildtype CFTR ORF. This polypeptide chain is the cystic fibrosis transmembrane conductance regulator (CFTR).

Example 37: MAP3K1 SMC

The method of Example 32 was used to identify an SMC in the MAP3K1 gene. The MAP3K1 gene has a rs2229882 polymorphism that was identified as a susceptibility factor for the early onset of breast cancer. The rs2229882 polymorphism is a SMC as it is located in an ORF and changes the codon from ACC to ACT. Both the ACC and ACT codons code for the threonine amino acid, resulting in an identical polypeptide sequence at that position of the chain as that of the wildtype MAP3K1 ORF. This polypeptide chain is the Mitogen-Activated Protein Kinase Kinase Kinase 1 (MAP3K1), which is serine/threonine kinase that regulates the ERK and JNK MAPK pathways as well as the transcription factor NF-kappa-B pathway.

Example 38: Production of a candidate TREM complementary to the SMC through mammalian cell purification

This example describes the production of a TREM in mammalian host cells.

Plasmid generation

To generate a plasmid comprising a TREM which comprises a tRNA gene, in this example, tRNA-Ser-AGA, a DNA fragment containing at least one copy of the tRNA gene with the sequence GTAGTCGTGGCCGAGTGGTTAAGGCGATGGACTAGAAATCCATTGGGGTTTCCCCGCGCAGGTTCGAATCCTGCCGACTACG is synthesized and cloned into the pLKO.1 puro

backbone plasmid with a U6 promoter (or any other RNA polymerase III recruiting promoter) following the manufacturer's instructions and standard molecular cloning techniques.

Transfection

One (1) mg of plasmid described above is used to transfect a 1L culture of suspension-adapted HEK293T cells (Freestyle 293-F cells) at 1 X 10^5 cells/mL. Cells are harvested at 24, 48, 72, or 96 hours post-transfection to determine the optimized timepoint for TREM expression as determined by a quantitative method such as Northern blot, quantitative PCR (q-PCR) or Nanopore sequencing.

Purification

At the optimized harvest timepoint, the cells are lysed, and total RNA is purified using a method such as phenol chloroform. RNAs smaller than 200 nucleotides are separated from the lysate using a small RNA isolation kit per manufacturer's instructions, to generate a small RNA (sRNA) fraction.

The sRNA fraction is incubated with annealing buffer and the biotinylated capture probe corresponding to a DNA probe that is complementary to a unique region of the target TREM being purified, in this example, a probe with the sequence 3′ biotin-CCAATGGATTTCTATCCATCGCCTTAACCACTCGGCCACGACTACAAAA is used to purify the TREM comprising tRNA-Ser-AGA. The mixture is incubated at 90°C for 2-3 minutes and quickly cooled down to 45°C and incubated overnight at 45°C. The admixture is then incubated with binding buffer previously heated to 45°C and streptavidin-conjugated RNase-free magnetic beads for 3 hours to allow binding of the DNA-tRNA complexes to the beads. The mixture is then added to a pre-equilibrated column in a magnetic field separator rack and washed 4 times. The TREM retained on the beads are eluted three times by adding elution buffer pre-heated to 80°C and then admixed with a pharmaceutically acceptable excipient to make a test TREM product.

Example 39: Production of a candidate TREM complementary to the SMC through bacterial cell purification

This example describes the production of a TREM in bacterial host cells.

Plasmid generation

To generate a plasmid to produce a TREM in bacteria, a tRNA gene, in this example, a DNA fragment containing at least one copy of the tRNA-Lys-UUU gene with the sequence GCCCGGATAGCTCAGTCGGTAGAGCATCAGACTTTTAATCTGAGGGTCCAGGGTTCA AGTCCCTGTTCGGGCG is synthesized and cloned into a bacterial tRNA expression vector as previously described in Ponchon et al., *Nat Protoc* 4, 947-959 (2009).

Transformation

1 X 10^9 bacteria grown from TREM expression plasmid transformed competent bacteria will be harvested at different cell density points, in this example OD(600)=0.5, OD(600)=0.7, OD(600)=0.9 to determine the optimal point of TREM expression as determined by a quantitative method such as Northern blot, quantitative PCR (q-PCR) or Nanopore sequencing.

Purification

At the optimized harvest cell density point, the TREM is purified as previously described in Cayama et al., *Nucleic Acids Research.* 28 (12), e64 (2000). Briefly, short RNAs (e.g., tRNAs) are recovered from cells by phenol extraction and concentrated by ethanol precipitation. The total tRNA in the precipitate is then separated from larger nucleic acids (including rRNA and DNA) under high salt conditions by a stepwise isopropanol precipitation. The elution fraction containing the TREM is further purified through probe binding. The TREM fraction is incubated with annealing buffer and the biotinylated capture probe corresponding to a DNA probe that is complementary to a unique region of the target TREM being purified, in this example, a probe conjugated to biotin at the 3′ end with the sequence CAGAUUAAAAGUCUG, is used to purify the TREM comprising tRNA-Lys-UUU. The mixture is incubated at 90°C for 2-3 minutes and quickly cooled down to 45°C and incubated overnight at 45°C. The admixture is then incubated with binding buffer previously heated to 45°C and streptavidin-conjugated RNase-free magnetic beads for 3 hours to allow binding of the DNA-tRNA complexes to the beads. The mixture is

then added to a pre-equilibrated column in a magnetic field separator rack and washed 4 times. The TREM retained on the beads are eluted three times by adding elution buffer pre-heated to 80°C and then admixed with a pharmaceutically acceptable excipient to make a test TREM product.

Example 40: Production of a candidate TREM complementary to the SMC through chemical synthesis

This example describes production of a TREM using chemical synthesis.

The TREM, in this example, tRNA-Thr-CGT, is chemically synthesized with the sequence GGCUCUAUGGCUUAGUUGGUUAAAGCGCCUGUCUCGUAAACAGGAGAUCCUGGGUUCGACUCCCAGUGGGGCCUCAA. This TREM is produced by solid-phase chemical synthesis using phosphoroamedite chemistry as previously described, for example as in Zlatev et. al. (2012) *Current Protocols,* 50 (1), 1.28.1–1.28.16. Briefly, protected RNA phorphoroamedites are sequentially added in a desired order to a growing chain immobilized on a solid support (e.g. controlled pore glass). Each cycle of addition has multiple steps, including: (i) deblocking the DMT group protecting the 5′-hydroxyl of the growing chain, (ii) coupling the growing chain to an incoming phosphoramidite building block, (iii) capping any chain molecules still featuring a 5′-hydroxyl, i.e. those that failed to couple with the desired incoming building block, and (iv) oxidation of the newly formed tricoordinated phosphite triester linkage. After the final building block has been coupled and oxidized, the chain is cleaved from the solid support and all protecting groups except for the DMT group protecting the 5′-hydroxyl are removed. The chain is then purified by RP-HPLC (e.g., DMT-on purification) and the fraction containing the chain is subjected to deprotection of the DMT group under acidic conditions, affording the final TREM. The TREM will feature a 5′-phosphate and a 3′-OH. The TREM is then admixed with a pharmaceutically acceptable excipient to make a test TREM product.

If the TREM needs to be charged, the TREM produced by the chemical synthesis reaction is then aminoacylated in vitro using aminoacyl tRNA synthetase, as previously described in Stanley, *Methods Enzymol* 29:530–547 (1974). Briefly, the TREM is incubated for 30 min at 37 °C with its synthetase and its cognate amino, in this example, with threonyl-tRNA synthetase and threonine, respectively, and then phenol extracted, filtered using a Nuc-trap

column, and ethanol precipitated. The TREM is then admixed with a pharmaceutically acceptable excipient to make a test TREM product.

Example 41: Production of a candidate TREM complementary to the SMC through in vitro transcription

This example describes production of a TREM using in vitro transcription (IVT).

The TREM, in this example, tRNA-Leu-CAA, is produced using in vitro transcription with the sequence GUCAGGAUGGCCGAGUGGUCUAAGGCGCCAGACUCAAGUUCUGGUCUCCGUAUG GAGGCGUGGGUUCGAAUCCCACUUCUGACA as previously described in Pestova et al., *RNA* 7(10):1496-505 (2001). Briefly, a DNA plasmid containing a bacteriophage T7 promoter followed by the tRNA-Leu-CAA gene sequence is linearized and transcribed in vitro with T7 RNA polymerase at 37 °C for 45 min and then phenol extracted, filtered using a Nuc-trap column, and ethanol precipitated. The TREM is then admixed with a pharmaceutically acceptable excipient to make a test TREM product.

If the TREM needs to be charged, the TREM produced by the IVT reaction is then aminoacylated in vitro using aminoacyl tRNA synthetase, as previously described in Stanley, *Methods Enzymol* 29:530–547 (1974). Briefly, the TREM is incubated for 30 min at 37 °C with its synthetase and its cognate amino, in this example, with leucyl-tRNA synthetase and leucine, respectively, and then phenol extracted, filtered using a Nuc-trap column, and ethanol precipitated. The TREM is then admixed with a pharmaceutically acceptable excipient to make a test TREM product.

Example 42: Modulation of a tRNA pool through TREM administration to a cell

This example describes administration of a TREM to a cell to modulate tRNA pools in the cell.

TREMs produced as in Examples 38-41 are delivered to a cell through electroporation, as previously described in *Nature Methods* **3**, 67–68 (2006). Briefly, 10^6-10^7 cells, in this example the human epithelial MCF10A cells, are transferred in an electroporation cuvette and mixed gently after the addition of 1-30 ug of TREM, in this example tRNA-Thr-CGT with the sequence GGCUCUAUGGCUUAGUUGGUUAAAGCGCCUGUCUCGUAAACAGGAGAUCCUGGG

UUCGACUCCCAGUGGGGCCUCAA. The cuvette is transferred to the electroporator and the device is discharged (a voltage of 200-350V is used). Place cuvette on ice and transfer the electroporated cells to a culture dish with complete medium and transfer to an incubator for 24-48 hrs.

Once delivered, the change in tRNA pools can be quantified by methods such as Nanopore sequencing, tRNA-sequencing, Northern blotting or quantitative RT-PCR. In this example, the tRNA pool changes are monitored using Oxford Nanopore direct RNA sequencing, as previously described in Sadaoka et al., *Nature Communications* (2019) 10, 754.

Briefly, the TREM-transfected cells are lysed and total RNA is purified using a method such as phenol chloroform. RNAs smaller than 200 nucleotides are separated from the lysate using a small RNA isolation kit per manufacturer's instructions, to generate a small RNA (sRNA) fraction.

The sRNA fraction is de-acylated using 100mM Tris-HCl (pH 9.0) at 37°C for 30 minutes. The solution is neutralized by the addition of an equal volume of 100mM Na-acetate/acetic acid (pH 4.8) and 100mM NaCl, followed by ethanol precipitation. Deacylated sRNA is dissolved in water, and its integrity verified by agarose gel electrophoresis. Deacylated sRNA is then polyadenylated using yeast poly(A) tailing kit per manufacturer's instructions to generate a sRNA polyadenylated pool. Following polyadenylation, a reverse transcription reaction is performed to generate cDNA using SuperScript III Reverse Transcriptase (Thermo Fisher Scientific) or a thermostable group II intron RT (TGIRT, InGex LLC) that is less sensitive to RNA structure and modifications. A sequencing adapter is ligated onto the cDNA mixture by incubating the cDNA mixture with RNA adapter, T4 ligase and ligation buffer following the standard protocol for Oxford Nanopore. Nanopore sequencing is then performed on the libraries and the sequences are mapped to a genomic database, in this example to the genomic tRNA database, GtRNAdb. The methods described in this example can be adopted for use to evaluate the tRNA pool in the cells administered with a TREM compared to those not administered with a TREM.

Example 43: Modulation of a tRNA pool through TREM administration to a cell using liposome

This example describes administration of a TREM to a cell using liposome vesicles to modulate tRNA pools in the cell.

TREMs produced as in Examples 38-41 are delivered to a cell in a vesicle or other lipid-based carrier, such as liposomes or lipid nanoparticles. In this example, a liposome kit (from Sigma or other vendor) is used to prepare liposomes containing the TREM, in this example tRNA-Thr-CGT with the sequence GGCUCUAUGGCUUAGUUGGUUAAAGCGCCUGUCUCGUAAACAGGAGAUCCUGGG UUCGACUCCCAGUGGGGCCUCAA following manufacturer's directions. The human cell line, HEK293T, is used in this example. Cells are seeded to obtain 70-80% confluency the day of the transfection. The media is replaced 30 minutes prior to the transfection with serum-free media after which the liposomes are added to the cell media.

Once delivered, the change in tRNA pools can be quantified by methods such as Nanopore sequencing, tRNA-sequencing (Zheng et al., *Nature Methods* 12, 835-837 (2015)), Northern blotting or quantitative RT-PCR. In this example, the tRNA pool changes are monitored using tRNA-sequencing. Briefly, the TREM-transfected cells are lysed and total RNA is purified using a method such as phenol chloroform. RNAs smaller than 200 nucleotides are separated from the lysate using a small RNA isolation kit per manufacturer's instructions, to generate a small RNA (sRNA) fraction.

The sRNA fraction is treated with a demethylase mixture to remove m^1A, m^1G and m^3C modifications located at the Watson-Crick face. Following demethylation of the tRNA pool, a cDNA library is generated from the tRNAs using a thermostable group II intron RT (TGIRT) that is less sensitive to tRNA structure. This reverse transcriptase adds RNA-sequencing adaptors to the tRNAs by template-switching without requiring RNA ligation. Illumina sequencing is then performed on the libraries generated from the tRNAs and the sequencing reads are mapped to a genomic database, in this example to the genomic tRNA database, GtRNAdb. The methods described in this example can be adopted for use to evaluate the tRNA pool in the cells administered with a TREM compared to those not administered with a TREM.

Example 44: Modulation of a tRNA pool through delivery of TREM-encoding plasmid to a cell

This example describes delivery of TREM-encoding plasmid to a cell to modulate tRNA pools in the cell.

A TREM is expressed in cells through delivery of a TREM-encoding plasmid using a vesicle-based carrier. To express a TREM in human cells, a plasmid is created, which contains a tRNA gene, in this example, tRNA-Gly-GCC, with the sequence GCATTGGTGGTTCAGTGGTAGAATTCTCGCCTGCCACGCGGGAGGCCCGGGTTCGATTCCCGGCCAATGCA. The plasmid is generated using seamless assembly of DNA fragments, in this example using NEBuilder HiFi Assembly Master Mix, where a linearized mammalian expression vector of interest, in this example pLKO.1-puro-turboGFP linearized by PpuMI enzyme restriction, is fused with a DNA fragment that contains the tRNA gene. The DNA fragment in this example includes the following elements in 5′ to 3′ order: a 25 nucleotide-long sequence from the 3′ end of the vector linearization site, a U6 promoter, the tRNA sequence, a RNA polymerase III termination signal, a 25 nucleotide-long sequence from the 5′ end of the vector linearization site.

Once the plasmid is made, the human cell line, in this example HEK293T, is transfected with TREM-encoding plasmid, using Lipofactamine 3000 following manufacturer's directions. Once delivered, the change in tRNA pools can be quantified by methods such as Nanopore sequencing, tRNA-sequencing (Zheng et al., *Nature Methods* 12, 835-837 (2015)), Northern blotting or quantitative RT-PCR. In this example, the tRNA pool changes are monitored using tRNA-sequencing. Briefly, the TREM-transfected cells are lysed and total RNA is purified using a method such as phenol chloroform. RNAs smaller than 200 nucleotides are separated from the lysate using a small RNA isolation kit per manufacturer's instructions, to generate a small RNA (sRNA) fraction.

The sRNA fraction is treated with a demethylase mixture to remove m^1A, m^1G and m^3C modifications located at the Watson-Crick face. Following demethylation of the tRNA pool, a cDNA library is generated from the tRNAs using a thermostable group II intron RT (TGIRT) that is less sensitive to tRNA structure. This reverse transcriptase adds RNA-sequencing adaptors to the tRNAs by template-switching without requiring RNA ligation. Illumina sequencing is then performed on the libraries generated from the tRNAs and the sequencing reads are mapped to a

genomic database, in this example to the genomic tRNA database, GtRNAdb. The methods described in this example can be adopted for use to evaluate the tRNA pool in the cells administered with a TREM compared to those not administered with a TREM.

Example 45: Modulation of a tRNA pool through delivery of a TREM-encoding viral vector to a cell

This example describes delivery of a TREM-encoding viral vector to a cell to modulate tRNA pools in the cell.

A TREM is expressed in cells through delivery of a TREM-encoding viral vector. In this example, a lentivirus packaging and delivery system encoding a TREM is used. Briefly, the TREM-encoding viral vector is built by first generating a plasmid comprising a TREM, in this example, tRNA-Gly-GCC, with the sequence GCATTGGTGGTTCAGTGGTAGAATTCTCGCCTGCCACGCGGGAGGCCCGGGTTCGATTCCCGGCCAATGCA. The plasmid is generated using seamless assembly of DNA fragments where the pLKO.1-puro-turboGFP linearized vector is ligated to a DNA fragment containing the tRNA sequence as described in Example 25. To prepare a TREM expressing lentivirus, HEK293T cells are co-transfected with 3 μg of each packaging vector (pRSV-Rev, pCMV-VSVG-G and pCgpV) and 9 μg of the plasmid comprising a TREM, using Lipofectamine 3000 according to manufacturer's instructions. After 24 hours, the media is replaced with fresh antibiotic-free media and after 48 hours, virus-containing supernatant is collected and centrifuged for 10 min at 2000 rpm before being filtered through a 0.45 μm filter.

The cell of interest is then infected with the virus. In this example, 2 mL of virus prepared is used to transduce 100,000 HeLa cells, in the presence of 8 μg/mL polybrene. Forty-eight hours after transduction, puromycin (at 2 μg/mL) antibiotic selection is performed for 2–7 days alongside a population of untransduced control cells to select for cells that integrated the TREM in their genome for expression.

The change in tRNA pools can be quantified by methods such as Nanopore sequencing, tRNA-sequencing (Zheng et al., *Nature Methods* 12, 835-837 (2015)), Northern blotting or quantitative RT-PCR. In this example, the tRNA pool changes are monitored using quantitative RT-PCR (Korniy et al., Nucleic Acids Research (2019), gkz202). Briefly, the TREM-transfected cells are lysed and total RNA is purified using a method such as phenol chloroform. RNAs

smaller than 200 nucleotides are separated from the lysate using a small RNA isolation kit per manufacturer's instructions, to generate a small RNA (sRNA) fraction.

The sRNA fraction is treated with a demethylase mixture to remove m^1A, m^1G and m^3C modifications located at the Watson-Crick face. Following demethylation, the pool is reverse transcribed into cDNA using stem-loop adapters complimentary to the 3′-ends of the tRNAs of interest. In this step, reverse transcription (RT) is performed using the Superscript III first strand synthesis system (ThermoFisher Scientific). Quantitative PCR is then performed using the QuantiTect SYBR Green Kit (Qiagen) according to the manufacturer's protocol with forward primers complimentary to the region of cDNA encoded by the tRNAs of interest and a universal primer complimentary to the stem-loop adapter appended during RT. The methods described in this example can be adopted for use to evaluate the levels of glycine specifying molecule that can pair with the CGT codon in the cells administered with a TREM compared to those not administered with a TREM.

Example 46: System to test the effects of TREM administration on an SMC containing ORF

This example describes a system, in this example a cell line, that expresses an SMC-containing ORF to study the effects of TREM administration.

To study the effects of TREM administration on a SMC-containing ORF, in this example on the rs2229882 polymorphism of the MAP3K1 gene, an established cell line, in this example human breast epithelial cells, such as MCF10A or 184A1 cells, are genomically edited by CRISPR-Cas to knock out the expression of the endogenous gene of interest, in this example the MAP3K1 gene. MAP3K1 knockout cells were generated using the CRISPR-Cas9 system to insert 1bp in a coding exon of MAP3K1 to cause a frameshift mutation as previously described (for example, Bauer et al., *J. Vis. Exp.*, (95), doi:10.3791/52118 (2015)). Briefly, an online design tool that predicts the most effective guide RNA to use for genome editing, for example, https://portals.broadinstitute.org/gpp/public/analysis-tools/sgrna-design, is used to select a high-score guide RNA (gRNA) containing a 20-base pair (bp) target sequence that minimizes genomic matches to reduce the risk of off-target site cleavage. In this example, the targeting sequence is CAGTGTGTGAAGACGGCTGC. The targeting sequence is cloned into pSpCas9 (BB) plasmid (pX330) (Addgene plasmid ID 42230). HEK293T cells are transiently transfected

with the CRISPR/Cas9 construct targeting MAP3K1 and a puromycin expression construct for clone selection. The next day, cells are selected with puromycin for 2 days and subcloned to form single colonies. MAP3K1 KO clones are identified by PCR screen. The obtained clones are validated by qPCR and immunoblot using an antibody against MAP3K1.

Once created, this cell line is used to overexpress the WT or SMC-containing mRNA through transient plasmid transfection or through stable lentivirus transduction methods. The TREM of interest is then administered to each cell line and its effect on the SMC-containing ORF compared to the WT ORF is assessed using assays such as the ones described in Examples 25, 30 or 31.

Example 47: Evaluation of protein expression levels of SMC-containing ORF with administration of a TREM

This example describes administration of a TREM to alter expression levels of an SMC-containing ORF.

To create a system in which to study the effects of TREM administration on protein expression levels of an SMC-containing protein, in this example, from the PNPL3A gene coding for adiponutrin, a plasmid containing the PNPL3A rs738408 ORF sequence is transfected in the normal human hepatocyte cell line THLE-3, edited by CRISPR/Cas to contain a frameshift mutation in a coding exon of PNPLA3 to knock out endogenous PNPLA3 (THLE-3_PNPLA3KO cells). As a control, an aliquot of THLE-3_PNPLA3KO cells are transfected with a plasmid containing the wildtype PNPL3A ORF sequence.

Synthesis and preparation of TREM

An arginine TREM is synthesized as described in Examples **3-7** and quality control methods as described in Examples **8-10** are performed. To ensure proper folding, the TREM is heated at 85°C for 2 minutes and then snap cooled at 4°C for 5 minutes.

Evaluation of protein level of SMC-containing ORF

A TREM is delivered to the THLE-3_PNPLA3KO cells containing the rs738408 ORF sequence as well as to the THLE-3_PNPLA3KO cells containing the wildtype PNPL3A ORF sequence. In this example, the TREM contains a proline isoacceptor containing an AGG anticodon, that base pairs to the CCT codon, i.e. with the sequence

GGCUCGUUGGUCUAGGGGUAUGAUUCUCGCUUAGGGUGCGAGAGGUCCCGGGUU CAAAUCCCGGACGAGCCC. A time course is performed ranging from 30 minutes to 6 hours with hour-long interval time points. At each time point, cells are trypsinized, washed and lysed. Cell lysates are analyzed by Western blotting and blots are probed with antibodies against the adiponutrin protein. A total protein loading control, such as GAPDH, actin or tubulin, is also probed as a loading control.

The methods described in this example can be adopted for use to evaluate the expression levels of the adiponutrin protein in rs738408 ORF containing cells.

Example 48: Modulation of protein translation rate of SMC-containing ORF with TREM administration

This example describes administration of a TREM to alter the rate of protein translation of an SMC-containing ORF.

To monitor the effects of TREM addition on translation elongation rates, an in vitro translation system, in this example the RRL system from Promega, is used in which the fluorescence change over time of a reporter gene, in this example GFP, is a surrogate for translation rates.

Synthesis and preparation of TREM

An arginine TREM is synthesized as described in Examples **3-7** and quality control methods as described in Examples **8-10** are performed. To ensure proper folding, the TREM is heated at 85°C for 2 minutes and then snap cooled at 4°C for 5 minutes.

Evaluation of protein translation rate of SMC-containing ORF

First, a rabbit reticulocyte lysate that is depleted of the endogenous tRNA using an antisense oligonucleotide targeting the sequence between the anticodon and variable loop is generated (see, e.g., Cui et al. 2018. Nucleic Acids Res. 46(12):6387–6400). In this example, a TREM comprising an alanine isoacceptor containing an UGC anticodon, that base pairs to the GCA codon, i.e. with the sequence GGGGAUGUAGCUCAGUGGUAGAGCGCAUGCUUUGCAUGUAUGAGGUCCCGGGUU CGAUCCCCGGCAUCUCCA is added to the in vitro translation assay lysate in addition to 0.1-0.5 ug/uL of mRNA coding for the wildtype TERT ORF fused to the GFP ORF by a linker or an

mRNA coding for the rs2736098 TERT ORF fused to the GFP ORF by a linker. The progress of GFP mRNA translation is monitored by fluorescence increase on a microplate reader at 37 °C using $\lambda_{ex}485/\lambda_{em}528$ with data points collected every 30 seconds over a period of 1hour. The amount of fluorescence change over time is plotted to determine the rate of translation elongation of the wildtype ORF compared to the rs2736098 ORF with and without TREM addition. The methods described in this example can be adopted for use to evaluate the translation rate of the rs2736098 ORF and the wildtype ORF in the presence or absence of TREM.

Example 49: Determining that administration of a TREM affects protein expression levels of SMC-containing ORF

This example describes administration of a TREM to alter expression levels of an SMC-containing ORF.

To create a system in which to study the effects of TREM administration on protein expression levels of SMC-containing protein, in this example, from the PNPL3A gene coding for adiponutrin, a plasmid containing the PNPL3A rs738408 ORF sequence is transfected in the normal human hepatocyte cell line THLE-3, edited by CRISPR/Cas to contain a frameshift mutation in a coding exon of PNPLA3 to knock out endogenous PNPLA3 (THLE-3_PNPLA3KO cells). As a control, an aliquot of THLE-3_PNPLA3KO cells are transfected with a plasmid containing the wildtype PNPL3A ORF sequence.

A TREM is delivered to the THLE-3_PNPLA3KO cells containing the rs738408 ORF sequence as well as to the THLE-3_PNPLA3KO cells containing the wildtype PNPL3A ORF sequence. In this example, the TREM contains a proline isoacceptor containing an AGG anticodon, that base pairs to the CCT codon, i.e. with the sequence GGCUCGUUGGUCUAGGGGUAUGAUUCUCGCUUAGGGUGCGAGAGGUCCCGGGUUCAAAUCCCGGACGAGCCC. A time course is performed ranging from 30 minutes to 6 hours with hour-long interval time points. At each time point, cells are trypsinized, washed and lysed. Cell lysates are analyzed by Western blotting and blots are probed with antibodies against the adiponutrin protein. A total protein loading control, such as GAPDH, actin or tubulin, is also probed as a loading control.

The methods described in this example can be adopted for use to evaluate the expression levels of the adiponutrin protein in rs738408 ORF containing cells.

Example 50: TREM administration to change protein translation rate of SMC-containing ORF

This example describes administration of a TREM to alter the rate of protein translation of an SMC-containing ORF.

To monitor the effects of TREM addition on translation elongation rates, an in vitro translation system, in this example the RRL system from Promega, is used in which the fluorescence change over time of a reporter gene, in this example GFP, is a surrogate for translation rates. First, a rabbit reticulocyte lysate that is depleted of the endogenous tRNA using an antisense oligonucleotide targeting the sequence between the anticodon and variable loop is generated (see, e.g., Cui et al. 2018. Nucleic Acids Res. 46(12):6387–6400). In this example, a TREM comprising an alanine isoacceptor containing an UGC anticodon, that base pairs to the GCA codon, i.e. with the sequence GGGGAUGUAGCUCAGUGGUAGAGCGCAUGCUUUGCAUGUAUGAGGUCCCGGGUU CGAUCCCCGGCAUCUCCA is added to the in vitro translation assay lysate in addition to 0.1-0.5 ug/uL of mRNA coding for the wildtype TERT ORF fused to the GFP ORF by a linker or an mRNA coding for the rs2736098 TERT ORF fused to the GFP ORF by a linker. The progress of GFP mRNA translation is monitored by fluorescence increase on a microplate reader at 37 °C using $\lambda_{ex}485/\lambda_{em}528$ with data points collected every 30 seconds over a period of 1hour. The amount of fluorescence change over time is plotted to determine the rate of translation elongation of the wildtype ORF compared to the rs2736098 ORF with and without TREM addition. The methods described in this example can be adopted for use to evaluate the translation rate of the rs2736098 ORF and the wildtype ORF in the presence or absence of TREM.

Example 51: Determining that modulation of a TREM complementary to the SMC changes the function of the protein derived from the SMC-containing ORF

This example describes administration of a TREM to change the function of an SMC-containing ORF.

Using an in vitro translation (IVT) system (such as the RRL system from Promega), the wildtype and SMC containing mRNAs are translated in the presence and absence of a TREM. In this example the SMC-containing gene is AChE, coding for the acetylcholinesterase protein, and

the TREM contains a proline isoacceptor containing an AGG anticodon, that base pairs to the CCU codon, i.e. with the sequence GGCUCGUUGGUCUAGGGGUAUGAUCUCGCUUAGGGUGCGAGAGGUCCCGGGUUCAAAUCCCGGACGAGCCC.

To determine if addition of the TREM changes the functional activity of the SMC-containing protein, in this example the acetylcholinesterase protein, a functional assay that uses DTNB to quantify the thiocholine produced from the hydrolysis of acetylthiocholine by AChE is used. Briefly, the translation reactions are incubated at room temperature for 10-30 minutes with the kit AChE reaction mixture, after which the absorption intensity of DTNB adduct at OD 410 nm is used to measure the amount of thiocholine formed, which is proportional to the AChE activity. The methods described in this example can be adopted for use to evaluate AChE activity of the protein resulting from the translation of the rs7636 AChE mRNA or the wildtype AChE mRNA.

Example 52: Determining that modulation of a TREM complementary to an SMC changes the localization of the protein derived from the SMC-containing ORF

This example describes administration of a TREM to alter the localization of an SMC-containing ORF.

To create a system in which to study the effects of TREM administration on protein localization of an SMC-containing ORF, a plasmid containing the CFTR rs1042077 ORF sequence tagged with a reporter, such as GFP or myc, is transfected in the human lung epithelial cell line MRC-5. As a control, a plasmid containing the wildtype CFTR ORF sequence tagged with a reporter is also transfected in parallel in MRC-5 cells.

To determine if TREM addition changes the localization of CFTR, the cells are seeded on coverslips and 24 hours later are transfected with a TREM complementary to the CFTR SMC or a control TREM. In this example the TREM complementary to the CFTR SMC comprises a threonine isoacceptor containing an CGU anticodon, that base pairs to the ACG codon, i.e. with the sequence GGCUCUGUGGCUUAGUUGGCUAAAGCGCCUGUCUCGUAAACAGGAGAUCCUGGGUUCGAAUCCCAGCGGGGCCU. The control TREM consists of either a scrambled sequence or the threonine sequence where the 5′ end of the TREM has been changed to prevent charging.

After 24 hours, the cells are fixed, stained for CFTR and its reporter and visualized under a microscope. The methods described in this example can be adopted for use to evaluate the localization of wildtype CFTR and rs1042077 CFTR.

Example 53: Determining that modulation of a TREM complementary to an SMC changes folding of the protein translated from the SMC-containing ORF

This example describes administration of a TREM to alter the folding of an SMC-containing ORF.

Plasmid Generation and Transfection

To identify SMCs that result in protein misfolding, the SMC-ORF containing protein, in this example the rs7190458 BCAR1 ORF is synthesized and cloned into a plasmid containing a CMV promoter (or any other mammalian promoter) and a purification tag, in this example a FLAG tag (DYKDDDDK epitope), following the manufacturer's instructions and standard molecular cloning techniques. Here, the pFLAG-CMV-1 plasmid is used. The plasmid is transfected in the human HeLa cell line. A TREM, in this example comprising a leucine isoacceptor containing an UUG anticodon, that base pairs to the CUU codon, i.e. with the sequence GGUAGCGUGGCCGAGCGGUCUAAGGCGCUGGAUUAAGGCUCCAGUCUCUUCGGA GGCGUGGGUUCGAAUCCCACCGCUGCCA is also transfected into the HeLa cells. As a control, the BCAR1 KO cells are transfected with the SMC BCAR1 ORF containing plasmid alone and separately with a plasmid containing the wildtype BCAR1 ORF sequence.

Purification

At the optimized harvest timepoint, in this example 72 hours post-transfection, the cells are lysed, and centrifuged at 12,000 x g for 10 minutes. The supernatant is loaded under gravity flow onto a pre-packed and equilibrated anti-flag packed M2-agarose column. The column is washed with 10-20 column volumes of TBS (Tris HCl, NaCl) or with a salt containing buffer. To elute the FLAG-tagged protein from the beads, the beads are incubated with FLAG-tag peptide. The eluate is run on an SDS-PAGE gel for purity quality control. This purification is

performed on cells transfected with the WT BCAR1 ORF and the SMC BCAR1 ORF in the presence and absence of a TREM.

Initial examination of protein folding

To examine the effects of protein folding, the stability of the purified proteins derived from the WT and SMC containing ORFs are monitored using thermal melting. In this example, Differential Scanning Fluorimetry (DSF) with a fluorescent dye (Sypro Orange), which measures the changes of binding of the intercalator dye to the unfolding protein is used. Alterations in protein folding results in variations of the thermal melting curves. Using this methodology, the SMC ORF-derived protein with and without TREM addition is compared to the control wildtype BCAR1. The methods described in this example can be adopted for use to evaluate the thermal melting curve of proteins derived from SMC-containing ORFs.

Example 54: Determining that modulation of a TREM complementary to an SMC alters the cellular phenotype resulting from translation of the SMC-containing ORF

This example describes administration of a TREM to alter the cellular phenotype of an SMC-containing ORF.

To create a system in which to study the effects of TREM administration on cellular processes, in this example on cell migration, a plasmid containing the SMC-containing ORF, in this example the rs7190458 BCAR1 ORF sequence, is transfected in the human pancreatic cancer cell line PANC-1, in which BCAR1 has been knocked out using CRISPR/Cas. As a control, the PANC-1 BCAR1 KO cells are transfected with a plasmid containing the WT BCAR1 ORF sequence.

A TREM, in this example comprising a leucine isoacceptor containing an UUG anticodon, that base pairs to the CUU codon, i.e. with the sequence GGUAGCGUGGCCGAGCGGUCUAAGGCGCUGGAUUAAGGCUCCAGUCUCUUCGGA GGCGUGGGUUCGAAUCCCACCGCUGCCA is delivered to the PANC-1 cells. Delivery of a control TREM containing either a scrambled sequence or the leucine sequence where the 5′ end of the TREM has been changed to prevent charging are used as a control. The cells are grown to 80% confluency in a monolayer and scratched with a new 1 ml pipette tip across the center of the

well. The cells are rinsed twice to remove floating cells and the media is replenished. After 48 hours, the cells are fixed and stained with crystal violet. The stained monolayer is photographed, and the gap distance quantified. The methods described in this example can be adopted for use to evaluate the migratory phenotype of cells administered a TREM.

Example 55: Modulation of TREM to ameliorate a disease state resulting from translation of the SMC-containing ORF.

This example describes increasing TREM levels to ameliorate a disease state resulting from an SMC-containing ORF.

To create a system in which to study the effects of TREM administration on disease state, in this example on breast cancer onset, a plasmid containing the SMC-containing ORF, in this example the rs2229882 MAP3K1 ORF sequence, is transfected in the human non-transformed breast cell line MCF10A, in which MAP3K1 has been knocked out using CRISPR/Cas. As a control, the MCF10A MAP3K1 KO cells are transfected with a plasmid containing the wildtype MAP3K1 ORF sequence.

A TREM, in this example comprising a threonine isoacceptor containing an AGU anticodon, that base pairs to the ACU codon, i.e. with the sequence GGCGCCGUGGCUUAGUUGGUUAAAGCGCCUGUCUAGUAAACAGGAGAUCCUGGGUUCGAAUCCCAGCGGUGCCU is delivered to the MCF10A cells. Delivery of a control TREM containing either a scrambled sequence or the threonine sequence where the 5′ end of the TREM has been changed to prevent charging are used as a control. The cells are monitored for increased MAPK signaling by Western blotting using antibodies against the phosphorylation state of the ERK and JNK kinases. A total protein loading control, such as GAPDH, actin or tubulin, as well as the non-modified (i.e. non-phosphorylated) signaling protein, i.e. using ERK as a control for phospho-ERK, are probed as loading controls. The cells are also monitored for cell proliferation and invasion using standard proliferation and transwell invasion assays. To monitor breast cancer progression, the cells are injected subcutaneously or in the mammary fat pad of SCID mice and tumor volume is monitored daily using calipers to measure the length, width and height of the tumor(s). The methods described in this example can be adopted for use to evaluate tumor phenotype.

What is claimed is:

1. A method of evaluating a tRNA pool in a cell or subject comprising an endogenous open reading frame (ORF), which ORF comprises a codon having a first sequence, comprising acquiring, e.g., directly or indirectly acquiring, knowledge of the abundance of one or both of (i) and (ii), e.g., acquiring knowledge of the relative amounts of (i) and (ii) in the cell or subject wherein:

(i) is a tRNA moiety having an anticodon that pairs with the codon of the ORF having a first sequence (the first tRNA moiety); and

(ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the codon having the first sequence (the second tRNA moiety) in the cell or subject,

thereby evaluating the tRNA pool in the cell or subject.

2. The method of claim 1, comprising acquiring knowledge of (i).

3. The method of claim 1, comprising acquiring knowledge of (ii).

4. The method of claim 1, comprising acquiring knowledge of (i) and (ii).

5. The method of any one of claims 1-4, wherein:

acquiring knowledge of (i) comprises acquiring a value for the abundance, e.g., relative amount, of (i); and/or

acquiring knowledge of (ii) comprises acquiring a value for the abundance, e.g., relative amount, of (ii).

6. The method of claim 5, wherein responsive to said value, the method comprises administering a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, wherein the TREM, TREM core fragment or TREM fragment has an anticodon that pairs with: (a) the codon having the first sequence; or (b) the codon other than the codon having the first sequence, in an amount and for a time sufficient to modulate the relative amounts of the first tRNA moiety and the second tRNA moiety.

7. A method of modulating a tRNA pool in a cell comprising an endogenous open reading frame (ORF), which ORF comprises a codon having a first sequence, comprising:

optionally, acquiring knowledge of the abundance of one or both of (i) and (ii), e.g., acquiring knowledge of the relative amounts of: (i) and (ii) in the cell, wherein (i) is a tRNA moiety having an anticodon that pairs with the codon of the ORF having a first sequence (the first tRNA moiety) and (ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the codon having the first sequence (the second tRNA moiety) in the cell;

contacting the cell with a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, wherein the TREM, TREM core fragment or TREM fragment has an anticodon that pairs with: (a) the codon having the first sequence; or (b) the codon other than the codon having the first sequence, in an amount and/or for a time sufficient to modulate the relative amounts of the first tRNA moiety and the second tRNA moiety in the cell,

thereby modulating the tRNA pool in the cell.

8. The method of claim 7, wherein the TREM comprises an anticodon that pairs with (a).

9. The method of claim 7, wherein the TREM comprises an anticodon that pairs with (b).

10. A method of modulating a tRNA pool in a subject having an endogenous open reading frame (ORF), which ORF comprises a codon having a first sequence, comprising:

optionally, acquiring knowledge of the abundance of one or both of (i) and (ii), e.g., acquiring knowledge of the relative amounts of: (i) and (ii) in the subject, wherein (i) is a tRNA moiety having an anticodon that pairs with the codon of the ORF having a first sequence (the first tRNA moiety) and (ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the codon having the first sequence (the second tRNA moiety) in the subject;

contacting the subject with a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, wherein the TREM, TREM core fragment or TREM fragment has an anticodon that pairs with: (a) the codon having the first sequence; or (b) the codon other than the codon having the first sequence, in an amount and/or for a time

sufficient to modulate the relative amounts of the first tRNA moiety and the second tRNA moiety in the subject,

thereby modulating the tRNA pool in the subject.

11. The method of claim 10, wherein the TREM comprises an anticodon that pairs with (a).

12. The method of claim 10, wherein the TREM comprises an anticodon that pairs with (b).

13. The method of any one of claims 10-12, comprising acquiring knowledge of (i).

14. The method of any one of claims 10-12, comprising acquiring knowledge of (ii).

15. The method of any one of claims 10-12, comprising acquiring knowledge of (i) and (ii).

16. The method of any one of claims 13-15, wherein:

acquiring knowledge of (i) comprises acquiring a value for the abundance, e.g., relative amounts, of (i); and/or

acquiring knowledge of (ii) comprises acquiring a value for the abundance, e.g., relative amounts, of (ii).

17. The method of claim 16, wherein responsive to said value, the cell or subject is contacted with the TREM composition having an anticodon that pairs with (a) or (b).

18. A method of modulating a tRNA pool in a subject having an endogenous open reading frame (ORF) comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

providing a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, wherein the TREM, TREM core fragment or TREM fragment comprises an isoacceptor tRNA moiety comprising an anticodon sequence that pairs with the SMC (the TREM);

contacting the subject with the TREM composition in an amount and/or for a time sufficient to modulate the tRNA pool in the subject,

thereby modulating the tRNA pool in the subject.

19. A method of modulating a tRNA pool in a cell comprising an endogenous open reading frame (ORF) comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

providing a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, wherein the TREM, TREM core fragment or TREM fragment comprises an isoacceptor tRNA moiety comprising an anticodon sequence that pairs with the SMC (the TREM);

contacting the cell with the TREM composition in an amount and/or for a time sufficient to modulate the tRNA pool in the cell,

thereby modulating the tRNA pool in the cell.

20. The method of claim 19 or 18, comprising acquiring knowledge of the abundance of one or both of (i) and (ii) e.g., acquiring knowledge of the relative amounts of (i) and (ii) wherein (i) is a tRNA moiety having an anticodon that pairs with the SMC (the first tRNA moiety) and (ii) is an isoacceptor tRNA moiety having an anticodon that pairs with a codon other than the SMC (the second tRNA moiety), in the subject or cell.

21. The method of claim 20, comprising acquiring knowledge of (i).

22. The method of claim 20, comprising acquiring knowledge of (ii).

23. The method of claim 20, comprising acquiring knowledge of (i) and (ii).

24. The method of claim 20, wherein acquiring knowledge of (i) comprises acquiring a value for the abundance, e.g., relative amounts, of (i).

25. The method of claim 20, wherein acquiring knowledge of (ii) comprises acquiring a value for the abundance, e.g., relative amounts, of (ii).

26. The method of claim 24 or 25, wherein responsive to said value, the cell or subject is contacted with the TREM composition.

27. A method of treating a subject having an endogenous open reading frame (ORF) comprising a codon having a first sequence, wherein:

(i) acquiring, e.g., directly or indirectly acquiring, a value for the status of the codon having the first sequence in the subject, wherein said value comprises a measure of the presence or absence of the codon having the first sequence in a sample from the subject; and identifying the subject as having the codon having the first sequence; and

(ii) responsive to said value, administering a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, wherein the TREM, TREM core fragment or TREM fragment comprises an isoacceptor tRNA moiety having an anticodon that pairs with the codon having the first sequence, to the subject,

thereby treating the subject.

28. A method of treating a subject having an endogenous open reading frame (ORF) comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

(i) acquiring, e.g., directly or indirectly acquiring, a value for the SMC status of the subject, wherein said value comprises a measure of the presence or absence of SMC in a sample from the subject, and identifying the subject as having a SMC; and

(ii) responsive to said value, administering a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, wherein the TREM, TREM core fragment or TREM fragment comprises comprising an isoacceptor tRNA moiety having an anticodon that pairs with the SMC, to the subject,

thereby treating the subject.

29. A method of evaluating a subject having an endogenous open reading frame (ORF) comprising a codon having a first sequence, comprising:

acquiring, e.g., directly or indirectly acquiring, a value for the status of the codon having the first sequence in the subject, wherein said value comprises a measure of the presence or absence of the codon having the first sequence in a sample from the subject; and

identifying the subject as having a codon having the first sequence,

thereby evaluating the subject.

30. A method of evaluating a subject having an endogenous open reading frame (ORF) comprising a codon comprising a synonymous mutation (a synonymous mutation codon or SMC), comprising:

acquiring, e.g., directly or indirectly acquiring, a value for the SMC status of the subject, wherein said value comprises a measure of the presence or absence of SMC in a sample from the subject; and

identifying the subject as having a SMC,

thereby evaluating the subject.

31. The method of claim 29 or 30, wherein the TREM, TREM core fragment or TREM fragment does not comprise an anticodon that pairs with a stop codon.

32. The method of any one of claims 29-31, wherein: (a) the ORF codon having the first sequence; or (b) the SMC; is other than a stop codon, e.g., TAA, TGA or TAG.

33. The method of any one of claims 1-32, wherein: (a) the ORF codon having the first sequence; or (b) the SMC; in the absence of contact with the composition comprising a TREM, is associated with a phenotype, e.g., an unwanted phenotype, e.g., a disorder or symptom, e.g., a disorder or symptom chosen from Table 1 or Fig. 4.

34. The method of claim 32, wherein the disorder or symptom is chosen from a disease group provided in Table 1, e.g., cardiovascular, dermatology, endocrine, immunology, neurology, oncology, ophthalmology, or respiratory.

35. A method of modulating a production parameter of an RNA, or a protein encoded by an RNA, in a target cell or tissue, comprising:

providing, *e.g.*, administering, to the target cell or tissue, or contacting the target cell or tissue with, an effective amount of a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, which TREM, TREM core fragment or TREM fragment corresponds to a contextually-rare codon ("con-rare codon") of the RNA,

thereby modulating the production parameter of the RNA, or protein encoded by the RNA in the target cell or tissue.

36. The method of claim 35, wherein the target cell or tissue is obtained from a subject.

37. The method of claim 36, comprising administering the TREM composition to a subject.

38. The method of claim 37, comprising contacting the TREM composition with the target tissue or cell ex vivo.

39. The method of claim 38, comprising introducing the ex vivo-contacted target tissue or cell into a subject, *e.g.*, an allogeneic or autologous subject.

40. The method of any one of claims 35-39, wherein the target cell or tissue is a specific or selected target cell or tissue, *e.g.*, a cell or tissue type in a particular developmental stage; a cell or tissue type in a particular disease state; or a cell present in a particular extracellular milieu.

41. The method of any one of claims 35-40, wherein the production parameter comprises an expression parameter or a signaling parameter, *e.g.*, as described herein.

42. The method of any one of claims 35-41, wherein the production parameter of the RNA is modulated, *e.g.*, an RNA that can be translated into a polypeptide, *e.g.*, a messenger RNA.

43. The method of claim 42, wherein the production parameter of the RNA is increased or decreased.

44. The method of any one of claims 35-43, wherein the production parameter of the protein encoded by the RNA is modulated.

45. The method of claim 44, wherein the production parameter of the protein is increased.

46. The method of claim 45, wherein the production parameter of the protein is decreased.

47. A method of determining the presence of a nucleic acid sequence, *e.g.*, a DNA or RNA, having a contextually-rare codon ("con-rare codon nucleic acid sequence"), comprising:

acquiring knowledge of the presence of the con-rare codon nucleic acid sequence in a sample from a subject, *e.g.*, a target cell or tissue sample,

wherein responsive to the acquisition of knowledge of the presence of the con-rare codon nucleic acid sequence:

(1) the subject is classified as being a candidate to receive administration of an effective amount of a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, which TREM, TREM core fragment or TREM fragment corresponds to a contextually-rare codon ("con-rare codon") of the nucleic acid sequence; or

(2) the subject is identified as likely to respond to a treatment comprising the TREM composition.

48. A method of treating a subject having a disease associated with a contextually-rare codon ("con-rare codon"), comprising:

acquiring knowledge of the presence of a nucleic acid sequence, *e.g.*, a DNA or RNA, having the con-rare codon ("con-rare codon nucleic acid sequence") in a target cell or tissue sample from the subject; and

administering to the subject an effective amount of a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, which TREM, TREM

core fragment or TREM fragment corresponds to the con-rare codon of the nucleic acid sequence,

thereby treating the disease in the subject.

49. A method of providing a tRNA effector molecule (TREM) to a subject, comprising:

providing, *e.g.*, administering, to the subject, an effective amount of a TREM composition comprising a TREM, a TREM core fragment, or a TREM fragment described herein, which TREM, TREM core fragment or TREM fragment corresponds to a contextually-rare codon ("con-rare codon") for a nucleic acid sequence in a target cell or tissue in the subject,

thereby providing a TREM composition to the subject.

50. A method of manufacturing a tRNA effector molecule (TREM) composition comprising:

identifying a TREM corresponding to a contextually-rare (con-rare) codon;

combining the TREM with a component, *e.g.*, a carrier or excipient.

thereby manufacturing a TREM composition.

51. The method of any one of claims 35-50, wherein the method comprises acquiring a value for a con-rare codon in the nucleic acid sequence, *e.g.*, DNA or RNA, wherein the value is a function of one or more of the following factors, *e.g.*, by evaluating or determining one or more of the following factors:

(1) the sequence of the codon;

(2) the availability of a corresponding tRNA, *e.g.*, charged tRNA, for that con-rare codon in a target cell or tissue, *e.g.*, one or more iso-acceptor tRNA molecules;

(3) the expression profile (or proteomic properties) of the target cell or tissue (*e.g.*, the abundance of expression of other proteins which include the con-rare codon);

(4) the proportion of the tRNAs corresponding to the con-rare codon which are charged; and

(5) the iso-decoder isotype of the tRNA corresponding to the con-rare codon.

52. The method of claim 51, wherein (1) comprises determining the presence or absence of a con-rare codon.

53. The method of claim 52, wherein a determination of the availability of a tRNA comprises acquiring a measure of one, two, three or all of the following parameters:

(a) level of a tRNA corresponding to the con-rare codon ("con-rare codon tRNA") compared to a tRNA corresponding to a different codon;

(b) function, *e.g.*, polypeptide chain elongation function, of a con-rare codon tRNA compared to a tRNA corresponding to a different codon;

(c) modification, *e.g.*, aminoacylation or post-transcriptional modification, of a con-rare codon tRNA compared to a tRNA corresponding to a different codon; and/or

(d) sequence of a con-rare codon tRNA.

54. The method of claim 53, wherein a measure of availability (*e.g.*, level) of a con-rare codon tRNA comprises a measure of the con-rare codon tRNA that is charged, *e.g.*, aminoacylated, compared to: (1) the proportion of the con-rare codon tRNA that is not charged; or (2) the proportion of charged tRNA corresponding to a different codon.

55. The method of any one of claims 51-54, wherein responsive to said value, the target cell, or tissue, is identified as having a nucleic acid sequence having a con-rare codon ("con-rare codon nucleic acid sequence") or an RNA having a con-rare codon ("con-rare codon RNA").

56. The method of any one of claims 51-55, wherein responsive to said value, the RNA is identified as, an RNA having a con-rare codon.

57. The method of any one of claims 35-56, wherein modulation of a production parameter of the con-rare codon RNA comprises increasing a production parameter, *e.g.*, an expression parameter or signaling parameter of the protein encoded by the con-rare codon RNA, *e.g.*, increasing the expression level of the protein encoded by the con-rare codon RNA.

58. The method of any one of claims 35-57, wherein modulation of a production parameter of the con-rare codon RNA comprises decreasing a production parameter, *e.g.*, an expression parameter

or signaling parameter, of the protein encoded by the con-rare codon RNA, *e.g.*, decreasing the expression level of the protein encoded by the con-rare codon RNA.

59. The method of any one of claims 51-54, wherein a determination of the expression profile (or proteome codon count) of the target cell or tissue, comprises a measure of:

(a) the abundance (*e.g.*, expression) of proteins in a target cell or tissue; and

(b) a protein codon count for expressed proteins in a target cell or tissue.

60. The method of any one of claims 35-59, wherein the target cell or tissue is identified as comprising a con-rare-codon nucleic acid, *e.g.*, RNA.

61. The method of any one of claims 35-60, wherein the con-rare codon meets a reference value for one or more of the following:

(1) the sequence of the codon;

(2) the availability of a corresponding tRNA, *e.g.*, charged tRNA, for that con-rare codon in a target cell or tissue, *e.g.*, one or more iso-acceptor tRNA molecules;

(3) the expression profile (or proteomic properties) of the target cell or tissue (*e.g.*, the abundance of expression of other proteins which include the con-rare codon);

(4) the proportion of the tRNAs corresponding to the con-rare codon which are charged; and

(5) the iso-decoder isotype of the tRNA corresponding to the con-rare codon.

62. The method of any of claims 35-61, wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the TREMs, TREM core fragments or TREM fragments in the TREM composition correspond to a con-rare codon.

63. The method of any one of claims 35-62, wherein the TREM composition comprises TREMs, TREM core fragments or TREM fragments that correspond to a plurality of con-rare codons.

64. The method of any of claims 35-63, wherein the TREM composition comprises: a first TREM which corresponds to a first con-rare codon; and an additional TREM which corresponds to a different con-rare codon.

65. The method of any of claims 35-64, wherein the TREM composition comprises: a first TREM which corresponds to a first con-rare codon; and a second TREM which corresponds to a second con-rare codon.

66. The method of any of claims 35-65, wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the TREMs in the composition are charged.

67. The method of any of claims 35-66, wherein at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 95%, 99%, or 100% (by weight or number) of the TREMs in the composition are of the same iso-decoder isotype.

68. The method of any one of claims 35-67, wherein the cell is a host cell.

69. The method of any one of claims 35-68, wherein the cell is a host cell chosen from: a HeLa cell, a HEK293T cell (*e.g.*, a Freestyle 293-F cell), a HT-1080 cell, a PER.C6 cell, a HKB-11 cell, a CAP cell, a HuH-7 cell, a BHK 21 cell, an MRC-S cell, a MDCK cell, a VERO cell, a WI-38 cell, or a Chinese Hamster Ovary (CHO) cell.

70. The method of any one of claims 35-69, wherein the cell comprises an exogenous nucleic acid sequence.

71. The method of any one of claims 35-71, wherein the cell is autologous to the exogenous nucleic acid sequence.

72. The method of any one of claims 35-71, wherein the cell is allogeneic to the exogenous nucleic acid sequence.

73. The method of any one of claims 35-72, wherein the exogenous nucleic acid sequence (*e.g.*, DNA or RNA) comprises a con-rare codon.

74. The method of any one of claims 70-73, wherein administration of a TREM composition corresponding to the con-rare codon to the cell, modulates a production parameter, *e.g.*, expression parameter or signaling parameter, of a product, *e.g.*, RNA or polypeptide, of the exogenous nucleic sequence.

75. The method of any one of the preceding embodiments, wherein the TREM comprises a sequence of Formula A:

[L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2],

wherein:

independently, [L1] and [VL Domain], are optional;

one of [L1], [ASt Domain1], [L2]-[DH Domain], [L3], [ACH Domain], [VL Domain], [TH Domain], [L4], and [ASt Domain2] comprises a nucleotide having a non-naturally occurring modification; and

wherein:

(a) the TREM retains the ability to: support protein synthesis, be charged by a synthetase, be bound by an elongation factor, introduce an amino acid into a peptide chain, support elongation, or support initiation;

(b) the TREM comprises at least X contiguous nucleotides without a non-naturally occurring modification, wherein X is greater than 10;

(c) at least 3, but less than all of the nucleotides of a type (e.g., A, T, C, G or U) comprise the same non-naturally occurring modification;

(d) at least X nucleotides of a type (e.g., A, T, C, G or U) do not comprise a non-naturally occurring modification, wherein X=1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50;

(e) no more than 5, 10, or 15 nucleotides of a type (e.g., A, T, C, G or U) comprise a non-naturally occurring modification; and/or

(f) no more than 5, 10, or 15 nucleotides of a type (e.g., A, T, C, G or U) do not comprise a non-naturally occurring modification.

76. The method of claim 75, wherein the Domain comprising the non-naturally occurring modification retains a function, e.g., a domain function described herein.

77. The method of any one of the preceding embodiments, wherein the TREM core fragment comprises a sequence of Formula B:

[L1] $_y$-[ASt Domain1] $_x$-[L2] $_y$-[DH Domain]$_y$-[L3] $_y$-[ACH Domain]$_x$-[VL Domain] $_y$-[TH Domain] $_y$-[L4] $_y$-[ASt Domain2] $_x$,

wherein:

x=1 and y=0 or 1;

one of [ASt Domain1], [ACH Domain], and [ASt Domain2] comprises a nucleotide having a non-naturally occurring modification; and

the TREM retains the ability to: support protein synthesis; be able to be charged by a synthetase, be bound by an elongation factor, introduce an amino acid into a peptide chain, support elongation, or support initiation.

78. The method of any one of the preceding embodiments, wherein the TREM fragment comprises a portion of a TREM, wherein the TREM comprises a sequence of Formula A:

[L1]-[ASt Domain1]-[L2]-[DH Domain]-[L3]-[ACH Domain] -[VL Domain]-[TH Domain]-[L4]-[ASt Domain2], and wherein:

the TREM fragment comprises:

a non-naturally occurring modification; and

one, two, three or all or any combination of the following:

(a) a TREM half (*e.g.*, from a cleavage in the ACH Domain, *e.g.*, in the anticodon sequence, *e.g.*, a 5'half or a 3' half);

(b) a 5' fragment (*e.g.*, a fragment comprising the 5' end, *e.g.*, from a cleavage in a DH Domain or the ACH Domain);

(c) a 3' fragment (*e.g.*, a fragment comprising the 3' end, *e.g.*, from a cleavage in the TH Domain); or

(d) an internal fragment (*e.g.*, from a cleavage in any one of the ACH Domain, DH Domain or TH Domain).

79. The method of any one of claims 75-78, wherein the TREM Domain comprises a plurality of nucleotides each having a non-naturally occurring modification.

80. The method of any one of claims 75-79, wherein the non-naturally occurring modification is a modification in a base or a backbone of a nucleotide, e.g., a modification chosen from any one of Tables 5, 6, 7, 8 or 9.

81. The method of any one of claims 75-80, wherein the TREM, TREM core fragment or TREM fragment recognizes a codon provided in Table 2 or Table 3.

82. The method of any one of claims 75-80, wherein the TREM, TREM core fragment or TREM fragment is a cognate TREM.

83. The method of any one of claims 75-80, wherein the TREM, TREM core fragment or TREM fragment is a non-cognate TREM.

84. The method of any one of claims 75-80, wherein the TREM, TREM core fragment or TREM fragment is encoded by a sequence provided in Table 4, e.g., any one of SEQ ID NOs 1-451.

85. The method of any one of claims 75-80, wherein the TREM, TREM core fragment or TREM fragment is encoded by a consensus sequence chosen from any one of SEQ ID NOs: 562-621.

86. A pharmaceutical composition comprising a TREM, TREM core fragment or TREM fragment described herein.

87. A method of making a TREM, TREM core fragment or TREM fragment, comprising linking a first nucleotide to a second nucleotide to form the TREM.

88. The method of claim 87, wherein the TREM, TREM core fragment or TREM fragment is synthetic.

89. The method of claim 88, wherein the TREM, TREM core fragment or TREM fragment is made by cell-free solid phase synthesis.

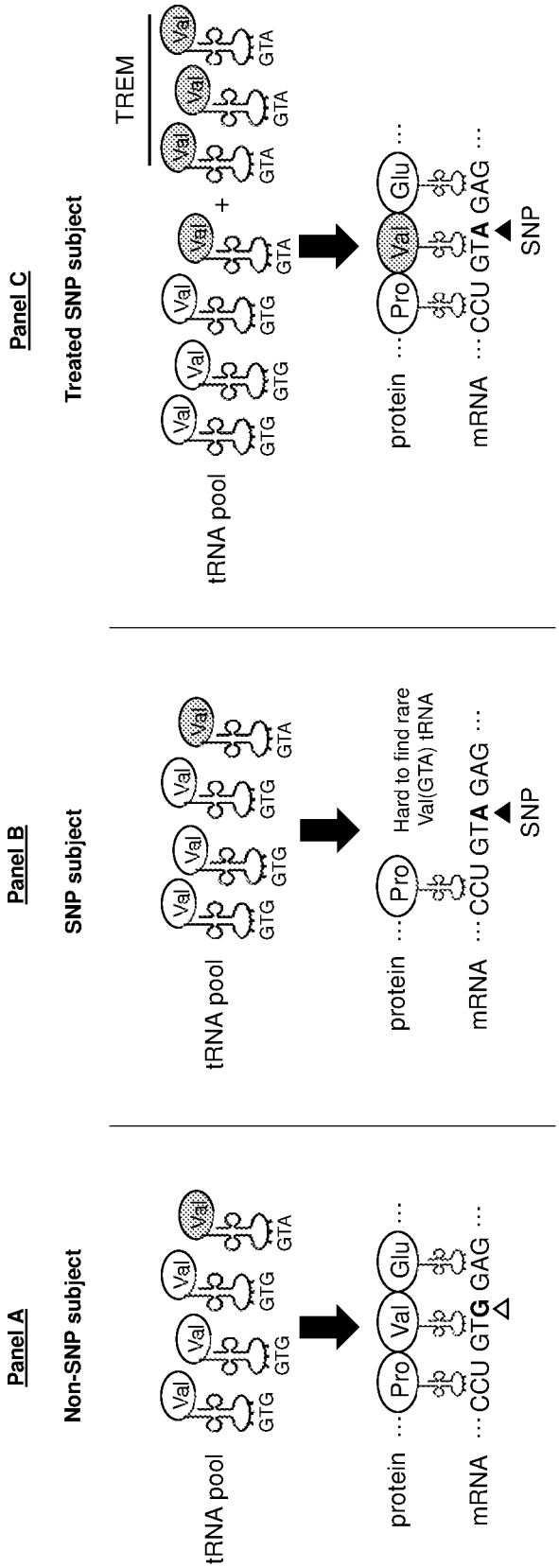

Panel A
Non-SNP subject
tRNA pool
protein
mRNA
Pro
Val
Glu
CCU GTG GAG
Panel B
SNP subject
Hard to find rare Val(GTA) tRNA
CCU GTA GAG
SNP
Panel C
Treated SNP subject
TREM

FIGURE 1

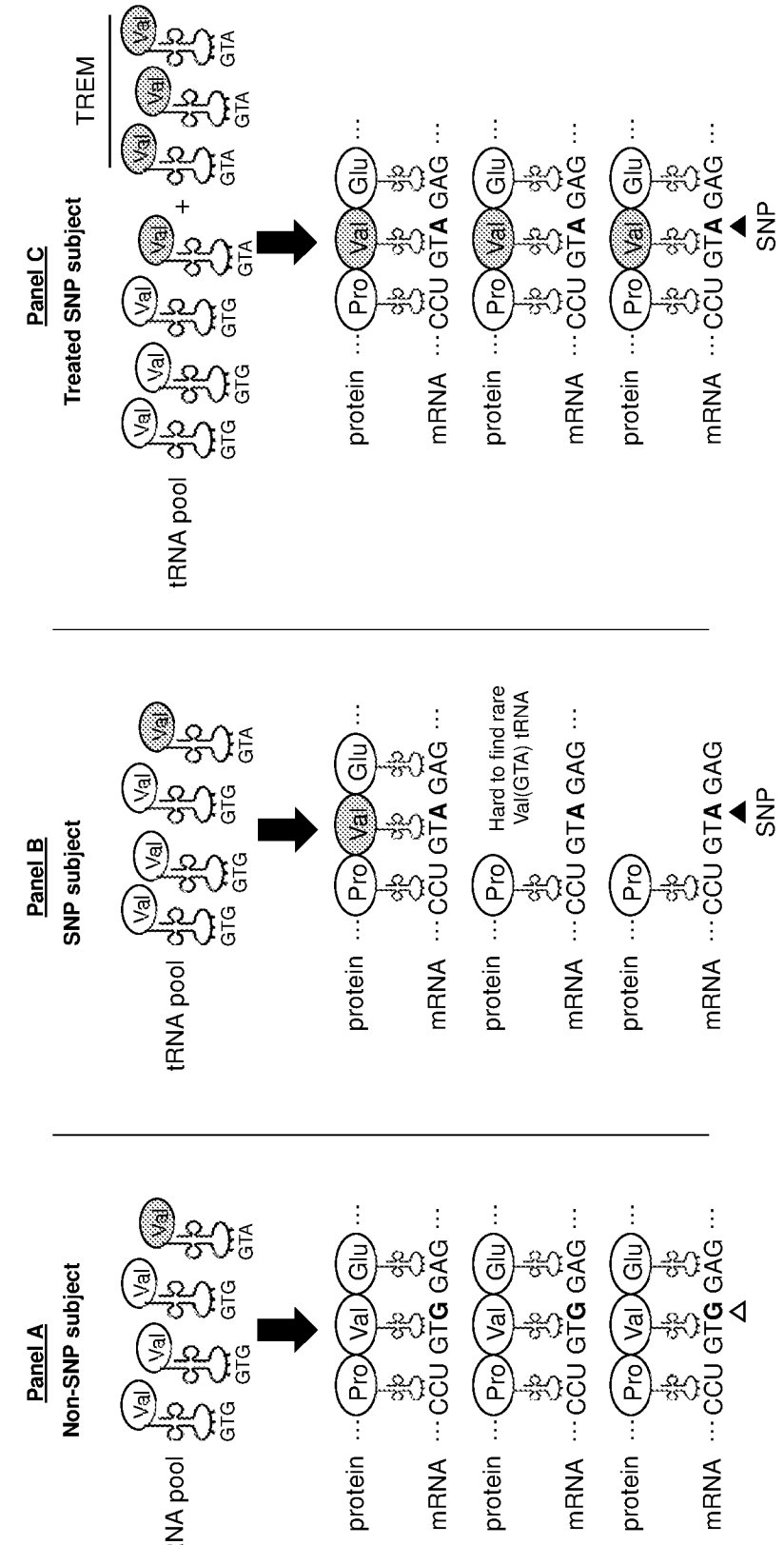

Panel A
Non-SNP subject
tRNA pool
GTG GTG GTG GTA
protein ... Pro Val Glu ...
mRNA ... CCU GTG GAG ...
protein ... Pro Val Glu ...
mRNA ... CCU GTG GAG ...
protein ... Pro Val Glu ...
mRNA ... CCU GTG GAG ...
Panel B
SNP subject
tRNA pool
GTG GTG GTG GTA
protein ... Pro Val Glu ...
mRNA ... CCU GTA GAG ...
protein ... Pro
Hard to find rare Val(GTA) tRNA
mRNA ... CCU GTA GAG ...
protein ... Pro
mRNA ... CCU GTA GAG
SNP
Panel C
Treated SNP subject
TREM
tRNA pool
GTG GTG GTG GTA + GTA GTA GTA
protein ... Pro Val Glu ...
mRNA ... CCU GTA GAG ...
protein ... Pro Val Glu ...
mRNA ... CCU GTA GAG ...
protein ... Pro Val Glu ...
mRNA ... CCU GTA GAG ...
SNP

FIGURE 2

FIGURE 3

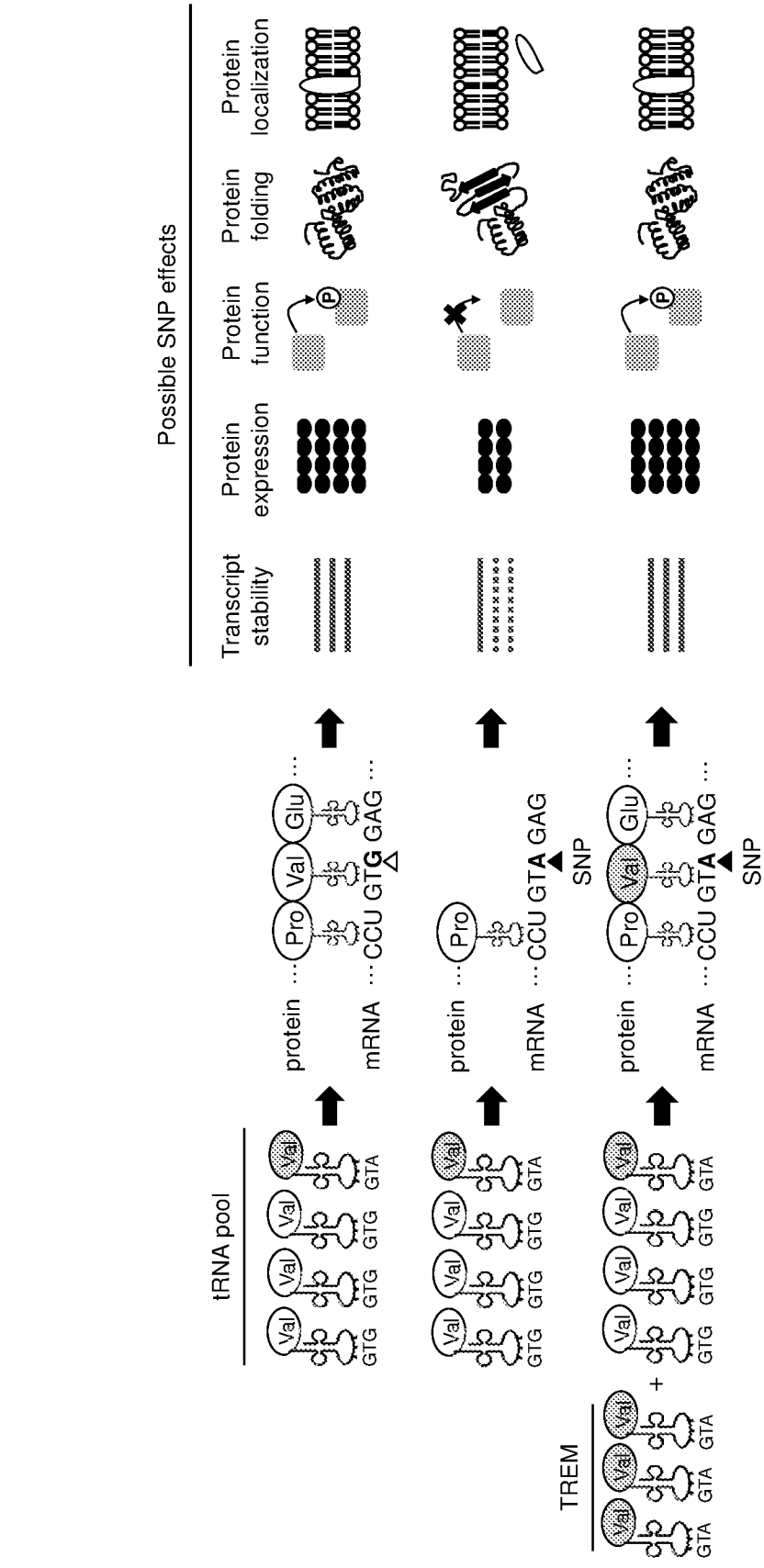

Possible SNP effects
Transcript stability
Protein expression
Protein function
Protein folding
Protein localization
Non-SNP subject
SNP subject
Treated SNP subject
tRNA pool
TREM
protein
mRNA
Pro
Val
Glu
GTG
GTA
GAG
CCU GTG GAG
CCU GTA GAG
SNP

FIG. 4

Gene	ensembl gene ID	Clinvar variant name	Original codon	New codon	Condition	Fold change	Log2 fold change
MLH1	ENSG00000076242	NM_000249.4(MLH1):c.1959G>T (p.Leu653=)	CTG	CTT	Lynch syndrome;Hereditary cancer-predisposing syndrome;Lynch syndrome I (COCA1);Hereditary nonpolyposis colorectal neoplasms;Lynch syndrome II (HNPCC2);	0.39	-1.35
PMS2	ENSG00000122512	NM_000535.7(PMS2):c.2253T>C (p.Phe751=)	TTT	TTC	Lynch syndrome;Lynch syndrome I (COCA1);Hereditary cancer-predisposing syndrome; ;Hereditary nonpolyposis colorectal cancer type 4 (HNPCC4);Hereditary nonpolyposis colorectal neoplasms;none provided	1.02	0.02
CYP11B1	ENSG00000160882	NM_000497.3(CYP11B1):c.243C>T (p.Tyr81=)	TAC	TAT	Congenital adrenal hyperplasia (CAH);Hyperaldosteronism, familial, type I (HALD1); Deficiency of steroid 11-beta-monooxygenase (CYP11B1)	0.9	-0.15
KCNJ11	ENSG00000187486	NM_000525.3(KCNJ11):c.801C>G (p.Leu267=)	CTC	CTG	;Maturity-onset diabetes of the young, type 13 (MODY13);Transient neonatal diabetes mellitus 3 (TNDM3);Islet cell hyperplasia (HHF2);Permanent neonatal diabetes mellitus (PNDM)	2.02	1.02
KCNJ11	ENSG00000187486	NM_000525.3(KCNJ11):c.1143G>A (p.Lys381=)	AAG	AAA	;Transient neonatal diabetes mellitus 3 (TNDM3);Maturity-onset diabetes of the young, type 13 (MODY13);Islet cell hyperplasia (HHF2);Permanent neonatal diabetes mellitus (PNDM)	0.87	-0.2
ABCC9	ENSG00000069431	NM_005691.3(ABCC9):c.2523C>T (p.Ala841=)	GCC	GCT	Primary dilated cardiomyopathy (DCM); Cardiovascular phenotype;Dilated cardiomyopathy 1O (CMD1O);Hypertrichotic osteochondrodysplasia Cantu type;Cardiomyopathy (CMYO)	0.74	-0.44
MSH2	ENSG00000095002	NM_000251.3(MSH2):c.339G>A (p.Lys113=)	AAG	AAA	Lynch syndrome;Hereditary cancer-predisposing syndrome; Lynch syndrome I (COCA1);Hereditary nonpolyposis colorectal neoplasms	0.87	-0.2
PAH	ENSG00000171759	NM_000277.3(PAH):c.735G>A (p.Val245=)	GTG	GTA	Phenylketonuria (PKU);Phenylketonuria (PKU)	0.3	-1.74
CSRP3	ENSG00000129170	NM_003476.5(CSRP3):c.336G>A (p.Ala112=)	GCG	GCA	Cardiovascular phenotype;Familial hypertrophic cardiomyopathy 12 (CMH12);Primary dilated cardiomyopathy (DCM);Familial hypertrophic cardiomyopathy 12 (CMH12);Dilated cardiomyopathy 1M (CMD1M);Cardiomyopathy (CMYO);none provided	2.88	1.52
ALAS2	ENSG00000158578	NM_000032.5(ALAS2):c.1560C>A (p.Pro520=)	CCC	CCA	Anemia, sideroblastic, 1 (SIDBA1);	1	-0.01
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.4377G>A (p.Gln1459=)	CAG	CAA	Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	0.4	-1.32
FANCB	ENSG00000181544	NM_001018113.3(FANCB):c.1371C>T (p.Val457=)	GTC	GTT	Fanconi anemia, complementation group B (FANCB);VACTERL association, X-linked, with or without hydrocephalus; Fanconi anemia (FA)	0.88	-0.19
DSG2	ENSG00000046604	NM_001943.5(DSG2):c.2484T>C (p.Asp828=)	GAT	GAC	Cardiovascular phenotype;Arrhythmogenic right ventricular cardiomyopathy, type 10 (ARVD10);Cardiomyopathy (CMYO)	1.01	0.01
ABCC9	ENSG00000069431	NM_005691.3(ABCC9):c.3768T>C (p.Leu1256=)	CTT	CTC	Cardiomyopathy (CMYO); Dilated cardiomyopathy 1O (CMD1O);Hypertrichotic osteochondrodysplasia Cantu type;none provided	1.26	0.33
SPINK1	ENSG00000164266	NM_003122.4(SPINK1):c.75C>T (p.Ser25=)	TCC	TCT	Inborn genetic diseases;Hereditary pancreatitis (PCTT)	0.98	-0.03
CYP11B1	ENSG00000160882	NM_000497.3(CYP11B1):c.1144C>T (p.Leu382=)	CTG	TTG	Congenital adrenal hyperplasia (CAH);Hyperaldosteronism, familial, type I (HALD1); Deficiency of steroid 11-beta-monooxygenase (CYP11B1)	0.37	-1.42
SOX10	ENSG00000100146	NM_006941.4(SOX10):c.753G>A (p.Ser251=)	TCG	TCA	Waardenburg syndrome;Peripheral demyelinating neuropathy, central dysmyelination, Waardenburg syndrome, and Hirschsprung disease (PCWH);	3.5	1.81
NDRG1	ENSG00000104419	NM_006096.3(NDRG1):c.789G>A (p.Ser263=)	TCG	TCA	Charcot-Marie-Tooth disease type 4;Charcot-Marie-Tooth disease, type 4D (CMT4D);Charcot-Marie-Tooth disease	3.5	1.81

MYH11	ENSG00000133392	NM_002474.3(MYH11):c.1212G>C (p.Gly404=)	GGG	GGC	Familial thoracic aortic aneurysm and aortic dissection (TAAD); Cardiovascular phenotype;Aortic aneurysm, familial thoracic 4 (AAT4)	1.29	0.37
SCN9A	ENSG00000169432	NM_001365536.1(SCN9A):c.1464C>T (p.Leu488=)	CTC	CTT	Primary erythromelalgia;Paroxysmal extreme pain disorder (PEXPD); Inherited Erythromelalgia;Indifference to pain, congenital, autosomal recessive (CIP); Hereditary sensory and autonomic neuropathy type IIA (HSAN2A);Generalized epilepsy with febrile seizures plus, type 7 (GEFSP7)	0.8	-0.33
ITPR1	ENSG00000150995	NM_002222.6(ITPR1):c.3822C>T (p.Asn1274=)	AAC	AAT	Autosomal dominant cerebellar ataxia; Spinocerebellar ataxia type 15/16;	1.01	0.02
HRAS	ENSG00000174775	NM_005343.4(HRAS):c.81T>C (p.His27=)	CAT	CAC	Rasopathy; Costello syndrome (CSTLO);Squamous cell lung carcinoma;none provided	1.23	0.3
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.12G>A (p.Lys4=)	AAG	AAA	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Aortic aneurysm, familial thoracic 4 (AAT4);Cardiovascular phenotype;Connective tissue disease;	0.87	-0.2
POLG	ENSG00000140521	NM_002693.2(POLG):c.2541C>T (p.Ala847=)	GCC	GCT	Progressive sclerosing poliodystrophy (MTDPS4A); Seizures;POLG-Related Spectrum Disorders	0.74	-0.44
GRIN2A	ENSG00000183454	NM_001134407.3(GRIN2A):c.2883C>T (p.Asn961=)	AAC	AAT	Epilepsy, focal, with speech disorder and with or without mental retardation (FESD);History of neurodevelopmental disorder;	1.01	0.02
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.3816G>A (p.Glu1272=)	GAG	GAA	Familial aortopathy; Cardiovascular phenotype; Familial thoracic aortic aneurysm and aortic dissection (TAAD);Aortic aneurysm, familial thoracic 4 (AAT4)	0.86	-0.22
MYH7	ENSG00000092054	NM_000257.4(MYH7):c.2769C>T (p.Asn923=)	AAC	AAT	Hypertrophic cardiomyopathy;Cardiovascular phenotype;Scapuloperoneal myopathy;Dilated Cardiomyopathy, Dominant;Myosin storage myopathy (MSMA);Myopathy, distal, 1 (MPD1);Cardiomyopathy, left ventricular noncompaction; Cardiomyopathy (CMYO)	1.01	0.02
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.777C>T (p.Ile259=)	ATC	ATT	Qualitative or quantitative defects of dysferlin	0.89	-0.17
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.609C>T (p.Cys203=)	TGC	TGT	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD)	0.97	-0.05
SLC20A2	ENSG00000168575	NM_001257180.2(SLC20A2):c.846C>T (p.Asp282=)	GAC	GAT	Idiopathic basal ganglia calcification 1 (IBGC1);	0.99	-0.01
PCDH19	ENSG00000165194	NM_001184880.2(PCDH19):c.1209C>T (p.Ser403=)	TCC	TCT		0.98	-0.03
HLCS	ENSG00000159267	NM_001352514.2(HLCS):c.2151C>T (p.Asn717=)	AAC	AAT	Holocarboxylase synthetase deficiency	1.01	0.02
OPA1	ENSG00000198836	NM_015560.2(OPA1):c.2256G>T (p.Leu752=)	CTG	CTT		0.39	-1.35
SPG7	ENSG00000197912	NM_003119.4(SPG7):c.199C>T (p.Leu67=)	CTG	TTG	Hereditary spastic paraplegia 7 (SPG7)	0.37	-1.42
ITPR1	ENSG00000150995	NM_002222.6(ITPR1):c.3849C>T (p.His1283=)	CAC	CAT		0.81	-0.3
FBP1	ENSG00000165140	NM_000507.4(FBP1):c.237C>T (p.Asn79=)	AAC	AAT	Fructose-biphosphatase deficiency (FBP1D)	1.01	0.02
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.2757C>T (p.Asn919=)	AAC	AAT	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD)	1.01	0.02
DNAI1	ENSG00000122735	NM_012144.4(DNAI1):c.297A>G (p.Gln99=)	CAA	CAG	Primary ciliary dyskinesia (PCD)	2.49	1.32
COL5A1	ENSG00000130635	NM_001278074.1(COL5A1):c.1896C>T (p.Phe632=)	TTC	TTT		0.98	-0.02
ADSL	ENSG00000239900	NM_000026.4(ADSL):c.363G>A (p.Leu121=)	TTG	TTA	Adenylosuccinate lyase deficiency (ADSLD)	0.65	-0.61
JAK3	ENSG00000105639	NM_000215.3(JAK3):c.108G>C (p.Gly36=)	GGG	GGC	Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-negative	1.29	0.37
ITPR1	ENSG00000150995	NM_002222.6(ITPR1):c.7770C>T (p.Ile2590=)	ATC	ATT		0.89	-0.17
HUWE1	ENSG00000086758	NM_031407.7(HUWE1):c.3663G>A (p.Ser1221=)	TCG	TCA		3.5	1.81
RP1L1	ENSG00000183638	NM_178857.6(RP1L1):c.168C>A (p.Arg56=)	CGC	CGA	Occult macular dystrophy (OCMD);	0.74	-0.44

ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.2292C>T (p.Phe764=)	TTC	TTT	Wilson disease (WND)	0.98	-0.02
SCN1A	ENSG00000144285	NM_001165963.4(SCN1A):c.579C>T (p.Leu193=)	CTC	CTT		0.8	-0.33
LYST	ENSG00000143669	NM_000081.4(LYST):c.9C>T (p.Thr3=)	ACC	ACT	Chédiak-Higashi syndrome (CHS)	0.8	-0.31
MFSD8	ENSG00000164073	NM_152778.3(MFSD8):c.1287C>T (p.Gly429=)	GGC	GGT	Neuronal ceroid lipofuscinosis 7 (CLN7)	0.55	-0.87
ABCA3	ENSG00000167972	NM_001089.3(ABCA3):c.393C>T (p.Ala131=)	GCC	GCT	Surfactant metabolism dysfunction, pulmonary, 3 (SMDP3)	0.74	-0.44
RP1L1	ENSG00000183638	NM_178857.6(RP1L1):c.273C>T (p.Ser91=)	AGC	AGT	Occult macular dystrophy (OCMD);	0.72	-0.48
LMBR1	ENSG00000105983	NM_022458.4(LMBR1):c.843G>A (p.Arg281=)	AGG	AGA	Polydactyly, preaxial II (PPD2);	1.1	0.14
AP5Z1	ENSG00000242802	NM_014855.3(AP5Z1):c.126C>T (p.Leu42=)	CTC	CTT	Spastic paraplegia 48, autosomal recessive (SPG48)	0.8	-0.33
BIN1	ENSG00000136717	NM_139343.3(BIN1):c.888C>T (p.Ser296=)	AGC	AGT	Myopathy, centronuclear, 2 (CNM2)	0.72	-0.48
SLC2A10	ENSG00000197496	NM_030777.4(SLC2A10):c.780C>T (p.Ser260=)	TCC	TCT	Arterial tortuosity syndrome (ATORS)	0.98	-0.03
PRF1	ENSG00000180644	NM_001083116.3(PRF1):c.630C>T (p.Pro210=)	CCC	CCT	Familial hemophagocytic lymphohistiocytosis 2 (FHL2)	1.02	0.02
AGA	ENSG00000038002	NM_000027.4(AGA):c.303A>T (p.Ala101=)	GCA	GCT	Aspartylglucosaminuria (AGU)	1.11	0.14
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.1134T>C (p.Pro378=)	CCT	CCC	Qualitative or quantitative defects of dysferlin	0.98	-0.02
NHLRC1	ENSG00000187566	NM_198586.3(NHLRC1):c.969C>T (p.Ser323=)	TCC	TCT	Lafora disease	0.98	-0.03
LGI1	ENSG00000108231	NM_005097.4(LGI1):c.1155A>C (p.Leu385=)	CTA	CTC	Familial temporal lobe epilepsy 1 (ETL1)	2.38	1.25
SAMHD1	ENSG00000101347	NM_015474.3(SAMHD1):c.195G>T (p.Leu65=)	CTG	CTT	Chilblain lupus 2 (CHBL2);Aicardi Goutieres syndrome 5 (AGS5)	0.39	-1.35
CBS	ENSG00000160200	NM_000071.2(CBS):c.612G>T (p.Val204=)	GTG	GTT	Classic homocystinuria	0.46	-1.13
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.3498T>C (p.Ser1166=)	AGT	AGC	Wilson disease (WND)	1.4	0.48
CNTNAP2	ENSG00000174469	NM_014141.6(CNTNAP2):c.3174C>G (p.Thr1058=)	ACC	ACG	Pitt-Hopkins-like syndrome 1 (PTHSL1)	0.31	-1.67
MCEE	ENSG00000124370	NM_032601.4(MCEE):c.102C>G (p.Pro34=)	CCC	CCG	Methylmalonyl-CoA epimerase deficiency	0.33	-1.62
LPIN2	ENSG00000101577	NM_014646.2(LPIN2):c.2568C>T (p.Leu856=)	CTC	CTT	Majeed syndrome (MJDS)	0.8	-0.33
PC	ENSG00000173599	NM_001040716.2(PC):c.2550C>T (p.Cys850=)	TGC	TGT	Pyruvate carboxylase deficiency	0.97	-0.05
AP5Z1	ENSG00000242802	NM_014855.3(AP5Z1):c.2400G>A (p.Arg800=)	AGG	AGA	Spastic paraplegia 48, autosomal recessive (SPG48)	1.1	0.14
PINK1	ENSG00000158828	NM_032409.3(PINK1):c.936G>A (p.Arg312=)	CGG	CGA	Parkinson disease 6, autosomal recessive early-onset (PARK6)	0.6	-0.73
AP5Z1	ENSG00000242802	NM_014855.3(AP5Z1):c.1794C>T (p.Ala598=)	GCC	GCT	Spastic paraplegia 48, autosomal recessive (SPG48)	0.74	-0.44
COQ8B	ENSG00000123815	NM_024876.4(COQ8B):c.1305C>T (p.Ser435=)	TCC	TCT		0.98	-0.03
KMT2D	ENSG00000167548	NM_003482.3(KMT2D):c.4986C>T (p.Cys1662=)	TGC	TGT		0.97	-0.05
CNTNAP2	ENSG00000174469	NM_014141.6(CNTNAP2):c.273T>C (p.Asn91=)	AAT	AAC		0.99	-0.02
COL6A1	ENSG00000142156	NM_001848.2(COL6A1):c.261C>T (p.Asn87=)	AAC	AAT	Collagen VI-related myopathy (COL6-RM);	1.01	0.02
MEN1	ENSG00000133895	NM_000244.3(MEN1):c.1449C>T (p.Gly483=)	GGC	GGT	Multiple endocrine neoplasia, type 1 (MEN1);Hereditary cancer-predisposing syndrome	0.55	-0.87
SPG7	ENSG00000197912	NM_003119.4(SPG7):c.120G>A (p.Gly40=)	GGG	GGA	Hereditary spastic paraplegia 7 (SPG7)	1.13	0.17
CLN6	ENSG00000128973	NM_017882.3(CLN6):c.213C>G (p.Leu71=)	CTC	CTG	Neuronal ceroid lipofuscinosis	2.02	1.02
TNFRSF1A	ENSG00000067182	NM_001065.4(TNFRSF1A):c.645C>T (p.Pro215=)	CCC	CCT	TNF receptor-associated periodic fever syndrome (TRAPS) (FPF)	1.02	0.02
TYMP	ENSG00000025708	NM_001953.5(TYMP):c.1290G>A (p.Arg430=)	AGG	AGA		1.1	0.14
CLN6	ENSG00000128973	NM_017882.3(CLN6):c.585C>T (p.Gly195=)	GGC	GGT	Neuronal ceroid lipofuscinosis	0.55	-0.87
ELP1	ENSG00000070061	NM_003640.5(ELP1):c.1230G>A (p.Pro410=)	CCG	CCA	Familial dysautonomia (HSAN3);	3.05	1.61
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.6777C>T (p.Phe2259=)	TTC	TTT	Autosomal recessive polycystic kidney disease (ARPKD);Polycystic kidney disease	0.98	-0.02
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.3525C>T (p.Asp1175=)	GAC	GAT	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Aortic aneurysm, familial thoracic 7 (AAT7)	0.99	-0.01
DHCR7	ENSG00000172893	NM_001360.2(DHCR7):c.126C>T (p.Ser42=)	AGC	AGT	Smith-Lemli-Opitz syndrome (SLOS);History of neurodevelopmental disorder	0.72	-0.48

PCSK9	ENSG00000169174	NM_174936.3(PCSK9):c.1026A>G (p.Gln342=)	CAA	CAG	Familial hypercholesterolemia 1 (FHCL1);Hypobetalipoproteinemia;Familial hypercholesterolemia 3 (FHCL3)	2.49	1.32
GLI3	ENSG00000106571	NM_000168.6(GLI3):c.1485G>A (p.Glu495=)	GAG	GAA	Greig cephalopolysyndactyly syndrome (GCPS); Pallister-Hall syndrome (PHS);Polydactyly	0.86	-0.22
CHD7	ENSG00000171316	NM_017780.4(CHD7):c.216T>C (p.Tyr72=)	TAT	TAC	CHARGE association (CHARGE);Hypogonadotropic hypogonadism 5 with or without anosmia (KAL5);History of neurodevelopmental disorder;	1.11	0.15
VCL	ENSG00000035403	NM_014000.3(VCL):c.1317T>C (p.Ser439=)	TCT	TCC	Dilated cardiomyopathy 1W (CMD1W);Cardiovascular phenotype;Cardiomyopathy (CMYO);none provided	1.02	0.03
PCSK9	ENSG00000169174	NM_174936.3(PCSK9):c.141C>T (p.Ser47=)	TCC	TCT	Familial hypercholesterolemia 1 (FHCL1);Hypobetalipoproteinemia;Familial hypercholesterolemia 3 (FHCL3);	0.98	-0.03
MFN2	ENSG00000116688	NM_014874.3(MFN2):c.1641C>T (p.Leu547=)	CTC	CTT	Charcot-Marie-Tooth disease, type 2;Charcot-Marie-Tooth disease	0.8	-0.33
RBM20	ENSG00000203867	NM_001134363.3(RBM20):c.1986G>A (p.Pro662=)	CCG	CCA	Dilated cardiomyopathy 1DD (CMD1DD);Cardiovascular phenotype;Cardiomyopathy (CMYO);	3.05	1.61
DMD	ENSG00000198947	NM_004006.2(DMD):c.2457A>C (p.Leu819=)	CTA	CTC	Duchenne muscular dystrophy (DMD);Dilated cardiomyopathy 3B (CMD3B)	2.38	1.25
SCN5A	ENSG00000183873	NM_000335.5(SCN5A):c.3360G>A (p.Ala1120=)	GCG	GCA	Brugada syndrome;Cardiovascular phenotype;Long QT syndrome (LQTS);Paroxysmal familial ventricular fibrillation;Romano-Ward syndrome (RWS);Progressive familial heart block;Dilated Cardiomyopathy, Dominant;Sick sinus syndrome; Arrhythmia	2.88	1.52
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.471C>T (p.Ile157=)	ATC	ATT	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Aortic aneurysm, familial thoracic 4 (AAT4); Cardiovascular phenotype	0.89	-0.17
LGI1	ENSG00000108231	NM_005097.4(LGI1):c.717A>C (p.Ile239=)	ATA	ATC	Familial temporal lobe epilepsy 1 (ETL1)	2.29	1.2
MFN2	ENSG00000116688	NM_014874.3(MFN2):c.756C>T (p.Asn252=)	AAC	AAT	Charcot-Marie-Tooth disease, type 2;Hereditary motor and sensory neuropathy with optic atrophy (HMSN6A);Charcot-Marie-Tooth disease	1.01	0.02
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.1623C>T (p.Ala541=)	GCC	GCT	Collagen VI-related myopathy (COL6-RM); Bethlem myopathy 1 (BTHLM1)	0.74	-0.44
GJB6	ENSG00000121742	NM_001110219.3(GJB6):c.15G>A (p.Thr5=)	ACG	ACA	Hidrotic ectodermal dysplasia syndrome (GJB6)	2.96	1.57
KCNQ2	ENSG00000075043	NM_172107.4(KCNQ2):c.1827C>T (p.Ala609=)	GCC	GCT	Early infantile epileptic encephalopathy with suppression bursts (EIEE)	0.74	-0.44
SCN2A	ENSG00000136531	NM_001040142.2(SCN2A):c.3579C>A (p.Leu1193=)	CTC	CTA	Seizures, benign familial infantile, 3 (BFIS3);Early infantile epileptic encephalopathy 11 (DEE11)	0.42	-1.25
DYNC2H1	ENSG00000187240	NM_001377.3(DYNC2H1):c.11703C>T (p.Asn3901=)	AAC	AAT	Short-rib thoracic dysplasia 3 with or without polydactyly (SRTD3);Jeune thoracic dystrophy (ATD1);	1.01	0.02
ALDH7A1	ENSG00000164904	NM_001182.5(ALDH7A1):c.615C>T (p.Asn205=)	AAC	AAT	Pyridoxine-dependent epilepsy (EPD);Seizures	1.01	0.02
DHCR7	ENSG00000172893	NM_001360.2(DHCR7):c.1092G>A (p.Thr364=)	ACG	ACA	Smith-Lemli-Opitz syndrome (SLOS);History of neurodevelopmental disorder	2.96	1.57
FBN2	ENSG00000138829	NM_001999.4(FBN2):c.2625T>C (p.Cys875=)	TGT	TGC	Congenital contractural arachnodactyly (CCA);Cardiovascular phenotype	1.03	0.05
NHLRC1	ENSG00000187566	NM_198586.3(NHLRC1):c.513C>T (p.Ala171=)	GCC	GCT	Lafora disease;Seizures	0.74	-0.44
RBM20	ENSG00000203867	NM_001134363.3(RBM20):c.1378T>C (p.Leu460=)	TTG	CTG	Dilated cardiomyopathy 1DD (CMD1DD);Cardiomyopathy (CMYO)	2.67	1.42
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.6852T>C (p.Pro2284=)	CCT	CCC	Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.98	-0.02
PEX1	ENSG00000127980	NM_000466.3(PEX1):c.330C>G (p.Pro110=)	CCC	CCG	Peroxisome biogenesis disorder 1A (Zellweger) (PBD1A);	0.33	-1.62

LGI1	ENSG00000108231	NM_005097.4(LGI1):c.345A>G (p.Pro115=)	CCA	CCG	Familial temporal lobe epilepsy 1 (ETL1);Seizures	0.33	-1.61
TTN	ENSG00000155657	NM_001267550.2(TTN):c.83133G>A (p.Lys27711=)	AAG	AAA	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.87	-0.2
TTN	ENSG00000155657	NM_001267550.2(TTN):c.87771C>A (p.Gly29257=)	GGC	GGA	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.87	-0.2
CLN6	ENSG00000128973	NM_017882.3(CLN6):c.282C>A (p.Pro94=)	CCC	CCA	Neuronal ceroid lipofuscinosis;Seizures	1	-0.01
SLC2A1	ENSG00000117394	NM_006516.3(SLC2A1):c.894C>T (p.Phe298=)	TTC	TTT	GLUT1 deficiency syndrome 1, autosomal recessive	0.98	-0.02
PKP2	ENSG00000057294	NM_004572.3(PKP2):c.387G>A (p.Gln129=)	CAG	CAA	Arrhythmogenic right ventricular dysplasia 9 (ARVD9);Cardiomyopathy (CMYO)	0.4	-1.32
TTN	ENSG00000155657	NM_001267550.2(TTN):c.21276C>T (p.Thr7092=)	ACC	ACT	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.8	-0.31
SYN1	ENSG00000008056	NM_006950.3(SYN1):c.1569G>A (p.Ala523=)	GCG	GCA	Epilepsy, X-linked, with variable learning disabilities and behavior disorders (EPILX)	2.88	1.52
VCL	ENSG00000035403	NM_014000.2(VCL):c.81C>T (p.His27=)	CAC	CAT	Dilated cardiomyopathy 1W (CMD1W);Cardiovascular phenotype	0.81	-0.3
TTN	ENSG00000155657	NM_001267550.2(TTN):c.66051G>A (p.Val22017=)	GTG	GTA	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.3	-1.74
TTN	ENSG00000155657	NM_001267550.2(TTN):c.30309T>C (p.Phe10103=)	TTT	TTC	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	1.02	0.02
CACNA1C	ENSG00000151067	NM_000719.7(CACNA1C):c.4659C>T (p.Asp1553=)	GAC	GAT	Cardiovascular phenotype;Long QT syndrome (LQTS)	0.99	-0.01
TTN	ENSG00000155657	NM_001267550.2(TTN):c.14424G>C (p.Val4808=)	GTG	GTC	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Cardiomyopathy (CMYO)	0.52	-0.94
APOB	ENSG00000084674	NM_000384.3(APOB):c.2706C>T (p.Asn902=)	AAC	AAT	Familial hypercholesterolemia 1 (FHCL1);Hypobetalipoproteinemia, familial, 1 (FHBL1);Familial hypercholesterolemia 2 (FCHL2);Hypobetalipoproteinemia, familial, 1 (FHBL1);Familial hypercholesterolemia (FH);Familial hypercholesterolemia 2 (FCHL2)	1.01	0.02
MUTYH	ENSG00000132781	NM_001048174.2(MUTYH):c.1347G>C (p.Thr449=)	ACG	ACC	Hereditary cancer-predisposing syndrome; MYH-associated polyposis (FAP2);none provided	3.18	1.67
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.3201C>T (p.Ser1067=)	TCC	TCT	History of neurodevelopmental disorder;Pitt-Hopkins-like syndrome 2 (PTHSL2)	0.98	-0.03
CBS	ENSG00000160200	NM_000071.2(CBS):c.1059G>A (p.Thr353=)	ACG	ACA	Classic homocystinuria;Cardiovascular phenotype;none provided	2.96	1.57
EYS	ENSG00000188107	NM_001142800.2(EYS):c.5601T>C (p.Ser1867=)	TCT	TCC	Retinitis pigmentosa 25 (RP25);Retinitis pigmentosa (RP)	1.02	0.03
RELN	ENSG00000189056	NM_005045.4(RELN):c.6141C>T (p.Phe2047=)	TTC	TTT	Norman-Roberts syndrome (LIS2);Epilepsy, familial temporal lobe, 7 (ETL7);Norman-Roberts syndrome (LIS2)	0.98	-0.02
PYGM	ENSG00000068976	NM_005609.4(PYGM):c.645G>A (p.Lys215=)	AAG	AAA	Glycogen storage disease, type V (GSD5);	0.87	-0.2
POLG	ENSG00000140521	NM_002693.2(POLG):c.3216C>G (p.Thr1072=)	ACC	ACG	Progressive sclerosing poliodystrophy (MTDPS4A);	0.31	-1.67
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.12453A>T (p.Pro4151=)	CCA	CCT	Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);Autosomal dominant cerebellar ataxia	1.02	0.03
MMUT	ENSG00000146085	NM_000255.4(MMUT):c.1629C>T (p.Ser543=)	AGC	AGT	Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency; Methylmalonic aciduria due to complete methylmalonyl-CoA mutase deficiency;none provided	0.72	-0.48
APOB	ENSG00000084674	NM_000384.3(APOB):c.8148C>T (p.Ile2716=)	ATC	ATT	Familial hypercholesterolemia 2 (FCHL2);Hypobetalipoproteinemia, familial, 1 (FHBL1);Familial hypercholesterolemia 1 (FHCL1);Hypobetalipoproteinemia, familial, 1 (FHBL1); Familial hypercholesterolemia (FH);Familial hypercholesterolemia 2 (FCHL2);none provided	0.89	-0.17
MFN2	ENSG00000116688	NM_014874.3(MFN2):c.1827C>T (p.Ser609=)	TCC	TCT	Charcot-Marie-Tooth disease, type 2;Hereditary motor and sensory neuropathy; Charcot-Marie-Tooth disease;none provided	0.98	-0.03

MYH11	ENSG00000133392	NM_002474.3(MYH11):c.5566C>T (p.Leu1856=)	CTG	TTG	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Lissencephaly, Recessive;Aortic aneurysm, familial thoracic 4 (AAT4);Cardiovascular phenotype;Connective tissue disease;	0.37	-1.42
PCDH19	ENSG00000165194	NM_001184880.2(PCDH19):c.1683G>A (p.Pro561=)	CCG	CCA	Early infantile epileptic encephalopathy 9 (DEE9); History of neurodevelopmental disorder	3.05	1.61
USH2A	ENSG00000042781	NM_206933.4(USH2A):c.4560C>T (p.Ile1520=)	ATC	ATT	Retinitis pigmentosa (RP);Usher syndrome, type 2A (USH2A);none provided	0.89	-0.17
CHST3	ENSG00000122863	NM_004273.5(CHST3):c.417C>T (p.Ala139=)	GCC	GCT	Spondyloepiphyseal dysplasia with congenital joint dislocations (SEDCJD);Larsen syndrome (LRS);Skeletal dysplasia;Spondyloepiphyseal dysplasia congenita (SEDC)	0.74	-0.44
SCN5A	ENSG00000183873	NM_000335.5(SCN5A):c.1068T>C (p.Asp356=)	GAT	GAC	Brugada syndrome;Dilated Cardiomyopathy, Dominant;Paroxysmal familial ventricular fibrillation;Long QT syndrome (LQTS);Sick sinus syndrome;Progressive familial heart block;Romano-Ward syndrome (RWS);Cardiovascular phenotype; Arrhythmia	1.01	0.01
SCN5A	ENSG00000183873	NM_000335.5(SCN5A):c.1569T>A (p.Arg523=)	CGT	CGA	Brugada syndrome;Long QT syndrome (LQTS);Romano-Ward syndrome (RWS);Sick sinus syndrome;Paroxysmal familial ventricular fibrillation;Progressive familial heart block;Dilated Cardiomyopathy, Dominant;Cardiovascular phenotype; Arrhythmia	1.41	0.49
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.8310C>T (p.His2770=)	CAC	CAT	Geleophysic dysplasia;Marfan syndrome (MFS);Weill-Marchesani syndrome;Acromicric dysplasia (ACMICD);Stiff skin syndrome (SSKS);Ectopia lentis, isolated, autosomal dominant (ECTOL1);Familial thoracic aortic aneurysm and aortic dissection (TAAD); Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.81	-0.3
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.8202C>T (p.Asn2734=)	AAC	AAT	Stiff skin syndrome (SSKS);Marfan syndrome (MFS);Geleophysic dysplasia;Ectopia lentis, isolated, autosomal dominant (ECTOL1);Acromicric dysplasia (ACMICD);Weill-Marchesani syndrome;Familial thoracic aortic aneurysm and aortic dissection (TAAD); Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	1.01	0.02
TTR	ENSG00000118271	NM_000371.4(TTR):c.417G>A (p.Thr139=)	ACG	ACA	Cardiovascular phenotype; Amyloidogenic transthyretin amyloidosis;Cardiomyopathy (CMYO);Charcot-Marie-Tooth disease;none provided	2.96	1.57
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.4584C>T (p.Ser1528=)	AGC	AGT	Hereditary breast and ovarian cancer syndrome (HBOC);Breast-ovarian cancer, familial 2 (BROVCA2); Hereditary cancer-predisposing syndrome;Fanconi anemia, complementation group D1 (FANCD1);Familial cancer of breast; Breast and/or ovarian cancer;none provided	0.72	-0.48
CBS	ENSG00000160200	NM_000071.2(CBS):c.1479G>A (p.Thr493=)	ACG	ACA	Cardiovascular phenotype;Classic homocystinuria	2.96	1.57
CACNA1D	ENSG00000157388	NM_001128840.3(CACNA1D):c.1998G>A (p.Leu666=)	TTG	TTA	Sinoatrial node dysfunction and deafness (SANDD);	0.65	-0.61
SCN2A	ENSG00000136531	NM_001040142.2(SCN2A):c.3456C>T (p.Ala1152=)	GCC	GCT	History of neurodevelopmental disorder;	0.74	-0.44
NSD1	ENSG00000165671	NM_022455.4(NSD1):c.3088T>C (p.Leu1030=)	TTG	CTG	History of neurodevelopmental disorder;	2.67	1.42
POLG	ENSG00000140521	NM_002693.2(POLG):c.1275C>T (p.Ala425=)	GCC	GCT	Progressive sclerosing poliodystrophy (MTDPS4A);	0.74	-0.44
SPTBN2	ENSG00000173898	NM_006946.3(SPTBN2):c.1719C>T (p.His573=)	CAC	CAT	Autosomal dominant cerebellar ataxia;	0.81	-0.3
FBN2	ENSG00000138829	NM_001999.4(FBN2):c.2508G>A (p.Thr836=)	ACG	ACA	Cardiovascular phenotype;Congenital contractural arachnodactyly (CCA)	2.96	1.57

RAX2	ENSG00000173976	NM_032753.4(RAX2):c.156G>A (p.Pro52=)	CCG	CCA	Cone-rod dystrophy 11 (CORD11);Age-related macular degeneration 6 (ARMD6);	3.05	1.61
SPG7	ENSG00000197912	NM_003119.4(SPG7):c.1032C>T (p.Gly344=)	GGC	GGT	Hereditary spastic paraplegia 7 (SPG7)	0.55	-0.87
AMT	ENSG00000145020	NM_000481.4(AMT):c.354G>A (p.Leu118=)	CTG	CTA	Non-ketotic hyperglycinemia (GCE)	0.21	-2.27
TMEM126A	ENSG00000171202	NM_032273.4(TMEM126A):c.96T>G (p.Leu32=)	CTT	CTG	Optic atrophy 7 (OPA7);	2.54	1.35
IGHMBP2	ENSG00000132740	NM_002180.2(IGHMBP2):c.741C>T (p.Ala247=)	GCC	GCT	Spinal muscular atrophy, distal, autosomal recessive, 1 (DSMA1); Spinal muscular atrophy, distal, autosomal recessive, 1 (DSMA1);Charcot-Marie-Tooth disease, axonal, type 2S (CMT2S);Charcot-Marie-Tooth disease;none provided	0.74	-0.44
IGHMBP2	ENSG00000132740	NM_002180.2(IGHMBP2):c.1104C>T (p.Tyr368=)	TAC	TAT	Spinal muscular atrophy, distal, autosomal recessive, 1 (DSMA1); Spinal muscular atrophy, distal, autosomal recessive, 1 (DSMA1);Charcot-Marie-Tooth disease, axonal, type 2S (CMT2S);Charcot-Marie-Tooth disease;none provided	0.9	-0.15
GABRA1	ENSG00000022355	NM_001127644.2(GABRA1):c.501G>A (p.Pro167=)	CCG	CCA	Seizures; Idiopathic generalized epilepsy;Epilepsy, juvenile myoclonic 5 (EIG13);Epilepsy, childhood absence 4 (ECA4);Epilepsy, juvenile myoclonic 5 (EIG13)	3.05	1.61
GABRA1	ENSG00000022355	NM_001127644.2(GABRA1):c.1155C>A (p.Gly385=)	GGC	GGA	Seizures; Idiopathic generalized epilepsy;Epilepsy, juvenile myoclonic 5 (EIG13);Epilepsy, childhood absence 4 (ECA4);Epilepsy, juvenile myoclonic 5 (EIG13)	0.87	-0.2
TTN	ENSG00000155657	NM_001267550.2(TTN):c.77043T>C (p.Tyr25681=)	TAT	TAC	Cardiovascular phenotype; Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	1.11	0.15
SLC25A22	ENSG00000177542	NM_001191061.2(SLC25A22):c.327G>A (p.Ala109=)	GCG	GCA	Seizures; Early infantile epileptic encephalopathy with suppression bursts (EIEE)	2.88	1.52
POLG	ENSG00000140521	NM_002693.2(POLG):c.975C>A (p.Pro325=)	CCC	CCA	Seizures; Progressive sclerosing poliodystrophy (MTDPS4A)	1	-0.01
KCNH2	ENSG00000055118	NM_000238.4(KCNH2):c.3111C>T (p.Asp1037=)	GAC	GAT	Cardiovascular phenotype; Long QT syndrome (LQTS);Arrhythmia	0.99	-0.01
MYBPC3	ENSG00000134571	NM_000256.3(MYBPC3):c.531C>T (p.Arg177=)	CGC	CGT	Hypertrophic cardiomyopathy;Familial hypertrophic cardiomyopathy 4 (CMH4);Cardiovascular phenotype;Left ventricular noncompaction 10 (LVNC10);Cardiomyopathy (CMYO)	0.52	-0.93
KCNH2	ENSG00000055118	NM_172056.2(KCNH2):c.1320G>T (p.Pro440=)	CCG	CCT	Long QT syndrome (LQTS);Cardiovascular phenotype; Arrhythmia;Long QT syndrome 2 (LQT2)	3.11	1.64
POLG	ENSG00000140521	NM_002693.2(POLG):c.1066C>T (p.Leu356=)	CTG	TTG	Progressive sclerosing poliodystrophy (MTDPS4A); POLG-Related Spectrum Disorders	0.37	-1.42
KCNH2	ENSG00000055118	NM_172056.2(KCNH2):c.2331C>T (p.Thr777=)	ACC	ACT	Long QT syndrome (LQTS); Long QT syndrome 2 (LQT2);Arrhythmia	0.8	-0.31
APC	ENSG00000134982	NM_000038.6(APC):c.6525A>G (p.Thr2175=)	ACA	ACG	Familial adenomatous polyposis 1 (FAP1);Hereditary cancer-predisposing syndrome; APC-Associated Polyposis Disorders;	0.34	-1.57
PSAP	ENSG00000197746	NM_002778.4(PSAP):c.189C>T (p.Cys63=)	TGC	TGT	Gaucher disease, atypical, due to saposin C deficiency;Krabbe disease, atypical, due to saposin A deficiency;Combined saposin deficiency;Sphingolipid activator protein 1 deficiency	0.97	-0.05
CDKN2A	ENSG00000147889	NM_000077.4(CDKN2A):c.273G>A (p.Leu91=)	CTG	CTA	Melanoma-pancreatic cancer syndrome;Hereditary cancer-predisposing syndrome; Hereditary melanoma	0.21	-2.27
FLNA	ENSG00000196924	NM_001110556.2(FLNA):c.1191C>T (p.Ile397=)	ATC	ATT	Cardiovascular phenotype;Connective tissue disease;History of neurodevelopmental disorder; Periventricular nodular heterotopia 1 (PVNH1);Melnick-Needles syndrome (MNS);Oto-palato-digital syndrome, type II (OPD2);Frontometaphyseal dysplasia (FMD1)	0.89	-0.17
FLNA	ENSG00000196924	NM_001110556.2(FLNA):c.1875C>T (p.Asp625=)	GAC	GAT	Cardiovascular phenotype;Connective tissue disease;History of neurodevelopmental disorder; Periventricular nodular heterotopia 1 (PVNH1);Melnick-Needles syndrome (MNS);Oto-palato-digital syndrome, type II (OPD2);Frontometaphyseal dysplasia (FMD1)	0.99	-0.01

ABCA4	ENSG00000198691	NM_000350.3(ABCA4):c.3759G>A (p.Thr1253=)	ACG	ACA	Macular degeneration;Cone-Rod Dystrophy, Recessive;Retinitis Pigmentosa, Recessive;Stargardt Disease, Recessive; ABCA4-Related Disorders	2.96	1.57
ACTA2	ENSG00000107796	NM_001613.4(ACTA2):c.201G>C (p.Leu67=)	CTG	CTC	Multisystemic smooth muscle dysfunction syndrome (MSMDS);Familial thoracic aortic aneurysm and aortic dissection (TAAD); Aortic aneurysm, familial thoracic 6 (AAT6)	0.49	-1.02
KCNQ2	ENSG00000075043	NM_172107.4(KCNQ2):c.1689C>T (p.Asp563=)	GAC	GAT	Early infantile epileptic encephalopathy 7 (DEE7);Seizures;Early infantile epileptic encephalopathy with suppression bursts (EIEE)	0.99	-0.01
TTN	ENSG00000155657	NM_001267550.2(TTN):c.97386C>T (p.Thr32462=)	ACC	ACT	Cardiovascular phenotype;Limb-girdle muscular dystrophy, type 2J (LGMDR10);Tibial muscular dystrophy (TMD);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Dilated cardiomyopathy 1G (CMD1G); Cardiomyopathy (CMYO);Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);none provided	0.8	-0.31
KCTD7	ENSG00000243335	NM_153033.4(KCTD7):c.687T>C (p.Asp229=)	GAT	GAC	Seizures; Epilepsy, progressive myoclonic 3 (EPM3)	1.01	0.01
CNTNAP2	ENSG00000174469	NM_014141.6(CNTNAP2):c.3927C>T (p.Ala1309=)	GCC	GCT	History of neurodevelopmental disorder; Pitt-Hopkins-like syndrome 1 (PTHSL1)	0.74	-0.44
FBN2	ENSG00000138829	NM_001999.4(FBN2):c.3013T>C (p.Leu1005=)	TTG	CTG	Cardiovascular phenotype; Congenital contractural arachnodactyly (CCA)	2.67	1.42
FOLR1	ENSG00000110195	NM_016729.3(FOLR1):c.157T>C (p.Leu53=)	TTG	CTG	History of neurodevelopmental disorder; Cerebral folate transport deficiency (NCFTD)	2.67	1.42
MAN1B1	ENSG00000177239	NM_016219.5(MAN1B1):c.1800C>T (p.Thr600=)	ACC	ACT	History of neurodevelopmental disorder; Mental retardation, autosomal recessive 15 (RAFQS)	0.8	-0.31
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.5070C>G (p.Val1690=)	GTC	GTG	Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	1.92	0.94
RYR2	ENSG00000198626	NM_001035.3(RYR2):c.2574G>A (p.Thr858=)	ACG	ACA	Catecholaminergic polymorphic ventricular tachycardia (CPVT1);Arrhythmogenic right ventricular dysplasia, familial, 2 (ARVD2);Cardiovascular phenotype;Cardiomyopathy (CMYO);Catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1);	2.96	1.57
DES	ENSG00000175084	NM_001927.4(DES):c.924C>T (p.Asn308=)	AAC	AAT	Neurogenic scapuloperoneal syndrome, Kaeser type (SCPNK); Dilated cardiomyopathy 1I (CMD1I);Myofibrillar myopathy 1 (MFM1);Myofibrillar Myopathy, Dominant; Myofibrillar myopathy 1 (MFM1);Muscular dystrophy, limb-girdle, type 2R (LGMD2R)	1.01	0.02
GALT	ENSG00000213930	NM_000155.4(GALT):c.1014C>G (p.Gly338=)	GGC	GGG	Deficiency of UDPglucose-hexose-1-phosphate uridylyltransferase (GALAC1);	0.77	-0.37
TSC2	ENSG00000103197	NM_000548.5(TSC2):c.1281C>A (p.Ile427=)	ATC	ATA	Tuberous sclerosis syndrome (TSC);Lymphangiomyomatosis (LAM);Hereditary cancer-predisposing syndrome; Tuberous sclerosis 2 (TSC2); none provided	0.44	-1.2
SMN1	ENSG00000172062	NM_000344.3(SMN1):c.840C>T (p.Phe280=)	TTC	TTT	Werdnig-Hoffmann disease (SMA1);Spinal muscular atrophy (SMA)	0.98	-0.02
NOS3	ENSG00000164867	NM_000603.5(NOS3):c.774T>C (p.Asp258=)	GAT	GAC	Metabolic syndrome, susceptibility to	1.01	0.01
TTN	ENSG00000155657	NM_001267550.2(TTN):c.102984C>T (p.Asp34328=)	GAC	GAT	Tibial muscular dystrophy (TMD);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Dilated cardiomyopathy 1G (CMD1G);	0.99	-0.01

POLG	ENSG00000140521	NM_002693.2(POLG):c.2028G>A (p.Ala676=)	GCG	GCA	POLG-Related Spectrum Disorders;Progressive sclerosing poliodystrophy (MTDPS4A);	2.88	1.52
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.12615G>A (p.Ser4205=)	TCG	TCA	Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);	3.5	1.81
CNTNAP2	ENSG00000174469	NM_014141.6(CNTNAP2):c.837G>A (p.Val279=)	GTG	GTA	Pitt-Hopkins-like syndrome;Pitt-Hopkins-like syndrome 1 (PTHSL1)	0.3	-1.74
ARFGEF2	ENSG00000124198	NM_006420.3(ARFGEF2):c.807C>T (p.Asp269=)	GAC	GAT	Heterotopia, periventricular, autosomal recessive (ARPHM);	0.99	-0.01
SPATA7	ENSG00000042317	NM_018418.5(SPATA7):c.729C>T (p.Arg243=)	CGC	CGT	Retinitis pigmentosa (RP);Leber congenital amaurosis 3 (LCA3)	0.52	-0.93
NOD2	ENSG00000167207	NM_001370466.1(NOD2):c.1200G>A (p.Pro400=)	CCG	CCA	Blau syndrome (BLAUS);Inflammatory bowel disease 1 (IBD1);	3.05	1.61
NPC1	ENSG00000141458	NM_000271.5(NPC1):c.3331C>T (p.Leu1111=)	CTG	TTG	Niemann-Pick disease type C1 (NPC1)	0.37	-1.42
FOXRED1	ENSG00000110074	NM_017547.4(FOXRED1):c.9G>A (p.Arg3=)	CGG	CGA	Mitochondrial complex I deficiency, nuclear type 1 (MC1DN1);	0.6	-0.73
SUCLG1	ENSG00000163541	NM_003849.4(SUCLG1):c.900C>T (p.Ala300=)	GCC	GCT	Mitochondrial DNA depletion syndrome;Mitochondrial DNA depletion syndrome 9 (encephalomyopathic with methylmalonic aciduria) (MTDPS9);	0.74	-0.44
CNTNAP2	ENSG00000174469	NM_014141.6(CNTNAP2):c.561T>C (p.Val187=)	GTT	GTC	Pitt-Hopkins-like syndrome;Pitt-Hopkins-like syndrome 1 (PTHSL1);History of neurodevelopmental disorder	1.14	0.19
ABCC9	ENSG00000069431	NM_005691.3(ABCC9):c.2826T>C (p.Tyr942=)	TAT	TAC	Hypertrichotic osteochondrodysplasia Cantu type;Dilated cardiomyopathy 1O (CMD1O);Cardiovascular phenotype;Cardiomyopathy (CMYO)	1.11	0.15
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.1038T>C (p.Asp346=)	GAT	GAC	Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	1.01	0.01
SLC25A22	ENSG00000177542	NM_001191061.2(SLC25A22):c.132C>T (p.Arg44=)	CGC	CGT	Early myoclonic encephalopathy (EIEE3);Seizures; Early infantile epileptic encephalopathy with suppression bursts (EIEE)	0.52	-0.93
POLG	ENSG00000140521	NM_002693.2(POLG):c.798G>T (p.Val266=)	GTG	GTT	POLG-Related Spectrum Disorders;Progressive sclerosing poliodystrophy (MTDPS4A);Seizures;	0.46	-1.13
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.3588C>T (p.Ile1196=)	ATC	ATT	Miyoshi myopathy;Limb-Girdle Muscular Dystrophy, Recessive; Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	0.89	-0.17
COL5A1	ENSG00000130635	NM_001278074.1(COL5A1):c.804C>T (p.Gly268=)	GGC	GGT	Ehlers-Danlos syndrome, type 7A (EDS7A);Cardiovascular phenotype;	0.55	-0.87
AARS1	ENSG00000090861	NM_001605.2(AARS1):c.2580G>A (p.Leu860=)	CTG	CTA	Charcot-Marie-Tooth disease, type 2; Charcot-Marie-Tooth disease;Charcot-Marie-Tooth disease, type 2N (CMT2N)	0.21	-2.27
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.4621C>T (p.Leu1541=)	CTG	TTG	Limb-Girdle Muscular Dystrophy, Recessive;Miyoshi myopathy;Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	0.37	-1.42
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.1944G>A (p.Pro648=)	CCG	CCA	Miyoshi myopathy;Limb-Girdle Muscular Dystrophy, Recessive;Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	3.05	1.61
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.4848G>A (p.Glu1616=)	GAG	GAA	Miyoshi myopathy;Limb-Girdle Muscular Dystrophy, Recessive;Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	0.86	-0.22
CHST3	ENSG00000122863	NM_004273.5(CHST3):c.561G>C (p.Val187=)	GTG	GTC	Skeletal dysplasia;Larsen syndrome (LRS);Spondyloepiphyseal dysplasia with congenital joint dislocations (SEDCJD);Spondyloepiphyseal dysplasia congenita (SEDC)	0.52	-0.94
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.6180C>T (p.Pro2060=)	CCC	CCT	Qualitative or quantitative defects of dysferlin	1.02	0.02

NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.3090A>C (p.Gly1030=)	GGA	GGC	Pitt-Hopkins-like syndrome 2 (PTHSL2)	1.15	0.2
MEFV	ENSG00000103313	NM_000243.2(MEFV):c.42G>A (p.Glu14=)	GAG	GAA	Familial Mediterranean fever (FMF)	0.86	-0.22
ZFYVE26	ENSG00000072121	NM_015346.4(ZFYVE26):c.4854C>T (p.Leu1618=)	CTC	CTT	Spastic paraplegia;Hereditary spastic paraplegia 15 (SPG15);	0.8	-0.33
LARGE1	ENSG00000133424	NM_004737.6(LARGE1):c.1644C>T (p.Asn548=)	AAC	AAT	Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B6 (MDDGB6);Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, type A6 (MDDGA6)	1.01	0.02
SCN5A	ENSG00000183873	NM_000335.5(SCN5A):c.3870G>A (p.Leu1290=)	CTG	CTA	Brugada syndrome;Cardiovascular phenotype;Sick sinus syndrome 1, autosomal recessive (SSS1);Dilated cardiomyopathy 1E (CMD1E);Progressive familial heart block, type 1A (PFHB1A);Paroxysmal familial ventricular fibrillation 1 (VF1);Romano-Ward syndrome (RWS);Long QT syndrome 3 (LQT3); Arrhythmia;Brugada syndrome 1 (BRGDA1)	0.21	-2.27
TTN	ENSG00000155657	NM_001267550.2(TTN):c.27498G>A (p.Ser9166=)	TCG	TCA	Tibial muscular dystrophy (TMD);Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Myopathy, early-onset, with fatal cardiomyopathy (SALMY); Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Cardiomyopathy (CMYO)	3.5	1.81
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.4992C>T (p.Leu1664=)	CTC	CTT	Hereditary cancer-predisposing syndrome;Hereditary breast and ovarian cancer syndrome (HBOC);Breast-ovarian cancer, familial 1 (BROVCA1);Familial cancer of breast;Breast-ovarian cancer, familial 1 (BROVCA1);Hereditary breast and ovarian cancer syndrome (HBOC)	0.8	-0.33
FBN1	ENSG00000166147	NM_000138.5(FBN1):c.8502T>C (p.Thr2834=)	ACT	ACC	Marfan syndrome (MFS); Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD);Familial thoracic aortic aneurysm and aortic dissection (TAAD);Acromicric dysplasia (ACMICD);Geleophysic dysplasia;Stiff skin syndrome (SSKS);Ectopia lentis, isolated, autosomal dominant (ECTOL1);Weill-Marchesani syndrome;Cardiovascular phenotype;none provided	1.24	0.31
ATM	ENSG00000149311	NM_000051.3(ATM):c.3342G>A (p.Lys1114=)	AAG	AAA	Hereditary cancer-predisposing syndrome; Ataxia-telangiectasia syndrome (AT)	0.87	-0.2
NTRK1	ENSG00000198400	NM_001007792.1(NTRK1):c.1800G>A (p.Ala600=)	GCG	GCA	Hereditary insensitivity to pain with anhidrosis (CIPA)	2.88	1.52
APC	ENSG00000134982	NM_000038.6(APC):c.1005A>G (p.Leu335=)	CTA	CTG	Hereditary cancer-predisposing syndrome; Familial adenomatous polyposis 1 (FAP1)	4.81	2.27
USH2A	ENSG00000042781	NM_206933.4(USH2A):c.2052A>G (p.Gln684=)	CAA	CAG	Usher syndrome, type 2A (USH2A);Retinitis pigmentosa (RP)	2.49	1.32
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.1167G>A (p.Pro389=)	CCG	CCA	Hereditary cancer-predisposing syndrome; Breast-ovarian cancer, familial 2 (BROVCA2); Hereditary breast and ovarian cancer syndrome (HBOC)	3.05	1.61
TGFBR1	ENSG00000106799	NM_004612.4(TGFBR1):c.528G>A (p.Thr176=)	ACG	ACA	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Loeys-Dietz syndrome 1 (LDS1);Loeys-Dietz syndrome (LDS); Cardiovascular phenotype	2.96	1.57
NEB	ENSG00000183091	NM_001271208.2(NEB):c.21825C>T (p.Tyr7275=)	TAC	TAT	Nemaline myopathy 2 (NEM2)	0.9	-0.15
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.5478C>T (p.Val1826=)	GTC	GTT	Qualitative or quantitative defects of dysferlin	0.88	-0.19
BIN1	ENSG00000136717	NM_139343.3(BIN1):c.906C>T (p.Gly302=)	GGC	GGT	Myopathy, centronuclear, 2 (CNM2)	0.55	-0.87
HPS6	ENSG00000166189	NM_024747.6(HPS6):c.2250G>A (p.Ser750=)	TCG	TCA		3.5	1.81
CLN6	ENSG00000128973	NM_017882.3(CLN6):c.339G>A (p.Thr113=)	ACG	ACA	Neuronal ceroid lipofuscinosis	2.96	1.57

DBT	ENSG00000137992	NM_001918.4(DBT):c.753C>T (p.Asp251=)	GAC	GAT	Maple syrup urine disease (MSUD)	0.99	-0.01
LAMC3	ENSG00000050555	NM_006059.4(LAMC3):c.2517G>A (p.Thr839=)	ACG	ACA		2.96	1.57
GRIN2A	ENSG00000183454	NM_001134407.3(GRIN2A):c.2664G>A (p.Thr888=)	ACG	ACA	Epilepsy, focal, with speech disorder and with or without mental retardation (FESD);	2.96	1.57
CAPN3	ENSG00000092529	NM_000070.3(CAPN3):c.930T>C (p.Asp310=)	GAT	GAC	Limb-girdle muscular dystrophy, type 2A (LGMDR1)	1.01	0.01
VCL	ENSG00000035403	NM_014000.3(VCL):c.2796T>C (p.Asp932=)	GAT	GAC	Dilated cardiomyopathy 1W (CMD1W)	1.01	0.01
RBM20	ENSG00000203867	NM_001134363.3(RBM20):c.280C>T (p.Leu94=)	CTG	TTG	Dilated cardiomyopathy 1DD (CMD1DD)	0.37	-1.42
USH2A	ENSG00000042781	NM_206933.4(USH2A):c.14517G>A (p.Thr4839=)	ACG	ACA		2.96	1.57
DOLK	ENSG00000175283	NM_014908.4(DOLK):c.186G>A (p.Arg62=)	CGG	CGA	Congenital disorder of glycosylation type 1M (CDG1M)	0.6	-0.73
DOLK	ENSG00000175283	NM_014908.3(DOLK):c.771C>T (p.Ile257=)	ATC	ATT	Congenital disorder of glycosylation type 1M (CDG1M)	0.89	-0.17
CLN6	ENSG00000128973	NM_017882.3(CLN6):c.822G>A (p.Ala274=)	GCG	GCA	Neuronal ceroid lipofuscinosis	2.88	1.52
DOLK	ENSG00000175283	NM_014908.4(DOLK):c.1437T>C (p.Ser479=)	TCT	TCC	Congenital disorder of glycosylation type 1M (CDG1M)	1.02	0.03
USH2A	ENSG00000042781	NM_206933.4(USH2A):c.12093C>T (p.Tyr4031=)	TAC	TAT	Usher syndrome, type 2A (USH2A)	0.9	-0.15
CHD7	ENSG00000171316	NM_017780.4(CHD7):c.657C>T (p.Gly219=)	GGC	GGT	CHARGE association (CHARGE);Hypogonadotropic hypogonadism 5 with or without anosmia (KAL5); History of neurodevelopmental disorder	0.55	-0.87
FBN1	ENSG00000166147	NM_000138.5(FBN1):c.6681A>C (p.Ser2227=)	TCA	TCC	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Ectopia lentis, isolated, autosomal dominant (ECTOL1);Stiff skin syndrome (SSKS);Weill-Marchesani syndrome;Acromicric dysplasia (ACMICD);Marfan syndrome (MFS);Geleophysic dysplasia;Cardiovascular phenotype; Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	1.22	0.29
FBN1	ENSG00000166147	NM_000138.5(FBN1):c.2175T>C (p.Asn725=)	AAT	AAC	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Ectopia lentis, isolated, autosomal dominant (ECTOL1);Marfan syndrome (MFS);Geleophysic dysplasia;Weill-Marchesani syndrome;Stiff skin syndrome (SSKS);Acromicric dysplasia (ACMICD);Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD);Cardiovascular phenotype;Connective tissue disease	0.99	-0.02
SLC26A4	ENSG00000091137	NM_000441.2(SLC26A4):c.15C>A (p.Gly5=)	GGC	GGA	Pendred syndrome (PDS); Deafness, autosomal recessive 4, with enlarged vestibular aqueduct (DFNB4)	0.87	-0.2
STK11	ENSG00000118046	NM_000455.4(STK11):c.825G>A (p.Pro275=)	CCG	CCA	Hereditary cancer-predisposing syndrome;Peutz-Jeghers syndrome (PJS);	3.05	1.61
NEB	ENSG00000183091	NM_001271208.2(NEB):c.19455G>A (p.Lys6485=)	AAG	AAA	Nemaline myopathy 2 (NEM2)	0.87	-0.2
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.1620C>T (p.Leu540=)	CTC	CTT	Wilson disease (WND)	0.8	-0.33
CAPN3	ENSG00000092529	NM_000070.3(CAPN3):c.2235C>T (p.Tyr745=)	TAC	TAT	Limb-girdle muscular dystrophy, type 2A (LGMDR1)	0.9	-0.15
MSH6	ENSG00000116062	NM_000179.2(MSH6):c.1050C>T (p.Ala350=)	GCC	GCT	Hereditary cancer-predisposing syndrome; Hereditary nonpolyposis colorectal cancer type 5 (HNPCC5); Hereditary nonpolyposis colorectal neoplasms	0.74	-0.44
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.3897C>T (p.Ala1299=)	GCC	GCT	Aortic aneurysm, familial thoracic 4 (AAT4);Lissencephaly 4 (LIS4);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.74	-0.44
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.4392T>C (p.His1464=)	CAT	CAC	Pitt-Hopkins-like syndrome 2 (PTHSL2);History of neurodevelopmental disorder	1.23	0.3
BLM	ENSG00000197299	NM_000057.4(BLM):c.2268A>G (p.Lys756=)	AAA	AAG	Bloom syndrome (BLM);Hereditary cancer-predisposing syndrome	1.15	0.2
PEX1	ENSG00000127980	NM_000466.3(PEX1):c.2442C>T (p.Phe814=)	TTC	TTT	Peroxisome biogenesis disorder 1A (Zellweger) (PBD1A);	0.98	-0.02

ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.3369G>A (p.Pro1123=)	CCG	CCA	Wilson disease (WND);	3.05	1.61
ATP2A1	ENSG00000196296	NM_004320.5(ATP2A1):c.1167C>T (p.Tyr389=)	TAC	TAT	Brody myopathy;	0.9	-0.15
DHCR7	ENSG00000172893	NM_001360.2(DHCR7):c.399C>T (p.Ala133=)	GCC	GCT	Smith-Lemli-Opitz syndrome (SLOS);History of neurodevelopmental disorder	0.74	-0.44
ABCC9	ENSG00000069431	NM_005691.3(ABCC9):c.2862C>T (p.Asp954=)	GAC	GAT	Dilated cardiomyopathy 1O (CMD1O);Hypertrichotic osteochondrodysplasia Cantu type	0.99	-0.01
TTN	ENSG00000155657	NM_001267550.2(TTN):c.44589G>A (p.Thr14863=)	ACG	ACA	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	2.96	1.57
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.11688C>T (p.Phe3896=)	TTC	TTT	Cohen syndrome (COH1);History of neurodevelopmental disorder	0.98	-0.02
TTN	ENSG00000155657	NM_001267550.2(TTN):c.77052C>T (p.Gly25684=)	GGC	GGT	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.55	-0.87
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.2961C>T (p.Ile987=)	ATC	ATT	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Cardiovascular phenotype;Aortic aneurysm, familial thoracic 4 (AAT4)	0.89	-0.17
SLC2A10	ENSG00000197496	NM_030777.4(SLC2A10):c.816C>G (p.Ala272=)	GCC	GCG	Arterial tortuosity syndrome (ATORS);Cardiovascular phenotype;Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.23	-2.11
VCL	ENSG00000035403	NM_014000.3(VCL):c.1290C>T (p.Asp430=)	GAC	GAT	Dilated cardiomyopathy 1W (CMD1W);Cardiovascular phenotype;Cardiomyopathy (CMYO)	0.99	-0.01
RBM20	ENSG00000203867	NM_001134363.3(RBM20):c.1992C>T (p.Pro664=)	CCC	CCT	Dilated cardiomyopathy 1DD (CMD1DD);Cardiovascular phenotype;Cardiomyopathy (CMYO)	1.02	0.02
RBM20	ENSG00000203867	NM_001134363.3(RBM20):c.1179C>T (p.Pro393=)	CCC	CCT	Dilated cardiomyopathy 1DD (CMD1DD);Cardiovascular phenotype;Cardiomyopathy (CMYO)	1.02	0.02
PCSK9	ENSG00000169174	NM_174936.3(PCSK9):c.720C>T (p.Gly240=)	GGC	GGT	Familial hypercholesterolemia 3 (FHCL3);Familial hypercholesterolemia 1 (FHCL1);Hypobetalipoproteinemia; Familial hypercholesterolemia (FH)	0.55	-0.87
TTN	ENSG00000155657	NM_001267550.2(TTN):c.23121G>A (p.Lys7707=)	AAG	AAA	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Tibial muscular dystrophy (TMD);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Cardiomyopathy (CMYO)	0.87	-0.2
SLC25A22	ENSG00000177542	NM_001191061.2(SLC25A22):c.495C>T (p.Ala165=)	GCC	GCT	Seizures;Early infantile epileptic encephalopathy with suppression bursts (EIEE);Early myoclonic encephalopathy (EIEE3)	0.74	-0.44
DHCR7	ENSG00000172893	NM_001163817.2(DHCR7):c.1341C>T (p.Asp447=)	GAC	GAT	History of neurodevelopmental disorder;Smith-Lemli-Opitz syndrome (SLOS)	0.99	-0.01
DSG2	ENSG00000046604	NM_001943.5(DSG2):c.2643C>T (p.Thr881=)	ACC	ACT	Arrhythmogenic right ventricular cardiomyopathy, type 10 (ARVD10);Cardiovascular phenotype;Cardiomyopathy (CMYO)	0.8	-0.31
BARD1	ENSG00000138376	NM_000465.4(BARD1):c.1977A>G (p.Arg659=)	AGA	AGG	Hereditary cancer-predisposing syndrome;Familial cancer of breast;	0.91	-0.14
CFTR	ENSG00000001626	NM_000492.3(CFTR):c.1920T>C (p.Phe640=)	TTT	TTC	Inborn genetic diseases;Cystic fibrosis (CF)	1.02	0.02
PKP2	ENSG00000057294	NM_001005242.3(PKP2):c.195C>T (p.Ala65=)	GCC	GCT	Arrhythmogenic right ventricular dysplasia 9 (ARVD9);Cardiovascular phenotype;Cardiomyopathy (CMYO)	0.74	-0.44
PLN	ENSG00000198523	NM_002667.5(PLN):c.27C>T (p.Arg9=)	CGC	CGT	Dilated cardiomyopathy 1P (CMD1P);Cardiovascular phenotype;Cardiomyopathy (CMYO)	0.52	-0.93
SLC2A10	ENSG00000197496	NM_030777.4(SLC2A10):c.1512G>A (p.Ser504=)	TCG	TCA	Arterial tortuosity syndrome (ATORS);Cardiovascular phenotype; Familial thoracic aortic aneurysm and aortic dissection (TAAD)	3.5	1.81
TTR	ENSG00000118271	NM_000371.3(TTR):c.384C>T (p.Ala128=)	GCC	GCT	Amyloidogenic transthyretin amyloidosis;Cardiomyopathy (CMYO);Charcot-Marie-Tooth disease	0.74	-0.44

DSC2	ENSG00000134755	NM_024422.6(DSC2):c.270G>A (p.Glu90=)	GAG	GAA	Arrhythmogenic right ventricular cardiomyopathy, type 11 (ARVD11);Cardiovascular phenotype;Cardiomyopathy (CMYO);	0.86	-0.22
CDH23	ENSG00000107736	NM_022124.6(CDH23):c.8022G>A (p.Gln2674=)	CAG	CAA	Usher syndrome type 1D (USH1D);Deafness, autosomal recessive 12 (DFNB12);Usher syndrome type 1 (USH1)	0.4	-1.32
GATA4	ENSG00000136574	NM_001308093.3(GATA4):c.825C>T (p.Cys275=)	TGC	TGT	Atrioventricular septal defect 4 (AVSD4);Cardiovascular phenotype;Tetralogy of Fallot (TOF);Atrial septal defect 2 (ASD2);Ventricular septal defect 1 (VSD1);Primary dilated cardiomyopathy (DCM)	0.97	-0.05
TTN	ENSG00000155657	NM_001267550.2(TTN):c.687T>C (p.Phe229=)	TTT	TTC	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Tibial muscular dystrophy (TMD);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Dilated cardiomyopathy 1G (CMD1G)	1.02	0.02
TMPRSS3	ENSG00000160183	NM_001256317.3(TMPRSS3):c.1125C>T (p.Tyr375=)	TAC	TAT	Deafness, autosomal recessive 8 (DFNB8)	0.9	-0.15
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.1776C>A (p.Val592=)	GTC	GTA	Usher syndrome, type 2C (USH2C)	0.57	-0.8
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.2112G>A (p.Pro704=)	CCG	CCA	Usher syndrome, type 2C (USH2C)	3.05	1.61
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.2310C>G (p.Leu770=)	CTC	CTG	Wilson disease (WND);	2.02	1.02
GPSM2	ENSG00000121957	NM_013296.5(GPSM2):c.2043G>A (p.Ser681=)	TCG	TCA	Chudley-McCullough syndrome (CMCS)	3.5	1.81
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.9213C>T (p.Asp3071=)	GAC	GAT	Usher syndrome, type 2C (USH2C);none provided	0.99	-0.01
CNTNAP2	ENSG00000174469	NM_014141.6(CNTNAP2):c.3522A>T (p.Gly1174=)	GGA	GGT	Pitt-Hopkins-like syndrome 1 (PTHSL1);Pitt-Hopkins-like syndrome;History of neurodevelopmental disorder;	0.63	-0.67
CNTNAP2	ENSG00000174469	NM_014141.6(CNTNAP2):c.2508T>C (p.Phe836=)	TTT	TTC	Pitt-Hopkins-like syndrome 1 (PTHSL1);Pitt-Hopkins-like syndrome;History of neurodevelopmental disorder;	1.02	0.02
MLH1	ENSG00000076242	NM_000249.3(MLH1):c.1266C>T (p.Gly422=)	GGC	GGT	Hereditary cancer-predisposing syndrome; Hereditary nonpolyposis colorectal neoplasms;Lynch syndrome II (HNPCC2)	0.55	-0.87
BRCA2	ENSG00000139618	NM_000059.4(BRCA2):c.4614T>C (p.Ser1538=)	TCT	TCC	Breast-ovarian cancer, familial 2 (BROVCA2);Hereditary cancer-predisposing syndrome;Hereditary breast and ovarian cancer syndrome (HBOC);	1.02	0.03
MEN1	ENSG00000133895	NM_000244.3(MEN1):c.30G>T (p.Leu10=)	CTG	CTT	Multiple endocrine neoplasia, type 1 (MEN1);Hereditary cancer-predisposing syndrome; Hyperparathyroidism	0.39	-1.35
HGF	ENSG00000019991	NM_000601.6(HGF):c.1008G>A (p.Glu336=)	GAG	GAA	Deafness, autosomal recessive 39 (DFNB39);	0.86	-0.22
VCL	ENSG00000035403	NM_014000.3(VCL):c.1716T>G (p.Leu572=)	CTT	CTG	Cardiovascular phenotype;Dilated cardiomyopathy 1W (CMD1W)	2.54	1.35
BARD1	ENSG00000138376	NM_000465.4(BARD1):c.783A>G (p.Leu261=)	CTA	CTG	Hereditary cancer-predisposing syndrome;Familial cancer of breast	4.81	2.27
POLE	ENSG00000177084	NM_006231.3(POLE):c.1347G>A (p.Thr449=)	ACG	ACA	Hereditary cancer-predisposing syndrome; Colorectal cancer, susceptibility to, 12 (CRCS12)	2.96	1.57
SLC2A10	ENSG00000197496	NM_030777.4(SLC2A10):c.765C>T (p.Ser255=)	TCC	TCT	Cardiovascular phenotype;Arterial tortuosity syndrome (ATORS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.98	-0.03
KCNT1	ENSG00000107147	NM_020822.3(KCNT1):c.99A>G (p.Gln33=)	CAA	CAG	Seizures; Early infantile epileptic encephalopathy 14 (DEE14);Epilepsy, nocturnal frontal lobe, 5 (ENFL5)	2.49	1.32
NOTCH3	ENSG00000074181	NM_000435.3(NOTCH3):c.4044C>T (p.Gly1348=)	GGC	GGT	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy type 1 (CADASIL1); none provided	0.55	-0.87

FBN1	ENSG00000166147	NM_000138.5(FBN1):c.2895G>A (p.Glu965=)	GAG		GAA	Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD);Familial thoracic aortic aneurysm and aortic dissection (TAAD);Geleophysic dysplasia;Weill-Marchesani syndrome;Marfan syndrome (MFS);Ectopia lentis, isolated, autosomal dominant (ECTOL1);Stiff skin syndrome (SSKS);Acromicric dysplasia (ACMICD);Cardiovascular phenotype;	0.86	-0.22
TTN	ENSG00000155657	NM_001267550.2(TTN):c.77205G>A (p.Val25735=)	GTG	GTA	Cardiovascular phenotype; Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Tibial muscular dystrophy (TMD);Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.3	-1.74
POLD1	ENSG00000062822	NM_002691.4(POLD1):c.1620C>T (p.Gly540=)	GGC	GGT	Hereditary cancer-predisposing syndrome; Colorectal cancer 10 (CRCS10)	0.55	-0.87
CACNA1A	ENSG00000141837	NM_001127222.2(CACNA1A):c.1395G>A (p.Ser465=)	TCG	TCA	History of neurodevelopmental disorder; Episodic ataxia type 2 (EA2);Epileptic encephalopathy, early infantile, 42 (DEE42)	3.5	1.81
EYA4	ENSG00000112319	NM_004100.5(EYA4):c.783G>A (p.Thr261=)	ACG	ACA	Cardiovascular phenotype;Dilated cardiomyopathy 1J (CMD1J);Deafness, autosomal dominant 10 (DFNA10)	2.96	1.57
PCSK9	ENSG00000169174	NM_174936.3(PCSK9):c.1929C>T (p.His643=)	CAC	CAT	Familial hypercholesterolemia (FH);Familial hypercholesterolemia 3 (FHCL3);Hypobetalipoproteinemia	0.81	-0.3
CAV3	ENSG00000182533	NM_033337.3(CAV3):c.201C>A (p.Val67=)	GTC	GTA	Cardiovascular phenotype; Long QT syndrome (LQTS);Caveolinopathy	0.57	-0.8
TTN	ENSG00000155657	NM_001267550.2(TTN):c.45273C>T (p.Asn15091=)	AAC	AAT	Cardiovascular phenotype; Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Tibial muscular dystrophy (TMD);Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	1.01	0.02
TTN	ENSG00000155657	NM_001267550.2(TTN):c.81105C>A (p.Thr27035=)	ACC	ACA	Cardiovascular phenotype; Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Tibial muscular dystrophy (TMD);Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Cardiomyopathy (CMYO)	0.93	-0.1
KIF1A	ENSG00000130294	NM_004321.7(KIF1A):c.3027G>A (p.Ala1009=)	GCG	GCA	History of neurodevelopmental disorder; Spastic paraplegia 30, autosomal recessive (SPG30);Hereditary sensory and autonomic neuropathy type IIC (HSN2C);Intellectual disability, autosomal dominant 9 (NESCAVS);Spastic paraplegia 30, autosomal recessive (SPG30);none provided	2.88	1.52
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.9720T>C (p.Val3240=)	GTT	GTC	Breast-ovarian cancer, familial 2 (BROVCA2);Hereditary cancer-predisposing syndrome;Hereditary breast and ovarian cancer syndrome (HBOC);Familial cancer of breast;	1.14	0.19
ABCC9	ENSG00000069431	NM_005691.3(ABCC9):c.2262T>C (p.Tyr754=)	TAT	TAC	Cardiovascular phenotype;Cardiomyopathy (CMYO);Dilated cardiomyopathy 1O (CMD1O);Hypertrichotic osteochondrodysplasia Cantu type	1.11	0.15

PMS2	ENSG00000122512	NM_000535.7(PMS2):c.2187C>G (p.Leu729=)	CTC	CTG	Hereditary cancer-predisposing syndrome;Lynch syndrome; Hereditary nonpolyposis colorectal cancer type 4 (HNPCC4);Hereditary nonpolyposis colorectal neoplasms	2.02	1.02
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.3438C>T (p.Leu1146=)	CTC	CTT	Cardiovascular phenotype; Aortic aneurysm, familial thoracic 7 (AAT7)	0.8	-0.33
DSG2	ENSG00000046604	NM_001943.5(DSG2):c.852T>C (p.Asn284=)	AAT	AAC	Cardiomyopathy (CMYO);Arrhythmogenic right ventricular cardiomyopathy, type 10 (ARVD10)	0.99	-0.02
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.999G>A (p.Pro333=)	CCG	CCA	Cardiovascular phenotype;Aortic aneurysm, familial thoracic 7 (AAT7);none provided	3.05	1.61
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.1866G>A (p.Ala622=)	GCG	GCA	Hereditary cancer-predisposing syndrome;Breast-ovarian cancer, familial 1 (BROVCA1); Hereditary breast and ovarian cancer syndrome (HBOC)	2.88	1.52
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.3031T>C (p.Leu1011=)	TTA	CTA	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Cardiovascular phenotype;Connective tissue disease;Aortic aneurysm, familial thoracic 4 (AAT4)	0.85	-0.24
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.5160C>T (p.Ser1720=)	AGC	AGT	Cardiovascular phenotype;Connective tissue disease;Familial thoracic aortic aneurysm and aortic dissection (TAAD);Aortic aneurysm, familial thoracic 4 (AAT4)	0.72	-0.48
MYH7	ENSG00000092054	NM_000257.4(MYH7):c.1191G>A (p.Lys397=)	AAG	AAA	Myopathy, distal, 1 (MPD1);Cardiomyopathy, left ventricular noncompaction;Hypertrophic cardiomyopathy;Dilated Cardiomyopathy, Dominant;Myosin storage myopathy (MSMA);Familial hypertrophic cardiomyopathy 1 (CMH1);Cardiovascular phenotype; Cardiomyopathy (CMYO)	0.87	-0.2
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.4254A>G (p.Pro1418=)	CCA	CCG	History of neurodevelopmental disorder; Pitt-Hopkins-like syndrome 2 (PTHSL2)	0.33	-1.61
BLM	ENSG00000197299	NM_000057.4(BLM):c.3798T>G (p.Val1266=)	GTT	GTG	Hereditary cancer-predisposing syndrome; Bloom syndrome (BLM)	2.18	1.13
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.1365T>C (p.Leu455=)	CTT	CTC	History of neurodevelopmental disorder; Pitt-Hopkins-like syndrome 2 (PTHSL2)	1.26	0.33
SGCD	ENSG00000170624	NM_000337.5(SGCD):c.213G>A (p.Arg71=)	AGG	AGA	Limb-Girdle Muscular Dystrophy, Recessive;Qualitative or quantitative defects of delta-sarcoglycan; Cardiomyopathy (CMYO);Autosomal recessive limb-girdle muscular dystrophy type 2F (LGMD2F)	1.1	0.14
KCNJ10	ENSG00000177807	NM_002241.5(KCNJ10):c.219G>A (p.Ala73=)	GCG	GCA	History of neurodevelopmental disorder; EAST syndrome (SESAMES);Deafness, autosomal recessive 4, with enlarged vestibular aqueduct (DFNB4)	2.88	1.52
TCAP	ENSG00000173991	NM_003673.4(TCAP):c.60C>G (p.Ala20=)	GCC	GCG	Cardiovascular phenotype;Hypertrophic cardiomyopathy 25 (CMH25);Autosomal recessive limb-girdle muscular dystrophy type 2G (LGMD2G); Hypertrophic cardiomyopathy 25 (CMH25);Primary familial hypertrophic cardiomyopathy (HCM)	0.23	-2.11
LARGE1	ENSG00000133424	NM_004737.6(LARGE1):c.1788G>A (p.Ala596=)	GCG	GCA	Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, type A6 (MDDGA6); Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B6 (MDDGB6)	2.88	1.52
RYR2	ENSG00000198626	NM_001035.3(RYR2):c.4734C>T (p.Pro1578=)	CCC	CCT	Arrhythmogenic right ventricular dysplasia, familial, 2 (ARVD2);Catecholaminergic polymorphic ventricular tachycardia (CPVT1); Cardiovascular phenotype;Cardiomyopathy (CMYO);Catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1)	1.02	0.02

TTN	ENSG00000155657	NM_001267550.2(TTN):c.51678C>T (p.Asn17226=)	AAC	AAT	Dilated cardiomyopathy 1G (CMD1G);Tibial muscular dystrophy (TMD);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9); Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	1.01	0.02
NEB	ENSG00000183091	NM_001271208.2(NEB):c.4272G>C (p.Thr1424=)	ACG	ACC	Nemaline myopathy 2 (NEM2)	3.18	1.67
PCDH15	ENSG00000150275	NM_033056.4(PCDH15):c.5565C>T (p.Ala1855=)	GCC	GCT	Usher syndrome type 1 (USH1);	0.74	-0.44
OTOF	ENSG00000115155	NM_194248.3(OTOF):c.5742G>A (p.Leu1914=)	CTG	CTA	Deafness, autosomal recessive 9 (DFNB9);	0.21	-2.27
MARVELD2	ENSG00000152939	NM_001038603.3(MARVELD2):c.1407C>T (p.Tyr469=)	TAC	TAT	Deafness, autosomal recessive 49 (DFNB49);	0.9	-0.15
SPG7	ENSG00000197912	NM_003119.4(SPG7):c.1083G>A (p.Ala361=)	GCG	GCA	Hereditary spastic paraplegia 7 (SPG7)	2.88	1.52
MYO15A	ENSG00000091536	NM_016239.4(MYO15A):c.6186C>A (p.Ala2062=)	GCC	GCA	Deafness, autosomal recessive 3 (DFNB3);	0.67	-0.59
MYBPC3	ENSG00000134571	NM_000256.3(MYBPC3):c.471C>T (p.Phe157=)	TTC	TTT	Dilated Cardiomyopathy, Dominant;Hypertrophic cardiomyopathy;Cardiomyopathy, left ventricular noncompaction;Cardiovascular phenotype;Cardiomyopathy (CMYO);	0.98	-0.02
SCN1A	ENSG00000144285	NM_001165963.4(SCN1A):c.4731T>C (p.Asn1577=)	AAT	AAC	Epilepsy;Familial hemiplegic migraine type 3 (FHM3);Early infantile epileptic encephalopathy with suppression bursts (EIEE);History of neurodevelopmental disorder;Generalized epilepsy with febrile seizures plus, type 2 (GEFSP2);	0.99	-0.02
SLC25A22	ENSG00000177542	NM_001191061.2(SLC25A22):c.876G>A (p.Ala292=)	GCG	GCA	Early myoclonic encephalopathy (EIEE3);Seizures; Early infantile epileptic encephalopathy with suppression bursts (EIEE)	2.88	1.52
COL5A2	ENSG00000204262	NM_000393.5(COL5A2):c.75A>G (p.Lys25=)	AAA	AAG	Ehlers-Danlos syndrome, type 7A (EDS7A);Cardiovascular phenotype; Ehlers-Danlos syndrome, classic type (cEDS);Ehlers-Danlos syndrome classic type 2 (EDSCL2)	1.15	0.2
ABCC9	ENSG00000069431	NM_005691.3(ABCC9):c.1557G>A (p.Glu519=)	GAG	GAA	Hypertrichotic osteochondrodysplasia Cantu type; Cardiovascular phenotype;Cardiomyopathy (CMYO);Dilated cardiomyopathy 1O (CMD1O)	0.86	-0.22
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.4428C>T (p.Ile1476=)	ATC	ATT	Miyoshi myopathy;Limb-Girdle Muscular Dystrophy, Recessive;Qualitative or quantitative defects of dysferlin	0.89	-0.17
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.2334C>T (p.Leu778=)	CTC	CTT	Limb-Girdle Muscular Dystrophy, Recessive;Miyoshi myopathy;Qualitative or quantitative defects of dysferlin	0.8	-0.33
WHRN	ENSG00000095397	NM_015404.4(WHRN):c.1365T>C (p.Ser455=)	TCT	TCC	Usher syndrome, type 2D (USH2D);Deafness, autosomal recessive 31 (DFNB31);	1.02	0.03
MYBPC3	ENSG00000134571	NM_000256.3(MYBPC3):c.1812C>T (p.Asp604=)	GAC	GAT	Cardiomyopathy, left ventricular noncompaction;Dilated Cardiomyopathy, Dominant;Hypertrophic cardiomyopathy;Cardiovascular phenotype;Cardiomyopathy (CMYO)	0.99	-0.01
TTN	ENSG00000155657	NM_001267550.2(TTN):c.21148C>T (p.Leu7050=)	CTG	TTG	Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Dilated cardiomyopathy 1G (CMD1G);Tibial muscular dystrophy (TMD);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9); Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Cardiomyopathy (CMYO)	0.37	-1.42

SCN5A	ENSG00000183873	NM_000335.5(SCN5A):c.1044C>T (p.Pro348=)	CCC	CCT	Progressive familial heart block, type 1A (PFHB1A);Long QT syndrome 3 (LQT3);Sick sinus syndrome 1, autosomal recessive (SSS1);Brugada syndrome;Dilated cardiomyopathy 1E (CMD1E);Romano-Ward syndrome (RWS);Paroxysmal familial ventricular fibrillation 1 (VF1);Cardiovascular phenotype; Arrhythmia;Brugada syndrome 1 (BRGDA1)	1.02	0.02
DAG1	ENSG00000173402	NM_004393.6(DAG1):c.804G>A (p.Gln268=)	CAG	CAA		0.4	-1.32
SERPINA1	ENSG00000197249	NM_000295.5(SERPINA1):c.967C>T (p.Leu323=)	CTG	TTG	Alpha-1-antitrypsin deficiency (A1ATD)	0.37	-1.42
PNPLA6	ENSG00000032444	NM_001166114.2(PNPLA6):c.4077C>T (p.Pro1359=)	CCC	CCT	Hereditary spastic paraplegia 39 (SPG39)	1.02	0.02
SERPINA1	ENSG00000197249	NM_000295.5(SERPINA1):c.450A>G (p.Leu150=)	CTA	CTG		4.81	2.27
STIL	ENSG00000123473	NM_001048166.1(STIL):c.3156C>T (p.Ser1052=)	AGC	AGT		0.72	-0.48
FLNB	ENSG00000136068	NM_001457.4(FLNB):c.6843C>T (p.Ile2281=)	ATC	ATT		0.89	-0.17
AHCY	ENSG00000101444	NM_000687.4(AHCY):c.390C>T (p.Asp130=)	GAC	GAT	Hypermethioninemia with s-adenosylhomocysteine hydrolase deficiency	0.99	-0.01
GLUL	ENSG00000135821	NM_001033044.4(GLUL):c.880C>T (p.Leu294=)	CTG	TTG	Congenital brain dysgenesis due to glutamine synthetase deficiency	0.37	-1.42
HADHB	ENSG00000138029	NM_000183.3(HADHB):c.1206C>T (p.Tyr402=)	TAC	TAT	Mitochondrial trifunctional protein deficiency (MTPD)	0.9	-0.15
GAA	ENSG00000171298	NM_000152.5(GAA):c.2319C>T (p.Tyr773=)	TAC	TAT	Glycogen storage disease, type II (GSD2)	0.9	-0.15
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.1140C>T (p.Asp380=)	GAC	GAT		0.99	-0.01
CACNA1C	ENSG00000151067	NM_000719.7(CACNA1C):c.927A>G (p.Ala309=)	GCA	GCG		0.35	-1.52
AGL	ENSG00000162688	NM_000642.3(AGL):c.4575T>A (p.Ile1525=)	ATT	ATA	Glycogen storage disease type III (GSD3)	0.49	-1.02
BIN1	ENSG00000136717	NM_139343.3(BIN1):c.681G>A (p.Leu227=)	CTG	CTA	Myopathy, centronuclear, 2 (CNM2)	0.21	-2.27
HLCS	ENSG00000159267	NM_001352514.2(HLCS):c.609C>T (p.Asp203=)	GAC	GAT	Holocarboxylase synthetase deficiency	0.99	-0.01
ITGB2	ENSG00000160255	NM_000211.5(ITGB2):c.537C>T (p.Phe179=)	TTC	TTT	Leukocyte adhesion deficiency 1	0.98	-0.02
ADGRG1	ENSG00000205336	NM_201525.4(ADGRG1):c.1356G>A (p.Thr452=)	ACG	ACA		2.96	1.57
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.316C>T (p.Leu106=)	CTG	TTG		0.37	-1.42
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.655C>T (p.Leu219=)	CTG	TTG		0.37	-1.42
TJP2	ENSG00000119139	NM_004817.4(TJP2):c.1473C>A (p.Ala491=)	GCC	GCA		0.67	-0.59
VIPAS39	ENSG00000151445	NM_022067.4(VIPAS39):c.972C>T (p.Arg324=)	CGC	CGT		0.52	-0.93
PCCA	ENSG00000175198	NM_000282.4(PCCA):c.1896A>G (p.Thr632=)	ACA	ACG	Propionic acidemia (PROP)	0.34	-1.57
AP3B1	ENSG00000132842	NM_003664.4(AP3B1):c.303C>T (p.Tyr101=)	TAC	TAT	Hermansky-Pudlak syndrome 2 (HPS2)	0.9	-0.15
MEFV	ENSG00000103313	NM_000243.2(MEFV):c.1173T>C (p.Asp391=)	GAT	GAC	Familial Mediterranean fever (FMF)	1.01	0.01
VIPAS39	ENSG00000151445	NM_022067.4(VIPAS39):c.1071C>T (p.Asn357=)	AAC	AAT		1.01	0.02
SLC12A6	ENSG00000140199	NM_001365088.1(SLC12A6):c.3249G>A (p.Arg1083=)	CGG	CGA		0.6	-0.73
IMPDH1	ENSG00000106348	NM_000883.4(IMPDH1):c.1173A>G (p.Thr391=)	ACA	ACG		0.34	-1.57
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.897G>A (p.Thr299=)	ACG	ACA		2.96	1.57
AGL	ENSG00000162688	NM_000642.3(AGL):c.609A>G (p.Lys203=)	AAA	AAG	Glycogen storage disease type III (GSD3)	1.15	0.2
CNKSR2	ENSG00000149970	NM_014927.5(CNKSR2):c.2199G>A (p.Thr733=)	ACG	ACA		2.96	1.57
IL12RB1	ENSG00000096996	NM_005535.3(IL12RB1):c.930G>A (p.Ser310=)	TCG	TCA	Immunodeficiency 30 (IMD30)	3.5	1.81
PCDH15	ENSG00000150275	NM_033056.4(PCDH15):c.4320G>A (p.Pro1440=)	CCG	CCA		3.05	1.61
LARS1	ENSG00000133706	NM_020117.11(LARS1):c.1500C>T (p.Asp500=)	GAC	GAT		0.99	-0.01
NEB	ENSG00000183091	NM_001271208.2(NEB):c.2739C>T (p.Ser913=)	AGC	AGT	Nemaline myopathy 2 (NEM2)	0.72	-0.48

NEB	ENSG00000183091	NM_001271208.2(NEB):c.1182A>C (p.Thr394=)	ACA	ACC	Nemaline myopathy 2 (NEM2)	1.07	0.1
DMD	ENSG00000198947	NM_004006.2(DMD):c.4851T>G (p.Thr1617=)	ACT	ACG		0.39	-1.36
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.7887C>T (p.Asn2629=)	AAC	AAT		1.01	0.02
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.192C>T (p.Asn64=)	AAC	AAT	Autosomal recessive polycystic kidney disease (ARPKD)	1.01	0.02
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.10314C>T (p.Asp3438=)	GAC	GAT		0.99	-0.01
LYST	ENSG00000143669	NM_000081.4(LYST):c.7911G>A (p.Thr2637=)	ACG	ACA	Chédiak-Higashi syndrome (CHS)	2.96	1.57
LYST	ENSG00000143669	NM_001301365.1(LYST):c.2700A>G (p.Leu900=)	CTA	CTG	Chédiak-Higashi syndrome (CHS)	4.81	2.27
DGKD	ENSG00000077044	NM_152879.3(DGKD):c.2925G>A (p.Glu975=)	GAG	GAA		0.86	-0.22
SCP2	ENSG00000116171	NM_002979.5(SCP2):c.900C>T (p.Asp300=)	GAC	GAT		0.99	-0.01
BIN1	ENSG00000136717	NM_139343.3(BIN1):c.675G>A (p.Glu225=)	GAG	GAA	Myopathy, centronuclear, 2 (CNM2)	0.86	-0.22
NEB	ENSG00000183091	NM_001271208.2(NEB):c.7623C>T (p.Ala2541=)	GCC	GCT	Nemaline myopathy 2 (NEM2)	0.74	-0.44
ACOX1	ENSG00000161533	NM_004035.7(ACOX1):c.912C>T (p.Ser304=)	AGC	AGT	Peroxisomal acyl-CoA oxidase deficiency	0.72	-0.48
DMD	ENSG00000198947	NM_004006.2(DMD):c.4080G>A (p.Arg1360=)	AGG	AGA		1.1	0.14
ELAC2	ENSG00000006744	NM_018127.7(ELAC2):c.1458T>C (p.Leu486=)	CTT	CTC		1.26	0.33
CARD9	ENSG00000187796	NM_052813.4(CARD9):c.960G>A (p.Glu320=)	GAG	GAA	Candidiasis, familial, 2 (CANDF2)	0.86	-0.22
DCDC2	ENSG00000146038	NM_016356.5(DCDC2):c.888A>G (p.Lys296=)	AAA	AAG		1.15	0.2
PRF1	ENSG00000180644	NM_001083116.3(PRF1):c.519G>A (p.Thr173=)	ACG	ACA	Familial hemophagocytic lymphohistiocytosis 2 (FHL2)	2.96	1.57
FGFR3	ENSG00000068078	NM_000142.5(FGFR3):c.1752G>A (p.Pro584=)	CCG	CCA		3.05	1.61
CBS	ENSG00000160200	NM_000071.2(CBS):c.600G>A (p.Pro200=)	CCG	CCA	Classic homocystinuria	3.05	1.61
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.2217C>T (p.Asp739=)	GAC	GAT		0.99	-0.01
PROM1	ENSG00000007062	NM_006017.3(PROM1):c.2319C>T (p.Thr773=)	ACC	ACT		0.8	-0.31
DCDC2	ENSG00000146038	NM_016356.5(DCDC2):c.402G>A (p.Pro134=)	CCG	CCA		3.05	1.61
NEB	ENSG00000183091	NM_001271208.2(NEB):c.1953G>A (p.Glu651=)	GAG	GAA	Nemaline myopathy 2 (NEM2)	0.86	-0.22
FLNB	ENSG00000136068	NM_001457.4(FLNB):c.6154C>T (p.Leu2052=)	CTG	TTG		0.37	-1.42
POMGNT1	ENSG00000085998	NM_017739.3(POMGNT1):c.444G>A (p.Val148=)	GTG	GTA		0.3	-1.74
SPART	ENSG00000133104	NM_015087.5(SPART):c.627G>A (p.Pro209=)	CCG	CCA	Troyer syndrome (SPG20)	3.05	1.61
TRPV4	ENSG00000111199	NM_021625.4(TRPV4):c.2247C>T (p.Pro749=)	CCC	CCT		1.02	0.02
DAG1	ENSG00000173402	NM_004393.6(DAG1):c.222C>T (p.Val74=)	GTC	GTT		0.88	-0.19
SCN3A	ENSG00000153253	NM_006922.4(SCN3A):c.3087C>G (p.Ala1029=)	GCC	GCG		0.23	-2.11
HLCS	ENSG00000159267	NM_001352514.2(HLCS):c.1074G>A (p.Thr358=)	ACG	ACA	Holocarboxylase synthetase deficiency	2.96	1.57
STRA6	ENSG00000137868	NM_022369.4(STRA6):c.993G>A (p.Thr331=)	ACG	ACA	Matthew-Wood syndrome (MCOPS9)	2.96	1.57
RBM10	ENSG00000182872	NM_005676.5(RBM10):c.1104A>G (p.Pro368=)	CCA	CCG		0.33	-1.61
NR1H4	ENSG00000012504	NM_001206979.2(NR1H4):c.438G>A (p.Gly146=)	GGG	GGA		1.13	0.17
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.2289C>T (p.Asn763=)	AAC	AAT	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD)	1.01	0.02
TOPORS	ENSG00000197579	NM_005802.5(TOPORS):c.2115T>C (p.Thr705=)	ACT	ACC		1.24	0.31
ALDH5A1	ENSG00000112294	NM_001080.3(ALDH5A1):c.525C>T (p.Tyr175=)	TAC	TAT	Succinate-semialdehyde dehydrogenase deficiency (SSADHD)	0.9	-0.15
SLC1A4	ENSG00000115902	NM_003038.5(SLC1A4):c.1182G>A (p.Ala394=)	GCG	GCA		2.88	1.52
MTMR14	ENSG00000163719	NM_001077525.3(MTMR14):c.480C>T (p.Asn160=)	AAC	AAT		1.01	0.02
MITF	ENSG00000187098	NM_001354604.2(MITF):c.639C>T (p.Asn213=)	AAC	AAT		1.01	0.02
BCOR	ENSG00000183337	NM_001123385.2(BCOR):c.2910G>A (p.Ala970=)	GCG	GCA		2.88	1.52
LRSAM1	ENSG00000148356	NM_138361.5(LRSAM1):c.1515G>A (p.Ser505=)	TCG	TCA	Charcot-Marie-Tooth disease type 2P (CMT2P)	3.5	1.81

IL1RN	ENSG00000136689	NM_173842.3(IL1RN):c.414T>C (p.Ser138=)	TCT	TCC	Osteomyelitis, sterile multifocal, with periostitis and pustulosis (OMPP)	1.02	0.03
ABCB4	ENSG00000005471	NM_000443.4(ABCB4):c.3111T>C (p.Asn1037=)	AAT	AAC		0.99	-0.02
PC	ENSG00000173599	NM_001040716.2(PC):c.879C>T (p.Ser293=)	AGC	AGT	Pyruvate carboxylase deficiency	0.72	-0.48
AFF2	ENSG00000155966	NM_002025.4(AFF2):c.2424C>T (p.Asp808=)	GAC	GAT		0.99	-0.01
FAT4	ENSG00000196159	NM_024582.4(FAT4):c.12060C>T (p.Gly4020=)	GGC	GGT		0.55	-0.87
ITGB2	ENSG00000160255	NM_000211.5(ITGB2):c.681C>T (p.Ser227=)	TCC	TCT	Leukocyte adhesion deficiency 1	0.98	-0.03
KCNMA1	ENSG00000156113	NM_001161352.2(KCNMA1):c.1056C>T (p.Thr352=)	ACC	ACT	Paroxysmal nonkinesigenic dyskinesia, 3, with or without generalized epilepsy (PNKD3)	0.8	-0.31
SP110	ENSG00000135899	NM_004509.4(SP110):c.1200C>T (p.Asp400=)	GAC	GAT	Hepatic veno-occlusive disease-immunodeficiency syndrome	0.99	-0.01
IL36RN	ENSG00000136695	NM_173170.1(IL36RN):c.363G>A (p.Leu121=)	CTG	CTA	Pustular psoriasis, generalized (PSORS14)	0.21	-2.27
IRAK4	ENSG00000198001	NM_016123.3(IRAK4):c.720T>C (p.Cys240=)	TGT	TGC	Immunodeficiency due to interleukin-1 receptor-associated kinase-4 deficiency (IMD67)	1.03	0.05
VIPAS39	ENSG00000151445	NM_022067.4(VIPAS39):c.558A>G (p.Glu186=)	GAA	GAG		1.16	0.22
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.9951T>G (p.Val3317=)	GTT	GTG	Cohen syndrome (COH1)	2.18	1.13
SPG11	ENSG00000104133	NM_025137.4(SPG11):c.2082C>T (p.Ser694=)	AGC	AGT	Spastic paraplegia 11, autosomal recessive (SPG11)	0.72	-0.48
LYST	ENSG00000143669	NM_001301365.1(LYST):c.6291C>T (p.Ala2097=)	GCC	GCT	Chédiak-Higashi syndrome (CHS)	0.74	-0.44
NEK1	ENSG00000137601	NM_012224.3(NEK1):c.3483C>T (p.Asn1161=)	AAC	AAT	Short rib-polydactyly syndrome, Majewski type (SRTD6)	1.01	0.02
SIK1	ENSG00000142178	NM_173354.5(SIK1):c.408C>T (p.Ala136=)	GCC	GCT		0.74	-0.44
GAD1	ENSG00000128683	NM_000817.3(GAD1):c.399T>C (p.Asp133=)	GAT	GAC	Cerebral palsy, spastic quadriplegic, 1 (CPSQ1)	1.01	0.01
SPG11	ENSG00000104133	NM_025137.4(SPG11):c.5796T>C (p.His1932=)	CAT	CAC	Spastic paraplegia 11, autosomal recessive (SPG11)	1.23	0.3
CREBBP	ENSG00000005339	NM_004380.3(CREBBP):c.711C>T (p.Ser237=)	AGC	AGT		0.72	-0.48
NEB	ENSG00000183091	NM_001271208.2(NEB):c.6624G>A (p.Pro2208=)	CCG	CCA	Nemaline myopathy 2 (NEM2)	3.05	1.61
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.1095G>A (p.Glu365=)	GAG	GAA		0.86	-0.22
CACNA1F	ENSG00000102001	NM_001256789.3(CACNA1F):c.3930C>A (p.Ile1310=)	ATC	ATA		0.44	-1.2
LYST	ENSG00000143669	NM_001301365.1(LYST):c.2313G>A (p.Gln771=)	CAG	CAA	Chédiak-Higashi syndrome (CHS)	0.4	-1.32
WDR35	ENSG00000118965	NM_020779.4(WDR35):c.1227A>G (p.Thr409=)	ACA	ACG		0.34	-1.57
ST3GAL5	ENSG00000115525	NM_003896.4(ST3GAL5):c.390G>A (p.Ala130=)	GCG	GCA	GM3 synthase deficiency (SPDRS)	2.88	1.52
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.5250A>G (p.Pro1750=)	CCA	CCG		0.33	-1.61
SPG11	ENSG00000104133	NM_025137.4(SPG11):c.4755A>C (p.Ala1585=)	GCA	GCC	Spastic paraplegia 11, autosomal recessive (SPG11)	1.5	0.59
TCN2	ENSG00000185339	NM_000355.4(TCN2):c.882C>T (p.Pro294=)	CCC	CCT	Transcolabamin II deficiency	1.02	0.02
MEFV	ENSG00000103313	NM_000243.2(MEFV):c.1038C>G (p.Gly346=)	GGC	GGG	Familial Mediterranean fever (FMF)	0.77	-0.37
COL12A1	ENSG00000111799	NM_004370.6(COL12A1):c.8856C>T (p.Ser2952=)	AGC	AGT		0.72	-0.48
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.11343C>T (p.Gly3781=)	GGC	GGT		0.55	-0.87
MYH14	ENSG00000105357	NM_001145809.2(MYH14):c.615G>A (p.Thr205=)	ACG	ACA		2.96	1.57
NPHP1	ENSG00000144061	NM_000272.4(NPHP1):c.336G>A (p.Gly112=)	GGG	GGA		1.13	0.17
IL12RB1	ENSG00000096996	NM_005535.3(IL12RB1):c.261C>T (p.Cys87=)	TGC	TGT	Immunodeficiency 30 (IMD30)	0.97	-0.05
IL12RB1	ENSG00000096996	NM_005535.3(IL12RB1):c.390C>T (p.Thr130=)	ACC	ACT	Immunodeficiency 30 (IMD30)	0.8	-0.31
FAT4	ENSG00000196159	NM_024582.4(FAT4):c.5367C>T (p.Ile1789=)	ATC	ATT		0.89	-0.17
TCN2	ENSG00000185339	NM_000355.4(TCN2):c.810G>A (p.Ala270=)	GCG	GCA	Transcolabamin II deficiency	2.88	1.52
MAGI2	ENSG00000187391	NM_012301.4(MAGI2):c.2142G>A (p.Pro714=)	CCG	CCA		3.05	1.61
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.14106C>T (p.Thr4702=)	ACC	ACT		0.8	-0.31

INSR	ENSG00000171105	NM_000208.4(INSR):c.1179G>A (p.Gly393=)	GGG	GGA		1.13	0.17
SMARCAL1	ENSG00000138375	NM_014140.4(SMARCAL1):c.1785C>T (p.Ile595=)	ATC	ATT	Schimke immuno-osseous dysplasia (SIOD)	0.89	-0.17
DHCR7	ENSG00000172893	NM_001360.3(DHCR7):c.765C>T (p.Phe255=)	TTC	TTT	Smith-Lemli-Opitz syndrome (SLOS)	0.98	-0.02
PCCA	ENSG00000175198	NM_000282.4(PCCA):c.945G>A (p.Ala315=)	GCG	GCA	Propionic acidemia (PROP)	2.88	1.52
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.2463C>G (p.Ala821=)	GCC	GCG	Autosomal recessive polycystic kidney disease (ARPKD)	0.23	-2.11
SCN3A	ENSG00000153253	NM_006922.4(SCN3A):c.3933T>C (p.Pro1311=)	CCT	CCC		0.98	-0.02
IL12RB1	ENSG00000096996	NM_005535.3(IL12RB1):c.1914T>C (p.Pro638=)	CCT	CCC	Immunodeficiency 30 (IMD30)	0.98	-0.02
NEB	ENSG00000183091	NM_001271208.2(NEB):c.5616G>A (p.Pro1872=)	CCG	CCA	Nemaline myopathy 2 (NEM2)	3.05	1.61
L1CAM	ENSG00000198910	NM_001278116.2(L1CAM):c.3192G>T (p.Ser1064=)	TCG	TCT		4.18	2.06
NEB	ENSG00000183091	NM_001271208.2(NEB):c.6513T>C (p.Asp2171=)	GAT	GAC	Nemaline myopathy 2 (NEM2)	1.01	0.01
ITGB2	ENSG00000160255	NM_000211.5(ITGB2):c.1575C>T (p.Pro525=)	CCC	CCT	Leukocyte adhesion deficiency 1	1.02	0.02
FRAS1	ENSG00000138759	NM_025074.7(FRAS1):c.990A>G (p.Glu330=)	GAA	GAG		1.16	0.22
ATP2B3	ENSG00000067842	NM_001001344.2(ATP2B3):c.1099C>T (p.Leu367=)	CTA	TTA		1.18	0.24
LIPA	ENSG00000107798	NM_000235.4(LIPA):c.714G>A (p.Ala238=)	GCG	GCA		2.88	1.52
NEB	ENSG00000183091	NM_001271208.2(NEB):c.11361G>A (p.Pro3787=)	CCG	CCA	Nemaline myopathy 2 (NEM2)	3.05	1.61
NEB	ENSG00000183091	NM_001271208.2(NEB):c.20853C>T (p.Ile6951=)	ATC	ATT	Nemaline myopathy 2 (NEM2)	0.89	-0.17
HSPG2	ENSG00000142798	NM_005529.7(HSPG2):c.9060G>A (p.Arg3020=)	AGG	AGA		1.1	0.14
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.4917C>T (p.Asn1639=)	AAC	AAT		1.01	0.02
ATP2A1	ENSG00000196296	NM_004320.6(ATP2A1):c.765G>A (p.Glu255=)	GAG	GAA	Brody myopathy	0.86	-0.22
SPINK5	ENSG00000133710	NM_006846.3(SPINK5):c.750C>T (p.Asp250=)	GAC	GAT	Netherton syndrome (NETH)	0.99	-0.01
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.786C>G (p.Gly262=)	GGC	GGG		0.77	-0.37
DOCK8	ENSG00000107099	NM_203447.3(DOCK8):c.1098G>A (p.Thr366=)	ACG	ACA	Hyperimmunoglobulin E recurrent infection syndrome, autosomal recessive (HIES2)	2.96	1.57
DNM2	ENSG00000079805	NM_001005360.2(DNM2):c.216G>A (p.Gln72=)	CAG	CAA		0.4	-1.32
FUCA1	ENSG00000179163	NM_000147.4(FUCA1):c.936G>A (p.Leu312=)	TTG	TTA	Fucosidosis	0.65	-0.61
UBR1	ENSG00000159459	NM_174916.3(UBR1):c.264G>A (p.Glu88=)	GAG	GAA		0.86	-0.22
PHKB	ENSG00000102893	NM_000293.3(PHKB):c.2445T>C (p.Phe815=)	TTT	TTC		1.02	0.02
SPG11	ENSG00000104133	NM_025137.4(SPG11):c.4578A>G (p.Thr1526=)	ACA	ACG	Spastic paraplegia 11, autosomal recessive (SPG11)	0.34	-1.57
VPS33B	ENSG00000184056	NM_018668.4(VPS33B):c.1362C>T (p.Ala454=)	GCC	GCT		0.74	-0.44
ITGB2	ENSG00000160255	NM_000211.5(ITGB2):c.1725C>T (p.Cys575=)	TGC	TGT	Leukocyte adhesion deficiency 1	0.97	-0.05
PCDH19	ENSG00000165194	NM_001184880.2(PCDH19):c.2721T>C (p.Ser907=)	AGT	AGC		1.4	0.48
TMEM237	ENSG00000155755	NM_001044385.3(TMEM237):c.183C>T (p.Pro61=)	CCC	CCT	Joubert syndrome 14 (JBTS14)	1.02	0.02
ROR2	ENSG00000169071	NM_004560.4(ROR2):c.234G>A (p.Thr78=)	ACG	ACA		2.96	1.57
PRF1	ENSG00000180644	NM_001083116.3(PRF1):c.1620A>G (p.Gln540=)	CAA	CAG	Familial hemophagocytic lymphohistiocytosis 2 (FHL2)	2.49	1.32
MAGI2	ENSG00000187391	NM_012301.4(MAGI2):c.2454C>T (p.Arg818=)	CGC	CGT		0.52	-0.93
LYST	ENSG00000143669	NM_001301365.1(LYST):c.2946T>C (p.Tyr982=)	TAT	TAC	Chédiak-Higashi syndrome (CHS)	1.11	0.15
TDRD7	ENSG00000196116	NM_014290.3(TDRD7):c.231C>T (p.Cys77=)	TGC	TGT	Cataract, autosomal recessive congenital 4 (CTRCT36)	0.97	-0.05
MLH3	ENSG00000119684	NM_001040108.1(MLH3):c.3576C>T (p.Leu1192=)	CTC	CTT	Hereditary nonpolyposis colorectal cancer type 7 (HNPCC7)	0.8	-0.33
PEX5	ENSG00000139197	NM_001131025.1(PEX5):c.543C>T (p.Thr181=)	ACC	ACT		0.8	-0.31
GALC	ENSG00000054983	NM_000153.4(GALC):c.1272G>A (p.Gln424=)	CAG	CAA	Galactosylceramide beta-galactosidase deficiency	0.4	-1.32
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.2145G>T (p.Ser715=)	TCG	TCT		4.18	2.06
NIPBL	ENSG00000164190	NM_133433.4(NIPBL):c.7728T>C (p.Tyr2576=)	TAT	TAC		1.11	0.15

SCN3A	ENSG00000153253	NM_006922.4(SCN3A):c.2121C>T (p.Ser707=)	AGC	AGT		0.72	-0.48
VCP	ENSG00000165280	NM_007126.5(VCP):c.732C>T (p.Tyr244=)	TAC	TAT		0.9	-0.15
LRP5	ENSG00000162337	NM_002335.4(LRP5):c.2124G>A (p.Ser708=)	TCG	TCA		3.5	1.81
KMT2D	ENSG00000167548	NM_003482.3(KMT2D):c.2551C>T (p.Leu851=)	CTG	TTG		0.37	-1.42
EPS8	ENSG00000151491	NM_004447.6(EPS8):c.1230A>C (p.Gly410=)	GGA	GGC		1.15	0.2
COL6A1	ENSG00000142156	NM_001848.2(COL6A1):c.519G>A (p.Glu173=)	GAG	GAA		0.86	-0.22
LYST	ENSG00000143669	NM_001301365.1(LYST):c.196T>C (p.Leu66=)	TTG	CTG	Chédiak-Higashi syndrome (CHS)	2.67	1.42
SMARCAL1	ENSG00000138375	NM_014140.3(SMARCAL1):c.1413C>T (p.Ile471=)	ATC	ATT	Schimke immuno-osseous dysplasia (SIOD)	0.89	-0.17
AP3B1	ENSG00000132842	NM_003664.5(AP3B1):c.1749G>A (p.Pro583=)	CCG	CCA	Hermansky-Pudlak syndrome 2 (HPS2)	3.05	1.61
IL36RN	ENSG00000136695	NM_173170.1(IL36RN):c.6C>T (p.Val2=)	GTC	GTT	Pustular psoriasis, generalized (PSORS14)	0.88	-0.19
SPINK5	ENSG00000133710	NM_006846.4(SPINK5):c.1732C>A (p.Arg578=)	CGA	AGA	Netherton syndrome (NETH)	2.09	1.06
LYST	ENSG00000143669	NM_000081.4(LYST):c.4548C>T (p.Ser1516=)	AGC	AGT	Chédiak-Higashi syndrome (CHS)	0.72	-0.48
ACAN	ENSG00000157766	NM_001369268.1(ACAN):c.7092G>A (p.Lys2364=)	AAG	AAA		0.87	-0.2
MAGI2	ENSG00000187391	NM_012301.4(MAGI2):c.1425T>C (p.Tyr475=)	TAT	TAC		1.11	0.15
HEXB	ENSG00000049860	NM_000521.4(HEXB):c.918G>C (p.Leu306=)	CTG	CTC	Sandhoff disease	0.49	-1.02
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.19180T>C (p.Leu6394=)	TTG	CTG		2.67	1.42
RIMS1	ENSG00000079841	NM_014989.5(RIMS1):c.1764A>G (p.Gln588=)	CAA	CAG		2.49	1.32
SCN3A	ENSG00000153253	NM_006922.4(SCN3A):c.5889T>C (p.Ser1963=)	TCT	TCC		1.02	0.03
HLCS	ENSG00000159267	NM_001352514.2(HLCS):c.2352C>T (p.Ile784=)	ATC	ATT	Holocarboxylase synthetase deficiency	0.89	-0.17
ERCC6	ENSG00000225830	NM_000124.4(ERCC6):c.2124C>T (p.Ser708=)	TCC	TCT		0.98	-0.03
ACVR2B	ENSG00000114739	NM_001106.4(ACVR2B):c.1269G>A (p.Ser423=)	TCG	TCA	Heterotaxy, visceral, 4, autosomal (HTX4)	3.5	1.81
CFTR	ENSG00000001626	NM_000492.3(CFTR):c.2280G>A (p.Thr760=)	ACG	ACA		2.96	1.57
RBM20	ENSG00000203867	NM_001134363.3(RBM20):c.1161G>A (p.Ala387=)	GCG	GCA	Dilated cardiomyopathy 1DD (CMD1DD)	2.88	1.52
TGFB1	ENSG00000105329	NM_000660.7(TGFB1):c.918C>T (p.Leu306=)	CTC	CTT		0.8	-0.33
JAK3	ENSG00000105639	NM_000215.3(JAK3):c.1551T>A (p.Pro517=)	CCT	CCA	Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-negative	0.98	-0.03
SLC22A5	ENSG00000197375	NM_003060.4(SLC22A5):c.414C>T (p.Asp138=)	GAC	GAT	Renal carnitine transport defect (CDSP)	0.99	-0.01
PRF1	ENSG00000180644	NM_001083116.3(PRF1):c.286C>A (p.Arg96=)	CGG	AGG	Familial hemophagocytic lymphohistiocytosis 2 (FHL2)	1.15	0.2
CREBBP	ENSG00000005339	NM_004380.3(CREBBP):c.2526G>A (p.Gln842=)	CAG	CAA		0.4	-1.32
CARD9	ENSG00000187796	NM_052813.4(CARD9):c.801C>T (p.Ser267=)	TCC	TCT	Candidiasis, familial, 2 (CANDF2)	0.98	-0.03
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.2637G>A (p.Thr879=)	ACG	ACA		2.96	1.57
AP3B1	ENSG00000132842	NM_003664.4(AP3B1):c.3207G>A (p.Gln1069=)	CAG	CAA	Hermansky-Pudlak syndrome 2 (HPS2)	0.4	-1.32
HSPG2	ENSG00000142798	NM_005529.7(HSPG2):c.1086G>A (p.Lys362=)	AAG	AAA		0.87	-0.2
SIL1	ENSG00000120725	NM_022464.5(SIL1):c.849C>T (p.Leu283=)	CTC	CTT		0.8	-0.33
INSR	ENSG00000171105	NM_000208.4(INSR):c.2970G>A (p.Pro990=)	CCG	CCA		3.05	1.61
PAPSS2	ENSG00000198682	NM_001015880.2(PAPSS2):c.1167C>T (p.Asp389=)	GAC	GAT		0.99	-0.01
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.9219C>T (p.Ser3073=)	AGC	AGT		0.72	-0.48
NHS	ENSG00000188158	NM_001291867.2(NHS):c.618G>A (p.Pro206=)	CCG	CCA		3.05	1.61
POMGNT1	ENSG00000085998	NM_017739.3(POMGNT1):c.1536T>C (p.Phe512=)	TTT	TTC		1.02	0.02
DNAL1	ENSG00000119661	NM_031427.4(DNAL1):c.517C>T (p.Leu173=)	CTG	TTG		0.37	-1.42
PCNT	ENSG00000160299	NM_006031.6(PCNT):c.5940C>T (p.Gly1980=)	GGC	GGT		0.55	-0.87
TCTN3	ENSG00000119977	NM_015631.6(TCTN3):c.1569A>G (p.Leu523=)	CTA	CTG		4.81	2.27

HGF	ENSG00000019991	NM_000601.6(HGF):c.2019T>C (p.Tyr673=)	TAT	TAC		1.11	0.15
WRN	ENSG00000165392	NM_000553.6(WRN):c.1302G>A (p.Thr434=)	ACG	ACA	Werner syndrome (WRN)	2.96	1.57
CYP27A1	ENSG00000135929	NM_000784.4(CYP27A1):c.504A>T (p.Pro168=)	CCA	CCT	Cholestanol storage disease (CTX)	1.02	0.03
ABCG8	ENSG00000143921	NM_022437.3(ABCG8):c.729C>T (p.Leu243=)	CTC	CTT		0.8	-0.33
USH1C	ENSG00000006611	NM_153676.4(USH1C):c.2265C>T (p.Leu755=)	CTC	CTT		0.8	-0.33
CIITA	ENSG00000179583	NM_000246.3(CIITA):c.2892G>A (p.Leu964=)	CTG	CTA	Bare lymphocyte syndrome 2	0.21	-2.27
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.6180C>T (p.Tyr2060=)	TAC	TAT		0.9	-0.15
ITGB2	ENSG00000160255	NM_000211.5(ITGB2):c.525C>T (p.Thr175=)	ACC	ACT	Leukocyte adhesion deficiency 1	0.8	-0.31
KCND3	ENSG00000171385	NM_004980.4(KCND3):c.1041G>A (p.Ser347=)	TCG	TCA		3.5	1.81
COL11A1	ENSG00000060718	NM_001854.4(COL11A1):c.3231G>A (p.Pro1077=)	CCG	CCA		3.05	1.61
NR1H4	ENSG00000012504	NM_001206979.2(NR1H4):c.18T>C (p.Asn6=)	AAT	AAC		0.99	-0.02
ALG8	ENSG00000159063	NM_024079.5(ALG8):c.441A>T (p.Val147=)	GTA	GTT	ALG8-CDG	1.53	0.62
MAN2B1	ENSG00000104774	NM_000528.4(MAN2B1):c.1158G>A (p.Gln386=)	CAG	CAA	Deficiency of alpha-mannosidase (MANSA)	0.4	-1.32
SLC22A5	ENSG00000197375	NM_003060.4(SLC22A5):c.522C>T (p.Phe174=)	TTC	TTT	Renal carnitine transport defect (CDSP)	0.98	-0.02
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.7584G>A (p.Gln2528=)	CAG	CAA		0.4	-1.32
XPNPEP3	ENSG00000196236	NM_022098.4(XPNPEP3):c.597G>A (p.Thr199=)	ACG	ACA	Nephronophthisis-like nephropathy 1 (NPHPL1)	2.96	1.57
TNFRSF11B	ENSG00000164761	NM_002546.4(TNFRSF11B):c.69G>A (p.Thr23=)	ACG	ACA		2.96	1.57
DBH	ENSG00000123454	NM_000787.4(DBH):c.354C>T (p.Asp118=)	GAC	GAT	Orthostatic hypotension 1 (ORTHYP1)	0.99	-0.01
FRMPD4	ENSG00000169933	NM_001368397.1(FRMPD4):c.2829C>T (p.Tyr943=)	TAC	TAT		0.9	-0.15
CPT2	ENSG00000157184	NM_000098.3(CPT2):c.321A>G (p.Lys107=)	AAA	AAG	Carnitine palmitoyltransferase II deficiency (CPT2)	1.15	0.2
NLRP12	ENSG00000142405	NM_144687.3(NLRP12):c.858C>T (p.Pro286=)	CCC	CCT	Familial cold autoinflammatory syndrome 2 (FCAS2)	1.02	0.02
OCA2	ENSG00000104044	NM_000275.3(OCA2):c.45G>A (p.Pro15=)	CCG	CCA		3.05	1.61
INSR	ENSG00000171105	NM_000208.4(INSR):c.3165G>A (p.Ala1055=)	GCG	GCA		2.88	1.52
INSR	ENSG00000171105	NM_000208.4(INSR):c.1665T>C (p.Ser555=)	AGT	AGC		1.4	0.48
LRP5	ENSG00000162337	NM_002335.4(LRP5):c.1818G>A (p.Ala606=)	GCG	GCA		2.88	1.52
SLC22A5	ENSG00000197375	NM_003060.4(SLC22A5):c.1440C>T (p.Phe480=)	TTC	TTT	Renal carnitine transport defect (CDSP)	0.98	-0.02
TGM6	ENSG00000166948	NM_198994.3(TGM6):c.1431G>A (p.Gly477=)	GGG	GGA		1.13	0.17
IL17RA	ENSG00000177663	NM_014339.6(IL17RA):c.1407C>T (p.Cys469=)	TGC	TGT	Immunodeficiency 51 (IMD51)	0.97	-0.05
PYGL	ENSG00000100504	NM_002863.5(PYGL):c.603G>T (p.Val201=)	GTG	GTT	Glycogen storage disease, type VI (GSD6)	0.46	-1.13
WDR81	ENSG00000167716	NM_001163809.1(WDR81):c.5118T>C (p.Leu1706=)	CTT	CTC		1.26	0.33
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.8644C>T (p.Leu2882=)	CTG	TTG		0.37	-1.42
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.5787G>A (p.Ala1929=)	GCG	GCA		2.88	1.52
NPHP4	ENSG00000131697	NM_015102.5(NPHP4):c.1935A>G (p.Leu645=)	CTA	CTG		4.81	2.27
PRF1	ENSG00000180644	NM_001083116.3(PRF1):c.1140G>A (p.Pro380=)	CCG	CCA	Familial hemophagocytic lymphohistiocytosis 2 (FHL2)	3.05	1.61
SPG11	ENSG00000104133	NM_025137.4(SPG11):c.4410C>T (p.Leu1470=)	CTC	CTT	Spastic paraplegia 11, autosomal recessive (SPG11)	0.8	-0.33
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.12798T>A (p.Ser4266=)	TCT	TCA		0.84	-0.26
ACOX1	ENSG00000161533	NM_004035.7(ACOX1):c.1068C>T (p.Asn356=)	AAC	AAT	Peroxisomal acyl-CoA oxidase deficiency	1.01	0.02
RD3	ENSG00000198570	NM_183059.2(RD3):c.519G>A (p.Val173=)	GTG	GTA	Leber congenital amaurosis 12 (LCA12)	0.3	-1.74
MLH3	ENSG00000119684	NM_001040108.1(MLH3):c.2838C>A (p.Ser946=)	TCC	TCA	Hereditary nonpolyposis colorectal cancer type 7 (HNPCC7)	0.82	-0.29
TYK2	ENSG00000105397	NM_003331.5(TYK2):c.783C>G (p.Ala261=)	GCC	GCG	Tyrosine kinase 2 deficiency (IMD35)	0.23	-2.11
PHGDH	ENSG00000092621	NM_006623.4(PHGDH):c.372G>A (p.Ala124=)	GCG	GCA	Phosphoglycerate dehydrogenase deficiency (PHGDHD)	2.88	1.52
CDH15	ENSG00000129910	NM_004933.3(CDH15):c.132G>T (p.Arg44=)	CGG	CGT		0.43	-1.22

IFNGR1	ENSG00000027697	NM_000416.2(IFNGR1):c.609G>A (p.Ala203=)	GCG	GCA	Disseminated atypical mycobacterial infection (IMD27A)	2.88	1.52	
FANCE	ENSG00000112039	NM_021922.2(FANCE):c.552A>C (p.Pro184=)	CCA	CCC	Fanconi anemia, complementation group E (FANCE)	1	0.01	
FAM126A	ENSG00000122591	NM_032581.4(FAM126A):c.582C>T (p.Tyr194=)	TAC	TAT	Hypomyelination and Congenital Cataract (HLD5)	0.9	-0.15	
TYK2	ENSG00000105397	NM_003331.5(TYK2):c.1869C>T (p.Asp623=)	GAC	GAT	Tyrosine kinase 2 deficiency (IMD35)	0.99	-0.01	
ABCG8	ENSG00000143921	NM_022437.3(ABCG8):c.1200G>A (p.Thr400=)	ACG	ACA		2.96	1.57	
CD3G	ENSG00000160654	NM_000073.2(CD3G):c.496C>A (p.Arg166=)	CGA	AGA	Immunodeficiency 17 (IMD17)	2.09	1.06	
MTOR	ENSG00000198793	NM_004958.4(MTOR):c.1821G>A (p.Ala607=)	GCG	GCA		2.88	1.52	
NIPBL	ENSG00000164190	NM_133433.4(NIPBL):c.2448T>C (p.Arg816=)	CGT	CGC	Cornelia de Lange syndrome 1 (CDLS1)	1.91	0.93	
KMT2D	ENSG00000167548	NM_003482.3(KMT2D):c.7629G>A (p.Gly2543=)	GGG	GGA		1.13	0.17	
IFNGR1	ENSG00000027697	NM_000416.2(IFNGR1):c.1341C>T (p.Thr447=)	ACC	ACT	Disseminated atypical mycobacterial infection (IMD27A)	0.8	-0.31	
LYST	ENSG00000143669	NM_000081.4(LYST):c.10758C>T (p.Cys3586=)	TGC	TGT	Chédiak-Higashi syndrome (CHS)	0.97	-0.05	
ALDOB	ENSG00000136872	NM_000035.4(ALDOB):c.582T>C (p.Asp194=)	GAT	GAC		1.01	0.01	
PRPF8	ENSG00000174231	NM_006445.4(PRPF8):c.4524C>T (p.Gly1508=)	GGC	GGT		0.55	-0.87	
GAN	ENSG00000261609	NM_022041.3(GAN):c.1323T>C (p.Tyr441=)	TAT	TAC	Giant axonal neuropathy 1 (GAN1)	1.11	0.15	
GUSB	ENSG00000169919	NM_000181.4(GUSB):c.1240C>T (p.Leu414=)	CTG	TTG	Mucopolysaccharidosis type 7 (MPS7)	0.37	-1.42	
MBD5	ENSG00000204406	NM_018328.4(MBD5):c.2904G>T (p.Ser968=)	TCG	TCT		4.18	2.06	
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.7188G>A (p.Gln2396=)	CAG	CAA		0.4	-1.32	
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.7098G>T (p.Arg2366=)	CGG	CGT		0.43	-1.22	
SPG11	ENSG00000104133	NM_025137.4(SPG11):c.2169C>T (p.Gly723=)	GGC	GGT	Spastic paraplegia 11, autosomal recessive (SPG11)	0.55	-0.87	
RELN	ENSG00000189056	NM_005045.4(RELN):c.6519C>T (p.Phe2173=)	TTC	TTT		0.98	-0.02	
BIN1	ENSG00000136717	NM_139343.3(BIN1):c.1629T>G (p.Ala543=)	GCT	GCG	Myopathy, centronuclear, 2 (CNM2)	0.31	-1.67	
DOCK8	ENSG00000107099	NM_203447.3(DOCK8):c.5892C>T (p.Asn1964=)	AAC	AAT	Hyperimmunoglobulin E recurrent infection syndrome, autosomal recessive (HIES2)	1.01	0.02	
CNTNAP2	ENSG00000174469	NM_014141.6(CNTNAP2):c.354C>T (p.Ser118=)	AGC	AGT		0.72	-0.48	
ATP6V0A2	ENSG00000185344	NM_012463.4(ATP6V0A2):c.1458G>A (p.Ser486=)	TCG	TCA		3.5	1.81	
SERPINC1	ENSG00000117601	NM_000488.3(SERPINC1):c.870C>T (p.Phe290=)	TTC	TTT	Antithrombin III deficiency (AT3D)	0.98	-0.02	
BRWD3	ENSG00000165288	NM_153252.5(BRWD3):c.4377A>G (p.Leu1459=)	TTA	TTG		1.53	0.61	
GLDC	ENSG00000178445	NM_000170.3(GLDC):c.2328C>T (p.Leu776=)	CTC	CTT	Non-ketotic hyperglycinemia (GCE)	0.8	-0.33	
TTC37	ENSG00000198677	NM_014639.3(TTC37):c.3603A>G (p.Arg1201=)	CGA	CGG		1.65	0.73	
LRP2	ENSG00000081479	NM_004525.3(LRP2):c.8070G>A (p.Lys2690=)	AAG	AAA		0.87	-0.2	
ADGRG1	ENSG00000205336	NM_201525.4(ADGRG1):c.243C>T (p.Phe81=)	TTC	TTT		0.98	-0.02	
SLC34A3	ENSG00000198569	NM_001177316.2(SLC34A3):c.1464T>C (p.Ala488=)	GCT	GCC		1.36	0.44	
GRIP1	ENSG00000155974	NM_001366722.1(GRIP1):c.3207C>T (p.Pro1069=)	CCC	CCT		1.02	0.02	
SPG11	ENSG00000104133	NM_025137.4(SPG11):c.4026A>G (p.Gln1342=)	CAA	CAG	Spastic paraplegia 11, autosomal recessive (SPG11)	2.49	1.32	
CTDP1	ENSG00000060069	NM_004715.4(CTDP1):c.669G>A (p.Thr223=)	ACG	ACA		2.96	1.57	
ITK	ENSG00000113263	NM_005546.3(ITK):c.1276C>T (p.Leu426=)	CTG	TTG	Lymphoproliferative syndrome 1 (LPFS1)	0.37	-1.42	
SLC10A2	ENSG00000125255	NM_000452.3(SLC10A2):c.175C>T (p.Leu59=)	CTA	TTA		1.18	0.24	
LITAF	ENSG00000189067	NM_001136473.1(LITAF):c.147G>A (p.Thr49=)	ACG	ACA	Charcot-Marie-Tooth disease, type 1C (CMT1C)	2.96	1.57	
VWA3B	ENSG00000168658	NM_144992.5(VWA3B):c.1296C>T (p.Ser432=)	TCC	TCT		0.98	-0.03	
ABCA7	ENSG00000064687	NM_019112.4(ABCA7):c.5037G>A (p.Glu1679=)	GAG	GAA		0.86	-0.22	
IFT140	ENSG00000187535	NM_014714.4(IFT140):c.1593G>T (p.Gly531=)	GGG	GGT	Saldino-Mainzer syndrome (SRTD9)	0.71	-0.5	
FLNB	ENSG00000136068	NM_001457.4(FLNB):c.6000T>C (p.Gly2000=)	GGT	GGC		1.82	0.87	

CCT5	ENSG00000150753	NM_012073.5(CCT5):c.954C>T (p.Asn318=)	AAC	AAT	Neuropathy, hereditary sensory, with spastic paraplegia, autosomal recessive	1.01	0.02
LYST	ENSG00000143669	NM_001301365.1(LYST):c.7806A>G (p.Gln2602=)	CAA	CAG	Chédiak-Higashi syndrome (CHS)	2.49	1.32
AHCY	ENSG00000101444	NM_000687.4(AHCY):c.882C>G (p.Ala294=)	GCC	GCG	Hypermethioninemia with s-adenosylhomocysteine hydrolase deficiency	0.23	-2.11
FRMPD4	ENSG00000169933	NM_001368397.1(FRMPD4):c.3738C>T (p.His1246=)	CAC	CAT		0.81	-0.3
KMT2D	ENSG00000167548	NM_003482.3(KMT2D):c.6264C>T (p.Thr2088=)	ACC	ACT		0.8	-0.31
RAD50	ENSG00000113522	NM_005732.4(RAD50):c.2970C>T (p.Cys990=)	TGC	TGT	Hereditary cancer-predisposing syndrome	0.97	-0.05
OBSL1	ENSG00000124006	NM_015311.3(OBSL1):c.2466C>T (p.Ser822=)	TCC	TCT		0.98	-0.03
FANCE	ENSG00000112039	NM_021922.2(FANCE):c.696G>A (p.Glu232=)	GAG	GAA	Fanconi anemia, complementation group E (FANCE)	0.86	-0.22
KMT2D	ENSG00000167548	NM_003482.3(KMT2D):c.192G>A (p.Arg64=)	CGG	CGA		0.6	-0.73
NOTCH2	ENSG00000134250	NM_024408.4(NOTCH2):c.5103A>G (p.Lys1701=)	AAA	AAG		1.15	0.2
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.4407C>T (p.Gly1469=)	GGC	GGT		0.55	-0.87
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.10566G>A (p.Thr3522=)	ACG	ACA		2.96	1.57
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.8871G>A (p.Lys2957=)	AAG	AAA		0.87	-0.2
CCBE1	ENSG00000183287	NM_133459.4(CCBE1):c.966G>A (p.Ala322=)	GCG	GCA	Hennekam lymphangiectasia-lymphedema syndrome 1 (HKLLS1)	2.88	1.52
ABCG8	ENSG00000143921	NM_022437.3(ABCG8):c.1473A>G (p.Pro491=)	CCA	CCG		0.33	-1.61
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.13212C>T (p.Gly4404=)	GGC	GGT		0.55	-0.87
ALDH4A1	ENSG00000159423	NM_003748.4(ALDH4A1):c.1098G>A (p.Gly366=)	GGG	GGA	Deficiency of pyrroline-5-carboxylate reductase (HYRPRO2)	1.13	0.17
ANK3	ENSG00000151150	NM_020987.5(ANK3):c.3822C>G (p.Ser1274=)	TCC	TCG		0.23	-2.09
LYST	ENSG00000143669	NM_001301365.1(LYST):c.10221C>T (p.Tyr3407=)	TAC	TAT	Chédiak-Higashi syndrome (CHS)	0.9	-0.15
NPHP4	ENSG00000131697	NM_015102.5(NPHP4):c.2952G>A (p.Thr984=)	ACG	ACA		2.96	1.57
KCNA5	ENSG00000130037	NM_002234.4(KCNA5):c.615G>C (p.Leu205=)	CTG	CTC	Atrial fibrillation, familial, 7 (ATFB7)	0.49	-1.02
CACNA2D4	ENSG00000151062	NM_172364.5(CACNA2D4):c.1509C>T (p.Ser503=)	AGC	AGT		0.72	-0.48
UNC13D	ENSG00000092929	NM_199242.2(UNC13D):c.972C>T (p.Asp324=)	GAC	GAT	Familial hemophagocytic lymphohistiocytosis 3 (FHL3)	0.99	-0.01
PAH	ENSG00000171759	NM_000277.3(PAH):c.399T>C (p.Asn133=)	AAT	AAC	Phenylketonuria (PKU)	0.99	-0.02
CNGB3	ENSG00000170289	NM_019098.4(CNGB3):c.2007A>G (p.Lys669=)	AAA	AAG		1.15	0.2
WRN	ENSG00000165392	NM_000553.6(WRN):c.2985C>T (p.Ala995=)	GCC	GCT	Werner syndrome (WRN)	0.74	-0.44
WNT7A	ENSG00000154764	NM_004625.4(WNT7A):c.213C>T (p.Asp71=)	GAC	GAT		0.99	-0.01
IL12RB1	ENSG00000096996	NM_005535.3(IL12RB1):c.1269C>T (p.His423=)	CAC	CAT	Immunodeficiency 30 (IMD30)	0.81	-0.3
SCN3A	ENSG00000153253	NM_006922.4(SCN3A):c.4335T>C (p.Tyr1445=)	TAT	TAC		1.11	0.15
SPTBN2	ENSG00000173898	NM_006946.4(SPTBN2):c.3717A>G (p.Val1239=)	GTA	GTG		3.34	1.74
FUCA1	ENSG00000179163	NM_000147.4(FUCA1):c.1119A>G (p.Lys373=)	AAA	AAG	Fucosidosis	1.15	0.2
GAD1	ENSG00000128683	NM_000817.3(GAD1):c.1173C>T (p.Asn391=)	AAC	AAT	Cerebral palsy, spastic quadriplegic, 1 (CPSQ1)	1.01	0.02
CIITA	ENSG00000179583	NM_000246.3(CIITA):c.456G>A (p.Pro152=)	CCG	CCA	Bare lymphocyte syndrome 2	3.05	1.61
SCN3A	ENSG00000153253	NM_006922.4(SCN3A):c.5469T>A (p.Pro1823=)	CCT	CCA		0.98	-0.03
HDAC4	ENSG00000068024	NM_006037.3(HDAC4):c.3159C>T (p.Ala1053=)	GCC	GCT		0.74	-0.44
CEP290	ENSG00000198707	NM_025114.4(CEP290):c.3408A>G (p.Gln1136=)	CAA	CAG		2.49	1.32
ZNF335	ENSG00000198026	NM_022095.4(ZNF335):c.2280G>A (p.Gln760=)	CAG	CAA		0.4	-1.32
LRP5	ENSG00000162337	NM_002335.4(LRP5):c.4272C>T (p.His1424=)	CAC	CAT		0.81	-0.3
IFT140	ENSG00000187535	NM_014714.4(IFT140):c.3501C>T (p.Thr1167=)	ACC	ACT	Saldino-Mainzer syndrome (SRTD9)	0.8	-0.31
IMPG2	ENSG00000081148	NM_016247.4(IMPG2):c.1794C>T (p.Asp598=)	GAC	GAT		0.99	-0.01

HGD	ENSG00000113924	NM_000187.4(HGD):c.1206A>G (p.Ser402=)	TCA	TCG	Alkaptonuria (AKU)	0.29	-1.81
MAT1A	ENSG00000151224	NM_000429.3(MAT1A):c.981G>A (p.Pro327=)	CCG	CCA	Hepatic methionine adenosyltransferase deficiency	3.05	1.61
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.6987G>A (p.Ala2329=)	GCG	GCA		2.88	1.52
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.9750G>A (p.Thr3250=)	ACG	ACA		2.96	1.57
PHKB	ENSG00000102893	NM_000293.3(PHKB):c.3216G>A (p.Ala1072=)	GCG	GCA	Glycogen storage disease IXb (GSD9B)	2.88	1.52
CIITA	ENSG00000179583	NM_000246.3(CIITA):c.384C>T (p.Ile128=)	ATC	ATT	Bare lymphocyte syndrome 2	0.89	-0.17
CIITA	ENSG00000179583	NM_000246.3(CIITA):c.3003C>T (p.Asp1001=)	GAC	GAT	Bare lymphocyte syndrome 2	0.99	-0.01
FBP1	ENSG00000165140	NM_000507.4(FBP1):c.102G>C (p.Leu34=)	CTG	CTC	Fructose-biphosphatase deficiency (FBP1D)	0.49	-1.02
SUMF1	ENSG00000144455	NM_182760.4(SUMF1):c.891C>T (p.Asn297=)	AAC	AAT	Multiple sulfatase deficiency (MSD)	1.01	0.02
BMP2	ENSG00000125845	NM_001200.4(BMP2):c.561C>T (p.Pro187=)	CCC	CCT		1.02	0.02
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.21819C>T (p.Asp7273=)	GAC	GAT		0.99	-0.01
LYST	ENSG00000143669	NM_001301365.1(LYST):c.8487C>T (p.Ile2829=)	ATC	ATT	Chédiak-Higashi syndrome (CHS)	0.89	-0.17
PHGDH	ENSG00000092621	NM_006623.4(PHGDH):c.1257G>A (p.Gly419=)	GGG	GGA	Phosphoglycerate dehydrogenase deficiency (PHGDHD)	1.13	0.17
NPC1	ENSG00000141458	NM_000271.5(NPC1):c.2775C>T (p.Asn925=)	AAC	AAT	Niemann-Pick disease type C1 (NPC1)	1.01	0.02
HDAC4	ENSG00000068024	NM_006037.3(HDAC4):c.1443C>T (p.Val481=)	GTC	GTT		0.88	-0.19
TBX15	ENSG00000092607	NM_001330677.2(TBX15):c.1728A>G (p.Gln576=)	CAA	CAG		2.49	1.32
UNC13D	ENSG00000092929	NM_199242.2(UNC13D):c.1215C>T (p.Tyr405=)	TAC	TAT	Familial hemophagocytic lymphohistiocytosis 3 (FHL3)	0.9	-0.15
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.2817C>T (p.Ser939=)	TCC	TCT	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS)	0.98	-0.03
JAK3	ENSG00000105639	NM_000215.3(JAK3):c.2079C>T (p.Pro693=)	CCC	CCT	Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-negative	1.02	0.02
ABCA4	ENSG00000198691	NM_000350.3(ABCA4):c.3468C>T (p.Tyr1156=)	TAC	TAT		0.9	-0.15
ZMYM3	ENSG00000147130	NM_201599.3(ZMYM3):c.4065C>T (p.Arg1355=)	CGC	CGT		0.52	-0.93
KCNMA1	ENSG00000156113	NM_001161352.2(KCNMA1):c.2946C>T (p.Ser982=)	AGC	AGT	Paroxysmal nonkinesigenic dyskinesia, 3, with or without generalized epilepsy (PNKD3)	0.72	-0.48
ASL	ENSG00000126522	NM_000048.4(ASL):c.75C>T (p.Asn25=)	AAC	AAT	Argininosuccinate lyase deficiency	1.01	0.02
WRN	ENSG00000165392	NM_000553.6(WRN):c.3738G>A (p.Leu1246=)	CTG	CTA	Werner syndrome (WRN)	0.21	-2.27
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.933C>T (p.Phe311=)	TTC	TTT		0.98	-0.02
VWA3B	ENSG00000168658	NM_144992.5(VWA3B):c.3471G>A (p.Ala1157=)	GCG	GCA		2.88	1.52
PEX26	ENSG00000215193	NM_001127649.3(PEX26):c.540A>G (p.Leu180=)	CTA	CTG		4.81	2.27
NIPBL	ENSG00000164190	NM_133433.4(NIPBL):c.2256A>G (p.Glu752=)	GAA	GAG	Cornelia de Lange syndrome 1 (CDLS1)	1.16	0.22
GALNS	ENSG00000141012	NM_000512.5(GALNS):c.921G>T (p.Leu307=)	CTG	CTT	Mucopolysaccharidosis, MPS-IV-A (MPS4A)	0.39	-1.35
CUL7	ENSG00000044090	NM_014780.4(CUL7):c.2754G>A (p.Thr918=)	AAG	AAA		0.87	-0.2
GALNS	ENSG00000141012	NM_000512.5(GALNS):c.324C>T (p.Tyr108=)	TAC	TAT	Mucopolysaccharidosis, MPS-IV-A (MPS4A)	0.9	-0.15
PCCB	ENSG00000114054	NM_000532.5(PCCB):c.180G>A (p.Lys60=)	AAG	AAA	Propionic acidemia (PROP)	0.87	-0.2
RFXAP	ENSG00000133111	NM_000538.3(RFXAP):c.666A>G (p.Ala222=)	GCA	GCG	Bare lymphocyte syndrome 2	0.35	-1.52
COL6A1	ENSG00000142156	NM_001848.2(COL6A1):c.696C>T (p.Ile232=)	ATC	ATT		0.89	-0.17
AGPS	ENSG00000018510	NM_003659.4(AGPS):c.1335C>T (p.Asp445=)	GAC	GAT		0.99	-0.01
KMT2D	ENSG00000167548	NM_003482.3(KMT2D):c.2847G>A (p.Pro949=)	CCG	CCA		3.05	1.61
JAK3	ENSG00000105639	NM_000215.3(JAK3):c.1581G>A (p.Leu527=)	CTG	CTA	Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-negative	0.21	-2.27
COL6A1	ENSG00000142156	NM_001848.2(COL6A1):c.609C>T (p.Ile203=)	ATC	ATT		0.89	-0.17
SRCAP	ENSG00000080603	NM_006662.3(SRCAP):c.5610C>T (p.Pro1870=)	CCC	CCT		1.02	0.02
GNS	ENSG00000135677	NM_002076.4(GNS):c.1434C>G (p.Val478=)	GTC	GTG	Mucopolysaccharidosis, MPS-III-D (MPS3D)	1.92	0.94

EPS8	ENSG00000151491	NM_004447.6(EPS8):c.1638C>T (p.Asn546=)	AAC	AAT		1.01	0.02
KDM5C	ENSG00000126012	NM_004187.5(KDM5C):c.465C>T (p.Ser155=)	TCC	TCT		0.98	-0.03
AP3B1	ENSG00000132842	NM_003664.4(AP3B1):c.2310C>T (p.Asp770=)	GAC	GAT	Hermansky-Pudlak syndrome 2 (HPS2)	0.99	-0.01
SRCAP	ENSG00000080603	NM_006662.3(SRCAP):c.5019G>A (p.Pro1673=)	CCG	CCA		3.05	1.61
SETBP1	ENSG00000152217	NM_015559.3(SETBP1):c.2934C>T (p.His978=)	CAC	CAT		0.81	-0.3
LRRK2	ENSG00000188906	NM_198578.4(LRRK2):c.6801C>T (p.Thr2267=)	ACC	ACT	Parkinson disease 8, autosomal dominant (PARK8)	0.8	-0.31
DSG2	ENSG00000046604	NM_001943.5(DSG2):c.390C>T (p.Tyr130=)	TAC	TAT	Arrhythmogenic right ventricular cardiomyopathy, type 10 (ARVD10)	0.9	-0.15
DCTN1	ENSG00000204843	NM_004082.4(DCTN1):c.2511C>T (p.Val837=)	GTC	GTT		0.88	-0.19
WNT7A	ENSG00000154764	NM_004625.4(WNT7A):c.555C>T (p.Asn185=)	AAC	AAT		1.01	0.02
IFT140	ENSG00000187535	NM_014714.4(IFT140):c.1788T>C (p.Asp596=)	GAT	GAC	Saldino-Mainzer syndrome (SRTD9)	1.01	0.01
FRAS1	ENSG00000138759	NM_025074.7(FRAS1):c.2862G>A (p.Thr954=)	ACG	ACA		2.96	1.57
AGA	ENSG00000038002	NM_000027.4(AGA):c.885G>A (p.Lys295=)	AAG	AAA	Aspartylglucosaminuria (AGU)	0.87	-0.2
TRPS1	ENSG00000104447	NM_014112.5(TRPS1):c.2976G>A (p.Pro992=)	CCG	CCA		3.05	1.61
BAAT	ENSG00000136881	NM_001701.4(BAAT):c.165C>T (p.Phe55=)	TTC	TTT		0.98	-0.02
FSCN2	ENSG00000186765	NM_012418.4(FSCN2):c.492C>T (p.Asp164=)	GAC	GAT		0.99	-0.01
ATP13A2	ENSG00000159363	NM_022089.4(ATP13A2):c.1080G>C (p.Gly360=)	GGG	GGC		1.29	0.37
GALNS	ENSG00000141012	NM_000512.5(GALNS):c.1071G>A (p.Pro357=)	CCG	CCA	Mucopolysaccharidosis, MPS-IV-A (MPS4A)	3.05	1.61
AGA	ENSG00000038002	NM_000027.4(AGA):c.1023A>G (p.Glu341=)	GAA	GAG	Aspartylglucosaminuria (AGU)	1.16	0.22
AP5Z1	ENSG00000242802	NM_014855.3(AP5Z1):c.417G>A (p.Ala139=)	GCG	GCA	Spastic paraplegia 48, autosomal recessive (SPG48)	2.88	1.52
WASHC5	ENSG00000164961	NM_014846.4(WASHC5):c.1779C>T (p.Leu593=)	CTC	CTT		0.8	-0.33
SLC10A2	ENSG00000125255	NM_000452.3(SLC10A2):c.108G>A (p.Thr36=)	ACG	ACA		2.96	1.57
COL9A3	ENSG00000092758	NM_001853.4(COL9A3):c.1242C>T (p.Pro414=)	CCC	CCT		1.02	0.02
FAM20C	ENSG00000177706	NM_020223.4(FAM20C):c.1152C>T (p.Ile384=)	ATC	ATT		0.89	-0.17
IFT140	ENSG00000187535	NM_014714.4(IFT140):c.3693G>A (p.Thr1231=)	ACG	ACA	Saldino-Mainzer syndrome (SRTD9)	2.96	1.57
KCNA5	ENSG00000130037	NM_002234.4(KCNA5):c.570C>T (p.Asn190=)	AAC	AAT	Atrial fibrillation, familial, 7 (ATFB7)	1.01	0.02
RNASEL	ENSG00000135828	NM_021133.4(RNASEL):c.1179G>A (p.Thr393=)	ACG	ACA		2.96	1.57
HDAC4	ENSG00000068024	NM_006037.3(HDAC4):c.681C>T (p.His227=)	CAC	CAT		0.81	-0.3
WRN	ENSG00000165392	NM_000553.6(WRN):c.3162T>C (p.Ala1054=)	GCT	GCC	Werner syndrome (WRN)	1.36	0.44
GLDC	ENSG00000178445	NM_000170.2(GLDC):c.2955G>A (p.Thr985=)	ACG	ACA	Non-ketotic hyperglycinemia (GCE)	2.96	1.57
MMP13	ENSG00000137745	NM_002427.4(MMP13):c.1251G>A (p.Pro417=)	CCG	CCA		3.05	1.61
IFT140	ENSG00000187535	NM_014714.4(IFT140):c.1824A>G (p.Thr608=)	ACA	ACG	Saldino-Mainzer syndrome (SRTD9)	0.34	-1.57
VPS33B	ENSG00000184056	NM_018668.4(VPS33B):c.1207T>C (p.Leu403=)	TTG	CTG		2.67	1.42
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.6204G>A (p.Thr2068=)	ACG	ACA		2.96	1.57
SUMF1	ENSG00000144455	NM_182760.4(SUMF1):c.606G>A (p.Pro202=)	CCG	CCA	Multiple sulfatase deficiency (MSD)	3.05	1.61
SP7	ENSG00000170374	NM_001173467.3(SP7):c.1272G>A (p.Glu424=)	GAG	GAA		0.86	-0.22
AHCY	ENSG00000101444	NM_000687.4(AHCY):c.1008C>T (p.Ile336=)	ATC	ATT	Hypermethioninemia with s-adenosylhomocysteine hydrolase deficiency	0.89	-0.17
ZMPSTE24	ENSG00000084073	NM_005857.5(ZMPSTE24):c.933A>G (p.Glu311=)	GAA	GAG		1.16	0.22
ABCA3	ENSG00000167972	NM_001089.3(ABCA3):c.753C>T (p.Ile251=)	ATC	ATT	Surfactant metabolism dysfunction, pulmonary, 3 (SMDP3)	0.89	-0.17
JAK3	ENSG00000105639	NM_000215.3(JAK3):c.3267C>T (p.Ser1089=)	AGC	AGT	Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-negative	0.72	-0.48
FAH	ENSG00000103876	NM_000137.4(FAH):c.741C>T (p.Leu247=)	CTC	CTT	Tyrosinemia type I (TYRSN1)	0.8	-0.33

GABRD	ENSG00000187730	NM_000815.5(GABRD):c.147C>T (p.Ala49=)	GCC	GCT		0.74	-0.44
ENPP1	ENSG00000197594	NM_006208.3(ENPP1):c.2088C>T (p.Thr696=)	ACC	ACT		0.8	-0.31
STAT2	ENSG00000170581	NM_005419.4(STAT2):c.903C>T (p.Asn301=)	AAC	AAT	Immunodeficiency 44 (IMD44)	1.01	0.02
CACNB4	ENSG00000182389	NM_000726.4(CACNB4):c.1437G>A (p.Gln479=)	CAG	CAA		0.4	-1.32
ALG12	ENSG00000182858	NM_024105.4(ALG12):c.1299C>T (p.Leu433=)	CTC	CTT	ALG12-congenital disorder of glycosylation (CDG1G)	0.8	-0.33
NGF	ENSG00000134259	NM_002506.2(NGF):c.165G>A (p.Pro55=)	CCG	CCA	Congenital sensory neuropathy with selective loss of small myelinated fibers (HSAN5)	3.05	1.61
RNASEL	ENSG00000135828	NM_021133.4(RNASEL):c.354C>T (p.Val118=)	GTC	GTT		0.88	-0.19
ACOX1	ENSG00000161533	NM_004035.7(ACOX1):c.405T>C (p.Thr135=)	ACT	ACC	Peroxisomal acyl-CoA oxidase deficiency	1.24	0.31
TRIOBP	ENSG00000100106	NM_001039141.3(TRIOBP):c.3309C>T (p.His1103=)	CAC	CAT		0.81	-0.3
MAN2B1	ENSG00000104774	NM_000528.4(MAN2B1):c.1437G>T (p.Ala479=)	GCG	GCT	Deficiency of alpha-mannosidase (MANSA)	3.18	1.67
DCAF17	ENSG00000115827	NM_025000.4(DCAF17):c.792T>C (p.Thr264=)	ACT	ACC	Hypogonadism, diabetes mellitus, alopecia, mental retardation and electrocardiographic abnormalities (WDSKS)	1.24	0.31
TBCE	ENSG00000116957	NM_003193.5(TBCE):c.708T>G (p.Leu236=)	CTT	CTG		2.54	1.35
SYNE2	ENSG00000054654	NM_182914.2(SYNE2):c.12738C>T (p.Ala4246=)	GCC	GCT		0.74	-0.44
ITGB2	ENSG00000160255	NM_000211.5(ITGB2):c.162G>A (p.Pro54=)	CCG	CCA	Leukocyte adhesion deficiency 1	3.05	1.61
ACOX1	ENSG00000161533	NM_004035.7(ACOX1):c.1368C>T (p.Asn456=)	AAC	AAT	Peroxisomal acyl-CoA oxidase deficiency	1.01	0.02
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.3457C>T (p.Leu1153=)	CTG	TTG		0.37	-1.42
PCCB	ENSG00000114054	NM_000532.5(PCCB):c.603T>C (p.Ala201=)	GCT	GCC	Propionic acidemia (PROP)	1.36	0.44
CACNA1A	ENSG00000141837	NM_001127222.2(CACNA1A):c.3525A>C (p.Pro1175=)	CCA	CCC		1	0.01
MYLK2	ENSG00000101306	NM_033118.3(MYLK2):c.1356G>A (p.Glu452=)	GAG	GAA	Familial hypertrophic cardiomyopathy 1 (CMH1)	0.86	-0.22
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.885C>T (p.Gly295=)	GGC	GGT	Cohen syndrome (COH1)	0.55	-0.87
ALDH4A1	ENSG00000159423	NM_003748.4(ALDH4A1):c.1377G>C (p.Pro459=)	CCG	CCC	Deficiency of pyrroline-5-carboxylate reductase (HYRPRO2)	3.07	1.62
CIITA	ENSG00000179583	NM_000246.3(CIITA):c.1926C>T (p.Val642=)	GTC	GTT	Bare lymphocyte syndrome 2	0.88	-0.19
SLC3A1	ENSG00000138079	NM_000341.4(SLC3A1):c.66C>T (p.Asn22=)	AAC	AAT	Cystinuria (CSNU)	1.01	0.02
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.20556A>G (p.Gln6852=)	CAA	CAG		2.49	1.32
ALDH4A1	ENSG00000159423	NM_003748.4(ALDH4A1):c.228G>A (p.Ser76=)	TCG	TCA	Deficiency of pyrroline-5-carboxylate reductase (HYRPRO2)	3.5	1.81
ANO5	ENSG00000171714	NM_213599.2(ANO5):c.2610A>G (p.Leu870=)	TTA	TTG		1.53	0.61
MAN2B1	ENSG00000104774	NM_000528.4(MAN2B1):c.1521G>T (p.Ala507=)	GCG	GCT	Deficiency of alpha-mannosidase (MANSA)	3.18	1.67
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.2604C>T (p.Asp868=)	GAC	GAT	Aortic aneurysm, familial thoracic 7 (AAT7)	0.99	-0.01
NLGN4X	ENSG00000146938	NM_181332.3(NLGN4X):c.999G>A (p.Pro333=)	CCG	CCA		3.05	1.61
NEB	ENSG00000183091	NM_001271208.2(NEB):c.2250G>A (p.Thr750=)	ACG	ACA	Nemaline myopathy 2 (NEM2)	2.96	1.57
KCNA5	ENSG00000130037	NM_002234.4(KCNA5):c.1539C>T (p.Pro513=)	CCC	CCT	Atrial fibrillation, familial, 7 (ATFB7)	1.02	0.02
GLDC	ENSG00000178445	NM_000170.2(GLDC):c.2487C>T (p.Ala829=)	GCC	GCT	Non-ketotic hyperglycinemia (GCE)	0.74	-0.44
RUNX1	ENSG00000159216	NM_001754.4(RUNX1):c.981G>C (p.Leu327=)	CTG	CTC	Familial platelet disorder with associated myeloid malignancy (FPDMM)	0.49	-1.02
TJP2	ENSG00000119139	NM_004817.4(TJP2):c.2034C>T (p.Asn678=)	AAC	AAT		1.01	0.02
BIN1	ENSG00000136717	NM_139343.3(BIN1):c.1473T>C (p.Pro491=)	CCT	CCC	Myopathy, centronuclear, 2 (CNM2)	0.98	-0.02
CIITA	ENSG00000179583	NM_000246.3(CIITA):c.1047T>C (p.Tyr349=)	TAT	TAC	Bare lymphocyte syndrome 2	1.11	0.15
TP53	ENSG00000141510	NM_000546.5(TP53):c.663G>A (p.Glu221=)	GAG	GAA		0.86	-0.22
IGF1R	ENSG00000140443	NM_000875.5(IGF1R):c.3918C>T (p.Asp1306=)	GAC	GAT		0.99	-0.01
SLC7A7	ENSG00000155465	NM_003982.4(SLC7A7):c.549A>C (p.Val183=)	GTA	GTC	Lysinuric protein intolerance (LPI)	1.74	0.8

TYK2	ENSG00000105397	NM_003331.5(TYK2):c.2985C>T (p.Ile995=)	ATC	ATT	Tyrosine kinase 2 deficiency (IMD35)	0.89	-0.17
ASPM	ENSG00000066279	NM_018136.5(ASPM):c.2103G>A (p.Gln701=)	CAG	CAA		0.4	-1.32
TRIOBP	ENSG00000100106	NM_001039141.3(TRIOBP):c.6360C>T (p.Ser2120=)	TCC	TCT		0.98	-0.03
FBLN1	ENSG00000077942	NM_006486.3(FBLN1):c.279G>T (p.Thr93=)	ACG	ACT		2.56	1.36
SYNJ1	ENSG00000159082	NM_203446.3(SYNJ1):c.384T>C (p.Phe128=)	TTT	TTC		1.02	0.02
KCNQ2	ENSG00000075043	NM_172107.4(KCNQ2):c.2316G>A (p.Pro772=)	CCG	CCA		3.05	1.61
DMD	ENSG00000198947	NM_004006.2(DMD):c.5187A>G (p.Pro1729=)	CCA	CCG		0.33	-1.61
IL2RA	ENSG00000134460	NM_000417.3(IL2RA):c.693G>A (p.Glu231=)	GAG	GAA	Interleukin 2 receptor, alpha, deficiency of (IMD41)	0.86	-0.22
FXN	ENSG00000165060	NM_000144.5(FXN):c.123C>T (p.Gly41=)	GGC	GGT		0.55	-0.87
SLC34A3	ENSG00000198569	NM_001177316.2(SLC34A3):c.1149C>T (p.Ala383=)	GCC	GCT		0.74	-0.44
CUL7	ENSG00000044090	NM_014780.4(CUL7):c.2163T>C (p.Asp721=)	CGG	CGC		0.82	-0.29
AP3B1	ENSG00000132842	NM_003664.4(AP3B1):c.2340C>T (p.Ser780=)	TCC	TCT	Hermansky-Pudlak syndrome 2 (HPS2)	0.98	-0.03
DIS3L2	ENSG00000144535	NM_152383.5(DIS3L2):c.795C>T (p.Tyr265=)	TAC	TAT	Perlman syndrome (PRLMNS)	0.9	-0.15
TCN2	ENSG00000185339	NM_000355.4(TCN2):c.903C>T (p.Tyr301=)	TAC	TAT	Transcolabamin II deficiency	0.9	-0.15
ALG12	ENSG00000182858	NM_024105.4(ALG12):c.1362C>T (p.Val454=)	GTC	GTT	ALG12-congenital disorder of glycosylation (CDG1G)	0.88	-0.19
CHRNA4	ENSG00000101204	NM_000744.7(CHRNA4):c.1494C>T (p.Ala498=)	GCC	GCT		0.74	-0.44
TTN	ENSG00000155657	NM_001267550.2(TTN):c.81393A>G (p.Lys27131=)	AAA	AAG		1.15	0.2
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.3321C>T (p.Phe1107=)	TTC	TTT	Qualitative or quantitative defects of dysferlin	0.98	-0.02
ATP13A2	ENSG00000159363	NM_022089.4(ATP13A2):c.3222G>A (p.Pro1074=)	CCG	CCA		3.05	1.61
DMD	ENSG00000198947	NM_004006.2(DMD):c.8418G>A (p.Gln2806=)	CAG	CAA		0.4	-1.32
CIB2	ENSG00000136425	NM_006383.4(CIB2):c.231G>A (p.Ala77=)	GCG	GCA		2.88	1.52
SERPINA1	ENSG00000197249	NM_000295.5(SERPINA1):c.1095C>T (p.Asp365=)	GAC	GAT	Alpha-1-antitrypsin deficiency (A1ATD)	0.99	-0.01
ALDH4A1	ENSG00000159423	NM_003748.4(ALDH4A1):c.1218C>T (p.His406=)	CAC	CAT	Deficiency of pyrroline-5-carboxylate reductase (HYRPRO2)	0.81	-0.3
TTN	ENSG00000155657	NM_001267550.2(TTN):c.75099C>T (p.Asp25033=)	GAC	GAT		0.99	-0.01
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.2145C>T (p.Cys715=)	TGC	TGT	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS)	0.97	-0.05
SCN3A	ENSG00000153253	NM_006922.4(SCN3A):c.1773T>C (p.Asn591=)	AAT	AAC		0.99	-0.02
UBE3A	ENSG00000114062	NM_130839.5(UBE3A):c.1272C>T (p.Pro424=)	CCC	CCT		1.02	0.02
MPI	ENSG00000178802	NM_002435.3(MPI):c.573C>T (p.Ala191=)	GCC	GCT	MPI-CDG	0.74	-0.44
CIITA	ENSG00000179583	NM_000246.3(CIITA):c.1542G>A (p.Thr514=)	ACG	ACA	Bare lymphocyte syndrome 2	2.96	1.57
DAG1	ENSG00000173402	NM_004393.6(DAG1):c.1695C>T (p.Pro565=)	CCC	CCT		1.02	0.02
BLM	ENSG00000197299	NM_000057.4(BLM):c.3267A>G (p.Gln1089=)	CAA	CAG	Bloom syndrome (BLM)	2.49	1.32
ALDH4A1	ENSG00000159423	NM_003748.4(ALDH4A1):c.648C>T (p.Gly216=)	GGC	GGT	Deficiency of pyrroline-5-carboxylate reductase (HYRPRO2)	0.55	-0.87
PCCA	ENSG00000175198	NM_000282.4(PCCA):c.2037C>T (p.Asp679=)	GAC	GAT	Propionic acidemia (PROP)	0.99	-0.01
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.4254G>A (p.Lys1418=)	AAG	AAA		0.87	-0.2
ALK	ENSG00000171094	NM_004304.5(ALK):c.4425C>T (p.His1475=)	CAC	CAT	Neuroblastoma 3 (NBLST3)	0.81	-0.3
SCN1A	ENSG00000144285	NM_001165963.4(SCN1A):c.135C>T (p.Asp45=)	GAC	GAT		0.99	-0.01
WNT7A	ENSG00000154764	NM_004625.4(WNT7A):c.861G>A (p.Val287=)	GTG	GTA		0.3	-1.74
SLC34A3	ENSG00000198569	NM_001177316.2(SLC34A3):c.1074G>A (p.Val358=)	GTG	GTA		0.3	-1.74
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.1053G>A (p.Lys351=)	AAG	AAA		0.87	-0.2
ITK	ENSG00000113263	NM_005546.3(ITK):c.150G>A (p.Thr50=)	ACG	ACA	Lymphoproliferative syndrome 1 (LPFS1)	2.96	1.57
TJP2	ENSG00000119139	NM_004817.4(TJP2):c.705G>T (p.Arg235=)	CGG	CGT		0.43	-1.22

LAMA2	ENSG00000196569	NM_000426.3(LAMA2):c.8211A>C (p.Pro2737=)	CCA	CCC		1	0.01
CUL7	ENSG00000044090	NM_014780.4(CUL7):c.2802C>A (p.Leu934=)	CGC	CGA		0.74	-0.44
IGF1R	ENSG00000140443	NM_000875.5(IGF1R):c.1956T>G (p.Pro652=)	CCT	CCG		0.32	-1.64
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.6921G>A (p.Leu2307=)	TTG	TTA		0.65	-0.61
TTN	ENSG00000155657	NM_001267550.2(TTN):c.210G>T (p.Val70=)	GTG	GTT		0.46	-1.13
CACNA1C	ENSG00000151067	NM_000719.7(CACNA1C):c.792C>A (p.Ala264=)	GCC	GCA		0.67	-0.59
DBH	ENSG00000123454	NM_000787.4(DBH):c.291C>T (p.Asn97=)	AAC	AAT	Orthostatic hypotension 1 (ORTHYP1)	1.01	0.02
LAMA1	ENSG00000101680	NM_005559.4(LAMA1):c.6354C>T (p.Val2118=)	GTC	GTT		0.88	-0.19
SYP	ENSG00000102003	NM_003179.2(SYP):c.612G>A (p.Ser204=)	TCG	TCA		3.5	1.81
CHD7	ENSG00000171316	NM_017780.4(CHD7):c.5439C>T (p.Pro1813=)	CCC	CCT		1.02	0.02
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.601C>T (p.Leu201=)	CTG	TTG	Aortic aneurysm, familial thoracic 7 (AAT7)	0.37	-1.42
ALK	ENSG00000171094	NM_004304.5(ALK):c.4608G>A (p.Glu1536=)	GAG	GAA	Neuroblastoma 3 (NBLST3)	0.86	-0.22
LMNA	ENSG00000160789	NM_170707.4(LMNA):c.498G>A (p.Arg166=)	CGG	CGA		0.6	-0.73
MANBA	ENSG00000109323	NM_005908.4(MANBA):c.531T>C (p.His177=)	CAT	CAC	Beta-D-mannosidosis (MANSB)	1.23	0.3
KIF7	ENSG00000166813	NM_198525.3(KIF7):c.2586C>T (p.Arg862=)	CGC	CGT		0.52	-0.93
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.12585C>T (p.Ile4195=)	ATC	ATT		0.89	-0.17
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.1848A>T (p.Ala616=)	GCA	GCT	Autosomal recessive polycystic kidney disease (ARPKD)	1.11	0.14
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.3336C>A (p.Gly1112=)	GGC	GGA	Aortic aneurysm, familial thoracic 7 (AAT7)	0.87	-0.2
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.9345G>A (p.Pro3115=)	CCG	CCA		3.05	1.61
GALC	ENSG00000054983	NM_000153.4(GALC):c.450A>T (p.Pro150=)	CCA	CCT	Galactosylceramide beta-galactosidase deficiency	1.02	0.03
FGFR3	ENSG00000068078	NM_000142.5(FGFR3):c.150C>T (p.Val50=)	GTC	GTT		0.88	-0.19
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.2244T>C (p.Asp748=)	GAT	GAC	Cohen syndrome (COH1)	1.01	0.01
ITGB2	ENSG00000160255	NM_000211.5(ITGB2):c.1464G>A (p.Arg488=)	CGG	CGA	Leukocyte adhesion deficiency 1	0.6	-0.73
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.6237C>T (p.Asn2079=)	AAC	AAT		1.01	0.02
TJP2	ENSG00000119139	NM_004817.4(TJP2):c.2751C>T (p.Arg917=)	CGC	CGT		0.52	-0.93
ERCC6	ENSG00000225830	NM_000124.4(ERCC6):c.2479C>T (p.Leu827=)	CTA	TTA		1.18	0.24
ALG12	ENSG00000182858	NM_024105.4(ALG12):c.1155C>T (p.Pro385=)	CCC	CCT		1.02	0.02
SLC3A1	ENSG00000138079	NM_000341.4(SLC3A1):c.300C>T (p.Leu100=)	CTC	CTT	Cystinuria (CSNU)	0.8	-0.33
SIX1	ENSG00000126778	NM_005982.4(SIX1):c.402G>A (p.Lys134=)	AAG	AAA		0.87	-0.2
SGSH	ENSG00000181523	NM_000199.5(SGSH):c.411G>A (p.Ala137=)	GCG	GCA	Mucopolysaccharidosis, MPS-III-A (MPS3A)	2.88	1.52
SGSH	ENSG00000181523	NM_000199.5(SGSH):c.390C>T (p.Thr130=)	ACC	ACT	Mucopolysaccharidosis, MPS-III-A (MPS3A)	0.8	-0.31
ABHD12	ENSG00000100997	NM_001042472.3(ABHD12):c.1113G>A (p.Arg371=)	AGG	AGA		1.1	0.14
VIPAS39	ENSG00000151445	NM_022067.4(VIPAS39):c.171C>G (p.Val57=)	GTC	GTG		1.92	0.94
SERPINA1	ENSG00000197249	NM_000295.5(SERPINA1):c.324C>T (p.Leu108=)	CTC	CTT		0.8	-0.33
JAK3	ENSG00000105639	NM_000215.3(JAK3):c.252G>A (p.Pro84=)	CCG	CCA	Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-negative	3.05	1.61
RFXAP	ENSG00000133111	NM_000538.3(RFXAP):c.312C>T (p.Ser104=)	AGC	AGT	Bare lymphocyte syndrome 2	0.72	-0.48
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.3228C>G (p.Thr1076=)	ACC	ACG		0.31	-1.67
NEB	ENSG00000183091	NM_001271208.2(NEB):c.7875G>A (p.Lys2625=)	AAG	AAA	Nemaline myopathy 2 (NEM2)	0.87	-0.2
DMD	ENSG00000198947	NM_004006.2(DMD):c.8322G>T (p.Leu2774=)	CTG	CTT		0.39	-1.35
GALNS	ENSG00000141012	NM_000512.5(GALNS):c.303C>T (p.Asn101=)	AAC	AAT	Mucopolysaccharidosis, MPS-IV-A (MPS4A)	1.01	0.02
CACNA1A	ENSG00000141837	NM_001127222.2(CACNA1A):c.924G>A (p.Val308=)	GTG	GTA		0.3	-1.74

NEB	ENSG00000183091	NM_001271208.2(NEB):c.1119G>A (p.Arg373=)	AGG	AGA	Nemaline myopathy 2 (NEM2)	1.1	0.14
DNMT1	ENSG00000130816	NM_001130823.3(DNMT1):c.4173G>A (p.Pro1391=)	CCG	CCA	Hereditary sensory neuropathy type IE (HSN1E)	3.05	1.61
NGF	ENSG00000134259	NM_002506.2(NGF):c.174G>A (p.Ala58=)	GCG	GCA	Congenital sensory neuropathy with selective loss of small myelinated fibers (HSAN5)	2.88	1.52
SYP	ENSG00000102003	NM_003179.2(SYP):c.687C>T (p.Ala229=)	GCC	GCT		0.74	-0.44
FAH	ENSG00000103876	NM_000137.3(FAH):c.249G>A (p.Val83=)	GTG	GTA	Tyrosinemia type I (TYRSN1)	0.3	-1.74
DMD	ENSG00000198947	NM_004006.2(DMD):c.6195T>C (p.Ser2065=)	AGT	AGC		1.4	0.48
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.9630G>A (p.Arg3210=)	AGG	AGA		1.1	0.14
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.3465C>T (p.Ile1155=)	ATC	ATT		0.89	-0.17
CREBBP	ENSG00000005339	NM_004380.3(CREBBP):c.423T>G (p.Ser141=)	TCT	TCG		0.24	-2.06
GARS1	ENSG00000106105	NM_002047.4(GARS1):c.786T>C (p.Asn262=)	AAT	AAC		0.99	-0.02
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.150T>G (p.Leu50=)	CTT	CTG	Autosomal recessive polycystic kidney disease (ARPKD)	2.54	1.35
GAA	ENSG00000171298	NM_000152.5(GAA):c.687C>T (p.Arg229=)	CGC	CGT	Glycogen storage disease, type II (GSD2)	0.52	-0.93
DMD	ENSG00000198947	NM_004006.2(DMD):c.4698G>A (p.Leu1566=)	TTG	TTA		0.65	-0.61
ITK	ENSG00000113263	NM_005546.3(ITK):c.237G>A (p.Pro79=)	CCG	CCA	Lymphoproliferative syndrome 1 (LPFS1)	3.05	1.61
TRPM4	ENSG00000130529	NM_017636.4(TRPM4):c.657C>T (p.Asp219=)	GAC	GAT	Progressive familial heart block type IB (PFHB1B)	0.99	-0.01
PNPLA6	ENSG00000032444	NM_001166114.2(PNPLA6):c.3450G>A (p.Gly1150=)	GGG	GGA	Hereditary spastic paraplegia 39 (SPG39)	1.13	0.17
COCH	ENSG00000100473	NM_004086.3(COCH):c.198A>T (p.Val66=)	GTA	GTT		1.53	0.62
ITGB2	ENSG00000160255	NM_000211.5(ITGB2):c.2283C>T (p.Val761=)	GTC	GTT	Leukocyte adhesion deficiency 1	0.88	-0.19
IFT122	ENSG00000163913	NM_052989.3(IFT122):c.978G>A (p.Thr326=)	ACG	ACA		2.96	1.57
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.744C>T (p.Thr248=)	ACC	ACT		0.8	-0.31
CP	ENSG00000047457	NM_000096.4(CP):c.1104G>C (p.Gly368=)	GGG	GGC	Deficiency of ferroxidase	1.29	0.37
TTN	ENSG00000155657	NM_001267550.2(TTN):c.61962C>T (p.Ile20654=)	ATC	ATT		0.89	-0.17
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.3279C>T (p.Asn1093=)	AAC	AAT		1.01	0.02
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.8673C>G (p.Gly2891=)	GGC	GGG		0.77	-0.37
ELOVL4	ENSG00000118402	NM_022726.4(ELOVL4):c.651C>T (p.Tyr217=)	TAC	TAT		0.9	-0.15
QDPR	ENSG00000151552	NM_000320.3(QDPR):c.450C>T (p.Tyr150=)	TAC	TAT	Dihydropteridine reductase deficiency (HPABH4C)	0.9	-0.15
ZIC3	ENSG00000156925	NM_003413.4(ZIC3):c.1194G>T (p.Thr398=)	ACG	ACT		2.56	1.36
COG7	ENSG00000168434	NM_153603.4(COG7):c.1113C>T (p.Leu371=)	CTC	CTT	COG7 congenital disorder of glycosylation (CDG2E)	0.8	-0.33
DNMT1	ENSG00000130816	NM_001130823.3(DNMT1):c.867C>T (p.Asp289=)	GAC	GAT	Hereditary sensory neuropathy type IE (HSN1E)	0.99	-0.01
SCN2A	ENSG00000136531	NM_001040142.2(SCN2A):c.5427G>A (p.Ala1809=)	GCG	GCA		2.88	1.52
SCN2A	ENSG00000136531	NM_001040142.2(SCN2A):c.5580T>G (p.Ala1860=)	GCT	GCG		0.31	-1.67
SALL4	ENSG00000101115	NM_020436.5(SALL4):c.2376T>C (p.Asn792=)	AAT	AAC		0.99	-0.02
GAA	ENSG00000171298	NM_000152.5(GAA):c.1245G>A (p.Thr415=)	ACG	ACA	Glycogen storage disease, type II (GSD2)	2.96	1.57
ABCB4	ENSG00000005471	NM_000443.4(ABCB4):c.3411G>C (p.Arg1137=)	CGG	CGC		0.82	-0.29
CDH23	ENSG00000107736	NM_022124.6(CDH23):c.7077A>C (p.Thr2359=)	ACA	ACC		1.07	0.1
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.2433A>T (p.Ile811=)	ATA	ATT	Cohen syndrome (COH1)	2.03	1.02
CHD7	ENSG00000171316	NM_017780.4(CHD7):c.6771C>T (p.Pro2257=)	CCC	CCT		1.02	0.02
KCNMA1	ENSG00000156113	NM_001161352.2(KCNMA1):c.771C>T (p.Pro257=)	CCC	CCT	Paroxysmal nonkinesigenic dyskinesia, 3, with or without generalized epilepsy (PNKD3)	1.02	0.02
RFXANK	ENSG00000064490	NM_003721.4(RFXANK):c.501C>A (p.Gly167=)	GGC	GGA	Bare lymphocyte syndrome 2	0.87	-0.2
UNC13D	ENSG00000092929	NM_199242.2(UNC13D):c.2241C>T (p.Ser747=)	AGC	AGT	Familial hemophagocytic lymphohistiocytosis 3 (FHL3)	0.72	-0.48

USH2A	ENSG00000042781	NM_206933.3(USH2A):c.8016G>A (p.Leu2672=)	CTG	CTA		0.21	-2.27
BLM	ENSG00000197299	NM_000057.4(BLM):c.3933C>T (p.Ala1311=)	GCC	GCT	Bloom syndrome (BLM)	0.74	-0.44
LIPA	ENSG00000107798	NM_000235.4(LIPA):c.1128C>T (p.Asp376=)	GAC	GAT		0.99	-0.01
NTRK1	ENSG00000198400	NM_001007792.1(NTRK1):c.285C>T (p.Asn95=)	AAC	AAT	Hereditary insensitivity to pain with anhidrosis (CIPA)	1.01	0.02
ALPL	ENSG00000162551	NM_000478.6(ALPL):c.921G>A (p.Pro307=)	CCG	CCA		3.05	1.61
KIF1A	ENSG00000130294	NM_004321.7(KIF1A):c.4531C>T (p.Leu1511=)	CTG	TTG		0.37	-1.42
CIITA	ENSG00000179583	NM_000246.3(CIITA):c.1068G>A (p.Pro356=)	CCG	CCA	Bare lymphocyte syndrome 2	3.05	1.61
CABP2	ENSG00000167791	NM_016366.3(CABP2):c.201C>A (p.Ala67=)	GCC	GCA		0.67	-0.59
VPS33B	ENSG00000184056	NM_018668.4(VPS33B):c.456G>T (p.Leu152=)	CTG	CTT		0.39	-1.35
PC	ENSG00000173599	NM_001040716.2(PC):c.3531C>T (p.Ile1177=)	ATC	ATT	Pyruvate carboxylase deficiency	0.89	-0.17
PCDH15	ENSG00000150275	NM_033056.4(PCDH15):c.3699C>T (p.Ser1233=)	AGC	AGT		0.72	-0.48
NLRP12	ENSG00000142405	NM_144687.3(NLRP12):c.654G>A (p.Ala218=)	GCG	GCA	Familial cold autoinflammatory syndrome 2 (FCAS2)	2.88	1.52
SCN3A	ENSG00000153253	NM_006922.4(SCN3A):c.363T>C (p.Ala121=)	GCT	GCC		1.36	0.44
ADGRG1	ENSG00000205336	NM_201525.4(ADGRG1):c.1191C>T (p.Ala397=)	GCC	GCT		0.74	-0.44
CTC1	ENSG00000178971	NM_025099.6(CTC1):c.597G>A (p.Thr199=)	ACG	ACA	Dyskeratosis congenita	2.96	1.57
SLC3A1	ENSG00000138079	NM_000341.4(SLC3A1):c.231T>A (p.Ser77=)	TCT	TCA	Cystinuria (CSNU)	0.84	-0.26
DAG1	ENSG00000173402	NM_004393.6(DAG1):c.384G>A (p.Val128=)	GTG	GTA		0.3	-1.74
VIPAS39	ENSG00000151445	NM_022067.4(VIPAS39):c.78C>T (p.Asp26=)	GAC	GAT		0.99	-0.01
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.3982C>T (p.Leu1328=)	CTG	TTG		0.37	-1.42
NEB	ENSG00000183091	NM_001271208.2(NEB):c.3399A>G (p.Thr1133=)	ACA	ACG	Nemaline myopathy 2 (NEM2)	0.34	-1.57
BLM	ENSG00000197299	NM_000057.4(BLM):c.4251A>C (p.Ser1417=)	TCA	TCC	Bloom syndrome (BLM)	1.22	0.29
FOXN1	ENSG00000109101	NM_001369369.1(FOXN1):c.1131G>A (p.Lys377=)	AAG	AAA	T-cell immunodeficiency, congenital alopecia, and nail dystrophy	0.87	-0.2
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.13596C>T (p.Ala4532=)	GCC	GCT		0.74	-0.44
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.741C>T (p.Asp247=)	GAC	GAT		0.99	-0.01
NTRK1	ENSG00000198400	NM_001007792.1(NTRK1):c.495G>A (p.Thr165=)	ACG	ACA	Hereditary insensitivity to pain with anhidrosis (CIPA)	2.96	1.57
TJP2	ENSG00000119139	NM_004817.4(TJP2):c.258C>T (p.Val86=)	GTC	GTT		0.88	-0.19
RETREG1	ENSG00000154153	NM_001034850.2(RETREG1):c.750G>T (p.Leu250=)	CTG	CTT		0.39	-1.35
RD3	ENSG00000198570	NM_183059.2(RD3):c.102G>A (p.Thr34=)	ACG	ACA	Leber congenital amaurosis 12 (LCA12)	2.96	1.57
RELN	ENSG00000189056	NM_005045.4(RELN):c.1482A>T (p.Ile494=)	ATA	ATT		2.03	1.02
FLNC	ENSG00000128591	NM_001458.4(FLNC):c.5544C>T (p.Ser1848=)	AGC	AGT		0.72	-0.48
ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.174C>T (p.Asp58=)	GAC	GAT		0.99	-0.01
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.1185C>T (p.Ala395=)	GCC	GCT		0.74	-0.44
DSP	ENSG00000096696	NM_004415.4(DSP):c.3282G>A (p.Lys1094=)	AAG	AAA	Cardiomyopathy (CMYO)	0.87	-0.2
ITGB2	ENSG00000160255	NM_000211.5(ITGB2):c.714C>T (p.Asp238=)	GAC	GAT	Leukocyte adhesion deficiency 1	0.99	-0.01
ILDR1	ENSG00000145103	NM_001199799.2(ILDR1):c.792G>A (p.Pro264=)	CCG	CCA		3.05	1.61
HLCS	ENSG00000159267	NM_001352514.2(HLCS):c.1857C>A (p.Ala619=)	GCC	GCA	Holocarboxylase synthetase deficiency	0.67	-0.59
MECP2	ENSG00000169057	NM_001110792.2(MECP2):c.633C>G (p.Pro211=)	CCC	CCG		0.33	-1.62
PCDH19	ENSG00000165194	NM_001184880.2(PCDH19):c.1401G>T (p.Thr467=)	ACG	ACT		2.56	1.36
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.9315C>T (p.Tyr3105=)	TAC	TAT		0.9	-0.15
PLEKHG5	ENSG00000171680	NM_020631.5(PLEKHG5):c.2610G>A (p.Pro870=)	CCA	CCA		1	0
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.6639C>A (p.Gly2213=)	GGC	GGA		0.87	-0.2

ABAT	ENSG00000183044	NM_020686.6(ABAT):c.978C>T (p.Asp326=)	GAC	GAT	Gamma-aminobutyric acid transaminase deficiency	0.99	-0.01
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.3582C>T (p.Ile1194=)	ATC	ATT	Wilson disease (WND)	0.89	-0.17
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.7590G>A (p.Val2530=)	GTG	GTA		0.3	-1.74
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.6519C>T (p.Thr2173=)	ACC	ACT		0.8	-0.31
HLCS	ENSG00000159267	NM_001352514.2(HLCS):c.918A>G (p.Gly306=)	GGA	GGG	Holocarboxylase synthetase deficiency	0.89	-0.17
TTN	ENSG00000155657	NM_001267550.2(TTN):c.8184C>G (p.Val2728=)	GTC	GTG		1.92	0.94
MEOX1	ENSG00000005102	NM_004527.4(MEOX1):c.126G>A (p.Pro42=)	CCG	CCA		3.05	1.61
VWF	ENSG00000110799	NM_000552.4(VWF):c.1614C>T (p.Pro538=)	CCC	CCT		1.02	0.02
CIITA	ENSG00000179583	NM_000246.3(CIITA):c.1518G>A (p.Ala506=)	GCG	GCA	Bare lymphocyte syndrome 2	2.88	1.52
DIS3L2	ENSG00000144535	NM_152383.5(DIS3L2):c.108G>A (p.Lys36=)	AAG	AAA	Perlman syndrome (PRLMNS)	0.87	-0.2
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.13470C>T (p.Arg4490=)	CGC	CGT		0.52	-0.93
FLNB	ENSG00000136068	NM_001457.4(FLNB):c.5220C>T (p.Asn1740=)	AAC	AAT		1.01	0.02
NEB	ENSG00000183091	NM_001271208.2(NEB):c.6369G>A (p.Thr2123=)	ACG	ACA	Nemaline myopathy 2 (NEM2)	2.96	1.57
DAG1	ENSG00000173402	NM_004393.6(DAG1):c.2124G>C (p.Thr708=)	ACG	ACC		3.18	1.67
NPHP3	ENSG00000113971	NM_153240.5(NPHP3):c.2688T>C (p.Tyr896=)	TAT	TAC		1.11	0.15
SH3PXD2B	ENSG00000174705	NM_001017995.3(SH3PXD2B):c.2541C>T (p.Ala847=)	GCC	GCT		0.74	-0.44
PEX1	ENSG00000127980	NM_000466.3(PEX1):c.2268A>G (p.Lys756=)	AAA	AAG		1.15	0.2
HLCS	ENSG00000159267	NM_001352514.2(HLCS):c.951C>T (p.Ser317=)	TCC	TCT	Holocarboxylase synthetase deficiency	0.98	-0.03
ARFGEF2	ENSG00000124198	NM_006420.3(ARFGEF2):c.1233C>T (p.Leu411=)	CTC	CTT		0.8	-0.33
FOXN1	ENSG00000109101	NM_001369369.1(FOXN1):c.321C>T (p.Ala107=)	GCC	GCT	T-cell immunodeficiency, congenital alopecia, and nail dystrophy	0.74	-0.44
STIL	ENSG00000123473	NM_001048166.1(STIL):c.1227T>C (p.Ser409=)	AGT	AGC		1.4	0.48
ARHGAP31	ENSG00000031081	NM_020754.4(ARHGAP31):c.435C>G (p.Thr145=)	ACC	ACG		0.31	-1.67
GRM6	ENSG00000113262	NM_000843.4(GRM6):c.1944G>T (p.Ala648=)	GCG	GCT		3.18	1.67
RAPSN	ENSG00000165917	NM_005055.5(RAPSN):c.567G>A (p.Ala189=)	GCG	GCA		2.88	1.52
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.19554C>T (p.Pro6518=)	CCC	CCT		1.02	0.02
DICER1	ENSG00000100697	NM_177438.2(DICER1):c.3690G>A (p.Gln1230=)	CAG	CAA	DICER1-related pleuropulmonary blastoma cancer predisposition syndrome (PPBFTDS)	0.4	-1.32
FKTN	ENSG00000106692	NM_001079802.2(FKTN):c.411C>T (p.Cys137=)	TGC	TGT		0.97	-0.05
OXCT1	ENSG00000083720	NM_000436.4(OXCT1):c.477A>G (p.Thr159=)	ACA	ACG	Succinyl-CoA acetoacetate transferase deficiency (SCOTD)	0.34	-1.57
OAT	ENSG00000065154	NM_000274.3(OAT):c.736C>T (p.Leu246=)	CTA	TTA	Ornithine aminotransferase deficiency (GACR)	1.18	0.24
IL17RA	ENSG00000177663	NM_014339.7(IL17RA):c.978G>A (p.Thr326=)	ACG	ACA	Immunodeficiency 51 (IMD51)	2.96	1.57
KIF7	ENSG00000166813	NM_198525.3(KIF7):c.2613G>A (p.Glu871=)	GAG	GAA	Acrocallosal syndrome (ACLS)	0.86	-0.22
D2HGDH	ENSG00000180902	NM_152783.5(D2HGDH):c.963C>T (p.Val321=)	GTC	GTT	D-2-hydroxyglutaric aciduria 1 (D2HGA1)	0.88	-0.19
COG1	ENSG00000166685	NM_018714.3(COG1):c.1230G>A (p.Pro410=)	CCG	CCA	COG1 congenital disorder of glycosylation (CDG2G)	3.05	1.61
IMPDH1	ENSG00000106348	NM_000883.4(IMPDH1):c.624C>G (p.Pro208=)	CCC	CCG		0.33	-1.62
NEB	ENSG00000183091	NM_001271208.2(NEB):c.4548T>C (p.Tyr1516=)	TAT	TAC	Nemaline myopathy 2 (NEM2)	1.11	0.15
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.6573G>A (p.Leu2191=)	CTG	CTA		0.21	-2.27
PLOD1	ENSG00000083444	NM_000302.4(PLOD1):c.1182G>C (p.Arg394=)	CGG	CGC	Ehlers-Danlos syndrome, hydroxylysine-deficient (EDSKSCL1)	0.82	-0.29
BCOR	ENSG00000183337	NM_001123385.2(BCOR):c.837C>T (p.Leu279=)	CTC	CTT		0.8	-0.33
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.3253C>T (p.Leu1085=)	CTG	TTG		0.37	-1.42
DMD	ENSG00000198947	NM_004006.2(DMD):c.8172C>T (p.Leu2724=)	CTC	CTT		0.8	-0.33
MCPH1	ENSG00000147316	NM_024596.5(MCPH1):c.90A>G (p.Thr30=)	ACA	ACG		0.34	-1.57

PNPLA6	ENSG00000032444	NM_001166114.2(PNPLA6):c.1962C>T (p.Ser654=)	TCC	TCT	Hereditary spastic paraplegia 39 (SPG39)	0.98	-0.03
MMAA	ENSG00000151611	NM_172250.3(MMAA):c.966A>G (p.Pro322=)	CCA	CCG	Vitamin B12-responsive methylmalonic acidemia type cblA	0.33	-1.61
UNG	ENSG00000076248	NM_080911.3(UNG):c.246G>C (p.Leu82=)	CTG	CTC	Hyper-IgM syndrome type 5 (HIGM5)	0.49	-1.02
SLC7A7	ENSG00000155465	NM_003982.4(SLC7A7):c.123C>T (p.Asn41=)	AAC	AAT	Lysinuric protein intolerance (LPI)	1.01	0.02
SMCHD1	ENSG00000101596	NM_015295.2(SMCHD1):c.2289G>A (p.Ser763=)	TCG	TCA		3.5	1.81
GALK1	ENSG00000108479	NM_000154.2(GALK1):c.66G>A (p.Glu22=)	GAG	GAA	Deficiency of galactokinase (GALAC2)	0.86	-0.22
TMEM138	ENSG00000149483	NM_016464.5(TMEM138):c.327C>T (p.Ser109=)	AGC	AGT	Joubert syndrome 16 (JBTS16)	0.72	-0.48
CACNB4	ENSG00000182389	NM_000726.4(CACNB4):c.288C>T (p.Ala96=)	GCC	GCT		0.74	-0.44
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.3501C>T (p.His1167=)	CAC	CAT		0.81	-0.3
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.12516C>T (p.Ser4172=)	TCC	TCT		0.98	-0.03
DOK7	ENSG00000175920	NM_173660.5(DOK7):c.1029C>T (p.Gly343=)	GGC	GGT		0.55	-0.87
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.612C>T (p.Ile204=)	ATC	ATT		0.89	-0.17
FLNA	ENSG00000196924	NM_001110556.2(FLNA):c.1107C>T (p.Pro369=)	CCC	CCT		1.02	0.02
MYO7A	ENSG00000137474	NM_000260.4(MYO7A):c.3729G>A (p.Pro1243=)	CCG	CCA		3.05	1.61
CPA6	ENSG00000165078	NM_020361.5(CPA6):c.1026C>G (p.Pro342=)	CCC	CCG		0.33	-1.62
CTC1	ENSG00000178971	NM_025099.6(CTC1):c.1734C>T (p.Ala578=)	GCC	GCT	Dyskeratosis congenita	0.74	-0.44
NTRK1	ENSG00000198400	NM_001007792.1(NTRK1):c.2247C>T (p.Ala749=)	GCC	GCT	Hereditary insensitivity to pain with anhidrosis (CIPA)	0.74	-0.44
PCDH15	ENSG00000150275	NM_033056.4(PCDH15):c.4608A>G (p.Val1536=)	GTA	GTG		3.34	1.74
ELP1	ENSG00000070061	NM_003640.5(ELP1):c.2598C>T (p.Pro866=)	CCC	CCT	Familial dysautonomia (HSAN3)	1.02	0.02
AGL	ENSG00000162688	NM_000642.3(AGL):c.1065G>A (p.Thr355=)	ACG	ACA	Glycogen storage disease type III (GSD3)	2.96	1.57
HSPG2	ENSG00000142798	NM_005529.7(HSPG2):c.9291C>T (p.Tyr3097=)	TAC	TAT		0.9	-0.15
SPG7	ENSG00000197912	NM_003119.4(SPG7):c.33C>T (p.Leu11=)	CTC	CTT		0.8	-0.33
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.13209G>A (p.Ser4403=)	TCG	TCA		3.5	1.81
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.10650C>T (p.Asn3550=)	AAC	AAT		1.01	0.02
EHMT1	ENSG00000181090	NM_024757.5(EHMT1):c.1425C>T (p.Asp475=)	GAC	GAT		0.99	-0.01
PKP2	ENSG00000057294	NM_001005242.3(PKP2):c.234C>T (p.His78=)	CAC	CAT		0.81	-0.3
MECP2	ENSG00000169057	NM_001110792.2(MECP2):c.564C>G (p.Pro188=)	CCC	CCG		0.33	-1.62
NEB	ENSG00000183091	NM_001271208.2(NEB):c.23091T>C (p.His7697=)	CAT	CAC	Nemaline myopathy 2 (NEM2)	1.23	0.3
EHHADH	ENSG00000113790	NM_001966.4(EHHADH):c.1608G>A (p.Gly536=)	GGG	GGA		1.13	0.17
MMAB	ENSG00000139428	NM_052845.4(MMAB):c.561C>T (p.Ala187=)	GCC	GCT	Vitamin B12-responsive methylmalonic acidemia type cblB	0.74	-0.44
IL10RA	ENSG00000110324	NM_001558.4(IL10RA):c.1539G>A (p.Thr513=)	ACG	ACA	Inflammatory bowel disease 28, autosomal recessive (IBD28)	2.96	1.57
TTN	ENSG00000155657	NM_001267550.2(TTN):c.543C>T (p.Ser181=)	AGC	AGT		0.72	-0.48
TTN	ENSG00000155657	NM_001267550.2(TTN):c.56118C>T (p.Ala18706=)	GCC	GCT		0.74	-0.44
RFXANK	ENSG00000064490	NM_003721.4(RFXANK):c.765G>A (p.Val255=)	GTG	GTA	Bare lymphocyte syndrome 2	0.3	-1.74
LRSAM1	ENSG00000148356	NM_138361.5(LRSAM1):c.894G>A (p.Thr298=)	ACG	ACA	Charcot-Marie-Tooth disease type 2P (CMT2P)	2.96	1.57
NEB	ENSG00000183091	NM_001271208.2(NEB):c.5853C>A (p.Ala1951=)	GCC	GCA	Nemaline myopathy 2 (NEM2)	0.67	-0.59
SLC22A5	ENSG00000197375	NM_003060.4(SLC22A5):c.1113C>T (p.Asp371=)	GAC	GAT	Renal carnitine transport defect (CDSP)	0.99	-0.01
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.9714A>G (p.Gly3238=)	GGA	GGG	Autosomal recessive polycystic kidney disease (ARPKD)	0.89	-0.17
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.3024G>A (p.Val1008=)	GTG	GTA	Aortic aneurysm, familial thoracic 7 (AAT7)	0.3	-1.74
ADGRG1	ENSG00000205336	NM_201525.4(ADGRG1):c.1537C>T (p.Leu513=)	CTG	TTG		0.37	-1.42
MMAA	ENSG00000151611	NM_172250.3(MMAA):c.102C>T (p.Leu34=)	CTC	CTT	Vitamin B12-responsive methylmalonic acidemia type cblA	0.8	-0.33
TJP2	ENSG00000119139	NM_004817.4(TJP2):c.2832G>A (p.Pro944=)	CCG	CCA		3.05	1.61

WDR62	ENSG00000075702	NM_001083961.2(WDR62):c.4122C>T (p.Gly1374=)	GGC	GGT		0.55	-0.87
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.624C>T (p.Cys208=)	TGC	TGT		0.97	-0.05
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.14808C>T (p.Ser4936=)	TCC	TCT		0.98	-0.03
PPP1R15B	ENSG00000158615	NM_032833.4(PPP1R15B):c.156C>T (p.Ser52=)	TCC	TCT		0.98	-0.03
RETREG1	ENSG00000154153	NM_001034850.2(RETREG1):c.1182T>C (p.Ala394=)	GCT	GCC		1.36	0.44
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.5160C>T (p.Asp1720=)	GAC	GAT	Autosomal recessive polycystic kidney disease (ARPKD)	0.99	-0.01
PLCB1	ENSG00000182621	NM_015192.4(PLCB1):c.3135C>T (p.Val1045=)	GTC	GTT		0.88	-0.19
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.9678A>G (p.Gly3226=)	GGA	GGG	Cohen syndrome (COH1)	0.89	-0.17
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.4626C>G (p.Arg1542=)	CGC	CGG	Cohen syndrome (COH1)	1.22	0.29
ATP8B1	ENSG00000081923	NM_005603.6(ATP8B1):c.433C>T (p.Leu145=)	CTA	TTA		1.18	0.24
AP3B2	ENSG00000103723	NM_001278512.2(AP3B2):c.2394C>T (p.Ser798=)	TCC	TCT		0.98	-0.03
LIM2	ENSG00000105370	NM_001161748.2(LIM2):c.57G>A (p.Leu19=)	CTG	CTA	Cataract 19, multiple types (CTRCT19)	0.21	-2.27
MAGI2	ENSG00000187391	NM_012301.4(MAGI2):c.1713C>T (p.Ser571=)	TCC	TCT		0.98	-0.03
PRF1	ENSG00000180644	NM_001083116.3(PRF1):c.519G>C (p.Thr173=)	ACG	ACC	Familial hemophagocytic lymphohistiocytosis 2 (FHL2)	3.18	1.67
CP	ENSG00000047457	NM_000096.4(CP):c.93G>A (p.Thr31=)	ACG	ACA	Deficiency of ferroxidase	2.96	1.57
DYNC2H1	ENSG00000187240	NM_001377.3(DYNC2H1):c.12006C>T (p.Ile4002=)	ATC	ATT		0.89	-0.17
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.11001C>T (p.Asp3667=)	GAC	GAT		0.99	-0.01
LARGE1	ENSG00000133424	NM_004737.6(LARGE1):c.1234C>T (p.Leu412=)	CTG	TTG		0.37	-1.42
PAPOLA	ENSG00000090060	NM_032632.4(PAPOLA):c.1464A>G (p.Val488=)	GTA	GTG		3.34	1.74
FKTN	ENSG00000106692	NM_001079802.2(FKTN):c.180A>G (p.Lys60=)	AAA	AAG		1.15	0.2
ACADM	ENSG00000117054	NM_000016.5(ACADM):c.624T>C (p.Asp208=)	GAT	GAC	Medium-chain acyl-coenzyme A dehydrogenase deficiency (ACADMD)	1.01	0.01
CACNA1A	ENSG00000141837	NM_001127222.2(CACNA1A):c.699A>G (p.Leu233=)	CTA	CTG		4.81	2.27
FKRP	ENSG00000181027	NM_024301.5(FKRP):c.336C>T (p.Ala112=)	GCC	GCT		0.74	-0.44
PCNT	ENSG00000160299	NM_006031.6(PCNT):c.1083A>G (p.Leu361=)	CTA	CTG	Microcephalic osteodysplastic primordial dwarfism type II (MOPD2)	4.81	2.27
ACAN	ENSG00000157766	NM_001369268.1(ACAN):c.894C>T (p.Ser298=)	AGC	AGT		0.72	-0.48
KCNQ2	ENSG00000075043	NM_172107.4(KCNQ2):c.2358G>A (p.Thr786=)	ACG	ACA		2.96	1.57
CTDP1	ENSG00000060069	NM_004715.4(CTDP1):c.2307C>T (p.Pro769=)	CCC	CCT		1.02	0.02
FGFR2	ENSG00000066468	NM_000141.5(FGFR2):c.2106G>A (p.Ser702=)	TCG	TCA		3.5	1.81
AP3B1	ENSG00000132842	NM_003664.5(AP3B1):c.1704C>T (p.Tyr568=)	TAC	TAT	Hermansky-Pudlak syndrome 2 (HPS2)	0.9	-0.15
FLNC	ENSG00000128591	NM_001458.4(FLNC):c.1632G>A (p.Lys544=)	AAG	AAA		0.87	-0.2
ASS1	ENSG00000130707	NM_054012.4(ASS1):c.1056C>T (p.Ser352=)	TCC	TCT	Citrullinemia type I (CTNL1)	0.98	-0.03
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.12930C>T (p.Asp4310=)	GAC	GAT		0.99	-0.01
SYNE2	ENSG00000054654	NM_182914.2(SYNE2):c.12189C>T (p.Thr4063=)	ACC	ACT		0.8	-0.31
ATP1A3	ENSG00000105409	NM_152296.5(ATP1A3):c.1296G>T (p.Val432=)	GTG	GTT		0.46	-1.13
ABAT	ENSG00000183044	NM_020686.6(ABAT):c.864C>T (p.Ala288=)	GCC	GCT	Gamma-aminobutyric acid transaminase deficiency	0.74	-0.44
SPG11	ENSG00000104133	NM_025137.4(SPG11):c.36C>T (p.Ser12=)	TCC	TCT	Spastic paraplegia 11, autosomal recessive (SPG11)	0.98	-0.03
LMNA	ENSG00000160789	NM_170707.4(LMNA):c.643C>T (p.Leu215=)	CTG	TTG		0.37	-1.42
MEF2C	ENSG00000081189	NM_002397.5(MEF2C):c.489A>G (p.Ser163=)	TCA	TCG		0.29	-1.81
ETHE1	ENSG00000105755	NM_014297.5(ETHE1):c.489G>A (p.Arg163=)	CGG	CGA	Ethylmalonic encephalopathy (EE)	0.6	-0.73

CLDN1	ENSG00000163347	NM_021101.5(CLDN1):c.195A>G (p.Lys65=)	AAA	AAG		1.15	0.2
CACNA1A	ENSG00000141837	NM_001127222.2(CACNA1A):c.6669C>T (p.Pro2223=)	CCC	CCT		1.02	0.02
NEK8	ENSG00000160602	NM_178170.3(NEK8):c.294C>G (p.Ser98=)	TCC	TCG		0.23	-2.09
TRAPPC11	ENSG00000168538	NM_021942.6(TRAPPC11):c.2817C>T (p.Thr939=)	ACC	ACT		0.8	-0.31
CHRNA1	ENSG00000138435	NM_001039523.3(CHRNA1):c.204G>A (p.Gln68=)	CAG	CAA		0.4	-1.32
PRF1	ENSG00000180644	NM_001083116.3(PRF1):c.132C>A (p.Ala44=)	GCC	GCA	Familial hemophagocytic lymphohistiocytosis 2 (FHL2)	0.67	-0.59
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.762G>A (p.Arg254=)	AGG	AGA	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS)	1.1	0.14
ABAT	ENSG00000183044	NM_020686.6(ABAT):c.645C>A (p.Gly215=)	GGC	GGA	Gamma-aminobutyric acid transaminase deficiency	0.87	-0.2
SCN10A	ENSG00000185313	NM_006514.3(SCN10A):c.4729C>T (p.Leu1577=)	CTG	TTG		0.37	-1.42
COLQ	ENSG00000206561	NM_005677.4(COLQ):c.912C>T (p.Tyr304=)	TAC	TAT	Endplate acetylcholinesterase deficiency (CMS5)	0.9	-0.15
MYH14	ENSG00000105357	NM_001145809.2(MYH14):c.4740C>T (p.Asp1580=)	GAC	GAT		0.99	-0.01
DBH	ENSG00000123454	NM_000787.4(DBH):c.807C>T (p.Cys269=)	TGC	TGT	Orthostatic hypotension 1 (ORTHYP1)	0.97	-0.05
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.7551C>T (p.Asn2517=)	AAC	AAT		1.01	0.02
MYO7A	ENSG00000137474	NM_000260.4(MYO7A):c.1209C>T (p.Tyr403=)	TAC	TAT		0.9	-0.15
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.13281C>T (p.Asp4427=)	GAC	GAT		0.99	-0.01
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.12861G>A (p.Glu4287=)	GAG	GAA		0.86	-0.22
SMCHD1	ENSG00000101596	NM_015295.2(SMCHD1):c.5625C>T (p.Gly1875=)	GGC	GGT		0.55	-0.87
AXIN2	ENSG00000168646	NM_004655.4(AXIN2):c.2124G>A (p.Ser708=)	TCG	TCA	Oligodontia-colorectal cancer syndrome (ODCRCS)	3.5	1.81
ALDOB	ENSG00000136872	NM_000035.4(ALDOB):c.486C>T (p.Leu162=)	CTC	CTT	Hereditary fructosuria (HFI)	0.8	-0.33
DMD	ENSG00000198947	NM_004006.2(DMD):c.2637G>T (p.Arg879=)	CGG	CGT		0.43	-1.22
CACNA1C	ENSG00000151067	NM_000719.7(CACNA1C):c.3258C>T (p.Ile1086=)	ATC	ATT		0.89	-0.17
ZMYM3	ENSG00000147130	NM_201599.3(ZMYM3):c.195C>G (p.Gly65=)	GGC	GGG		0.77	-0.37
FHL1	ENSG00000022267	NM_001159699.2(FHL1):c.447G>A (p.Lys149=)	AAG	AAA		0.87	-0.2
BIN1	ENSG00000136717	NM_139343.3(BIN1):c.1047G>A (p.Pro349=)	CCG	CCA	Myopathy, centronuclear, 2 (CNM2)	3.05	1.61
STXBP2	ENSG00000076944	NM_006949.4(STXBP2):c.333C>T (p.Pro111=)	CCC	CCT	Hemophagocytic lymphohistiocytosis, familial, 5 (FHL5)	1.02	0.02
PYGM	ENSG00000068976	NM_005609.4(PYGM):c.1266C>T (p.Asp422=)	GAC	GAT	Glycogen storage disease, type V (GSD5)	0.99	-0.01
LYST	ENSG00000143669	NM_001301365.1(LYST):c.2724C>T (p.Cys908=)	TGC	TGT	Chédiak-Higashi syndrome (CHS)	0.97	-0.05
DYNC2H1	ENSG00000187240	NM_001377.3(DYNC2H1):c.7149G>A (p.Thr2383=)	ACG	ACA		2.96	1.57
MYH2	ENSG00000125414	NM_017534.6(MYH2):c.3384C>T (p.Ile1128=)	ATC	ATT		0.89	-0.17
SH3PXD2B	ENSG00000174705	NM_001017995.3(SH3PXD2B):c.1398C>T (p.Pro466=)	CCC	CCT		1.02	0.02
CRB2	ENSG00000148204	NM_173689.7(CRB2):c.1110C>T (p.Gly370=)	GGC	GGT		0.55	-0.87
TCTN2	ENSG00000168778	NM_024809.5(TCTN2):c.429T>C (p.Ile143=)	ATT	ATC		1.13	0.17
TNFRSF11A	ENSG00000141655	NM_003839.4(TNFRSF11A):c.321G>A (p.Thr107=)	ACG	ACA		2.96	1.57
SP110	ENSG00000135899	NM_004509.4(SP110):c.459G>A (p.Ala153=)	GCG	GCA	Hepatic veno-occlusive disease-immunodeficiency syndrome	2.88	1.52
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.2487C>T (p.Leu829=)	CTC	CTT		0.8	-0.33
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.8805G>A (p.Ala2935=)	GCG	GCA		2.88	1.52
PCDH19	ENSG00000165194	NM_001184880.2(PCDH19):c.684G>A (p.Val228=)	GTG	GTA		0.3	-1.74
MEFV	ENSG00000103313	NM_000243.2(MEFV):c.801A>G (p.Thr267=)	ACA	ACG	Familial Mediterranean fever (FMF)	0.34	-1.57
NR1H4	ENSG00000012504	NM_001206979.2(NR1H4):c.750C>T (p.Thr250=)	ACC	ACT		0.8	-0.31
TRPM4	ENSG00000130529	NM_017636.4(TRPM4):c.3489A>G (p.Gly1163=)	GGA	GGG	Progressive familial heart block type IB (PFHB1B)	0.89	-0.17
TCN2	ENSG00000185339	NM_000355.4(TCN2):c.810G>T (p.Ala270=)	GCG	GCT	Transcolabamin II deficiency	3.18	1.67

CGNL1	ENSG00000128849	NM_001252335.2(CGNL1):c.2322T>C (p.His774=)	CAT	CAC		1.23	0.3
PLOD1	ENSG00000083444	NM_000302.4(PLOD1):c.1581C>T (p.Pro527=)	CCC	CCT	Ehlers-Danlos syndrome, hydroxylysine-deficient (EDSKSCL1)	1.02	0.02
NLRP7	ENSG00000167634	NM_001127255.1(NLRP7):c.531C>T (p.His177=)	CAC	CAT	Hydatidiform mole, recurrent, 1 (HYDM1)	0.81	-0.3
DHCR24	ENSG00000116133	NM_014762.4(DHCR24):c.102C>T (p.Phe34=)	TTC	TTT		0.98	-0.02
HDAC4	ENSG00000068024	NM_006037.3(HDAC4):c.2136G>A (p.Gln712=)	CAG	CAA		0.4	-1.32
DEPDC5	ENSG00000100150	NM_001242897.2(DEPDC5):c.501G>A (p.Thr167=)	ACG	ACA		2.96	1.57
KBTBD13	ENSG00000234438	NM_001101362.2(KBTBD13):c.1191G>C (p.Val397=)	GTG	GTC	Nemaline myopathy 6 (NEM6)	0.52	-0.94
CYP7B1	ENSG00000172817	NM_004820.5(CYP7B1):c.1036T>C (p.Leu346=)	TTG	CTG		2.67	1.42
IL17RA	ENSG00000177663	NM_014339.6(IL17RA):c.2466G>A (p.Gly822=)	GGG	GGA	Immunodeficiency 51 (IMD51)	1.13	0.17
LYST	ENSG00000143669	NM_001301365.1(LYST):c.4566A>C (p.Ala1522=)	GCA	GCC	Chédiak-Higashi syndrome (CHS)	1.5	0.59
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.10503A>G (p.Leu3501=)	CTA	CTG		4.81	2.27
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.180T>G (p.Gly60=)	GGT	GGG		1.41	0.5
MYO15A	ENSG00000091536	NM_016239.4(MYO15A):c.5193C>T (p.Phe1731=)	TTC	TTT		0.98	-0.02
MMUT	ENSG00000146085	NM_000255.4(MMUT):c.1614C>T (p.Thr538=)	ACC	ACT	Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency	0.8	-0.31
GAN	ENSG00000261609	NM_022041.3(GAN):c.1017G>A (p.Gln339=)	CAG	CAA	Giant axonal neuropathy 1 (GAN1)	0.4	-1.32
MRE11	ENSG00000020922	NM_005591.3(MRE11):c.1974C>T (p.Thr658=)	ACC	ACT	Hereditary cancer-predisposing syndrome	0.8	-0.31
COL5A1	ENSG00000130635	NM_001278074.1(COL5A1):c.2382C>T (p.Val794=)	GTC	GTT		0.88	-0.19
CHD8	ENSG00000100888	NM_001170629.2(CHD8):c.7620C>T (p.Asp2540=)	GAC	GAT		0.99	-0.01
LDLR	ENSG00000130164	NM_000527.4(LDLR):c.861C>T (p.Gly287=)	GGC	GGT	Familial hypercholesterolemia (FH)	0.55	-0.87
RELN	ENSG00000189056	NM_005045.4(RELN):c.5418C>T (p.Asp1806=)	GAC	GAT		0.99	-0.01
SMARCAL1	ENSG00000138375	NM_014140.3(SMARCAL1):c.1407C>T (p.Ile469=)	ATC	ATT	Schimke immuno-osseous dysplasia (SIOD)	0.89	-0.17
IQSEC2	ENSG00000124313	NM_001111125.3(IQSEC2):c.1926G>A (p.Pro642=)	CCG	CCA		3.05	1.61
MYO7A	ENSG00000137474	NM_000260.4(MYO7A):c.1299C>T (p.Ile433=)	ATC	ATT		0.89	-0.17
PCCA	ENSG00000175198	NM_000282.4(PCCA):c.432A>G (p.Gly144=)	GGA	GGG	Propionic acidemia (PROP)	0.89	-0.17
ALDH7A1	ENSG00000164904	NM_001182.5(ALDH7A1):c.423G>C (p.Val141=)	GTG	GTC	Pyridoxine-dependent epilepsy (EPD)	0.52	-0.94
PNPLA2	ENSG00000177666	NM_020376.4(PNPLA2):c.399C>T (p.Asn133=)	AAC	AAT	Neutral lipid storage myopathy (NLSDM)	1.01	0.02
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.18879C>T (p.Ile6293=)	ATC	ATT		0.89	-0.17
IL10RA	ENSG00000110324	NM_001558.4(IL10RA):c.1401G>A (p.Ser467=)	TCG	TCA	Inflammatory bowel disease 28, autosomal recessive (IBD28)	3.5	1.81
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.123C>T (p.Thr41=)	ACC	ACT		0.8	-0.31
ATL1	ENSG00000198513	NM_001127713.1(ATL1):c.756C>T (p.Asn252=)	AAC	AAT	Hereditary spastic paraplegia 3A (SPG3A)	1.01	0.02
COL2A1	ENSG00000139219	NM_001844.5(COL2A1):c.1962C>T (p.Gly654=)	GGC	GGT		0.55	-0.87
STRA6	ENSG00000137868	NM_022369.4(STRA6):c.1566G>T (p.Val522=)	GTG	GTT	Matthew-Wood syndrome (MCOPS9)	0.46	-1.13
TTN	ENSG00000155657	NM_001267550.2(TTN):c.9639C>T (p.Ser3213=)	AGC	AGT		0.72	-0.48
ASS1	ENSG00000130707	NM_054012.4(ASS1):c.858A>T (p.Ala286=)	GCA	GCT	Citrullinemia type I (CTNL1)	1.11	0.14
PLEKHG5	ENSG00000171680	NM_020631.5(PLEKHG5):c.1572C>T (p.His524=)	CTG	CTT		0.39	-1.35
CARD9	ENSG00000187796	NM_052813.5(CARD9):c.406C>T (p.Leu136=)	CTG	TTG	Candidiasis, familial, 2 (CANDF2)	0.37	-1.42
DOCK6	ENSG00000130158	NM_020812.4(DOCK6):c.906G>C (p.Ser302=)	TCG	TCC		4.26	2.09
HMGCS2	ENSG00000134240	NM_005518.4(HMGCS2):c.111T>C (p.Ser37=)	TCT	TCC	mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency (HMGCS2D)	1.02	0.03
PYGM	ENSG00000068976	NM_005609.4(PYGM):c.1110G>A (p.Val370=)	GTG	GTA	Glycogen storage disease, type V (GSD5)	0.3	-1.74
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.1497C>T (p.His499=)	CAC	CAT		0.81	-0.3

PLEC	ENSG00000178209	NM_201384.3(PLEC):c.6267G>A (p.Ala2089=)	GCG	GCA		2.88	1.52
TTN	ENSG00000155657	NM_001267550.2(TTN):c.11337C>T (p.Ala3779=)	GCC	GCT		0.74	-0.44
PNPLA2	ENSG00000177666	NM_020376.4(PNPLA2):c.492C>T (p.Tyr164=)	TAC	TAT	Neutral lipid storage myopathy (NLSDM)	0.9	-0.15
NSDHL	ENSG00000147383	NM_015922.3(NSDHL):c.816C>A (p.Pro272=)	CCC	CCA		1	-0.01
HSPG2	ENSG00000142798	NM_005529.7(HSPG2):c.4413C>T (p.Pro1471=)	CCC	CCT		1.02	0.02
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.2175C>T (p.Ser725=)	AGC	AGT	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD)	0.72	-0.48
MYO7A	ENSG00000137474	NM_000260.4(MYO7A):c.5004C>T (p.Tyr1668=)	TAC	TAT		0.9	-0.15
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.366T>C (p.Asn122=)	AAT	AAC		0.99	-0.02
NEB	ENSG00000183091	NM_001271208.2(NEB):c.12210C>G (p.Ala4070=)	GCC	GCG	Nemaline myopathy 2 (NEM2)	0.23	-2.11
L1CAM	ENSG00000198910	NM_001278116.2(L1CAM):c.1107C>T (p.Asn369=)	AAC	AAT		1.01	0.02
ALDH7A1	ENSG00000164904	NM_001182.5(ALDH7A1):c.528T>C (p.His176=)	CAT	CAC	Pyridoxine-dependent epilepsy (EPD)	1.23	0.3
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.7083G>A (p.Thr2361=)	ACG	ACA		2.96	1.57
SLC34A3	ENSG00000198569	NM_001177316.2(SLC34A3):c.978C>T (p.Ile326=)	ATC	ATT		0.89	-0.17
LIFR	ENSG00000113594	NM_001127671.2(LIFR):c.2937G>A (p.Ser979=)	TCG	TCA		3.5	1.81
AGA	ENSG00000038002	NM_000027.4(AGA):c.60A>G (p.Leu20=)	CTA	CTG	Aspartylglucosaminuria (AGU)	4.81	2.27
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.2919G>A (p.Val973=)	GTG	GTA	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD)	0.3	-1.74
EHHADH	ENSG00000113790	NM_001966.4(EHHADH):c.855C>T (p.Ser285=)	TCC	TCT		0.98	-0.03
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.3657G>A (p.Thr1219=)	ACG	ACA		2.96	1.57
KCNQ3	ENSG00000184156	NM_004519.4(KCNQ3):c.2391C>T (p.His797=)	CAC	CAT		0.81	-0.3
FLNA	ENSG00000196924	NM_001110556.2(FLNA):c.5448G>A (p.Ala1816=)	GCG	GCA		2.88	1.52
LYST	ENSG00000143669	NM_001301365.1(LYST):c.3030A>G (p.Gly1010=)	GGA	GGG	Chédiak-Higashi syndrome (CHS)	0.89	-0.17
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.3735C>T (p.Leu1245=)	CTC	CTT		0.8	-0.33
VCP	ENSG00000165280	NM_007126.5(VCP):c.1488T>C (p.Pro496=)	CCT	CCC		0.98	-0.02
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.8703T>C (p.Tyr2901=)	TAT	TAC		1.11	0.15
KCNMA1	ENSG00000156113	NM_001161352.2(KCNMA1):c.1227C>T (p.His409=)	CAC	CAT	Paroxysmal nonkinesigenic dyskinesia, 3, with or without generalized epilepsy (PNKD3)	0.81	-0.3
COL6A1	ENSG00000142156	NM_001848.2(COL6A1):c.531C>T (p.Asn177=)	AAC	AAT		1.01	0.02
LRPPRC	ENSG00000138095	NM_133259.4(LRPPRC):c.1419T>C (p.Asp473=)	GAT	GAC	Congenital lactic acidosis, Saguenay-Lac-Saint-Jean type (MC4DN5)	1.01	0.01
ICOS	ENSG00000163600	NM_012092.4(ICOS):c.375A>G (p.Gly125=)	GGA	GGG	Common variable immunodeficiency 1 (CVID1)	0.89	-0.17
MECP2	ENSG00000169057	NM_001110792.2(MECP2):c.1200A>C (p.Pro400=)	CCA	CCC		1	0.01
ADGRG1	ENSG00000205336	NM_201525.4(ADGRG1):c.1578G>A (p.Thr526=)	ACG	ACA		2.96	1.57
LDLR	ENSG00000130164	NM_000527.5(LDLR):c.48C>A (p.Leu16=)	CTC	CTA	Familial hypercholesterolemia 1 (FHCL1)	0.42	-1.25
ARSA	ENSG00000100299	NM_000487.6(ARSA):c.930C>T (p.Gly310=)	GGC	GGT		0.55	-0.87
PYCR1	ENSG00000183010	NM_006907.4(PYCR1):c.465C>T (p.Ser155=)	AGC	AGT		0.72	-0.48
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.2535C>T (p.Ser845=)	TCC	TCT		0.98	-0.03
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.4786C>T (p.Leu1596=)	CTG	TTG		0.37	-1.42
IFT140	ENSG00000187535	NM_014714.4(IFT140):c.2424G>A (p.Ala808=)	GCG	GCA	Saldino-Mainzer syndrome (SRTD9)	2.88	1.52
WDR62	ENSG00000075702	NM_001083961.2(WDR62):c.2040T>C (p.His680=)	CAT	CAC		1.23	0.3
VCL	ENSG00000035403	NM_014000.2(VCL):c.3186G>A (p.Gln1062=)	CAG	CAA	Dilated cardiomyopathy 1W (CMD1W)	0.4	-1.32
ELP1	ENSG00000070061	NM_003640.5(ELP1):c.2370A>G (p.Glu790=)	GAA	GAG	Familial dysautonomia (HSAN3)	1.16	0.22

ETFA	ENSG00000140374	NM_000126.4(ETFA):c.720A>G (p.Gln240=)	CAA	CAG	Multiple acyl-CoA dehydrogenase deficiency (MADD)	2.49	1.32
SCN11A	ENSG00000168356	NM_001349253.2(SCN11A):c.1986A>G (p.Gln662=)	CAA	CAG	Neuropathy, hereditary sensory and autonomic, type VII (HSAN7);Episodic pain syndrome, familial, 3 (FEPS3)	2.49	1.32
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.7635C>G (p.Thr2545=)	ACC	ACG	Autosomal recessive polycystic kidney disease (ARPKD)	0.31	-1.67
MAN2B1	ENSG00000104774	NM_000528.4(MAN2B1):c.1713C>T (p.Pro571=)	CCC	CCT	Deficiency of alpha-mannosidase (MANSA)	1.02	0.02
SLC22A5	ENSG00000197375	NM_003060.4(SLC22A5):c.453G>A (p.Val151=)	GTG	GTA	Renal carnitine transport defect (CDSP)	0.3	-1.74
SCP2	ENSG00000116171	NM_002979.5(SCP2):c.648T>C (p.Phe216=)	TTT	TTC		1.02	0.02
TCN2	ENSG00000185339	NM_000355.4(TCN2):c.522C>T (p.Ser174=)	AGC	AGT	Transcolabamin II deficiency	0.72	-0.48
DHCR7	ENSG00000172893	NM_001360.3(DHCR7):c.735C>T (p.Ile245=)	ATC	ATT	Smith-Lemli-Opitz syndrome (SLOS)	0.89	-0.17
CREBBP	ENSG00000005339	NM_004380.3(CREBBP):c.5334G>A (p.Ser1778=)	TCG	TCA		3.5	1.81
MYPN	ENSG00000138347	NM_032578.4(MYPN):c.1875C>G (p.Pro625=)	CCC	CCG		0.33	-1.62
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.1095G>C (p.Gly365=)	GGG	GGC		1.29	0.37
FUCA1	ENSG00000179163	NM_000147.4(FUCA1):c.405G>A (p.Thr135=)	ACG	ACA	Fucosidosis	2.96	1.57
SACS	ENSG00000151835	NM_014363.6(SACS):c.7713A>T (p.Pro2571=)	CCA	CCT	Charlevoix-Saguenay spastic ataxia (SACS)	1.02	0.03
IL17RA	ENSG00000177663	NM_014339.6(IL17RA):c.1728C>T (p.Asp576=)	GAC	GAT	Immunodeficiency 51 (IMD51)	0.99	-0.01
ALG8	ENSG00000159063	NM_024079.5(ALG8):c.1506C>T (p.Gly502=)	GGC	GGT	ALG8-CDG	0.55	-0.87
FSCN2	ENSG00000186765	NM_012418.4(FSCN2):c.867C>T (p.His289=)	CAC	CAT		0.81	-0.3
SBF1	ENSG00000100241	NM_002972.4(SBF1):c.738C>T (p.Leu246=)	CTC	CTT		0.8	-0.33
FYCO1	ENSG00000163820	NM_024513.4(FYCO1):c.3825G>A (p.Pro1275=)	CCG	CCA	Cataract 18 (CATC2)	3.05	1.61
LRPPRC	ENSG00000138095	NM_133259.4(LRPPRC):c.96C>T (p.Gly32=)	GGC	GGT	Congenital lactic acidosis, Saguenay-Lac-Saint-Jean type (MC4DN5)	0.55	-0.87
ACOX1	ENSG00000161533	NM_004035.7(ACOX1):c.825C>T (p.Tyr275=)	TAC	TAT	Peroxisomal acyl-CoA oxidase deficiency	0.9	-0.15
TAPBP	ENSG00000231925	NM_003190.4(TAPBP):c.591G>A (p.Pro197=)	CCG	CCA	Bare lymphocyte syndrome type 1	3.05	1.61
LYST	ENSG00000143669	NM_001301365.1(LYST):c.2517T>C (p.Ile839=)	ATT	ATC	Chédiak-Higashi syndrome (CHS)	1.13	0.17
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.462C>T (p.Ser154=)	TCC	TCT		0.98	-0.03
LARGE1	ENSG00000133424	NM_004737.6(LARGE1):c.72C>T (p.Ile24=)	ATC	ATT		0.89	-0.17
MUTYH	ENSG00000132781	NM_001048174.2(MUTYH):c.774G>A (p.Gly258=)	GGG	GGA		1.13	0.17
PEX5	ENSG00000139197	NM_001131025.1(PEX5):c.660G>A (p.Arg220=)	CGG	CGA		0.6	-0.73
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.6840C>T (p.Ala2280=)	GCC	GCT		0.74	-0.44
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.1245C>G (p.Ala415=)	GCC	GCG		0.23	-2.11
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.5469C>T (p.Asp1823=)	GAC	GAT		0.99	-0.01
HSPG2	ENSG00000142798	NM_005529.7(HSPG2):c.8199A>G (p.Ser2733=)	TCA	TCG		0.29	-1.81
MAN2B1	ENSG00000104774	NM_000528.4(MAN2B1):c.1167C>T (p.Thr389=)	ACC	ACT	Deficiency of alpha-mannosidase (MANSA)	0.8	-0.31
COL4A5	ENSG00000188153	NM_033380.3(COL4A5):c.858T>C (p.Gly286=)	GGT	GGC		1.82	0.87
WDR62	ENSG00000075702	NM_001083961.2(WDR62):c.525C>T (p.Tyr175=)	TAC	TAT		0.9	-0.15
PCNT	ENSG00000160299	NM_006031.6(PCNT):c.405C>T (p.Val135=)	GTC	GTT		0.88	-0.19
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.3297A>C (p.Thr1099=)	ACA	ACC	Cohen syndrome (COH1)	1.07	0.1
ASS1	ENSG00000130707	NM_054012.4(ASS1):c.1083C>T (p.Leu361=)	CTC	CTT	Citrullinemia type I (CTNL1)	0.8	-0.33
HSD17B4	ENSG00000133835	NM_000414.4(HSD17B4):c.357C>A (p.Ile119=)	ATC	ATA		0.44	-1.2
BMPR1B	ENSG00000138696	NM_001203.3(BMPR1B):c.468A>G (p.Arg156=)	AGA	AGG		0.91	-0.14
NEB	ENSG00000183091	NM_001271208.2(NEB):c.23487G>A (p.Ser7829=)	TCG	TCA	Nemaline myopathy 2 (NEM2)	3.5	1.81
RBM20	ENSG00000203867	NM_001134363.3(RBM20):c.1053C>T (p.Asp351=)	GAC	GAT	Dilated cardiomyopathy 1DD (CMD1DD)	0.99	-0.01
PEX13	ENSG00000162928	NM_002618.4(PEX13):c.1095G>A (p.Thr365=)	ACG	ACA		2.96	1.57

DYM	ENSG00000141627	NM_017653.5(DYM):c.534A>G (p.Thr178=)	ACA	ACG		0.34	-1.57
ALDOB	ENSG00000136872	NM_000035.4(ALDOB):c.849C>T (p.Asn283=)	AAC	AAT	Hereditary fructosuria (HFI)	1.01	0.02
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.1140G>A (p.Glu380=)	GAG	GAA		0.86	-0.22
PYGM	ENSG00000068976	NM_005609.4(PYGM):c.606C>T (p.His202=)	CAC	CAT	Glycogen storage disease, type V (GSD5)	0.81	-0.3
ACADSB	ENSG00000196177	NM_001609.3(ACADSB):c.795C>T (p.Phe265=)	TTC	TTT	Deficiency of 2-methylbutyryl-CoA dehydrogenase (ACADSB)	0.98	-0.02
IDUA	ENSG00000127415	NM_000203.5(IDUA):c.630C>T (p.Arg210=)	CGC	CGT	Mucopolysaccharidosis type 1 (MPS1)	0.52	-0.93
CDC73	ENSG00000134371	NM_024529.5(CDC73):c.1047T>G (p.Pro349=)	CCT	CCG		0.32	-1.64
ALOX12B	ENSG00000179477	NM_001139.3(ALOX12B):c.1566G>T (p.Pro522=)	CCG	CCT		3.11	1.64
ARX	ENSG00000004848	NM_139058.3(ARX):c.303A>G (p.Ala101=)	GCA	GCG		0.35	-1.52
USH2A	ENSG00000042781	NM_206933.3(USH2A):c.14760C>T (p.Ser4920=)	TCC	TCT		0.98	-0.03
ALDOB	ENSG00000136872	NM_000035.4(ALDOB):c.243C>T (p.His81=)	CAC	CAT	Hereditary fructosuria (HFI)	0.81	-0.3
MYBPC3	ENSG00000134571	NM_000256.3(MYBPC3):c.1104G>A (p.Lys368=)	AAG	AAA	Cardiomyopathy (CMYO)	0.87	-0.2
ALDOB	ENSG00000136872	NM_000035.4(ALDOB):c.375T>C (p.Ile125=)	ATT	ATC	Hereditary fructosuria (HFI)	1.13	0.17
ALMS1	ENSG00000116127	NM_015120.4(ALMS1):c.12201G>A (p.Arg4067=)	GAG	GAA	Alstrom syndrome (ALMS)	0.86	-0.22
RBM20	ENSG00000203867	NM_001134363.3(RBM20):c.3609G>A (p.Lys1203=)	AAG	AAA	Dilated cardiomyopathy 1DD (CMD1DD)	0.87	-0.2
RFX5	ENSG00000143390	NM_001025603.2(RFX5):c.477T>C (p.Tyr159=)	TAT	TAC	Bare lymphocyte syndrome 2	1.11	0.15
ADSL	ENSG00000239900	NM_000026.4(ADSL):c.763C>T (p.Leu255=)	CTG	TTG	Adenylosuccinate lyase deficiency (ADSLD)	0.37	-1.42
ATP1A2	ENSG00000018625	NM_000702.4(ATP1A2):c.2187T>C (p.Ile729=)	ATT	ATC		1.13	0.17
CNTNAP2	ENSG00000174469	NM_014141.6(CNTNAP2):c.1566G>A (p.Gln522=)	CAG	CAA		0.4	-1.32
GLDC	ENSG00000178445	NM_000170.3(GLDC):c.1554G>C (p.Pro518=)	CCG	CCC	Non-ketotic hyperglycinemia (GCE)	3.07	1.62
MBD5	ENSG00000204406	NM_018328.4(MBD5):c.720G>A (p.Arg240=)	AGG	AGA		1.1	0.14
BLM	ENSG00000197299	NM_000057.4(BLM):c.204C>A (p.Thr68=)	ACC	ACA	Bloom syndrome (BLM)	0.93	-0.1
ABCG5	ENSG00000138075	NM_022436.3(ABCG5):c.828G>A (p.Thr276=)	ACG	ACA		2.96	1.57
NCF2	ENSG00000116701	NM_000433.4(NCF2):c.918G>A (p.Gln306=)	CAG	CAA	Chronic granulomatous disease, autosomal recessive cytochrome b-positive, type 2 (CGD2)	0.4	-1.32
POLE	ENSG00000177084	NM_006231.4(POLE):c.5562T>C (p.Ala1854=)	GCT	GCC		1.36	0.44
FBLN5	ENSG00000140092	NM_006329.3(FBLN5):c.894G>A (p.Thr298=)	ACG	ACA		2.96	1.57
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.11724G>T (p.Ala3908=)	GCG	GCT		3.18	1.67
IFT122	ENSG00000163913	NM_052989.3(IFT122):c.2181C>T (p.Thr727=)	ACC	ACT	Cranioectodermal dysplasia 1 (CED1)	0.8	-0.31
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.9933C>T (p.Ser3311=)	TCC	TCT		0.98	-0.03
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.2580G>A (p.Pro860=)	CCG	CCA		3.05	1.61
POLG	ENSG00000140521	NM_002693.2(POLG):c.3024G>A (p.Leu1008=)	TTG	TTA		0.65	-0.61
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.2604C>T (p.Ala868=)	GCC	GCT		0.74	-0.44
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.2391C>T (p.Arg797=)	CGC	CGT		0.52	-0.93
EPCAM	ENSG00000119888	NM_002354.2(EPCAM):c.171C>A (p.Val57=)	GTC	GTA		0.57	-0.8
STRA6	ENSG00000137868	NM_022369.4(STRA6):c.1242C>T (p.Arg414=)	CGC	CGT	Matthew-Wood syndrome (MCOPS9)	0.52	-0.93
TTN	ENSG00000155657	NM_001267550.2(TTN):c.44790G>A (p.Lys14930=)	AAG	AAA		0.87	-0.2
ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.2523G>A (p.Gly841=)	GGG	GGA		1.13	0.17
LDLRAP1	ENSG00000157978	NM_015627.2(LDLRAP1):c.45C>T (p.Pro15=)	CCC	CCT	Familial hypercholesterolemia 4 (FHCL4)	1.02	0.02
RAD50	ENSG00000113522	NM_005732.4(RAD50):c.2646A>G (p.Gln882=)	CAA	CAG	Hereditary cancer-predisposing syndrome	2.49	1.32
WRN	ENSG00000165392	NM_000553.6(WRN):c.1296C>T (p.Asn432=)	AAC	AAT	Werner syndrome (WRN)	1.01	0.02
WRN	ENSG00000165392	NM_000553.6(WRN):c.3582G>A (p.Thr1194=)	ACG	ACA	Werner syndrome (WRN)	2.96	1.57

SCN3A	ENSG00000153253	NM_006922.4(SCN3A):c.5172C>T (p.Pro1724=)	CCC	CCT		1.02	0.02
SUMF1	ENSG00000144455	NM_182760.4(SUMF1):c.16C>T (p.Leu6=)	CTA	TTA	Multiple sulfatase deficiency (MSD)	1.18	0.24
PARK7	ENSG00000116288	NM_007262.5(PARK7):c.501A>G (p.Ala167=)	GCA	GCG	Parkinson disease 7 (PARK7)	0.35	-1.52
COL3A1	ENSG00000168542	NM_000090.3(COL3A1):c.792A>G (p.Gly264=)	GGA	GGG		0.89	-0.17
CFTR	ENSG00000001626	NM_000492.3(CFTR):c.2055A>G (p.Gln685=)	CAA	CAG		2.49	1.32
ALK	ENSG00000171094	NM_004304.5(ALK):c.1044C>T (p.Ala348=)	GCC	GCT	Neuroblastoma 3 (NBLST3)	0.74	-0.44
ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.3246T>C (p.Asp1082=)	GAT	GAC		1.01	0.01
AP5Z1	ENSG00000242802	NM_014855.3(AP5Z1):c.780C>A (p.Thr260=)	ACC	ACA	Spastic paraplegia 48, autosomal recessive (SPG48)	0.93	-0.1
MBD5	ENSG00000204406	NM_018328.4(MBD5):c.258C>T (p.Thr86=)	ACC	ACT		0.8	-0.31
COL4A4	ENSG00000081052	NM_000092.4(COL4A4):c.90C>T (p.Leu30=)	CTC	CTT		0.8	-0.33
POMT2	ENSG00000009830	NM_013382.5(POMT2):c.1824C>T (p.Tyr608=)	TAC	TAT		0.9	-0.15
TTN	ENSG00000155657	NM_001267550.2(TTN):c.92871T>C (p.Ala30957=)	GCT	GCC		1.36	0.44
DNAH5	ENSG00000039139	NM_001369.2(DNAH5):c.13005C>T (p.Thr4335=)	ACC	ACT	Primary ciliary dyskinesia (PCD)	0.8	-0.31
GAA	ENSG00000171298	NM_000152.5(GAA):c.2151C>T (p.His717=)	CAC	CAT	Glycogen storage disease, type II (GSD2)	0.81	-0.3
GAA	ENSG00000171298	NM_000152.5(GAA):c.2154C>T (p.Val718=)	GTC	GTT	Glycogen storage disease, type II (GSD2)	0.88	-0.19
ALK	ENSG00000171094	NM_004304.5(ALK):c.2304T>C (p.Asp768=)	GAT	GAC	Neuroblastoma 3 (NBLST3)	1.01	0.01
JAK3	ENSG00000105639	NM_000215.3(JAK3):c.2391A>G (p.Ala797=)	GCA	GCG	Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-negative	0.35	-1.52
SMC3	ENSG00000108055	NM_005445.3(SMC3):c.1581T>C (p.His527=)	CAT	CAC	Cornelia de Lange syndrome 3 (CDLS3)	1.23	0.3
MTM1	ENSG00000171100	NM_000252.2(MTM1):c.1701C>T (p.Tyr567=)	TAC	TAT	Severe X-linked myotubular myopathy (CNMX)	0.9	-0.15
PNPLA6	ENSG00000032444	NM_001166114.2(PNPLA6):c.684C>T (p.Asp228=)	GAC	GAT	Hereditary spastic paraplegia 39 (SPG39)	0.99	-0.01
KCNMA1	ENSG00000156113	NM_001161352.2(KCNMA1):c.3588G>A (p.Ser1196=)	TCG	TCA	Paroxysmal nonkinesigenic dyskinesia, 3, with or without generalized epilepsy (PNKD3)	3.5	1.81
TTN	ENSG00000155657	NM_001267550.2(TTN):c.12564C>A (p.Ala4188=)	GCC	GCA		0.67	-0.59
LDLR	ENSG00000130164	NM_000527.5(LDLR):c.690C>T (p.Asn230=)	AAC	AAT	Familial hypercholesterolemia 1 (FHCL1)	1.01	0.02
DIS3L2	ENSG00000144535	NM_152383.5(DIS3L2):c.453G>A (p.Pro151=)	CCG	CCA	Perlman syndrome (PRLMNS)	3.05	1.61
GLDC	ENSG00000178445	NM_000170.3(GLDC):c.96G>T (p.Pro32=)	CCG	CCT	Non-ketotic hyperglycinemia (GCE)	3.11	1.64
EXT1	ENSG00000182197	NM_000127.3(EXT1):c.1743G>A (p.Val581=)	GTG	GTA	Multiple congenital exostosis (EXT)	0.3	-1.74
NGF	ENSG00000134259	NM_002506.2(NGF):c.93C>G (p.Thr31=)	ACC	ACG	Congenital sensory neuropathy with selective loss of small myelinated fibers (HSAN5)	0.31	-1.67
PRICKLE2	ENSG00000163637	NM_198859.4(PRICKLE2):c.516G>A (p.Leu172=)	CTG	CTA		0.21	-2.27
KMT2D	ENSG00000167548	NM_003482.3(KMT2D):c.11304T>C (p.Ala3768=)	GCT	GCC		1.36	0.44
NPHP4	ENSG00000131697	NM_015102.5(NPHP4):c.2892C>T (p.Ala964=)	GCC	GCT		0.74	-0.44
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.9906G>A (p.Pro3302=)	CCG	CCA	Cohen syndrome (COH1)	3.05	1.61
CHD7	ENSG00000171316	NM_017780.4(CHD7):c.1644G>A (p.Pro548=)	CCG	CCA		3.05	1.61
FLNA	ENSG00000196924	NM_001110556.2(FLNA):c.7092C>A (p.Ile2364=)	ATC	ATA		0.44	-1.2
G6PC1	ENSG00000131482	NM_000151.4(G6PC1):c.993G>A (p.Ala331=)	GCG	GCA	Glycogen storage disease due to glucose-6-phosphatase deficiency type IA (GSD1A)	2.88	1.52
SLC22A5	ENSG00000197375	NM_003060.4(SLC22A5):c.760C>A (p.Arg254=)	CGA	AGA	Renal carnitine transport defect (CDSP)	2.09	1.06
AP5Z1	ENSG00000242802	NM_014855.3(AP5Z1):c.1315C>T (p.Leu439=)	CTG	TTG	Spastic paraplegia 48, autosomal recessive (SPG48)	0.37	-1.42
KCNJ10	ENSG00000177807	NM_002241.5(KCNJ10):c.771T>C (p.His257=)	CAT	CAC		1.23	0.3
CTC1	ENSG00000178971	NM_025099.6(CTC1):c.663T>C (p.Gly221=)	GGT	GGC	Dyskeratosis congenita	1.82	0.87
CACNA1C	ENSG00000151067	NM_000719.7(CACNA1C):c.6090C>T (p.His2030=)	CAC	CAT		0.81	-0.3

MAN1B1	ENSG00000177239	NM_016219.5(MAN1B1):c.768C>T (p.Val256=)	GTC	GTT	Mental retardation, autosomal recessive 15 (RAFQS)	0.88	-0.19
PRPF8	ENSG00000174231	NM_006445.4(PRPF8):c.5943G>C (p.Val1981=)	GTG	GTC		0.52	-0.94
COL3A1	ENSG00000168542	NM_000090.3(COL3A1):c.2364A>G (p.Pro788=)	CCA	CCG	Ehlers-Danlos syndrome, type 4 (EDSVASC)	0.33	-1.61
HGD	ENSG00000113924	NM_000187.4(HGD):c.141G>A (p.Ser47=)	TCG	TCA	Alkaptonuria (AKU)	3.5	1.81
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.987C>T (p.Thr329=)	ACC	ACT		0.8	-0.31
CDH23	ENSG00000107736	NM_022124.6(CDH23):c.9759C>T (p.Asp3253=)	GAC	GAT		0.99	-0.01
SLC2A1	ENSG00000117394	NM_006516.3(SLC2A1):c.1467T>C (p.Asp489=)	GAT	GAC		1.01	0.01
IDUA	ENSG00000127415	NM_000203.5(IDUA):c.1002G>A (p.Leu334=)	CTG	CTA	Mucopolysaccharidosis type 1 (MPS1)	0.21	-2.27
ACOX1	ENSG00000161533	NM_004035.7(ACOX1):c.1344G>A (p.Val448=)	GTG	GTA	Peroxisomal acyl-CoA oxidase deficiency	0.3	-1.74
UBE3A	ENSG00000114062	NM_130839.5(UBE3A):c.1728G>A (p.Val576=)	GTG	GTA		0.3	-1.74
FSCN2	ENSG00000186765	NM_012418.4(FSCN2):c.1230C>T (p.Asp410=)	GAC	GAT		0.99	-0.01
VPS33B	ENSG00000184056	NM_018668.4(VPS33B):c.1749C>T (p.Ala583=)	GCC	GCT		0.74	-0.44
P3H1	ENSG00000117385	NM_022356.3(P3H1):c.756C>T (p.Tyr252=)	TAC	TAT		0.9	-0.15
G6PC1	ENSG00000131482	NM_000151.4(G6PC1):c.18T>C (p.Asn6=)	AAT	AAC	Glycogen storage disease due to glucose-6-phosphatase deficiency type IA (GSD1A)	0.99	-0.02
GALE	ENSG00000117308	NM_001008216.2(GALE):c.423C>T (p.Tyr141=)	TAC	TAT	UDPglucose-4-epimerase deficiency (GALAC3)	0.9	-0.15
SYNE2	ENSG00000054654	NM_182914.2(SYNE2):c.12660A>G (p.Gln4220=)	CAA	CAG	Emery-Dreifuss muscular dystrophy 5, autosomal dominant (EDMD5)	2.49	1.32
DBH	ENSG00000123454	NM_000787.4(DBH):c.1215C>T (p.His405=)	CAC	CAT	Orthostatic hypotension 1 (ORTHYP1)	0.81	-0.3
LRP5	ENSG00000162337	NM_002335.4(LRP5):c.639C>T (p.Asp213=)	GAC	GAT		0.99	-0.01
GJB1	ENSG00000169562	NM_000166.6(GJB1):c.297A>G (p.Gln99=)	CAA	CAG		2.49	1.32
CFTR	ENSG00000001626	NM_000492.3(CFTR):c.393T>C (p.Phe131=)	TTT	TTC		1.02	0.02
EXT1	ENSG00000182197	NM_000127.2(EXT1):c.2148G>A (p.Pro716=)	CCG	CCA		3.05	1.61
WRN	ENSG00000165392	NM_000553.6(WRN):c.16T>C (p.Leu6=)	TTG	CTG	Werner syndrome (WRN)	2.67	1.42
CTC1	ENSG00000178971	NM_025099.6(CTC1):c.2895C>T (p.Ala965=)	GCC	GCT	Dyskeratosis congenita	0.74	-0.44
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.1914C>T (p.Asp638=)	GAC	GAT	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS)	0.99	-0.01
CYP27A1	ENSG00000135929	NM_000784.4(CYP27A1):c.699C>A (p.Ile233=)	ATC	ATA		0.44	-1.2
GLDC	ENSG00000178445	NM_000170.2(GLDC):c.1453T>C (p.Leu485=)	TTG	CTG	Non-ketotic hyperglycinemia (GCE)	2.67	1.42
COL4A4	ENSG00000081052	NM_000092.4(COL4A4):c.2589C>T (p.Pro863=)	CCC	CCT		1.02	0.02
ALK	ENSG00000171094	NM_004304.5(ALK):c.4344C>T (p.Ser1448=)	TCC	TCT	Neuroblastoma 3 (NBLST3)	0.98	-0.03
LRPPRC	ENSG00000138095	NM_133259.4(LRPPRC):c.2385C>T (p.Gly795=)	GGC	GGT	Congenital lactic acidosis, Saguenay-Lac-Saint-Jean type (MC4DN5)	0.55	-0.87
RAD50	ENSG00000113522	NM_005732.4(RAD50):c.2454A>T (p.Gly818=)	GGA	GGT	Hereditary cancer-predisposing syndrome	0.63	-0.67
INSR	ENSG00000171105	NM_000208.4(INSR):c.2256C>G (p.Ala752=)	GCC	GCG		0.23	-2.11
CARD9	ENSG00000187796	NM_052813.4(CARD9):c.12C>T (p.Tyr4=)	TAC	TAT	Candidiasis, familial, 2 (CANDF2)	0.9	-0.15
TTN	ENSG00000155657	NM_001267550.2(TTN):c.103113T>C (p.Asn34371=)	AAT	AAC		0.99	-0.02
LRP5	ENSG00000162337	NM_002335.4(LRP5):c.1299C>T (p.Thr433=)	ACC	ACT		0.8	-0.31
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.339C>T (p.Ala113=)	GCC	GCT		0.74	-0.44
AGRN	ENSG00000188157	NM_198576.4(AGRN):c.526C>T (p.Leu176=)	CTG	TTG		0.37	-1.42
PYGL	ENSG00000100504	NM_002863.5(PYGL):c.1758G>A (p.Thr586=)	ACG	ACA		2.96	1.57
FOLR1	ENSG00000110195	NM_016729.3(FOLR1):c.507C>T (p.Cys169=)	TGC	TGT		0.97	-0.05
SPTAN1	ENSG00000197694	NM_001130438.3(SPTAN1):c.615T>A (p.Val205=)	GTT	GTA		0.65	-0.62

GALE	ENSG00000117308	NM_001008216.2(GALE):c.330C>T (p.Thr110=)	ACC	ACT	UDPglucose-4-epimerase deficiency (GALAC3)	0.8	-0.31
CHEK2	ENSG00000183765	NM_007194.4(CHEK2):c.126T>A (p.Ser42=)	TCT	TCA		0.84	-0.26
TTN	ENSG00000155657	NM_001267550.2(TTN):c.102025T>C (p.Leu34009=)	TTG	CTG		2.67	1.42
TTN	ENSG00000155657	NM_001267550.2(TTN):c.100467T>C (p.Ser33489=)	TCT	TCC		1.02	0.03
COL6A1	ENSG00000142156	NM_001848.2(COL6A1):c.1554C>T (p.Thr518=)	ACC	ACT		0.8	-0.31
CYP27A1	ENSG00000135929	NM_000784.4(CYP27A1):c.666C>T (p.Phe222=)	TTC	TTT	Cholestanol storage disease (CTX)	0.98	-0.02
SGSH	ENSG00000181523	NM_000199.5(SGSH):c.432C>T (p.Ser144=)	TCC	TCT	Mucopolysaccharidosis, MPS-III-A (MPS3A)	0.98	-0.03
CBL	ENSG00000110395	NM_005188.3(CBL):c.2190G>A (p.Thr730=)	ACG	ACA		2.96	1.57
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.774C>T (p.Phe258=)	TTC	TTT		0.98	-0.02
COL6A1	ENSG00000142156	NM_001848.2(COL6A1):c.2610C>T (p.Asp870=)	GAC	GAT		0.99	-0.01
COL3A1	ENSG00000168542	NM_000090.3(COL3A1):c.3117T>C (p.Ser1039=)	TCT	TCC	Familial thoracic aortic aneurysm and aortic dissection (TAAD)	1.02	0.03
PHGDH	ENSG00000092621	NM_006623.4(PHGDH):c.834C>A (p.Val278=)	GTC	GTA	Phosphoglycerate dehydrogenase deficiency (PHGDHD)	0.57	-0.8
AP5Z1	ENSG00000242802	NM_014855.3(AP5Z1):c.558C>T (p.Tyr186=)	TAC	TAT	Spastic paraplegia 48, autosomal recessive (SPG48)	0.9	-0.15
PFKM	ENSG00000152556	NM_000289.6(PFKM):c.2121G>A (p.Ser707=)	TCG	TCA	Glycogen storage disease, type VII (GSD7)	3.5	1.81
CNKSR2	ENSG00000149970	NM_014927.5(CNKSR2):c.1458A>G (p.Arg486=)	AGA	AGG		0.91	-0.14
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.21465A>T (p.Arg7155=)	CGA	CGT		0.71	-0.49
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.4923G>A (p.Ala1641=)	GCG	GCA		2.88	1.52
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.9363G>A (p.Lys3121=)	AAG	AAA		0.87	-0.2
CDH3	ENSG00000062038	NM_001793.6(CDH3):c.1704G>A (p.Thr568=)	ACG	ACA		2.96	1.57
PIGO	ENSG00000165282	NM_032634.4(PIGO):c.468C>T (p.His156=)	CAC	CAT	Hyperphosphatasia with mental retardation syndrome 2 (HPMRS2)	0.81	-0.3
ACTG1	ENSG00000184009	NM_001614.5(ACTG1):c.81C>T (p.Pro27=)	CCC	CCT		1.02	0.02
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.3375C>T (p.Leu1125=)	CTC	CTT		0.8	-0.33
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.13149C>T (p.Ala4383=)	GCC	GCT		0.74	-0.44
BMP2	ENSG00000125845	NM_001200.4(BMP2):c.891G>A (p.Lys297=)	AAG	AAA		0.87	-0.2
NEB	ENSG00000183091	NM_001271208.2(NEB):c.25212A>G (p.Pro8404=)	CCA	CCG	Nemaline myopathy 2 (NEM2)	0.33	-1.61
ASPA	ENSG00000108381	NM_000049.3(ASPA):c.906G>A (p.Thr302=)	ACG	ACA	Spongy degeneration of central nervous system	2.96	1.57
SERPINC1	ENSG00000117601	NM_000488.3(SERPINC1):c.594T>C (p.Tyr198=)	TAT	TAC	Antithrombin III deficiency (AT3D)	1.11	0.15
UNC13D	ENSG00000092929	NM_199242.2(UNC13D):c.1890G>A (p.Ala630=)	GCG	GCA	Familial hemophagocytic lymphohistiocytosis 3 (FHL3)	2.88	1.52
WRN	ENSG00000165392	NM_000553.6(WRN):c.3483A>T (p.Val1161=)	GTA	GTT	Werner syndrome (WRN)	1.53	0.62
AP5Z1	ENSG00000242802	NM_014855.3(AP5Z1):c.1473C>G (p.Ser491=)	TCC	TCG	Spastic paraplegia 48, autosomal recessive (SPG48)	0.23	-2.09
ALDH5A1	ENSG00000112294	NM_001080.3(ALDH5A1):c.651C>T (p.Ala217=)	GCC	GCT	Succinate-semialdehyde dehydrogenase deficiency (SSADHD)	0.74	-0.44
PMM2	ENSG00000140650	NM_000303.3(PMM2):c.441C>G (p.Leu147=)	CTC	CTG		2.02	1.02
PHGDH	ENSG00000092621	NM_006623.4(PHGDH):c.519G>A (p.Gly173=)	GGG	GGA	Phosphoglycerate dehydrogenase deficiency (PHGDHD)	1.13	0.17
ZMPSTE24	ENSG00000084073	NM_005857.5(ZMPSTE24):c.750G>A (p.Thr250=)	ACG	ACA		2.96	1.57
COL6A1	ENSG00000142156	NM_001848.2(COL6A1):c.624G>A (p.Thr208=)	ACG	ACA		2.96	1.57
CYP27A1	ENSG00000135929	NM_000784.4(CYP27A1):c.435G>T (p.Gly145=)	GGG	GGT	Cholestanol storage disease (CTX)	0.71	-0.5
SLC19A3	ENSG00000135917	NM_025243.4(SLC19A3):c.861C>T (p.Phe287=)	TTC	TTT	Biotin-responsive basal ganglia disease (THMD2)	0.98	-0.02
GLI3	ENSG00000106571	NM_000168.6(GLI3):c.4560G>A (p.Ser1520=)	TCG	TCA		3.5	1.81
TBC1D20	ENSG00000125875	NM_144628.4(TBC1D20):c.1143G>A (p.Ala381=)	GCG	GCA		2.88	1.52
EFEMP2	ENSG00000172638	NM_016938.5(EFEMP2):c.99C>T (p.Pro33=)	CCC	CCT	Autosomal recessive cutis laxa type 1B (ARCL1B)	1.02	0.02
MAN2B1	ENSG00000104774	NM_000528.4(MAN2B1):c.2007G>A (p.Pro669=)	CCG	CCA	Deficiency of alpha-mannosidase (MANSA)	3.05	1.61

TTN	ENSG00000155657	NM_001267550.2(TTN):c.55986C>T (p.Val18662=)	GTC	GTT		0.88	-0.19
AMT	ENSG00000145020	NM_000481.4(AMT):c.555C>T (p.Pro185=)	CCC	CCT	Non-ketotic hyperglycinemia (GCE)	1.02	0.02
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.24861C>T (p.His8287=)	CAC	CAT		0.81	-0.3
ABCA4	ENSG00000198691	NM_000350.3(ABCA4):c.4401C>T (p.Ser1467=)	TCC	TCT		0.98	-0.03
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.1662T>C (p.Cys554=)	TGT	TGC		1.03	0.05
ICOS	ENSG00000163600	NM_012092.3(ICOS):c.591G>A (p.Val197=)	GTG	GTA	Common variable immunodeficiency 1 (CVID1)	0.3	-1.74
FGD1	ENSG00000102302	NM_004463.3(FGD1):c.771C>T (p.Pro257=)	CCC	CCT		1.02	0.02
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.26100A>G (p.Arg8700=)	CGA	CGG		1.65	0.73
CACNA1H	ENSG00000196557	NM_021098.3(CACNA1H):c.4065C>T (p.Gly1355=)	GGC	GGT		0.55	-0.87
IFT140	ENSG00000187535	NM_014714.4(IFT140):c.2724C>T (p.Ala908=)	GCC	GCT	Saldino-Mainzer syndrome (SRTD9)	0.74	-0.44
UNC13D	ENSG00000092929	NM_199242.2(UNC13D):c.3033C>T (p.Ala1011=)	GCC	GCT	Familial hemophagocytic lymphohistiocytosis 3 (FHL3)	0.74	-0.44
WRN	ENSG00000165392	NM_000553.6(WRN):c.2784A>G (p.Gly928=)	GGA	GGG		0.89	-0.17
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.4491C>T (p.Ala1497=)	GCC	GCT		0.74	-0.44
CACNA1C	ENSG00000151067	NM_000719.7(CACNA1C):c.4380C>T (p.Tyr1460=)	TAC	TAT		0.9	-0.15
SCN3A	ENSG00000153253	NM_006922.4(SCN3A):c.4899T>A (p.Arg1633=)	CGT	CGA		1.41	0.49
CTSD	ENSG00000117984	NM_001909.5(CTSD):c.63C>T (p.Leu21=)	CTC	CTT		0.8	-0.33
GALK1	ENSG00000108479	NM_000154.2(GALK1):c.447G>A (p.Thr149=)	ACG	ACA	Deficiency of galactokinase (GALAC2)	2.96	1.57
WRN	ENSG00000165392	NM_000553.6(WRN):c.3972C>T (p.Pro1324=)	CCC	CCT	Werner syndrome (WRN)	1.02	0.02
ABCA4	ENSG00000198691	NM_000350.3(ABCA4):c.5880C>T (p.Val1960=)	GTC	GTT		0.88	-0.19
KIF7	ENSG00000166813	NM_198525.3(KIF7):c.1296G>A (p.Leu432=)	CTG	CTA	Acrocallosal syndrome (ACLS)	0.21	-2.27
USH2A	ENSG00000042781	NM_206933.3(USH2A):c.11013T>G (p.Pro3671=)	CCT	CCG		0.32	-1.64
BRIP1	ENSG00000136492	NM_032043.3(BRIP1):c.2958C>T (p.Ser986=)	TCC	TCT		0.98	-0.03
PROP1	ENSG00000175325	NM_006261.4(PROP1):c.423C>T (p.Ala141=)	GCC	GCT		0.74	-0.44
CYP27A1	ENSG00000135929	NM_000784.4(CYP27A1):c.1311C>T (p.Ala437=)	GCC	GCT		0.74	-0.44
GAD1	ENSG00000128683	NM_000817.3(GAD1):c.1251C>T (p.Leu417=)	CTC	CTT	Cerebral palsy, spastic quadriplegic, 1 (CPSQ1)	0.8	-0.33
AHCY	ENSG00000101444	NM_000687.4(AHCY):c.639C>T (p.Gly213=)	GGC	GGT		0.55	-0.87
GCDH	ENSG00000105607	NM_000159.4(GCDH):c.1197C>T (p.His399=)	CAC	CAT	Glutaric aciduria, type 1 (GA1)	0.81	-0.3
GAD1	ENSG00000128683	NM_000817.3(GAD1):c.807G>A (p.Pro269=)	CCG	CCA	Cerebral palsy, spastic quadriplegic, 1 (CPSQ1)	3.05	1.61
ASL	ENSG00000126522	NM_000048.4(ASL):c.1263G>A (p.Ser421=)	TCG	TCA	Argininosuccinate lyase deficiency	3.5	1.81
DNMT1	ENSG00000130816	NM_001130823.3(DNMT1):c.1314C>T (p.Ile438=)	ATC	ATT		0.89	-0.17
HES7	ENSG00000179111	NM_001165967.2(HES7):c.420G>A (p.Pro140=)	CCG	CCA		3.05	1.61
SCN1A	ENSG00000144285	NM_001165963.4(SCN1A):c.597A>G (p.Thr199=)	ACA	ACG		0.34	-1.57
LDLR	ENSG00000130164	NM_000527.5(LDLR):c.1383C>T (p.Gly461=)	GGC	GGT	Familial hypercholesterolemia 1 (FHCL1)	0.55	-0.87
COLQ	ENSG00000206561	NM_005677.4(COLQ):c.1350C>T (p.Pro450=)	CCC	CCT		1.02	0.02
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.2436T>C (p.Asn812=)	AAT	AAC	Wilson disease (WND)	0.99	-0.02
PITPNM3	ENSG00000091622	NM_031220.4(PITPNM3):c.2700C>T (p.Arg900=)	CGC	CGT		0.52	-0.93
PROC	ENSG00000115718	NM_000312.3(PROC):c.30C>T (p.Phe10=)	TTC	TTT	Thrombophilia, hereditary, due to protein C deficiency, autosomal dominant (THPH3)	0.98	-0.02
ALG6	ENSG00000088035	NM_013339.4(ALG6):c.156G>A (p.Pro52=)	CCG	CCA	Congenital disorder of glycosylation type 1C (CDG1C)	3.05	1.61
ABCC2	ENSG00000023839	NM_000392.5(ABCC2):c.2034C>T (p.Ser678=)	TCC	TCT		0.98	-0.03
GRIN2B	ENSG00000273079	NM_000834.4(GRIN2B):c.4077C>T (p.Ala1359=)	GCC	GCT		0.74	-0.44
FBN2	ENSG00000138829	NM_001999.4(FBN2):c.6438C>T (p.Asp2146=)	GAC	GAT	Congenital contractural arachnodactyly (CCA)	0.99	-0.01

SMCHD1	ENSG00000101596	NM_015295.2(SMCHD1):c.4827A>G (p.Leu1609=)	CTA	CTG		4.81	2.27
COL1A1	ENSG00000108821	NM_000088.3(COL1A1):c.3258C>T (p.Pro1086=)	CCC	CCT		1.02	0.02
ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.1248C>A (p.Ile416=)	ATC	ATA		0.44	-1.2
TARDBP	ENSG00000120948	NM_007375.3(TARDBP):c.87C>T (p.Ser29=)	TCC	TCT		0.98	-0.03
GLDC	ENSG00000178445	NM_000170.3(GLDC):c.78G>C (p.Ser26=)	TCG	TCC	Non-ketotic hyperglycinemia (GCE)	4.26	2.09
AXIN2	ENSG00000168646	NM_004655.4(AXIN2):c.1443C>T (p.Leu481=)	CTC	CTT	Oligodontia-colorectal cancer syndrome (ODCRCS)	0.8	-0.33
RAD50	ENSG00000113522	NM_005732.4(RAD50):c.477A>G (p.Gln159=)	CAA	CAG	Hereditary cancer-predisposing syndrome	2.49	1.32
ALDH5A1	ENSG00000112294	NM_001080.3(ALDH5A1):c.831G>A (p.Val277=)	GTG	GTA	Succinate-semialdehyde dehydrogenase deficiency (SSADHD)	0.3	-1.74
IRAK4	ENSG00000198001	NM_016123.3(IRAK4):c.291G>A (p.Ala97=)	GCG	GCA	Immunodeficiency due to interleukin-1 receptor-associated kinase-4 deficiency (IMD67)	2.88	1.52
PTPN11	ENSG00000179295	NM_002834.4(PTPN11):c.1740T>C (p.Tyr580=)	TAT	TAC		1.11	0.15
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.11037G>A (p.Ala3679=)	GCG	GCA		2.88	1.52
ALDH4A1	ENSG00000159423	NM_003748.4(ALDH4A1):c.135T>G (p.Pro45=)	CCT	CCG	Deficiency of pyrroline-5-carboxylate reductase (HYRPRO2)	0.32	-1.64
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.1311A>G (p.Lys437=)	AAA	AAG		1.15	0.2
RAD50	ENSG00000113522	NM_005732.4(RAD50):c.33C>T (p.Gly11=)	GGC	GGT	Hereditary cancer-predisposing syndrome	0.55	-0.87
PRPF3	ENSG00000117360	NM_004698.4(PRPF3):c.957T>C (p.Pro319=)	CCT	CCC		0.98	-0.02
ALK	ENSG00000171094	NM_004304.5(ALK):c.2073C>T (p.Ser691=)	AGC	AGT	Neuroblastoma 3 (NBLST3)	0.72	-0.48
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.2994G>T (p.Arg998=)	CGG	CGT	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS)	0.43	-1.22
SRCAP	ENSG00000080603	NM_006662.3(SRCAP):c.5838C>A (p.Pro1946=)	CCC	CCA		1	-0.01
JAK3	ENSG00000105639	NM_000215.3(JAK3):c.3213C>T (p.His1071=)	CAC	CAT	Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-negative	0.81	-0.3
RINT1	ENSG00000135249	NM_021930.6(RINT1):c.1155C>T (p.Ala385=)	GCC	GCT		0.74	-0.44
HEXB	ENSG00000049860	NM_000521.4(HEXB):c.1248G>A (p.Ala416=)	GCG	GCA	Sandhoff disease	2.88	1.52
UNC13D	ENSG00000092929	NM_199242.2(UNC13D):c.444G>A (p.Gly148=)	GGG	GGA	Familial hemophagocytic lymphohistiocytosis 3 (FHL3)	1.13	0.17
TAF1	ENSG00000147133	NM_004606.5(TAF1):c.297T>C (p.Asp99=)	TAT	TAC		1.11	0.15
LAMA4	ENSG00000112769	NM_001105206.3(LAMA4):c.3165C>T (p.Ser1055=)	TCC	TCT		0.98	-0.03
FRAS1	ENSG00000138759	NM_025074.7(FRAS1):c.39G>A (p.Ala13=)	GCG	GCA		2.88	1.52
MCCC1	ENSG00000078070	NM_020166.5(MCCC1):c.1281C>T (p.Ser427=)	TCC	TCT	3 Methylcrotonyl-CoA carboxylase 1 deficiency (MCC1D)	0.98	-0.03
PANK2	ENSG00000125779	NM_153638.3(PANK2):c.1074A>C (p.Ser358=)	TCA	TCC		1.22	0.29
IFT140	ENSG00000187535	NM_014714.4(IFT140):c.3147C>T (p.Asn1049=)	AAC	AAT	Saldino-Mainzer syndrome (SRTD9)	1.01	0.02
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.24723C>T (p.His8241=)	CAC	CAT		0.81	-0.3
PEX5	ENSG00000139197	NM_001131025.1(PEX5):c.129A>G (p.Gly43=)	GGA	GGG		0.89	-0.17
AGPS	ENSG00000018510	NM_003659.4(AGPS):c.891T>C (p.Cys297=)	TGT	TGC		1.03	0.05
JAK3	ENSG00000105639	NM_000215.3(JAK3):c.1653A>G (p.Thr551=)	ACA	ACG	Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-negative	0.34	-1.57
IL2RA	ENSG00000134460	NM_000417.3(IL2RA):c.777C>A (p.Leu259=)	CTC	CTA	Interleukin 2 receptor, alpha, deficiency of (IMD41)	0.42	-1.25
MAN2B1	ENSG00000104774	NM_000528.4(MAN2B1):c.1383C>T (p.Tyr461=)	TAC	TAT	Deficiency of alpha-mannosidase (MANSA)	0.9	-0.15
JAK3	ENSG00000105639	NM_000215.3(JAK3):c.696C>T (p.His232=)	CAC	CAT	Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-negative	0.81	-0.3
FOXC1	ENSG00000054598	NM_001453.3(FOXC1):c.279C>T (p.Asn93=)	AAC	AAT		1.01	0.02
MCOLN1	ENSG00000090674	NM_020533.3(MCOLN1):c.177G>A (p.Lys59=)	AAG	AAA	Mucolipidosis type IV (ML4)	0.87	-0.2
UNC13D	ENSG00000092929	NM_199242.2(UNC13D):c.273G>A (p.Val91=)	GTG	GTA	Familial hemophagocytic lymphohistiocytosis 3 (FHL3)	0.3	-1.74
IFT140	ENSG00000187535	NM_014714.4(IFT140):c.1272G>A (p.Pro424=)	CCG	CCA		3.05	1.61

NF1	ENSG00000196712	NM_001042492.3(NF1):c.3831C>T (p.Gly1277=)	GGC	GGT	Neurofibromatosis, type 1 (NF1)	0.55	-0.87
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.24867T>C (p.Tyr8289=)	TAT	TAC		1.11	0.15
TTN	ENSG00000155657	NM_001267550.2(TTN):c.70137C>A (p.Thr23379=)	ACC	ACA		0.93	-0.1
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.777C>T (p.Asp259=)	GAC	GAT		0.99	-0.01
ALDH7A1	ENSG00000164904	NM_001182.5(ALDH7A1):c.1176T>C (p.Gly392=)	GGT	GGC		1.82	0.87
ACOX1	ENSG00000161533	NM_004035.7(ACOX1):c.1695T>C (p.Tyr565=)	TAT	TAC	Peroxisomal acyl-CoA oxidase deficiency	1.11	0.15
ITGB2	ENSG00000160255	NM_000211.5(ITGB2):c.159G>A (p.Gly53=)	GGG	GGA	Leukocyte adhesion deficiency 1	1.13	0.17
GALE	ENSG00000117308	NM_001008216.2(GALE):c.369G>A (p.Gly123=)	GGG	GGA	UDPglucose-4-epimerase deficiency (GALAC3)	1.13	0.17
AP5Z1	ENSG00000242802	NM_014855.3(AP5Z1):c.1062C>T (p.His354=)	CAC	CAT	Spastic paraplegia 48, autosomal recessive (SPG48)	0.81	-0.3
SMARCB1	ENSG00000099956	NM_003073.5(SMARCB1):c.585C>T (p.Ile195=)	ATC	ATT		0.89	-0.17
NF1	ENSG00000196712	NM_000267.3(NF1):c.1998T>C (p.Ser666=)	TCT	TCC		1.02	0.03
ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.711G>A (p.Arg237=)	AGG	AGA		1.1	0.14
EHMT1	ENSG00000181090	NM_024757.5(EHMT1):c.2961C>T (p.Ser987=)	AGC	AGT		0.72	-0.48
KBTBD13	ENSG00000234438	NM_001101362.2(KBTBD13):c.162C>T (p.Ser54=)	AGC	AGT	Nemaline myopathy 6 (NEM6)	0.72	-0.48
SLC25A15	ENSG00000102743	NM_014252.4(SLC25A15):c.345C>T (p.Phe115=)	TTC	TTT	Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (HHHS)	0.98	-0.02
PRF1	ENSG00000180644	NM_001083116.3(PRF1):c.111C>T (p.Phe37=)	TTC	TTT	Familial hemophagocytic lymphohistiocytosis 2 (FHL2)	0.98	-0.02
CUL7	ENSG00000044090	NM_014780.4(CUL7):c.981C>T (p.Pro327=)	CCG	CCT		3.11	1.64
ATP2A1	ENSG00000196296	NM_173201.4(ATP2A1):c.1935C>T (p.Asn645=)	AAC	AAT	Brody myopathy	1.01	0.02
TTN	ENSG00000155657	NM_001267550.2(TTN):c.6690C>T (p.Phe2230=)	TTC	TTT		0.98	-0.02
VPS33B	ENSG00000184056	NM_018668.4(VPS33B):c.198A>G (p.Leu66=)	CTA	CTG		4.81	2.27
GAA	ENSG00000171298	NM_000152.5(GAA):c.18G>C (p.Pro6=)	CCG	CCC		3.07	1.62
MLYCD	ENSG00000103150	NM_012213.3(MLYCD):c.1236C>T (p.Arg412=)	CGC	CGT	Deficiency of malonyl-CoA decarboxylase	0.52	-0.93
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.6054C>T (p.Tyr2018=)	TAC	TAT	Autosomal recessive polycystic kidney disease (ARPKD)	0.9	-0.15
SHOX	ENSG00000185960	NM_000451.3(SHOX):c.144G>A (p.Glu48=)	GAG	GAA		0.86	-0.22
ALG12	ENSG00000182858	NM_024105.4(ALG12):c.189C>T (p.Val63=)	GTC	GTT	ALG12-congenital disorder of glycosylation (CDG1G)	0.88	-0.19
AGA	ENSG00000038002	NM_000027.4(AGA):c.675T>C (p.Asn225=)	AAT	AAC	Aspartylglucosaminuria (AGU)	0.99	-0.02
WRN	ENSG00000165392	NM_000553.6(WRN):c.3417T>C (p.Ser1139=)	AGT	AGC	Werner syndrome (WRN)	1.4	0.48
ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.2037G>A (p.Ala679=)	GCG	GCA		2.88	1.52
ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.126C>T (p.Gly42=)	GGC	GGT		0.55	-0.87
LDLRAP1	ENSG00000157978	NM_015627.2(LDLRAP1):c.201G>A (p.Ser67=)	TCG	TCA	Familial hypercholesterolemia 4 (FHCL4)	3.5	1.81
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.2811G>A (p.Val937=)	GTG	GTA	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS)	0.3	-1.74
LPIN2	ENSG00000101577	NM_014646.2(LPIN2):c.840A>G (p.Arg280=)	CGA	CGG	Majeed syndrome (MJDS)	1.65	0.73
GDI1	ENSG00000203879	NM_001493.3(GDI1):c.1167C>T (p.Pro389=)	CCC	CCT		1.02	0.02
NPHP4	ENSG00000131697	NM_015102.5(NPHP4):c.2238C>T (p.Thr746=)	ACC	ACT		0.8	-0.31
TCN2	ENSG00000185339	NM_000355.4(TCN2):c.138C>T (p.Ser46=)	TCC	TCT	Transcolabamin II deficiency	0.98	-0.03
TTN	ENSG00000155657	NM_001267550.2(TTN):c.23091A>G (p.Thr7697=)	ACA	ACG		0.34	-1.57
PEX1	ENSG00000127980	NM_000466.3(PEX1):c.3633T>C (p.Ser1211=)	AGT	AGC		1.4	0.48
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.6957A>G (p.Pro2319=)	CCA	CCG		0.33	-1.61
KDM5C	ENSG00000126012	NM_004187.4(KDM5C):c.4338C>T (p.His1446=)	CAC	CAT		0.81	-0.3
TNPO3	ENSG00000064419	NM_012470.3(TNPO3):c.1179T>C (p.Thr393=)	ACT	ACC		1.24	0.31
HEXB	ENSG00000049860	NM_000521.4(HEXB):c.1035A>C (p.Pro345=)	CCA	CCC	Sandhoff disease	1	0.01

CHRNA2	ENSG00000120903	NM_000742.4(CHRNA2):c.987C>T (p.Gly329=)	GGC	GGT		0.55	-0.87
ATL1	ENSG00000198513	NM_001127713.1(ATL1):c.1608T>G (p.Ala536=)	GCT	GCG	Hereditary spastic paraplegia 3A (SPG3A)	0.31	-1.67
KIF7	ENSG00000166813	NM_198525.3(KIF7):c.3795G>A (p.Thr1265=)	ACG	ACA		2.96	1.57
HCFC1	ENSG00000172534	NM_005334.3(HCFC1):c.6042C>T (p.Asn2014=)	AAC	AAT		1.01	0.02
SCN1A	ENSG00000144285	NM_001165963.4(SCN1A):c.5346C>T (p.Ile1782=)	ATC	ATT		0.89	-0.17
HOMER2	ENSG00000103942	NM_004839.4(HOMER2):c.33G>A (p.Ala11=)	GCG	GCA		2.88	1.52
PSTPIP1	ENSG00000140368	NM_003978.5(PSTPIP1):c.1146G>A (p.Ala382=)	GCG	GCA	Pyogenic arthritis-pyoderma gangrenosum-acne syndrome	2.88	1.52
GDNF	ENSG00000168621	NM_000514.4(GDNF):c.138G>A (p.Ala46=)	GCG	GCA		2.88	1.52
SMCHD1	ENSG00000101596	NM_015295.2(SMCHD1):c.1164G>A (p.Lys388=)	AAG	AAA		0.87	-0.2
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.4524C>G (p.Leu1508=)	CTC	CTG		2.02	1.02
GALC	ENSG00000054983	NM_000153.4(GALC):c.120C>T (p.Gly40=)	GGC	GGT	Galactosylceramide beta-galactosidase deficiency	0.55	-0.87
G6PC3	ENSG00000141349	NM_138387.3(G6PC3):c.201C>T (p.Leu67=)	CTC	CTT	Severe congenital neutropenia 4, autosomal recessive (SCN4)	0.8	-0.33
GCDH	ENSG00000105607	NM_000159.4(GCDH):c.627C>T (p.Thr209=)	ACC	ACT	Glutaric aciduria, type 1 (GA1)	0.8	-0.31
SLC7A7	ENSG00000155465	NM_003982.4(SLC7A7):c.1263G>A (p.Pro421=)	CCG	CCA	Lysinuric protein intolerance (LPI)	3.05	1.61
ALK	ENSG00000171094	NM_004304.5(ALK):c.4275G>A (p.Leu1425=)	CTG	CTA	Neuroblastoma 3 (NBLST3)	0.21	-2.27
SLC24A5	ENSG00000188467	NM_205850.3(SLC24A5):c.534G>A (p.Ala178=)	GCG	GCA		2.88	1.52
B3GLCT	ENSG00000187676	NM_194318.4(B3GLCT):c.39G>C (p.Pro13=)	CCG	CCC	Peters plus syndrome (PTRPLS)	3.07	1.62
ABCD1	ENSG00000101986	NM_000033.4(ABCD1):c.1914C>T (p.Asp638=)	GAC	GAT	Adrenoleukodystrophy (ALD)	0.99	-0.01
IFT140	ENSG00000187535	NM_014714.4(IFT140):c.1230G>A (p.Ser410=)	TCG	TCA	Saldino-Mainzer syndrome (SRTD9)	3.5	1.81
KIF7	ENSG00000166813	NM_198525.3(KIF7):c.3264C>T (p.Leu1088=)	CTC	CTT		0.8	-0.33
PC	ENSG00000173599	NM_001040716.2(PC):c.1530C>T (p.Asn510=)	AAC	AAT	Pyruvate carboxylase deficiency	1.01	0.02
POLG	ENSG00000140521	NM_002693.2(POLG):c.3630C>T (p.Tyr1210=)	TAC	TAT		0.9	-0.15
ACVRL1	ENSG00000139567	NM_000020.3(ACVRL1):c.9G>A (p.Leu3=)	TTG	TTA	Telangiectasia, hereditary hemorrhagic, type 2 (HHT2)	0.65	-0.61
PCCB	ENSG00000114054	NM_000532.5(PCCB):c.45C>T (p.Ser15=)	AGC	AGT	Propionic acidemia (PROP)	0.72	-0.48
AGA	ENSG00000038002	NM_000027.4(AGA):c.657T>C (p.Ala219=)	GCT	GCC	Aspartylglucosaminuria (AGU)	1.36	0.44
TTN	ENSG00000155657	NM_001267550.2(TTN):c.17910T>C (p.His5970=)	CAT	CAC		1.23	0.3
POMT1	ENSG00000130714	NM_001077365.2(POMT1):c.1746C>T (p.Ser582=)	AGC	AGT		0.72	-0.48
RBM20	ENSG00000203867	NM_001134363.3(RBM20):c.2991G>A (p.Val997=)	GTG	GTA	Dilated cardiomyopathy 1DD (CMD1DD)	0.3	-1.74
TTN	ENSG00000155657	NM_001267550.2(TTN):c.30282T>G (p.Ser10094=)	TCT	TCG		0.24	-2.06
PTS	ENSG00000150787	NM_000317.3(PTS):c.132C>T (p.Asn44=)	AAC	AAT	BH4-deficient hyperphenylalaninemia A	1.01	0.02
KIF7	ENSG00000166813	NM_198525.3(KIF7):c.3021C>T (p.Ile1007=)	ATC	ATT		0.89	-0.17
MYOT	ENSG00000120729	NM_006790.2(MYOT):c.1398T>G (p.Leu466=)	CTT	CTG		2.54	1.35
TNFRSF13(	ENSG00000159958	NM_052945.3(TNFRSF13C):c.375G>A (p.Glu125=)	GAG	GAA	Common variable immunodeficiency 4 (CVID4)	0.86	-0.22
SGSH	ENSG00000181523	NM_000199.5(SGSH):c.534C>T (p.His178=)	CAC	CAT	Mucopolysaccharidosis, MPS-III-A (MPS3A)	0.81	-0.3
SRD5A3	ENSG00000128039	NM_024592.5(SRD5A3):c.108G>T (p.Pro36=)	CCG	CCT	Congenital disorder of glycosylation type 1Q (CDG1Q)	3.11	1.64
OFD1	ENSG00000046651	NM_003611.3(OFD1):c.276T>C (p.Ser92=)	TCT	TCC		1.02	0.03
COL6A1	ENSG00000142156	NM_001848.2(COL6A1):c.1911C>T (p.Phe637=)	TTC	TTT		0.98	-0.02
FOXN1	ENSG00000109101	NM_001369369.1(FOXN1):c.987C>T (p.Phe329=)	TTC	TTT	T-cell immunodeficiency, congenital alopecia, and nail dystrophy	0.98	-0.02
HMGCL	ENSG00000117305	NM_000191.3(HMGCL):c.501C>T (p.Tyr167=)	TAC	TAT	Deficiency of hydroxymethylglutaryl-CoA lyase (HMGCLD)	0.9	-0.15
SMCHD1	ENSG00000101596	NM_015295.2(SMCHD1):c.1191C>T (p.Asp397=)	GAC	GAT		0.99	-0.01
GJB4	ENSG00000189433	NM_153212.3(GJB4):c.495C>T (p.Ser165=)	TCC	TCT		0.98	-0.03
MCOLN1	ENSG00000090674	NM_020533.3(MCOLN1):c.216G>A (p.Lys72=)	AAG	AAA	Mucolipidosis type IV (ML4)	0.87	-0.2

CD19	ENSG00000177455	NM_001770.5(CD19):c.390T>A (p.Gly130=)	GGT	GGA	Common variable immunodeficiency 3 (CVID3)	1.59	0.67
SGCA	ENSG00000108823	NM_000023.4(SGCA):c.408C>T (p.Ala136=)	GCC	GCT		0.74	-0.44
CIITA	ENSG00000179583	NM_000246.3(CIITA):c.3357C>T (p.His1119=)	CAC	CAT	Bare lymphocyte syndrome 2	0.81	-0.3
DMD	ENSG00000198947	NM_004006.2(DMD):c.159C>A (p.Leu53=)	CTC	CTA		0.42	-1.25
TTN	ENSG00000155657	NM_001267550.2(TTN):c.53185C>T (p.Leu17729=)	CTA	TTA		1.18	0.24
SMCHD1	ENSG00000101596	NM_015295.2(SMCHD1):c.4161C>T (p.Phe1387=)	TTC	TTT		0.98	-0.02
FAH	ENSG00000103876	NM_000137.3(FAH):c.696C>T (p.Asn232=)	AAC	AAT	Tyrosinemia type I (TYRSN1)	1.01	0.02
FKBP10	ENSG00000141756	NM_021939.3(FKBP10):c.174A>G (p.Glu58=)	GAA	GAG		1.16	0.22
TTN	ENSG00000155657	NM_001267550.2(TTN):c.52242C>T (p.Pro17414=)	CCC	CCT		1.02	0.02
FAM126A	ENSG00000122591	NM_032581.4(FAM126A):c.1044C>T (p.Asp348=)	GAC	GAT	Hypomyelination and Congenital Cataract (HLD5)	0.99	-0.01
MLH3	ENSG00000119684	NM_001040108.1(MLH3):c.4032C>T (p.Gly1344=)	GGC	GGT	Hereditary nonpolyposis colorectal cancer type 7 (HNPCC7)	0.55	-0.87
ALDOB	ENSG00000136872	NM_000035.4(ALDOB):c.282C>T (p.Phe94=)	TTC	TTT	Hereditary fructosuria (HFI)	0.98	-0.02
POMT2	ENSG00000009830	NM_013382.5(POMT2):c.795C>T (p.Phe265=)	TTC	TTT		0.98	-0.02
GNS	ENSG00000135677	NM_002076.4(GNS):c.285A>G (p.Arg95=)	AGA	AGG	Mucopolysaccharidosis, MPS-III-D (MPS3D)	0.91	-0.14
MCOLN1	ENSG00000090674	NM_020533.3(MCOLN1):c.1038G>A (p.Glu346=)	GAG	GAA	Mucolipidosis type IV (ML4)	0.86	-0.22
PC	ENSG00000173599	NM_001040716.2(PC):c.1233C>T (p.Ser411=)	TCC	TCT	Pyruvate carboxylase deficiency	0.98	-0.03
SCN8A	ENSG00000196876	NM_001330260.2(SCN8A):c.5847T>C (p.Ser1949=)	AGT	AGC		1.4	0.48
OBSL1	ENSG00000124006	NM_015311.3(OBSL1):c.342C>T (p.Ala114=)	GCC	GCT		0.74	-0.44
SLC29A3	ENSG00000198246	NM_018344.6(SLC29A3):c.1347G>A (p.Thr449=)	ACG	ACA	Histiocytosis-lymphadenopathy plus syndrome (HJCD)	2.96	1.57
HCN4	ENSG00000138622	NM_005477.3(HCN4):c.1227C>T (p.Tyr409=)	TAC	TAT		0.9	-0.15
CHST3	ENSG00000122863	NM_004273.5(CHST3):c.1135C>T (p.Leu379=)	CTG	TTG	Spondyloepiphyseal dysplasia with congenital joint dislocations (SEDCJD)	0.37	-1.42
TULP1	ENSG00000112041	NM_003322.6(TULP1):c.327C>G (p.Ala109=)	GCC	GCG		0.23	-2.11
TTN	ENSG00000155657	NM_001267550.2(TTN):c.28200C>T (p.Asp9400=)	GAC	GAT		0.99	-0.01
ASS1	ENSG00000130707	NM_054012.4(ASS1):c.39C>T (p.Gly13=)	GGC	GGT	Citrullinemia type I (CTNL1)	0.55	-0.87
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.6291T>C (p.Ala2097=)	GCT	GCC		1.36	0.44
PEX10	ENSG00000157911	NM_153818.1(PEX10):c.378C>T (p.Pro126=)	CCC	CCT		1.02	0.02
SMCHD1	ENSG00000101596	NM_015295.2(SMCHD1):c.3414G>A (p.Ala1138=)	GCG	GCA		2.88	1.52
GRM6	ENSG00000113262	NM_000843.4(GRM6):c.588C>T (p.Pro196=)	CCC	CCT		1.02	0.02
SLC39A13	ENSG00000165915	NM_001128225.3(SLC39A13):c.222T>A (p.Gly74=)	GGT	GGA		1.59	0.67
SRCAP	ENSG00000080603	NM_006662.3(SRCAP):c.7248C>T (p.Ser2416=)	TCC	TCT		0.98	-0.03
SMCHD1	ENSG00000101596	NM_015295.2(SMCHD1):c.1479T>C (p.Thr493=)	ACT	ACC		1.24	0.31
ALK	ENSG00000171094	NM_004304.5(ALK):c.4809T>C (p.His1603=)	CAT	CAC	Neuroblastoma 3 (NBLST3)	1.23	0.3
IDUA	ENSG00000127415	NM_000203.5(IDUA):c.1332C>T (p.Asp444=)	GAC	GAT	Mucopolysaccharidosis type 1 (MPS1)	0.99	-0.01
POR	ENSG00000127948	NM_000941.3(POR):c.1953T>G (p.Ala651=)	GCT	GCG	Disordered steroidogenesis due to cytochrome p450 oxidoreductase deficiency (ABS1)	0.31	-1.67
DIS3L2	ENSG00000144535	NM_152383.5(DIS3L2):c.1158C>T (p.Thr386=)	ACC	ACT	Perlman syndrome (PRLMNS)	0.8	-0.31
PC	ENSG00000173599	NM_001040716.2(PC):c.3483T>C (p.His1161=)	CAT	CAC	Pyruvate carboxylase deficiency	1.23	0.3
CLCN1	ENSG00000188037	NM_000083.3(CLCN1):c.799C>T (p.Leu267=)	CTG	TTG		0.37	-1.42
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.3963C>G (p.Ser1321=)	TCC	TCG		0.23	-2.09
DGUOK	ENSG00000114956	NM_080916.3(DGUOK):c.405G>A (p.Lys135=)	AAG	AAA		0.87	-0.2
ABCC2	ENSG00000023839	NM_000392.5(ABCC2):c.306C>A (p.Thr102=)	ACC	ACA		0.93	-0.1
CPT2	ENSG00000157184	NM_000098.3(CPT2):c.45G>T (p.Ala15=)	GCG	GCT	Carnitine palmitoyltransferase II deficiency (CPT2)	3.18	1.67

ST3GAL3	ENSG00000126091	NM_006279.5(ST3GAL3):c.1068A>G (p.Lys356=)	AAA	AAG		1.15	0.2
AMACR	ENSG00000242110	NM_014324.6(AMACR):c.90T>G (p.Arg30=)	CGT	CGG		2.33	1.22
ATP8B1	ENSG00000081923	NM_005603.6(ATP8B1):c.2358G>A (p.Val786=)	GTG	GTA		0.3	-1.74
TTN	ENSG00000155657	NM_001267550.2(TTN):c.54054G>A (p.Lys18018=)	AAG	AAA		0.87	-0.2
RIMS1	ENSG00000079841	NM_014989.5(RIMS1):c.1533G>A (p.Pro511=)	CCG	CCA		3.05	1.61
SOX9	ENSG00000125398	NM_000346.4(SOX9):c.531G>A (p.Arg177=)	CGG	CGA		0.6	-0.73
NOTCH1	ENSG00000148400	NM_017617.5(NOTCH1):c.1725C>T (p.Cys575=)	TGC	TGT		0.97	-0.05
DPM1	ENSG00000000419	NM_003859.2(DPM1):c.84G>A (p.Ser28=)	TCG	TCA	Congenital disorder of glycosylation type 1E (CDG1E)	3.5	1.81
USH2A	ENSG00000042781	NM_206933.3(USH2A):c.4071G>A (p.Thr1357=)	ACG	ACA		2.96	1.57
SH3PXD2B	ENSG00000174705	NM_001017995.3(SH3PXD2B):c.1542C>T (p.Pro514=)	CCC	CCT		1.02	0.02
VCP	ENSG00000165280	NM_007126.5(VCP):c.258A>G (p.Arg86=)	AGA	AGG		0.91	-0.14
RNASEH2A	ENSG00000104889	NM_006397.2(RNASEH2A):c.36C>T (p.Gly12=)	GGC	GGT	Aicardi Goutieres syndrome 4 (AGS4)	0.55	-0.87
PEX19	ENSG00000162735	NM_002857.3(PEX19):c.159A>G (p.Arg53=)	AGA	AGG		0.91	-0.14
MMAA	ENSG00000151611	NM_172250.3(MMAA):c.912G>A (p.Ala304=)	GCG	GCA	Vitamin B12-responsive methylmalonic acidemia type cblA	2.88	1.52
CTC1	ENSG00000178971	NM_025099.6(CTC1):c.1548G>A (p.Pro516=)	CCG	CCA	Dyskeratosis congenita	3.05	1.61
NKX3-2	ENSG00000109705	NM_001189.4(NKX3-2):c.873A>G (p.Arg291=)	AGA	AGG		0.91	-0.14
TTN	ENSG00000155657	NM_001267550.2(TTN):c.99996G>A (p.Glu33332=)	GAG	GAA		0.86	-0.22
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.8568C>G (p.Leu2856=)	CTC	CTG		2.02	1.02
TTN	ENSG00000155657	NM_001267550.2(TTN):c.100167A>G (p.Pro33389=)	CCA	CCG		0.33	-1.61
LHCGR	ENSG00000138039	NM_000233.4(LHCGR):c.1797C>A (p.Ile599=)	ATC	ATA		0.44	-1.2
PDX1	ENSG00000139515	NM_000209.4(PDX1):c.285G>A (p.Pro95=)	CCG	CCA		3.05	1.61
KCNV2	ENSG00000168263	NM_133497.4(KCNV2):c.168G>A (p.Glu56=)	GAG	GAA		0.86	-0.22
CFTR	ENSG00000001626	NM_000492.4(CFTR):c.1518C>A (p.Ile506=)	ATC	ATA		0.44	-1.2
PNPLA2	ENSG00000177666	NM_020376.4(PNPLA2):c.591C>T (p.Asp197=)	GAC	GAT	Neutral lipid storage myopathy (NLSDM)	0.99	-0.01
CTC1	ENSG00000178971	NM_025099.6(CTC1):c.1500C>T (p.Pro500=)	CCC	CCT	Dyskeratosis congenita	1.02	0.02
CHD7	ENSG00000171316	NM_017780.4(CHD7):c.5973A>G (p.Gln1991=)	CAA	CAG		2.49	1.32
PNPLA2	ENSG00000177666	NM_020376.4(PNPLA2):c.747G>A (p.Leu249=)	CTG	CTA	Neutral lipid storage myopathy (NLSDM)	0.21	-2.27
MCOLN1	ENSG00000090674	NM_020533.3(MCOLN1):c.1032G>A (p.Leu344=)	CTG	CTA	Mucolipidosis type IV (ML4)	0.21	-2.27
ADA	ENSG00000196839	NM_000022.4(ADA):c.927G>A (p.Gln309=)	CAG	CAA	Severe combined immunodeficiency due to ADA deficiency	0.4	-1.32
THPO	ENSG00000090534	NM_000460.4(THPO):c.639T>A (p.Thr213=)	ACT	ACA		1.16	0.21
MCOLN1	ENSG00000090674	NM_020533.3(MCOLN1):c.1077C>T (p.Val359=)	GTC	GTT	Mucolipidosis type IV (ML4)	0.88	-0.19
HYAL1	ENSG00000114378	NM_033159.4(HYAL1):c.1041C>T (p.Phe347=)	TTC	TTT	Deficiency of hyaluronoglucosaminidase (MPS9)	0.98	-0.02
GCDH	ENSG00000105607	NM_000159.4(GCDH):c.885C>T (p.Tyr295=)	TAC	TAT	Glutaric aciduria, type 1 (GA1)	0.9	-0.15
HBB	ENSG00000244734	NM_000518.5(HBB):c.45G>A (p.Leu15=)	CTG	CTA		0.21	-2.27
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.11157C>A (p.Ile3719=)	ATC	ATA		0.44	-1.2
NPHP3	ENSG00000113971	NM_153240.5(NPHP3):c.1083T>C (p.Ser361=)	TCT	TCC		1.02	0.03
MYOT	ENSG00000120729	NM_006790.2(MYOT):c.61T>C (p.Leu21=)	TTG	CTG		2.67	1.42
PNPLA6	ENSG00000032444	NM_001166114.2(PNPLA6):c.162C>T (p.Ile54=)	ATC	ATT	Hereditary spastic paraplegia 39 (SPG39)	0.89	-0.17
SGSH	ENSG00000181523	NM_000199.5(SGSH):c.1302G>A (p.Ala434=)	GCG	GCA	Mucopolysaccharidosis, MPS-III-A (MPS3A)	2.88	1.52
TTN	ENSG00000155657	NM_001267550.2(TTN):c.47766C>T (p.Thr15922=)	ACC	ACT		0.8	-0.31
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.26355C>T (p.His8785=)	CAC	CAT		0.81	-0.3

CHD7	ENSG00000171316	NM_017780.4(CHD7):c.5496G>A (p.Glu1832=)	GAG	GAA		0.86	-0.22
IL17RA	ENSG00000177663	NM_014339.7(IL17RA):c.30T>A (p.Ala10=)	GCT	GCA	Immunodeficiency 51 (IMD51)	0.9	-0.14
CHD2	ENSG00000173575	NM_001271.4(CHD2):c.4482C>T (p.Asn1494=)	AAC	AAT		1.01	0.02
MAN2B1	ENSG00000104774	NM_000528.4(MAN2B1):c.744G>A (p.Pro248=)	CCG	CCA	Deficiency of alpha-mannosidase (MANSA)	3.05	1.61
DIS3L2	ENSG00000144535	NM_152383.5(DIS3L2):c.2637C>T (p.Pro879=)	CCC	CCT	Perlman syndrome (PRLMNS)	1.02	0.02
IQSEC2	ENSG00000124313	NM_001111125.3(IQSEC2):c.3663A>G (p.Pro1221=)	CCA	CCG		0.33	-1.61
DIS3L2	ENSG00000144535	NM_152383.5(DIS3L2):c.519C>T (p.Ser173=)	AGC	AGT	Perlman syndrome (PRLMNS)	0.72	-0.48
CP	ENSG00000047457	NM_000096.4(CP):c.3006C>T (p.Ser1002=)	AGC	AGT	Deficiency of ferroxidase	0.72	-0.48
CIITA	ENSG00000179583	NM_000246.3(CIITA):c.2442C>T (p.His814=)	CAC	CAT	Bare lymphocyte syndrome 2	0.81	-0.3
CIITA	ENSG00000179583	NM_000246.3(CIITA):c.492C>G (p.Pro164=)	CCC	CCG	Bare lymphocyte syndrome 2	0.33	-1.62
GAA	ENSG00000171298	NM_000152.5(GAA):c.36C>T (p.Leu12=)	CTC	CTT	Glycogen storage disease, type II (GSD2)	0.8	-0.33
RAD50	ENSG00000113522	NM_005732.4(RAD50):c.633A>G (p.Lys211=)	AAA	AAG	Hereditary cancer-predisposing syndrome	1.15	0.2
PNPLA2	ENSG00000177666	NM_020376.4(PNPLA2):c.903C>T (p.Pro301=)	CCC	CCT	Neutral lipid storage myopathy (NLSDM)	1.02	0.02
CTSA	ENSG00000064601	NM_000308.3(CTSA):c.1113G>A (p.Pro371=)	CGC	CGA	Combined deficiency of sialidase AND beta galactosidase (GSL)	0.74	-0.44
XPC	ENSG00000154767	NM_004628.5(XPC):c.1185G>A (p.Lys395=)	AAG	AAA	Xeroderma pigmentosum, group C (XPC)	0.87	-0.2
RHO	ENSG00000163914	NM_000539.3(RHO):c.1020G>A (p.Thr340=)	ACG	ACA		2.96	1.57
AXIN2	ENSG00000168646	NM_004655.4(AXIN2):c.174C>T (p.Asn58=)	AAC	AAT	Oligodontia-colorectal cancer syndrome (ODCRCS)	1.01	0.02
PNPLA2	ENSG00000177666	NM_020376.4(PNPLA2):c.165G>T (p.Ala55=)	GCG	GCT	Neutral lipid storage myopathy (NLSDM)	3.18	1.67
MLH3	ENSG00000119684	NM_001040108.1(MLH3):c.423C>T (p.Ser141=)	AGC	AGT	Hereditary nonpolyposis colorectal cancer type 7 (HNPCC7)	0.72	-0.48
ROR2	ENSG00000169071	NM_004560.4(ROR2):c.2445G>A (p.Pro815=)	CCG	CCA		3.05	1.61
TTN	ENSG00000155657	NM_001267550.2(TTN):c.105999G>A (p.Gln35333=)	CAG	CAA		0.4	-1.32
TTN	ENSG00000155657	NM_001267550.2(TTN):c.99990A>G (p.Lys33330=)	AAA	AAG		1.15	0.2
HBB	ENSG00000244734	NM_000518.5(HBB):c.327C>T (p.Asn109=)	AAC	AAT		1.01	0.02
AMT	ENSG00000145020	NM_000481.4(AMT):c.84C>T (p.Cys28=)	TGC	TGT	Non-ketotic hyperglycinemia (GCE)	0.97	-0.05
MET	ENSG00000105976	NM_000245.4(MET):c.600C>G (p.Thr200=)	ACC	ACG	Renal cell carcinoma, papillary, 1 (RCCP1)	0.31	-1.67
SLC29A3	ENSG00000198246	NM_018344.6(SLC29A3):c.987C>T (p.Asn329=)	AAC	AAT	Histiocytosis-lymphadenopathy plus syndrome (HJCD)	1.01	0.02
CABP4	ENSG00000175544	NM_145200.4(CABP4):c.531C>A (p.Ile177=)	ATC	ATA		0.44	-1.2
PROC	ENSG00000115718	NM_000312.4(PROC):c.1326C>T (p.Leu442=)	CTC	CTT	Thrombophilia, hereditary, due to protein C deficiency, autosomal dominant (THPH3)	0.8	-0.33
G6PC1	ENSG00000131482	NM_000151.4(G6PC1):c.1056G>A (p.Pro352=)	CCG	CCA	Glycogen storage disease due to glucose-6-phosphatase deficiency type IA (GSD1A)	3.05	1.61
HMGCS2	ENSG00000134240	NM_001166107.1(HMGCS2):c.560-646C>T	CCC	CCT	mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency (HMGCS2D)	1.02	0.02
DIS3L2	ENSG00000144535	NM_152383.5(DIS3L2):c.1680G>A (p.Leu560=)	CTG	CTA	Perlman syndrome (PRLMNS)	0.21	-2.27
ACTG1	ENSG00000184009	NM_001614.5(ACTG1):c.1095G>A (p.Ser365=)	TCG	TCA		3.5	1.81
SGSH	ENSG00000181523	NM_000199.5(SGSH):c.1446C>T (p.Ala482=)	GCC	GCT	Mucopolysaccharidosis, MPS-III-A (MPS3A)	0.74	-0.44
RAX	ENSG00000134438	NM_013435.3(RAX):c.24A>G (p.Pro8=)	CCA	CCG	Microphthalmia, isolated 3 (MCOP3)	0.33	-1.61
DNAJB6	ENSG00000105993	NM_058246.4(DNAJB6):c.801G>A (p.Ser267=)	TCG	TCA		3.5	1.81
PNPLA2	ENSG00000177666	NM_020376.4(PNPLA2):c.597C>T (p.Ser199=)	TCC	TCT	Neutral lipid storage myopathy (NLSDM)	0.98	-0.03
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.12147G>A (p.Glu4049=)	GAG	GAA		0.86	-0.22
AXIN2	ENSG00000168646	NM_004655.4(AXIN2):c.1347C>T (p.Thr449=)	ACC	ACT	Oligodontia-colorectal cancer syndrome (ODCRCS)	0.8	-0.31

DLAT	ENSG00000150768	NM_001931.5(DLAT):c.423G>A (p.Glu141=)	GAG	GAA		0.86	-0.22
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.14931A>G (p.Leu4977=)	CTA	CTG		4.81	2.27
PRPF8	ENSG00000174231	NM_006445.4(PRPF8):c.6750C>T (p.Gly2250=)	GGC	GGT		0.55	-0.87
MMP9	ENSG00000100985	NM_004994.3(MMP9):c.1896C>T (p.Leu632=)	CTC	CTT		0.8	-0.33
PRICKLE2	ENSG00000163637	NM_198859.4(PRICKLE2):c.1962G>A (p.Leu654=)	CTG	CTA		0.21	-2.27
TTN	ENSG00000155657	NM_001267550.2(TTN):c.25035C>T (p.Val8345=)	GTC	GTT		0.88	-0.19
SYNE2	ENSG00000054654	NM_182914.2(SYNE2):c.18963G>T (p.Leu6321=)	CTG	CTT	Emery-Dreifuss muscular dystrophy 5, autosomal dominant (EDMD5)	0.39	-1.35
GALC	ENSG00000054983	NM_000153.4(GALC):c.81C>T (p.Ala27=)	GCC	GCT	Galactosylceramide beta-galactosidase deficiency	0.74	-0.44
ADA	ENSG00000196839	NM_000022.4(ADA):c.375C>G (p.Thr125=)	ACC	ACG	Severe combined immunodeficiency due to ADA deficiency	0.31	-1.67
G6PC1	ENSG00000131482	NM_000151.4(G6PC1):c.879A>G (p.Pro293=)	CCA	CCG	Glycogen storage disease due to glucose-6-phosphatase deficiency type IA (GSD1A)	0.33	-1.61
SGSH	ENSG00000181523	NM_000199.5(SGSH):c.1209C>T (p.Tyr403=)	TAC	TAT	Mucopolysaccharidosis, MPS-III-A (MPS3A)	0.9	-0.15
CTC1	ENSG00000178971	NM_025099.6(CTC1):c.3498G>A (p.Ser1166=)	TCG	TCA	Dyskeratosis congenita	3.5	1.81
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.26106G>A (p.Lys8702=)	AAG	AAA		0.87	-0.2
STXBP2	ENSG00000076944	NM_006949.4(STXBP2):c.1671C>T (p.Thr557=)	ACC	ACT	Hemophagocytic lymphohistiocytosis, familial, 5 (FHL5)	0.8	-0.31
TTN	ENSG00000155657	NM_001267550.2(TTN):c.67146C>T (p.Gly22382=)	GGC	GGT		0.55	-0.87
FOXC1	ENSG00000054598	NM_001453.3(FOXC1):c.597C>G (p.Arg199=)	CGC	CGG		1.22	0.29
SHOX	ENSG00000185960	NM_000451.3(SHOX):c.702G>A (p.Ala234=)	GCG	GCA		2.88	1.52
ETHE1	ENSG00000105755	NM_014297.5(ETHE1):c.9G>A (p.Glu3=)	GAG	GAA	Ethylmalonic encephalopathy (EE)	0.86	-0.22
POLG	ENSG00000140521	NM_002693.2(POLG):c.3468C>T (p.Thr1156=)	ACC	ACT		0.8	-0.31
ETFDH	ENSG00000171503	NM_004453.4(ETFDH):c.63T>C (p.Ile21=)	ATT	ATC	Multiple acyl-CoA dehydrogenase deficiency (MADD)	1.13	0.17
CACNA1B	ENSG00000148408	NM_000718.4(CACNA1B):c.30C>T (p.Gly10=)	GGC	GGT		0.55	-0.87
SPG11	ENSG00000104133	NM_025137.4(SPG11):c.60G>C (p.Ala20=)	GCG	GCC	Spastic paraplegia 11, autosomal recessive (SPG11)	4.32	2.11
DIS3L2	ENSG00000144535	NM_152383.5(DIS3L2):c.2424G>A (p.Gln808=)	CAG	CAA	Perlman syndrome (PRLMNS)	0.4	-1.32
ACADVL	ENSG00000072778	NM_000018.4(ACADVL):c.780G>A (p.Thr260=)	ACG	ACA	Very long chain acyl-CoA dehydrogenase deficiency (VLCAD)	2.96	1.57
SRCAP	ENSG00000080603	NM_006662.3(SRCAP):c.1545A>G (p.Glu515=)	GAA	GAG		1.16	0.22
UNG	ENSG00000076248	NM_080911.3(UNG):c.183G>A (p.Pro61=)	CCG	CCA	Hyper-IgM syndrome type 5 (HIGM5)	3.05	1.61
CPT2	ENSG00000157184	NM_000098.3(CPT2):c.1335C>T (p.Cys445=)	TGC	TGT	Carnitine palmitoyltransferase II deficiency (CPT2)	0.97	-0.05
CHMP1A	ENSG00000131165	NM_002768.5(CHMP1A):c.147C>T (p.Ala49=)	GCC	GCT		0.74	-0.44
GALK1	ENSG00000108479	NM_000154.2(GALK1):c.747G>A (p.Ala249=)	GCG	GCA	Deficiency of galactokinase (GALAC2)	2.88	1.52
ATP8B1	ENSG00000081923	NM_005603.6(ATP8B1):c.903G>A (p.Arg301=)	AGG	AGA		1.1	0.14
CFTR	ENSG00000001626	NM_000492.3(CFTR):c.2736G>C (p.Ser912=)	TCG	TCC		4.26	2.09
FOXC1	ENSG00000054598	NM_001453.3(FOXC1):c.171G>C (p.Pro57=)	CCG	CCC		3.07	1.62
MYH7	ENSG00000092054	NM_000257.4(MYH7):c.3147G>A (p.Glu1049=)	GAG	GAA	Cardiomyopathy (CMYO)	0.86	-0.22
SLC25A15	ENSG00000102743	NM_014252.4(SLC25A15):c.255C>T (p.Tyr85=)	TAC	TAT	Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (HHHS)	0.9	-0.15
HOXA1	ENSG00000105991	NM_005522.4(HOXA1):c.684A>G (p.Gln228=)	CAA	CAG		2.49	1.32
NTRK1	ENSG00000198400	NM_001007792.1(NTRK1):c.1887G>A (p.Lys629=)	AAG	AAA	Hereditary insensitivity to pain with anhidrosis (CIPA)	0.87	-0.2
VCAN	ENSG00000038427	NM_004385.5(VCAN):c.7065C>T (p.Ile2355=)	ATC	ATT		0.89	-0.17
LRP5	ENSG00000162337	NM_002335.4(LRP5):c.144C>T (p.Ala48=)	GCC	GCT		0.74	-0.44
TTN	ENSG00000155657	NM_001267550.2(TTN):c.39375A>G (p.Pro13125=)	CCA	CCG		0.33	-1.61
BSCL2	ENSG00000168000	NM_032667.6(BSCL2):c.228C>T (p.Ser76=)	TCC	TCT		0.98	-0.03

MCCC1	ENSG00000078070	NM_020166.5(MCCC1):c.1839C>A (p.Ile613=)	ATC	ATA	3 Methylcrotonyl-CoA carboxylase 1 deficiency (MCC1D)	0.44	-1.2
AMACR	ENSG00000242110	NM_014324.6(AMACR):c.714C>G (p.Pro238=)	CCC	CCG		0.33	-1.62
PINK1	ENSG00000158828	NM_032409.3(PINK1):c.165G>A (p.Glu55=)	GAG	GAA	Parkinson disease 6, autosomal recessive early-onset (PARK6)	0.86	-0.22
FZD4	ENSG00000174804	NM_012193.4(FZD4):c.1194T>C (p.Tyr398=)	TAT	TAC		1.11	0.15
SLC7A7	ENSG00000155465	NM_001126106.2(SLC7A7):c.1494T>C (p.Asp498=)	GAT	GAC	Lysinuric protein intolerance (LPI)	1.01	0.01
MAN1B1	ENSG00000177239	NM_016219.5(MAN1B1):c.882G>A (p.Ala294=)	GCG	GCA	Mental retardation, autosomal recessive 15 (RAFQS)	2.88	1.52
CACNB4	ENSG00000182389	NM_000726.4(CACNB4):c.36G>A (p.Ala12=)	GCG	GCA		2.88	1.52
TNFRSF1A	ENSG00000067182	NM_001065.4(TNFRSF1A):c.1206C>T (p.Ser402=)	AGC	AGT	TNF receptor-associated periodic fever syndrome (TRAPS) (FPF)	0.72	-0.48
DIS3L2	ENSG00000144535	NM_152383.5(DIS3L2):c.2124C>T (p.Asp708=)	GAC	GAT	Perlman syndrome (PRLMNS)	0.99	-0.01
TNFRSF11A	ENSG00000141655	NM_003839.4(TNFRSF11A):c.1296G>A (p.Pro432=)	CCG	CCA		3.05	1.61
TTN	ENSG00000155657	NM_001267550.2(TTN):c.35268G>A (p.Pro11756=)	CCG	CCA		3.05	1.61
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.2904C>T (p.Asn968=)	AAC	AAT		1.01	0.02
PNPLA2	ENSG00000177666	NM_020376.4(PNPLA2):c.1491C>T (p.Pro497=)	CCC	CCT	Neutral lipid storage myopathy (NLSDM)	1.02	0.02
LPIN2	ENSG00000101577	NM_014646.2(LPIN2):c.756G>A (p.Ala252=)	GCG	GCA	Majeed syndrome (MJDS)	2.88	1.52
PANK2	ENSG00000125779	NM_153638.3(PANK2):c.585G>T (p.Ser195=)	TCG	TCT	Pigmentary pallidal degeneration (NBIA1)	4.18	2.06
HTRA1	ENSG00000166033	NM_002775.5(HTRA1):c.957C>T (p.Thr319=)	ACC	ACT		0.8	-0.31
AP5Z1	ENSG00000242802	NM_014855.3(AP5Z1):c.1773C>T (p.Tyr591=)	TAC	TAT	Spastic paraplegia 48, autosomal recessive (SPG48)	0.9	-0.15
DIS3L2	ENSG00000144535	NM_152383.5(DIS3L2):c.2067C>T (p.Tyr689=)	TAC	TAT	Perlman syndrome (PRLMNS)	0.9	-0.15
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.2883G>A (p.Ala961=)	GCG	GCA		2.88	1.52
SLC25A15	ENSG00000102743	NM_014252.4(SLC25A15):c.216C>T (p.Ile72=)	ATC	ATT	Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (HHHS)	0.89	-0.17
JAG1	ENSG00000101384	NM_000214.3(JAG1):c.2298T>C (p.Phe766=)	TTT	TTC		1.02	0.02
HBA1	ENSG00000206172	NM_000558.5(HBA1):c.396T>C (p.Ser132=)	TCT	TCC		1.02	0.03
GALK1	ENSG00000108479	NM_000154.2(GALK1):c.1044C>T (p.Phe348=)	TTC	TTT	Deficiency of galactokinase (GALAC2)	0.98	-0.02
IDUA	ENSG00000127415	NM_000203.5(IDUA):c.663C>G (p.Pro221=)	CCC	CCG	Mucopolysaccharidosis type 1 (MPS1)	0.33	-1.62
MCPH1	ENSG00000147316	NM_024596.5(MCPH1):c.2274C>T (p.Asp758=)	GAC	GAT		0.99	-0.01
APC2	ENSG00000115266	NM_005883.2(APC2):c.6588C>A (p.Val2196=)	GTC	GTA		0.57	-0.8
SLC29A3	ENSG00000198246	NM_018344.6(SLC29A3):c.855G>A (p.Ser285=)	TCG	TCA	Histiocytosis-lymphadenopathy plus syndrome (HJCD)	3.5	1.81
DIS3L2	ENSG00000144535	NM_152383.5(DIS3L2):c.1908C>T (p.Ser636=)	TCC	TCT	Perlman syndrome (PRLMNS)	0.98	-0.03
SPG11	ENSG00000104133	NM_025137.4(SPG11):c.7146C>T (p.Ser2382=)	TCC	TCT	Spastic paraplegia 11, autosomal recessive (SPG11)	0.98	-0.03
HES7	ENSG00000179111	NM_001165967.2(HES7):c.591C>T (p.Pro197=)	CCC	CCT		1.02	0.02
NPC1	ENSG00000141458	NM_000271.5(NPC1):c.3321C>A (p.Gly1107=)	GGC	GGA	Niemann-Pick disease type C1 (NPC1)	0.87	-0.2
ATP8B1	ENSG00000081923	NM_005603.6(ATP8B1):c.3201C>T (p.Ser1067=)	TCC	TCT		0.98	-0.03
MPI	ENSG00000178802	NM_002435.3(MPI):c.849C>T (p.Cys283=)	TGC	TGT	MPI-CDG	0.97	-0.05
GRIN2D	ENSG00000105464	NM_000836.2(GRIN2D):c.2910G>A (p.Pro970=)	CCG	CCA		3.05	1.61
G6PC3	ENSG00000141349	NM_001319945.2(G6PC3):c.568C>T (p.Pro190Ser)	AGC	AGT	Severe congenital neutropenia 4, autosomal recessive (SCN4)	0.72	-0.48
FOXP2	ENSG00000128573	NM_014491.4(FOXP2):c.1434A>T (p.Arg478=)	CGA	CGT		0.71	-0.49
MCCC1	ENSG00000078070	NM_020166.5(MCCC1):c.156C>A (p.Val52=)	GTC	GTA		0.57	-0.8
SLC3A1	ENSG00000138079	NM_000341.4(SLC3A1):c.1398C>T (p.Asn466=)	AAC	AAT	Cystinuria (CSNU)	1.01	0.02
GALK1	ENSG00000108479	NM_000154.2(GALK1):c.864G>C (p.Thr288=)	ACG	ACC	Deficiency of galactokinase (GALAC2)	3.18	1.67
DOLK	ENSG00000175283	NM_014908.3(DOLK):c.633C>T (p.Arg211=)	CGC	CGT	Congenital disorder of glycosylation type 1M (CDG1M)	0.52	-0.93
NAGS	ENSG00000161653	NM_153006.3(NAGS):c.1281C>G (p.Ala427=)	GCC	GCG	Hyperammonemia, type III (NAGSD)	0.23	-2.11

TMEM70	ENSG00000175606	NM_017866.6(TMEM70):c.462C>A (p.Ile154=)	ATC	ATA	Nuclearly-encoded mitochondrial complex V (ATP synthase) deficiency 2 (MC5DN2)	0.44	-1.2
DIS3L2	ENSG00000144535	NM_152383.5(DIS3L2):c.1836G>A (p.Pro612=)	CCG	CCA	Perlman syndrome (PRLMNS)	3.05	1.61
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.2106G>A (p.Val702=)	GTG	GTA		0.3	-1.74
WDR81	ENSG00000167716	NM_001163809.1(WDR81):c.2871T>C (p.Asn957=)	AAT	AAC		0.99	-0.02
UNC13D	ENSG00000092929	NM_199242.2(UNC13D):c.114G>A (p.Pro38=)	CCG	CCA	Familial hemophagocytic lymphohistiocytosis 3 (FHL3)	3.05	1.61
MCOLN1	ENSG00000090674	NM_020533.3(MCOLN1):c.60C>T (p.Pro20=)	CCC	CCT	Mucolipidosis type IV (ML4)	1.02	0.02
AMT	ENSG00000145020	NM_000481.4(AMT):c.153G>A (p.Ala51=)	GCG	GCA	Non-ketotic hyperglycinemia (GCE)	2.88	1.52
POMT1	ENSG00000130714	NM_001077365.2(POMT1):c.30G>A (p.Val10=)	GTG	GTA		0.3	-1.74
RNASEH2C	ENSG00000172922	NM_032193.3(RNASEH2C):c.417C>G (p.Gly139=)	GGC	GGG	Aicardi Goutieres syndrome 3 (AGS3)	0.77	-0.37
IDUA	ENSG00000127415	NM_000203.5(IDUA):c.408C>T (p.Ala136=)	GCC	GCT	Mucopolysaccharidosis type 1 (MPS1)	0.74	-0.44
GLIS2	ENSG00000126603	NM_032575.2(GLIS2):c.1026C>T (p.Pro342=)	CCC	CCT		1.02	0.02
TOR1A	ENSG00000136827	NM_000113.3(TOR1A):c.990C>T (p.Tyr330=)	TAC	TAT		0.9	-0.15
TNFRSF13C	ENSG00000159958	NM_052945.3(TNFRSF13C):c.246C>T (p.Pro82=)	CCC	CCT	Common variable immunodeficiency 4 (CVID4)	1.02	0.02
ELP1	ENSG00000070061	NM_003640.5(ELP1):c.169T>C (p.Leu57=)	TTG	CTG	Familial dysautonomia (HSAN3)	2.67	1.42
SCN9A	ENSG00000169432	NM_001365536.1(SCN9A):c.4941C>T (p.Ile1647=)	ATC	ATT		0.89	-0.17
ELANE	ENSG00000197561	NM_001972.4(ELANE):c.558C>A (p.Val186=)	GTC	GTA		0.57	-0.8
SGSH	ENSG00000181523	NM_000199.5(SGSH):c.780C>T (p.Ala260=)	GCC	GCT	Mucopolysaccharidosis, MPS-III-A (MPS3A)	0.74	-0.44
DIS3L2	ENSG00000144535	NM_152383.5(DIS3L2):c.1599C>T (p.His533=)	CAC	CAT	Perlman syndrome (PRLMNS)	0.81	-0.3
EHMT1	ENSG00000181090	NM_024757.5(EHMT1):c.3555C>T (p.Tyr1185=)	TAC	TAT		0.9	-0.15
HEXB	ENSG00000049860	NM_000521.4(HEXB):c.1269A>G (p.Val423=)	GTA	GTG	Sandhoff disease	3.34	1.74
PYGM	ENSG00000068976	NM_005609.4(PYGM):c.2412G>A (p.Arg804=)	CGG	CGA	Glycogen storage disease, type V (GSD5)	0.6	-0.73
MYBPC3	ENSG00000134571	NM_000256.3(MYBPC3):c.534G>T (p.Val178=)	GTG	GTT	Cardiomyopathy (CMYO)	0.46	-1.13
CTCF	ENSG00000102974	NM_006565.4(CTCF):c.969G>A (p.Lys323=)	AAG	AAA		0.87	-0.2
DIS3L2	ENSG00000144535	NM_152383.5(DIS3L2):c.1839C>T (p.Pro613=)	CCC	CCT	Perlman syndrome (PRLMNS)	1.02	0.02
GRN	ENSG00000030582	NM_002087.4(GRN):c.102C>T (p.Pro34=)	CCC	CCT		1.02	0.02
TNFRSF13C	ENSG00000159958	NM_052945.3(TNFRSF13C):c.213G>A (p.Ala71=)	GCG	GCA	Common variable immunodeficiency 4 (CVID4)	2.88	1.52
POMT2	ENSG00000009830	NM_013382.5(POMT2):c.87A>T (p.Ala29=)	GCA	GCT		1.11	0.14
DOLK	ENSG00000175283	NM_014908.3(DOLK):c.192A>G (p.Leu64=)	CTA	CTG	Congenital disorder of glycosylation type 1M (CDG1M)	4.81	2.27
NDUFV1	ENSG00000167792	NM_007103.4(NDUFV1):c.249G>A (p.Ser83=)	TCG	TCA		3.5	1.81
NPHP3	ENSG00000113971	NM_153240.5(NPHP3):c.171C>A (p.Pro57=)	CCC	CCA		1	-0.01
PEX19	ENSG00000162735	NM_002857.3(PEX19):c.162G>T (p.Ser54=)	TCG	TCT		4.18	2.06
COG1	ENSG00000166685	NM_018714.3(COG1):c.2304A>G (p.Thr768=)	ACA	ACG	COG1 congenital disorder of glycosylation (CDG2G)	0.34	-1.57
POLR1D	ENSG00000186184	NM_015972.4(POLR1D):c.177C>T (p.Ile59=)	ATC	ATT		0.89	-0.17
PIGO	ENSG00000165282	NM_032634.4(PIGO):c.1416A>T (p.Ala472=)	GCA	GCT	Hyperphosphatasia with mental retardation syndrome 2 (HPMRS2)	1.11	0.14
BBS10	ENSG00000179941	NM_024685.4(BBS10):c.42G>A (p.Ala14=)	GCG	GCA	Bardet-Biedl syndrome (BBS)	2.88	1.52
ROGDI	ENSG00000067836	NM_024589.2(ROGDI):c.783C>T (p.Phe261=)	TTC	TTT	Kohlschutter's syndrome (KTZS)	0.98	-0.02
DIS3L2	ENSG00000144535	NM_152383.4(DIS3L2):c.1809G>A (p.Glu603=)	GAG	GAA	Perlman syndrome (PRLMNS)	0.86	-0.22
PGK1	ENSG00000102144	NM_000291.4(PGK1):c.1188T>A (p.Gly396=)	GGT	GGA		1.59	0.67
MCOLN1	ENSG00000090674	NM_020533.3(MCOLN1):c.1584C>T (p.Gly528=)	GGC	GGT	Mucolipidosis type IV (ML4)	0.55	-0.87
ACADVL	ENSG00000072778	NM_000018.4(ACADVL):c.963C>T (p.Asn321=)	AAC	AAT	Very long chain acyl-CoA dehydrogenase deficiency (VLCAD)	1.01	0.02
COG8	ENSG00000213380	NM_032382.4(COG8):c.249C>G (p.Ala83=)	GCC	GCG	Congenital disorder of glycosylation type 2H (CDG2H)	0.23	-2.11

TBX6	ENSG00000149922	NM_004608.3(TBX6):c.585C>T (p.Val195=)	GTC	GTT		0.88	-0.19
PNPLA2	ENSG00000177666	NM_020376.4(PNPLA2):c.912C>A (p.Leu304=)	CTC	CTA	Neutral lipid storage myopathy (NLSDM)	0.42	-1.25
TBX6	ENSG00000149922	NM_004608.3(TBX6):c.298C>T (p.Leu100=)	CTA	TTA		1.18	0.24
PANK2	ENSG00000125779	NM_153638.3(PANK2):c.588C>G (p.Val196=)	GTC	GTG	Pigmentary pallidal degeneration (NBIA1)	1.92	0.94
MYH7	ENSG00000092054	NM_000257.4(MYH7):c.5178G>A (p.Gln1726=)	CAG	CAA	Cardiomyopathy (CMYO)	0.4	-1.32
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.2968C>T (p.Leu990=)	CTG	TTG		0.37	-1.42
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.813C>T (p.Cys271=)	TGC	TGT	Wilson disease (WND)	0.97	-0.05
MCCC1	ENSG00000078070	NM_020166.5(MCCC1):c.144C>T (p.Asn48=)	AAC	AAT	3 Methylcrotonyl-CoA carboxylase 1 deficiency (MCC1D)	1.01	0.02
TBX6	ENSG00000149922	NM_004608.3(TBX6):c.408C>T (p.Arg136=)	CGC	CGT		0.52	-0.93
WDR81	ENSG00000167716	NM_001163809.1(WDR81):c.2136G>A (p.Gly712=)	GGG	GGA		1.13	0.17
MYH7	ENSG00000092054	NM_000257.4(MYH7):c.5013C>T (p.Ile1671=)	ATC	ATT	Cardiomyopathy (CMYO)	0.89	-0.17
DIS3L2	ENSG00000144535	NM_152383.5(DIS3L2):c.2151C>T (p.Ala717=)	GCC	GCT	Perlman syndrome (PRLMNS)	0.74	-0.44
SLC3A1	ENSG00000138079	NM_000341.4(SLC3A1):c.1767C>T (p.Ile589=)	ATC	ATT	Cystinuria (CSNU)	0.89	-0.17
PANK2	ENSG00000125779	NM_153638.3(PANK2):c.348G>A (p.Gly116=)	GGG	GGA	Pigmentary pallidal degeneration (NBIA1)	1.13	0.17
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.3024C>T (p.Pro1008=)	CCC	CCT		1.02	0.02
EFEMP2	ENSG00000172638	NM_016938.5(EFEMP2):c.363T>C (p.Cys121=)	TGT	TGC	Autosomal recessive cutis laxa type 1B (ARCL1B)	1.03	0.05
B3GALT6	ENSG00000176022	NM_080605.4(B3GALT6):c.585G>T (p.Gly195=)	GGG	GGT		0.71	-0.5
COQ8A	ENSG00000163050	NM_020247.5(COQ8A):c.1773T>C (p.Ile591=)	ATT	ATC		1.13	0.17
AMACR	ENSG00000242110	NM_014324.6(AMACR):c.1083C>T (p.Arg361=)	CGC	CGT		0.52	-0.93
YARS1	ENSG00000134684	NM_003680.3(YARS1):c.1464C>T (p.Phe488=)	TTC	TTT		0.98	-0.02
COL9A3	ENSG00000092758	NM_001853.4(COL9A3):c.1932C>T (p.Pro644=)	CCC	CCT		1.02	0.02
ALG12	ENSG00000182858	NM_024105.4(ALG12):c.57C>T (p.Ala19=)	GCC	GCT	ALG12-congenital disorder of glycosylation (CDG1G)	0.74	-0.44
TAT	ENSG00000198650	NM_000353.3(TAT):c.1290G>A (p.Ala430=)	GCG	GCA	Tyrosinemia type II (TYRSN2)	2.88	1.52
CPT2	ENSG00000157184	NM_000098.3(CPT2):c.1737C>T (p.Tyr579=)	TAC	TAT	Carnitine palmitoyltransferase II deficiency (CPT2)	0.9	-0.15
SGSH	ENSG00000181523	NM_000199.5(SGSH):c.798A>G (p.Thr266=)	ACA	ACG	Mucopolysaccharidosis, MPS-III-A (MPS3A)	0.34	-1.57
PANK2	ENSG00000125779	NM_153638.3(PANK2):c.12C>T (p.Leu4=)	CTC	CTT		0.8	-0.33
SGSH	ENSG00000181523	NM_000199.5(SGSH):c.1134C>T (p.Ser378=)	TCC	TCT	Mucopolysaccharidosis, MPS-III-A (MPS3A)	0.98	-0.03
NPC1	ENSG00000141458	NM_000271.5(NPC1):c.3312G>A (p.Val1104=)	GTG	GTA	Niemann-Pick disease type C1 (NPC1)	0.3	-1.74
IDH3B	ENSG00000101365	NM_006899.5(IDH3B):c.981G>A (p.Leu327=)	CTG	CTA		0.21	-2.27
TNFRSF1A	ENSG00000067182	NM_001065.4(TNFRSF1A):c.1329C>A (p.Gly443=)	GGC	GGA		0.87	-0.2
ADA	ENSG00000196839	NM_000022.4(ADA):c.642C>T (p.His214=)	CAC	CAT	Severe combined immunodeficiency due to ADA deficiency	0.81	-0.3
COG1	ENSG00000166685	NM_018714.3(COG1):c.2682C>T (p.Asn894=)	AAC	AAT	COG1 congenital disorder of glycosylation (CDG2G)	1.01	0.02
ACADVL	ENSG00000072778	NM_000018.4(ACADVL):c.216C>T (p.Ser72=)	TCC	TCT	Very long chain acyl-CoA dehydrogenase deficiency (VLCAD)	0.98	-0.03
TRMU	ENSG00000100416	NM_018006.5(TRMU):c.30C>T (p.Ala10=)	GCC	GCT		0.74	-0.44
FOXG1	ENSG00000176165	NM_005249.5(FOXG1):c.1119G>A (p.Pro373=)	CCG	CCA		3.05	1.61
TRMU	ENSG00000100416	NM_018006.5(TRMU):c.18C>T (p.His6=)	CAC	CAT		0.81	-0.3
ITK	ENSG00000113263	NM_005546.3(ITK):c.1455C>T (p.Ala485=)	GCC	GCT	Lymphoproliferative syndrome 1 (LPFS1)	0.74	-0.44
PNP	ENSG00000198805	NM_000270.3(PNP):c.678C>T (p.Ile226=)	ATC	ATT	Purine-nucleoside phosphorylase deficiency	0.89	-0.17
ROGDI	ENSG00000067836	NM_024589.2(ROGDI):c.378G>C (p.Leu126=)	CTG	CTC	Kohlschutter's syndrome (KTZS)	0.49	-1.02
NPC1	ENSG00000141458	NM_000271.5(NPC1):c.3393C>T (p.Ile1131=)	ATC	ATT		0.89	-0.17
UGT1A6	ENSG00000242366	NM_001072.4(UGT1A6):c.862-6588G>A	AGG	AGA		1.1	0.14
HSD3B7	ENSG00000099377	NM_025193.4(HSD3B7):c.1047G>C (p.Ser349=)	TCG	TCC		4.26	2.09

IDUA	ENSG00000127415	NM_000203.5(IDUA):c.1800G>A (p.Ser600=)	TCG	TCA	Mucopolysaccharidosis type 1 (MPS1)	3.5	1.81
ROGDI	ENSG00000067836	NM_024589.2(ROGDI):c.243C>T (p.Ala81=)	GCC	GCT	Kohlschutter's syndrome (KTZS)	0.74	-0.44
MAN1B1	ENSG00000177239	NM_016219.5(MAN1B1):c.426G>A (p.Ala142=)	GCG	GCA	Mental retardation, autosomal recessive 15 (RAFQS)	2.88	1.52
CLN6	ENSG00000128973	NM_017882.3(CLN6):c.831C>T (p.Val277=)	GTC	GTT	Neuronal ceroid lipofuscinosis	0.88	-0.19
IDUA	ENSG00000127415	NM_000203.5(IDUA):c.30G>A (p.Leu10=)	CTG	CTA	Mucopolysaccharidosis type 1 (MPS1)	0.21	-2.27
MMAB	ENSG00000139428	NM_052845.4(MMAB):c.150G>A (p.Ser50=)	TCG	TCA	Vitamin B12-responsive methylmalonic acidemia type cblB	3.5	1.81
SOX2	ENSG00000181449	NM_003106.4(SOX2):c.54G>C (p.Ser18=)	TCG	TCC		4.26	2.09
VPS37A	ENSG00000155975	NM_152415.3(VPS37A):c.99C>A (p.Ile33=)	ATC	ATA		0.44	-1.2
IDUA	ENSG00000127415	NM_000203.5(IDUA):c.249C>T (p.Arg83=)	CGC	CGT	Mucopolysaccharidosis type 1 (MPS1)	0.52	-0.93
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.489C>T (p.Ile163=)	ATC	ATT	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD);	0.89	-0.17
MECP2	ENSG00000169057	NM_001110792.2(MECP2):c.750G>A (p.Gly250=)	GGG	GGA		1.13	0.17
MID1	ENSG00000101871	NM_000381.4(MID1):c.1489C>T (p.Leu497=)	CTG	TTG		0.37	-1.42
ITPR1	ENSG00000150995	NM_002222.6(ITPR1):c.5076C>T (p.Asn1692=)	AAC	AAT	Autosomal dominant cerebellar ataxia	1.01	0.02
LRBA	ENSG00000198589	NM_001364905.1(LRBA):c.2340A>G (p.Thr780=)	ACA	ACG	Common variable immunodeficiency 8, with autoimmunity (CVID8)	0.34	-1.57
PITPNM3	ENSG00000091622	NM_031220.4(PITPNM3):c.2355G>A (p.Pro785=)	CCG	CCA	Cone-rod dystrophy 5 (CORD5)	3.05	1.61
SACS	ENSG00000151835	NM_014363.6(SACS):c.10668G>A (p.Leu3556=)	TTG	TTA	Spastic paraplegia	0.65	-0.61
FGFR3	ENSG00000068078	NM_000142.5(FGFR3):c.1497C>T (p.Ala499=)	GCC	GCT	Craniosynostosis syndrome	0.74	-0.44
WDR19	ENSG00000157796	NM_025132.4(WDR19):c.2715G>A (p.Lys905=)	AAG	AAA	Asphyxiating thoracic dystrophy 5 (SRTD5);Senior-Loken syndrome 8 (SLSN8)	0.87	-0.2
RTTN	ENSG00000176225	NM_173630.4(RTTN):c.5883G>A (p.Leu1961=)	TTG	TTA		0.65	-0.61
ELP1	ENSG00000070061	NM_003640.5(ELP1):c.3876T>G (p.Thr1292=)	ACT	ACG	Familial dysautonomia (HSAN3);	0.39	-1.36
HUWE1	ENSG00000086758	NM_031407.7(HUWE1):c.12573C>G (p.Pro4191=)	CCC	CCG	History of neurodevelopmental disorder	0.33	-1.62
MYOC	ENSG00000034971	NM_000261.2(MYOC):c.366C>T (p.Gly122=)	GGC	GGT	Glaucoma 1, open angle, A (GLC1A)	0.55	-0.87
EP300	ENSG00000100393	NM_001429.4(EP300):c.3105C>T (p.Thr1035=)	ACC	ACT	Rubinstein-Taybi syndrome 2 (RSTS2);Colorectal cancer	0.8	-0.31
ARFGEF2	ENSG00000124198	NM_006420.3(ARFGEF2):c.1185C>T (p.Asp395=)	GAC	GAT		0.99	-0.01
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.9558A>G (p.Thr3186=)	ACA	ACG	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.34	-1.57
POR	ENSG00000127948	NM_000941.3(POR):c.87G>A (p.Thr29=)	ACG	ACA	Disordered steroidogenesis due to cytochrome p450 oxidoreductase deficiency (ABS1);none provided	2.96	1.57
SMC3	ENSG00000108055	NM_005445.3(SMC3):c.1680T>C (p.Tyr560=)	TAT	TAC	Cornelia de Lange syndrome 3 (CDLS3);History of neurodevelopmental disorder	1.11	0.15
GLI2	ENSG00000074047	NM_001374353.1(GLI2):c.1080G>A (p.Ser360=)	TCG	TCA	Holoprosencephaly 9 (HPE9)	3.5	1.81
DST	ENSG00000151914	NM_015548.5(DST):c.645A>T (p.Ser215=)	TCA	TCT	Neuropathy, hereditary sensory and autonomic, type VI (HSAN6);Neuropathy, hereditary sensory and autonomic, type VI (HSAN6);Epidermolysis bullosa simplex, autosomal recessive 2 (EBSB2)	1.2	0.26
MECP2	ENSG00000169057	NM_001110792.2(MECP2):c.312A>G (p.Gly104=)	GGA	GGG		0.89	-0.17
ABCA3	ENSG00000167972	NM_001089.3(ABCA3):c.2268C>T (p.Ala756=)	GCC	GCT	Surfactant metabolism dysfunction, pulmonary, 3 (SMDP3);	0.74	-0.44
MYO15A	ENSG00000091536	NM_016239.4(MYO15A):c.4623G>A (p.Thr1541=)	ACG	ACA	Deafness, autosomal recessive 3 (DFNB3)	2.96	1.57
HCFC1	ENSG00000172534	NM_005334.3(HCFC1):c.3492C>T (p.Ser1164=)	TCC	TCT	Mental retardation 3, X-linked (MRX3)	0.98	-0.03

LARGE1	ENSG00000133424	NM_004737.6(LARGE1):c.1071T>C (p.Asn357=)	AAT	AAC	Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B6 (MDDGB6)	0.99	-0.02
OPHN1	ENSG00000079482	NM_002547.3(OPHN1):c.1830C>T (p.Ser610=)	AGC	AGT		0.72	-0.48
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.1518C>A (p.Ile506=)	ATC	ATA	Qualitative or quantitative defects of dysferlin	0.44	-1.2
OBSL1	ENSG00000124006	NM_015311.3(OBSL1):c.375G>A (p.Glu125=)	GAG	GAA	Three M syndrome 2 (3M2)	0.86	-0.22
HMGCL	ENSG00000117305	NM_000191.3(HMGCL):c.594C>T (p.Tyr198=)	TAC	TAT	Deficiency of hydroxymethylglutaryl-CoA lyase (HMGCLD);Deficiency of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase	0.9	-0.15
TTN	ENSG00000155657	NM_001267550.2(TTN):c.79410G>A (p.Gly26470=)	GGG	GGA	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	1.13	0.17
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.6162C>T (p.His2054=)	CAC	CAT	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.81	-0.3
TSC2	ENSG00000103197	NM_000548.5(TSC2):c.1818C>T (p.Ile606=)	ATC	ATT	Tuberous sclerosis 2 (TSC2)	0.89	-0.17
L1CAM	ENSG00000198910	NM_001278116.2(L1CAM):c.3015C>T (p.Ile1005=)	ATC	ATT	Spastic paraplegia	0.89	-0.17
BTD	ENSG00000169814	NM_001370658.1(BTD):c.339G>A (p.Pro113=)	GAG	GAA	Biotinidase deficiency	0.86	-0.22
CPS1	ENSG00000021826	NM_001875.5(CPS1):c.186C>T (p.Gly62=)	GCT	GCT	Congenital hyperammonemia, type I;Carbamoyl-phosphate synthase I deficiency	1	0
CYP27A1	ENSG00000135929	NM_000784.4(CYP27A1):c.792G>A (p.Val264=)	GTG	GTA	Cholestanol storage disease (CTX);	0.3	-1.74
SETX	ENSG00000107290	NM_015046.7(SETX):c.2502A>G (p.Gly834=)	GGA	GGG		0.89	-0.17
ATR	ENSG00000175054	NM_001184.4(ATR):c.2688G>A (p.Leu896=)	TTG	TTA	Seckel syndrome 1 (SCKL1);	0.65	-0.61
TNNI2	ENSG00000130598	NM_003282.4(TNNI2):c.354G>A (p.Ser118=)	TCG	TCA		3.5	1.81
CHMP1A	ENSG00000131165	NM_002768.5(CHMP1A):c.210C>T (p.Asp70=)	GAC	GAT		0.99	-0.01
SPG11	ENSG00000104133	NM_025137.4(SPG11):c.7023C>T (p.Tyr2341=)	TAC	TAT	Spastic paraplegia 11, autosomal recessive (SPG11);	0.9	-0.15
ASPM	ENSG00000066279	NM_018136.5(ASPM):c.5940C>T (p.Tyr1980=)	TAC	TAT		0.9	-0.15
COQ8A	ENSG00000163050	NM_020247.5(COQ8A):c.1800C>G (p.Val600=)	GTC	GTG		1.92	0.94
OBSL1	ENSG00000124006	NM_015311.3(OBSL1):c.1599G>A (p.Thr533=)	ACG	ACA	Three M syndrome 2 (3M2)	2.96	1.57
KIF7	ENSG00000166813	NM_198525.3(KIF7):c.3738C>G (p.Pro1246=)	CCC	CCG	Acrocallosal syndrome (ACLS)	0.33	-1.62
SPG11	ENSG00000104133	NM_025137.4(SPG11):c.7197G>A (p.Lys2399=)	AAG	AAA	Spastic paraplegia 11, autosomal recessive (SPG11);	0.87	-0.2
TTN	ENSG00000155657	NM_001267550.2(TTN):c.65187G>A (p.Glu21729=)	GAG	GAA	Cardiomyopathy (CMYO)	0.86	-0.22
CPT2	ENSG00000157184	NM_000098.3(CPT2):c.84C>T (p.Gly28=)	GGC	GGT	Carnitine palmitoyltransferase II deficiency (CPT2);	0.55	-0.87
TNFRSF1A	ENSG00000067182	NM_001065.4(TNFRSF1A):c.1110C>T (p.Arg370=)	CGC	CGT	TNF receptor-associated periodic fever syndrome (TRAPS) (FPF);	0.52	-0.93
AP5Z1	ENSG00000242802	NM_014855.3(AP5Z1):c.849C>T (p.Ala283=)	GCC	GCT	Spastic paraplegia 48, autosomal recessive (SPG48);	0.74	-0.44
PNKP	ENSG00000039650	NM_007254.4(PNKP):c.624C>T (p.Ala208=)	GCC	GCT		0.74	-0.44
SCN2A	ENSG00000136531	NM_001040142.2(SCN2A):c.2955C>T (p.Ser985=)	TCC	TCT	Seizures, benign familial infantile, 3 (BFIS3);Seizures, benign familial infantile, 3 (BFIS3);Early infantile epileptic encephalopathy 11 (DEE11)	0.98	-0.03
CEP152	ENSG00000103995	NM_001194998.2(CEP152):c.1866G>T (p.Leu622=)	CTG	CTT	Primary autosomal recessive microcephaly 9 (MCPH9); Seckel syndrome 5 (SCKL5)	0.39	-1.35
WWOX	ENSG00000186153	NM_016373.4(WWOX):c.885G>A (p.Arg295=)	AGG	AGA	Epileptic encephalopathy, early infantile, 1 (DEE1);Spinocerebellar ataxia, autosomal recessive 12 (SCAR12)	1.1	0.14
POMGNT2	ENSG00000144647	NM_032806.6(POMGNT2):c.450A>G (p.Pro150=)	CCA	CCG	Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type a, 8 (MDDGA8)	0.33	-1.61

BTD	ENSG00000169814	NM_001370658.1(BTD):c.585C>T (p.Leu195=)	CCC	CCT	Biotinidase deficiency;	1.02	0.02
ACTA1	ENSG00000143632	NM_001100.3(ACTA1):c.1125A>G (p.Lys375=)	AAA	AAG	Nemaline myopathy 3 (NEM3);Familial restrictive cardiomyopathy (RCM);Congenital myopathy with fiber type disproportion (CFTD)	1.15	0.2
LDLR	ENSG00000130164	NM_000527.5(LDLR):c.1194C>T (p.Ile398=)	ATC	ATT	Familial hypercholesterolemia 1 (FHCL1);Familial hypercholesterolemia (FH);Autosomal dominant familial hypercholesterolemia	0.89	-0.17
VCAN	ENSG00000038427	NM_004385.5(VCAN):c.927T>C (p.Thr309=)	ACT	ACC	Wagner syndrome (WGN1);Vitreoretinopathy	1.24	0.31
KMT2D	ENSG00000167548	NM_003482.3(KMT2D):c.6807C>T (p.Ser2269=)	TCC	TCT	Kabuki syndrome 1 (KABUK1); Kabuki syndrome	0.98	-0.03
FLNA	ENSG00000196924	NM_001110556.2(FLNA):c.2613C>T (p.Asp871=)	GAC	GAT	Periventricular nodular heterotopia 1 (PVNH1);Melnick-Needles syndrome (MNS);Oto-palato-digital syndrome, type II (OPD2);Frontometaphyseal dysplasia (FMD1)	0.99	-0.01
LDLR	ENSG00000130164	NM_000527.5(LDLR):c.1920C>T (p.Asn640=)	AAC	AAT	Familial hypercholesterolemia 1 (FHCL1); Familial hypercholesterolemia (FH)	1.01	0.02
MEFV	ENSG00000103313	NM_000243.2(MEFV):c.2118G>A (p.Pro706=)	CCG	CCA	Familial Mediterranean fever (FMF); none provided	3.05	1.61
DLG3	ENSG00000082458	NM_021120.4(DLG3):c.429C>T (p.Phe143=)	TTC	TTT	History of neurodevelopmental disorder;	0.98	-0.02
NKX2-5	ENSG00000183072	NM_004387.4(NKX2-5):c.861C>T (p.Ala287=)	GCC	GCT	Atrial septal defect 7 with or without atrioventricular conduction defects (ASD7);Cardiovascular phenotype	0.74	-0.44
EVC2	ENSG00000173040	NM_147127.5(EVC2):c.18C>T (p.Ser6=)	TCC	TCT	Ellis-van Creveld syndrome (EVC);Curry-Hall syndrome (WAD)	0.98	-0.03
ATP1A3	ENSG00000105409	NM_152296.5(ATP1A3):c.1323G>A (p.Ala441=)	GCG	GCA	Alternating hemiplegia of childhood 2 (AHC2);Dystonia 12 (DYT12);	2.88	1.52
LDLR	ENSG00000130164	NM_000527.5(LDLR):c.90C>T (p.Asn30=)	AAC	AAT	Familial hypercholesterolemia 1 (FHCL1); Familial hypercholesterolemia (FH)	1.01	0.02
ROR2	ENSG00000169071	NM_004560.4(ROR2):c.75G>A (p.Leu25=)	CTG	CTA	Robinow syndrome, autosomal recessive (RRS1); Brachydactyly type B1 (BDB1);	0.21	-2.27
SLC2A1	ENSG00000117394	NM_006516.3(SLC2A1):c.987G>A (p.Glu329=)	GAG	GAA	GLUT1 deficiency syndrome 1, autosomal recessive;GLUT1 deficiency syndrome 1 (GLUT1DS1);Dystonia 9 (DYT9)	0.86	-0.22
PCSK9	ENSG00000169174	NM_174936.3(PCSK9):c.705C>T (p.Ser235=)	AGC	AGT	Familial hypercholesterolemia 1 (FHCL1);Hypobetalipoproteinemia; Familial hypercholesterolemia 3 (FHCL3)	0.72	-0.48
SMARCA4	ENSG00000127616	NM_001128849.2(SMARCA4):c.1791T>G (p.Pro597=)	CCT	CCG	Rhabdoid tumor predisposition syndrome 2 (RTPS2);Coffin-Siris syndrome;Hereditary cancer-predisposing syndrome	0.32	-1.64
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.4515G>A (p.Ser1505=)	TCG	TCA	Autosomal dominant cerebellar ataxia;Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);Charcot-Marie-Tooth disease	3.5	1.81
LMNA	ENSG00000160789	NM_170707.4(LMNA):c.1851C>T (p.Ala617=)	GCC	GCT	Charcot-Marie-Tooth disease, type 2;Cardiomyopathy (CMYO);Charcot-Marie-Tooth disease	0.74	-0.44
NDUFAF5	ENSG00000101247	NM_024120.5(NDUFAF5):c.183G>C (p.Arg61=)	CGG	CGC	Mitochondrial complex 1 deficiency, nuclear type 16;Mitochondrial complex I deficiency	0.82	-0.29
GCK	ENSG00000106633	NM_000162.5(GCK):c.666C>T (p.Val222=)	GTC	GTT	Maturity-onset diabetes of the young, type 2 (MODY2); Hyperinsulinism due to glucokinase deficiency (HHF3);Transient Neonatal Diabetes, Recessive;Permanent neonatal diabetes mellitus (PNDM)	0.88	-0.19
PCNT	ENSG00000160299	NM_006031.6(PCNT):c.6933C>T (p.Val2311=)	GTC	GTT	Microcephalic osteodysplastic primordial dwarfism type II (MOPD2)	0.88	-0.19
APOB	ENSG00000084674	NM_000384.3(APOB):c.10131G>A (p.Leu3377=)	CTG	CTA	Familial hypercholesterolemia 1 (FHCL1); Familial hypercholesterolemia (FH);Familial hypercholesterolemia 2 (FCHL2);Hypobetalipoproteinemia, familial, 1 (FHBL1);Familial hypercholesterolemia 2 (FCHL2);Hypobetalipoproteinemia, familial, 1 (FHBL1)	0.21	-2.27
NF2	ENSG00000186575	NM_000268.4(NF2):c.1386C>T (p.Arg462=)	CGC	CGT	Neurofibromatosis, type 2 (NF2); Hereditary cancer-predisposing syndrome	0.52	-0.93

KNL1	ENSG00000137812	NM_144508.5(KNL1):c.5271C>T (p.Cys1757=)	TGC	TGT	Primary autosomal recessive microcephaly 4 (MCPH4)	0.97	-0.05
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.24C>G (p.Ala8=)	GCC	GCG	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Aortic aneurysm, familial thoracic 7 (AAT7);Cardiovascular phenotype	0.23	-2.11
GRIN2B	ENSG00000273079	NM_000834.4(GRIN2B):c.3747C>T (p.Gly1249=)	GGC	GGT	Mental retardation, autosomal dominant 6 (MRD6);Epileptic encephalopathy, early infantile, 27 (DEE27);History of neurodevelopmental disorder	0.55	-0.87
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.9138G>T (p.Ser3046=)	TCG	TCT	Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);History of neurodevelopmental disorder	4.18	2.06
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.7758C>T (p.Ala2586=)	GCC	GCT	Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);History of neurodevelopmental disorder	0.74	-0.44
CNTNAP2	ENSG00000174469	NM_014141.6(CNTNAP2):c.3675G>A (p.Ser1225=)	TCG	TCA	Pitt-Hopkins-like syndrome 1 (PTHSL1);History of neurodevelopmental disorder	3.5	1.81
NKX2-5	ENSG00000183072	NM_004387.4(NKX2-5):c.114G>A (p.Glu38=)	GAG	GAA	Atrial septal defect 7 with or without atrioventricular conduction defects (ASD7);Cardiovascular phenotype	0.86	-0.22
PDGFRA	ENSG00000134853	NM_006206.6(PDGFRA):c.276G>A (p.Ala92=)	GCG	GCA	Gastrointestinal stromal tumor (GIST);Idiopathic hypereosinophilic syndrome (HES);Hereditary cancer-predisposing syndrome	2.88	1.52
PDGFRA	ENSG00000134853	NM_006206.6(PDGFRA):c.801A>G (p.Pro267=)	CCA	CCG	Gastrointestinal stromal tumor (GIST);Idiopathic hypereosinophilic syndrome (HES);Hereditary cancer-predisposing syndrome	0.33	-1.61
MAOA	ENSG00000189221	NM_000240.3(MAOA):c.825G>A (p.Pro275=)	CCG	CCA	Brunner syndrome (BRNRS);History of neurodevelopmental disorder	3.05	1.61
CEP290	ENSG00000198707	NM_025114.4(CEP290):c.3955T>C (p.Leu1319=)	TTG	CTG	Joubert syndrome (JBTS);Meckel-Gruber syndrome;Nephronophthisis;Leber congenital amaurosis (LCA)	2.67	1.42
ACADVL	ENSG00000072778	NM_000018.4(ACADVL):c.1473A>G (p.Leu491=)	CTA	CTG	Very long chain acyl-CoA dehydrogenase deficiency (VLCAD);	4.81	2.27
ATL1	ENSG00000198513	NM_001127713.1(ATL1):c.1173C>T (p.His391=)	CAC	CAT	Hereditary spastic paraplegia 3A (SPG3A)	0.81	-0.3
PRICKLE1	ENSG00000139174	NM_153026.3(PRICKLE1):c.114G>A (p.Pro38=)	CCG	CCA	Seizures;Progressive myoclonus epilepsy with ataxia (EPM1B)	3.05	1.61
SCN2A	ENSG00000136531	NM_001040142.2(SCN2A):c.897A>G (p.Ser299=)	TCA	TCG	History of neurodevelopmental disorder;Seizures, benign familial infantile, 3 (BFIS3);Early infantile epileptic encephalopathy 11 (DEE11)	0.29	-1.81
MEFV	ENSG00000103313	NM_000243.2(MEFV):c.1467G>A (p.Gln489=)	CAG	CAA	Familial Mediterranean fever (FMF); none provided	0.4	-1.32
FBN2	ENSG00000138829	NM_001999.4(FBN2):c.8247A>G (p.Thr2749=)	ACA	ACG	Congenital contractural arachnodactyly (CCA);Cardiovascular phenotype;none provided	0.34	-1.57
SMARCA4	ENSG00000127616	NM_001128849.2(SMARCA4):c.2460C>T (p.Tyr820=)	TAC	TAT	Rhabdoid tumor predisposition syndrome 2 (RTPS2);Hereditary cancer-predisposing syndrome;Coffin-Siris syndrome	0.9	-0.15
GRIN1	ENSG00000176884	NM_007327.4(GRIN1):c.768G>C (p.Gly256=)	GGG	GGC	History of neurodevelopmental disorder;Neurodevelopmental disorder with or without hyperkinetic movements and seizures, autosomal dominant (NDHMSD)	1.29	0.37
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.4275G>T (p.Arg1425=)	CGG	CGT	History of neurodevelopmental disorder;Pitt-Hopkins-like syndrome 2 (PTHSL2)	0.43	-1.22
SLC2A1	ENSG00000117394	NM_006516.3(SLC2A1):c.777C>T (p.Ile259=)	ATC	ATT	GLUT1 deficiency syndrome 1 (GLUT1DS1); Dystonia 9 (DYT9); GLUT1 deficiency syndrome 1, autosomal recessive	0.89	-0.17
GRIN1	ENSG00000176884	NM_007327.4(GRIN1):c.1005T>C (p.Thr335=)	ACT	ACC	History of neurodevelopmental disorder;Neurodevelopmental disorder with or without hyperkinetic movements and seizures, autosomal dominant (NDHMSD)	1.24	0.31
SCN2A	ENSG00000136531	NM_001040142.2(SCN2A):c.24G>A (p.Pro8=)	CCG	CCA	Seizures, benign familial infantile, 3 (BFIS3);Seizures, benign familial infantile, 3 (BFIS3);Early infantile epileptic encephalopathy 11 (DEE11);History of neurodevelopmental disorder	3.05	1.61

GRIN2B	ENSG00000273079	NM_000834.4(GRIN2B):c.1851C>T (p.Ser617=)	TCC	TCT	Mental retardation, autosomal dominant 6 (MRD6);Epileptic encephalopathy, early infantile, 27 (DEE27);Mental retardation, autosomal dominant 6 (MRD6);History of neurodevelopmental disorder	0.98	-0.03
LDLR	ENSG00000130164	NM_000527.4(LDLR):c.2358C>T (p.Ser786=)	AGC	AGT	Familial hypercholesterolemia 1 (FHCL1);Familial hypercholesterolemia (FH);	0.72	-0.48
FBN2	ENSG00000138829	NM_001999.4(FBN2):c.5496C>T (p.Arg1832=)	CGC	CGT	Congenital contractural arachnodactyly (CCA);Cardiovascular phenotype;Connective tissue disease;none provided	0.52	-0.93
LMNA	ENSG00000160789	NM_170707.4(LMNA):c.1566C>T (p.Cys522=)	TGC	TGT	Charcot-Marie-Tooth disease, type 2;Cardiovascular phenotype;Dilated cardiomyopathy 1A (CMD1A);Hutchinson-Gilford syndrome (HGPS);Emery-Dreifuss muscular dystrophy (EDMD);Familial partial lipodystrophy 2 (FPLD2);Limb-Girdle Muscular Dystrophy, Recessive;Mandibuloacral dysplasia with type A lipodystrophy (MADA);Lipoatrophy with Diabetes, Hepatic Steatosis, Hypertrophic Cardiomyopathy, and Leukomelanodermic Papules;Congenital muscular dystrophy, LMNA-related (MDCL);Lethal tight skin contracture syndrome;Cardiomyopathy (CMYO);Charcot-Marie-Tooth disease type 2B1 (CMT2B1);Emery-Dreifuss muscular dystrophy 2, autosomal dominant (EDMD2);Charcot-Marie-Tooth disease;	0.97	-0.05
CDKL5	ENSG00000008086	NM_001323289.2(CDKL5):c.93A>G (p.Arg31=)	AGA	AGG	Early infantile epileptic encephalopathy 2 (DEE2);Angelman syndrome-like;History of neurodevelopmental disorder;	0.91	-0.14
KIF1A	ENSG00000130294	NM_004321.7(KIF1A):c.2655G>C (p.Val885=)	GTG	GTC	Spastic paraplegia 30, autosomal recessive (SPG30);Hereditary sensory and autonomic neuropathy type IIC (HSN2C);Intellectual disability, autosomal dominant 9 (NESCAVS);History of neurodevelopmental disorder;Spastic paraplegia 30, autosomal recessive (SPG30)	0.52	-0.94
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.2751G>T (p.Val917=)	GTG	GTT	Collagen VI-related myopathy (COL6-RM);Myosclerosis, autosomal recessive; Bethlem myopathy 1 (BTHLM1)	0.46	-1.13
SACS	ENSG00000151835	NM_014363.6(SACS):c.8022T>C (p.Phe2674=)	TTT	TTC	Spastic paraplegia;Charlevoix-Saguenay spastic ataxia (SACS)	1.02	0.02
COL2A1	ENSG00000139219	NM_001844.5(COL2A1):c.4116C>T (p.Asn1372=)	AAC	AAT	Type II Collagenopathies;Stickler syndrome type 1 (STL1)	1.01	0.02
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.4377C>T (p.Ser1459=)	TCC	TCT	Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Spinocerebellar ataxia, autosomal recessive 8 (SCAR8)	0.98	-0.03
MMP13	ENSG00000137745	NM_002427.4(MMP13):c.438C>T (p.Ser146=)	TCC	TCT	Metaphyseal anadysplasia;Spondyloepimetaphyseal dysplasia, Missouri type (SEMDM)	0.98	-0.03
ACTA1	ENSG00000143632	NM_001100.4(ACTA1):c.786G>C (p.Thr262=)	ACG	ACC	Nemaline myopathy 3 (NEM3);Congenital myopathy with fiber type disproportion (CFTD);Familial restrictive cardiomyopathy (RCM)	3.18	1.67
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.25575G>A (p.Ser8525=)	TCG	TCA	Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Spinocerebellar ataxia, autosomal recessive 8 (SCAR8)	3.5	1.81
CASK	ENSG00000147044	NM_001367721.1(CASK):c.891A>G (p.Lys297=)	AAA	AAG	History of neurodevelopmental disorder; Mental retardation, CASK-related, X-linked	1.15	0.2
PCDH19	ENSG00000165194	NM_001184880.2(PCDH19):c.2796C>T (p.Asn932=)	AAC	AAT	Early infantile epileptic encephalopathy 9 (DEE9); History of neurodevelopmental disorder	1.01	0.02
SPTAN1	ENSG00000197694	NM_001130438.3(SPTAN1):c.6234C>T (p.Ala2078=)	GCC	GCT	Early infantile epileptic encephalopathy with suppression bursts (EIEE);Generalized tonic-clonic seizures;Seizures	0.74	-0.44
COL4A3	ENSG00000169031	NM_000091.4(COL4A3):c.3825C>T (p.His1275=)	CAC	CAT	Alport syndrome;Alport syndrome 3, autosomal dominant (ATS3)	0.81	-0.3
ABCC8	ENSG00000006071	NM_000352.6(ABCC8):c.2610C>T (p.Ala870=)	GCC	GCT	Transient neonatal diabetes mellitus 2 (TNDM2);Permanent neonatal diabetes mellitus (PNDM);Hyperinsulinemic hypoglycemia, familial, 1 (HHF1);Hereditary hyperinsulinism	0.74	-0.44
IFT122	ENSG00000163913	NM_052989.3(IFT122):c.3129C>T (p.Arg1043=)	CGC	CGT	Cranioectodermal dysplasia 1 (CED1)	0.52	-0.93

PNPLA6	ENSG00000032444	NM_001166114.2(PNPLA6):c.3495C>T (p.Ser1165=)	TCC	TCT	Hereditary spastic paraplegia 39 (SPG39);	0.98	-0.03
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.2853C>T (p.Thr951=)	ACC	ACT	Autosomal recessive polycystic kidney disease (ARPKD);	0.8	-0.31
BTD	ENSG00000169814	NM_001370658.1(BTD):c.1041C>T (p.Gly347=)	AAC	AAT	Biotinidase deficiency;	1.01	0.02
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.1002C>T (p.His334=)	CAC	CAT	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD);	0.81	-0.3
SYNE2	ENSG00000054654	NM_182914.2(SYNE2):c.10392C>T (p.Cys3464=)	TGC	TGT	Emery-Dreifuss muscular dystrophy 5, autosomal dominant (EDMD5)	0.97	-0.05
ALDOB	ENSG00000136872	NM_000035.4(ALDOB):c.759C>T (p.Thr253=)	ACC	ACT	Hereditary fructosuria (HFI);	0.8	-0.31
KIF7	ENSG00000166813	NM_198525.3(KIF7):c.516G>A (p.Glu172=)	GAG	GAA	Acrocallosal syndrome (ACLS)	0.86	-0.22
MEFV	ENSG00000103313	NM_000243.3(MEFV):c.585G>A	GAG	GAA	Familial Mediterranean fever (FMF);	0.86	-0.22
CHD7	ENSG00000171316	NM_017780.4(CHD7):c.7590A>G (p.Lys2530=)	AAA	AAG	CHARGE association (CHARGE); History of neurodevelopmental disorder	1.15	0.2
ASPM	ENSG00000066279	NM_018136.5(ASPM):c.7554A>G (p.Arg2518=)	AGA	AGG	Primary autosomal recessive microcephaly 5 (MCPH5);	0.91	-0.14
MEFV	ENSG00000103313	NM_000243.2(MEFV):c.297C>T (p.Asn99=)	AAC	AAT	Familial Mediterranean fever (FMF); Familial mediterranean fever, autosomal dominant (DFMF)	1.01	0.02
ATM	ENSG00000149311	NM_000051.3(ATM):c.4473C>T (p.Phe1491=)	TTC	TTT	Ataxia-telangiectasia syndrome (AT);Hereditary cancer-predisposing syndrome;	0.98	-0.02
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.13440C>T (p.Ser4480=)	TCC	TCT	Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);Autosomal dominant cerebellar ataxia;Charcot-Marie-Tooth disease	0.98	-0.03
DSC2	ENSG00000134755	NM_024422.6(DSC2):c.1788G>A (p.Ala596=)	GCG	GCA	Arrhythmogenic right ventricular cardiomyopathy, type 11 (ARVD11); Cardiomyopathy (CMYO)	2.88	1.52
MUTYH	ENSG00000132781	NM_001048174.2(MUTYH):c.228C>T (p.Tyr76=)	TAC	TAT	MYH-associated polyposis (FAP2);Hereditary cancer-predisposing syndrome; none provided	0.9	-0.15
ATM	ENSG00000149311	NM_000051.3(ATM):c.162T>C (p.Tyr54=)	TAT	TAC	Ataxia-telangiectasia syndrome (AT);Hereditary cancer-predisposing syndrome; Familial cancer of breast;none provided	1.11	0.15
ATM	ENSG00000149311	NM_000051.3(ATM):c.609C>T (p.Asp203=)	GAC	GAT	Ataxia-telangiectasia syndrome (AT);Hereditary cancer-predisposing syndrome; none provided	0.99	-0.01
PALB2	ENSG00000083093	NM_024675.3(PALB2):c.1194G>A (p.Val398=)	GTG	GTA	Familial cancer of breast;Hereditary cancer-predisposing syndrome; Fanconi anemia, complementation group N (FANCN); Breast and/or ovarian cancer;none provided	0.3	-1.74
SMC3	ENSG00000108055	NM_005445.3(SMC3):c.255A>G (p.Ser85=)	TCA	TCG	Cornelia de Lange syndrome 3 (CDLS3); History of neurodevelopmental disorder	0.29	-1.81
EFEMP2	ENSG00000172638	NM_016938.5(EFEMP2):c.1188C>T (p.Ser396=)	AGC	AGT	Autosomal recessive cutis laxa type 1B (ARCL1B);	0.72	-0.48
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.2121C>A (p.Gly707=)	GGC	GGA	Neuromuscular disease, congenital, with uniform type 1 fiber (CNMDU1);Central core myopathy (CCD);Malignant hyperthermia, susceptibility to, 1 (MHS1);Minicore myopathy with external ophthalmoplegia;RYR1-Related Disorders	0.87	-0.2
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.267G>A (p.Pro89=)	CCG	CCA	Hereditary breast and ovarian cancer syndrome (HBOC); Hereditary cancer-predisposing syndrome;Breast-ovarian cancer, familial 2 (BROVCA2);Fanconi anemia (FA);	3.05	1.61
NEK1	ENSG00000137601	NM_012224.3(NEK1):c.3327G>A (p.Leu1109=)	CTG	CTA	Short rib-polydactyly syndrome, Majewski type (SRTD6)	0.21	-2.27
CDHR1	ENSG00000148600	NM_033100.4(CDHR1):c.1461G>A (p.Gly487=)	GGG	GGA	Cone-rod dystrophy 15 (CORD15);	1.13	0.17
CDHR1	ENSG00000148600	NM_033100.4(CDHR1):c.1071C>T (p.Ser357=)	AGC	AGT	Cone-rod dystrophy 15 (CORD15)	0.72	-0.48
ADGRG1	ENSG00000205336	NM_201525.4(ADGRG1):c.1983T>C (p.Gly661=)	GGT	GGC		1.82	0.87
OXCT1	ENSG00000083720	NM_000436.4(OXCT1):c.1491C>T (p.Asp497=)	GAC	GAT	Succinyl-CoA acetoacetate transferase deficiency (SCOTD)	0.99	-0.01
ABCA3	ENSG00000167972	NM_001089.3(ABCA3):c.2340C>T (p.His780=)	CAC	CAT	Surfactant metabolism dysfunction, pulmonary, 3 (SMDP3)	0.81	-0.3

TMEM237	ENSG00000155755	NM_001044385.3(TMEM237):c.1065C>G (p.Leu355=)	CTC	CTG	Joubert syndrome 14 (JBTS14)	2.02	1.02
BCKDHB	ENSG00000083123	NM_183050.4(BCKDHB):c.51A>C (p.Ala17=)	GCA	GCC	Maple syrup urine disease (MSUD);	1.5	0.59
ASPM	ENSG00000066279	NM_018136.5(ASPM):c.6702A>G (p.Gln2234=)	CAA	CAG		2.49	1.32
PINK1	ENSG00000158828	NM_032409.3(PINK1):c.858G>A (p.Pro286=)	CCG	CCA	Parkinson disease 6, autosomal recessive early-onset (PARK6)	3.05	1.61
TCIRG1	ENSG00000110719	NM_006019.4(TCIRG1):c.1800C>T (p.Ala600=)	GCC	GCT	Autosomal recessive osteopetrosis 1;	0.74	-0.44
FKBP10	ENSG00000141756	NM_021939.3(FKBP10):c.21C>T (p.Pro7=)	CCC	CCT	Osteogenesis imperfecta, type XI (OI11)	1.02	0.02
SPG11	ENSG00000104133	NM_025137.4(SPG11):c.6258G>T (p.Leu2086=)	CTG	CTT	Spastic paraplegia 11, autosomal recessive (SPG11);	0.39	-1.35
BARD1	ENSG00000138376	NM_000465.4(BARD1):c.144G>A (p.Leu48=)	CTG	CTA	Hereditary cancer-predisposing syndrome; Familial cancer of breast	0.21	-2.27
NEB	ENSG00000183091	NM_001271208.2(NEB):c.25143A>G (p.Gln8381=)	CAA	CAG	Nemaline myopathy 2 (NEM2)	2.49	1.32
CDKN2A	ENSG00000147889	NM_000077.4(CDKN2A):c.318G>A (p.Val106=)	GTG	GTA	Hereditary cancer-predisposing syndrome; Melanoma-pancreatic cancer syndrome;Hereditary melanoma	0.3	-1.74
LDLR	ENSG00000130164	NM_000527.5(LDLR):c.1836C>T (p.Ala612=)	GCC	GCT	Familial hypercholesterolemia 1 (FHCL1); Familial hypercholesterolemia (FH)	0.74	-0.44
DBT	ENSG00000137992	NM_001918.4(DBT):c.327C>T (p.Thr109=)	ACC	ACT	Maple syrup urine disease (MSUD);	0.8	-0.31
PEX1	ENSG00000127980	NM_000466.3(PEX1):c.3216T>C (p.Ser1072=)	AGT	AGC	Peroxisome biogenesis disorder 1A (Zellweger) (PBD1A);Zellweger syndrome (ZS)	1.4	0.48
NPC1	ENSG00000141458	NM_000271.5(NPC1):c.3561G>T (p.Ala1187=)	GCG	GCT	Niemann-Pick disease type C1 (NPC1);	3.18	1.67
CFTR	ENSG00000001626	NM_000492.3(CFTR):c.2559T>C (p.Ile853=)	ATT	ATC	Cystic fibrosis (CF); Inborn genetic diseases;none provided	1.13	0.17
POLG	ENSG00000140521	NM_002693.2(POLG):c.2724C>T (p.Ala908=)	GCC	GCT	Progressive sclerosing poliodystrophy (MTDPS4A);POLG-Related Spectrum Disorders	0.74	-0.44
POMT1	ENSG00000130714	NM_001077365.2(POMT1):c.2178G>A (p.Ter726=)	TAG	TAA	Limb-girdle muscular dystrophy-dystroglycanopathy, type C1 (MDDGC1);Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B1 (MDDGB1);Walker-Warburg congenital muscular dystrophy (MDDGA1);Limb-girdle muscular dystrophy-dystroglycanopathy, type C1 (MDDGC1);Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type A, 1 (MDDGA1)	1.26	0.33
MVK	ENSG00000110921	NM_000431.4(MVK):c.924C>T (p.Leu308=)	CTC	CTT	Mevalonic aciduria (MEVA);Porokeratosis 3, disseminated superficial actinic type (DSAP1);Hyperimmunoglobulin D with periodic fever (HIDS);Mevalonic aciduria (MEVA);Hyperimmunoglobulin D with periodic fever (HIDS);none provided	0.8	-0.33
BLM	ENSG00000197299	NM_000057.4(BLM):c.3879A>G (p.Glu1293=)	GAA	GAG	Bloom syndrome (BLM);Hereditary cancer-predisposing syndrome;	1.16	0.22
LARGE1	ENSG00000133424	NM_004737.6(LARGE1):c.1599C>T (p.Ile533=)	ATC	ATT	Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B6 (MDDGB6);Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, type A6 (MDDGA6)	0.89	-0.17
MEFV	ENSG00000103313	NM_000243.2(MEFV):c.2292G>T (p.Gly764=)	GGG	GGT	Familial Mediterranean fever (FMF);	0.71	-0.5
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.5529G>A (p.Ser1843=)	TCG	TCA	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Lissencephaly, Recessive;Cardiovascular phenotype;Aortic aneurysm, familial thoracic 4 (AAT4);	3.5	1.81
TP53	ENSG00000141510	NM_000546.6(TP53):c.66A>G (p.Leu22=)	CTA	CTG	Hereditary cancer-predisposing syndrome;Li-Fraumeni syndrome (LFS); Squamous cell carcinoma of the head and neck (HNSCC);	4.81	2.27
PALB2	ENSG00000083093	NM_024675.4(PALB2):c.2379C>T (p.Gly793=)	GGC	GGT	Hereditary cancer-predisposing syndrome;Familial cancer of breast; Fanconi anemia, complementation group N (FANCN);	0.55	-0.87

HBB	ENSG00000244734	NM_000518.5(HBB):c.274C>T (p.Leu92=)	CTG	TTG	Fetal hemoglobin quantitative trait locus 1 (HBFQTL1);Hemoglobin E;beta Thalassemia (BTHAL);Hb SS disease (SCD)	0.37	-1.42
AGL	ENSG00000162688	NM_000642.3(AGL):c.3231G>A (p.Lys1077=)	AAG	AAA	Glycogen storage disease type III (GSD3);	0.87	-0.2
BIN1	ENSG00000136717	NM_139343.3(BIN1):c.384G>A (p.Thr128=)	ACG	ACA	Myopathy, centronuclear, 2 (CNM2);	2.96	1.57
PCDH15	ENSG00000150275	NM_033056.4(PCDH15):c.2619A>G (p.Glu873=)	GAA	GAG	Usher syndrome type 1F (USH1F)	1.16	0.22
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.2829G>A (p.Ala943=)	GCG	GCA	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	2.88	1.52
HLCS	ENSG00000159267	NM_001352514.2(HLCS):c.1695C>T (p.Leu565=)	CTC	CTT	Holocarboxylase synthetase deficiency;	0.8	-0.33
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.2919G>A (p.Pro973=)	CCG	CCA	Aortic aneurysm, familial thoracic 7 (AAT7);	3.05	1.61
CACNA1C	ENSG00000151067	NM_000719.7(CACNA1C):c.2391G>A (p.Gly797=)	GGG	GGA	Long QT syndrome (LQTS)	1.13	0.17
NEK1	ENSG00000137601	NM_001199397.3(NEK1):c.1617G>A (p.Gln539=)	CAG	CAA	Short rib-polydactyly syndrome, Majewski type (SRTD6);none provided	0.4	-1.32
DAG1	ENSG00000173402	NM_004393.6(DAG1):c.2082C>T (p.Asn694=)	AAC	AAT	Limb-girdle muscular dystrophy-dystroglycanopathy, type C9 (MDDGC9);Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type a, 9 (MDDGA9)	1.01	0.02
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.2463C>T (p.Pro821=)	CCC	CCT	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD);	1.02	0.02
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.10800G>A (p.Leu3600=)	TTG	TTA	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	0.65	-0.61
PNPLA6	ENSG00000032444	NM_001166114.2(PNPLA6):c.3549T>C (p.Val1183=)	GTT	GTC	Hereditary spastic paraplegia 39 (SPG39);	1.14	0.19
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.3396C>T (p.Ser1132=)	AGC	AGT	Wilson disease (WND);	0.72	-0.48
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.2799G>A (p.Val933=)	GTG	GTA	Aortic aneurysm, familial thoracic 7 (AAT7);Cardiovascular phenotype	0.3	-1.74
DICER1	ENSG00000100697	NM_177438.2(DICER1):c.897G>A (p.Ser299=)	TCG	TCA	DICER1-related pleuropulmonary blastoma cancer predisposition syndrome (PPBFTDS);Hereditary cancer-predisposing syndrome	3.5	1.81
BLM	ENSG00000197299	NM_000057.4(BLM):c.3828G>A (p.Ala1276=)	GCG	GCA	Bloom syndrome (BLM);Hereditary cancer-predisposing syndrome	2.88	1.52
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.3105C>T (p.Gly1035=)	GGC	GGT	Wilson disease (WND);	0.55	-0.87
BLM	ENSG00000197299	NM_000057.4(BLM):c.4113G>A (p.Thr1371=)	ACG	ACA	Bloom syndrome (BLM);Hereditary cancer-predisposing syndrome	2.96	1.57
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.3588C>T (p.Asp1196=)	GAC	GAT	Wilson disease (WND);	0.99	-0.01
PRKN	ENSG00000185345	NM_004562.3(PRKN):c.919C>T (p.Leu307=)	CTG	TTG	Parkinson disease 2 (PARK2)	0.37	-1.42
ALPL	ENSG00000162551	NM_000478.6(ALPL):c.612C>T (p.Ile204=)	ATC	ATT	Hypophosphatasia	0.89	-0.17
ATP1A3	ENSG00000105409	NM_152296.5(ATP1A3):c.2226C>T (p.Asp742=)	GAC	GAT	Dystonia 12 (DYT12)	0.99	-0.01
TCN2	ENSG00000185339	NM_000355.4(TCN2):c.921A>C (p.Pro307=)	CCA	CCC	Transcolabamin II deficiency;	1	0.01
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.1779C>T (p.Asp593=)	GAC	GAT	Collagen VI-related myopathy (COL6-RM)	0.99	-0.01
DNMT1	ENSG00000130816	NM_001130823.3(DNMT1):c.2667C>T (p.Tyr889=)	TAC	TAT	Hereditary sensory neuropathy type IE (HSN1E);none provided	0.9	-0.15
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.1602C>T (p.Tyr534=)	TAC	TAT	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD);	0.9	-0.15
SPART	ENSG00000133104	NM_015087.5(SPART):c.360A>G (p.Lys120=)	AAA	AAG	Troyer syndrome (SPG20);	1.15	0.2
CACNA1A	ENSG00000141837	NM_001127222.2(CACNA1A):c.5259C>T (p.Thr1753=)	ACC	ACT		0.8	-0.31
ITGA7	ENSG00000135424	NM_002206.3(ITGA7):c.1317C>T (p.Phe439=)	TTC	TTT	Muscular dystrophy, congenital, due to integrin alpha-7 deficiency	0.98	-0.02

LYST	ENSG00000143669	NM_001301365.1(LYST):c.7368T>C (p.Asn2456=)	AAT	AAC	Chédiak-Higashi syndrome (CHS);	0.99	-0.02
AGL	ENSG00000162688	NM_000642.3(AGL):c.1908A>G (p.Ser636=)	TCA	TCG	Glycogen storage disease type III (GSD3);	0.29	-1.81
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.1149C>T (p.Thr383=)	ACC	ACT	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS);	0.8	-0.31
AP4E1	ENSG00000081014	NM_007347.5(AP4E1):c.258T>C (p.Tyr86=)	TAT	TAC	Spastic paraplegia	1.11	0.15
LCA5	ENSG00000135338	NM_001122769.3(LCA5):c.1215T>G (p.Val405=)	GTT	GTG	Leber congenital amaurosis (LCA)	2.18	1.13
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.2301C>T (p.His767=)	CAC	CAT	Bethlem myopathy 1 (BTHLM1)	0.81	-0.3
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.3786C>T (p.Val1262=)	GTC	GTT	Wilson disease (WND)	0.88	-0.19
NSD1	ENSG00000165671	NM_022455.4(NSD1):c.3150C>T (p.Thr1050=)	ACC	ACT	History of neurodevelopmental disorder	0.8	-0.31
ARHGEF9	ENSG00000131089	NM_001353921.2(ARHGEF9):c.372C>T (p.His124=)	CAC	CAT	Early infantile epileptic encephalopathy 8 (DEE8)	0.81	-0.3
PCCA	ENSG00000175198	NM_000282.4(PCCA):c.1236A>G (p.Pro412=)	CCA	CCG	Propionic acidemia (PROP);	0.33	-1.61
EVC2	ENSG00000173040	NM_147127.5(EVC2):c.2304G>C (p.Val768=)	GTG	GTC	Ellis-van Creveld syndrome (EVC);Curry-Hall syndrome (WAD)	0.52	-0.94
SMS	ENSG00000102172	NM_004595.5(SMS):c.978G>A (p.Ser326=)	TCG	TCA	History of neurodevelopmental disorder	3.5	1.81
SLC22A5	ENSG00000197375	NM_003060.4(SLC22A5):c.1377A>G (p.Arg459=)	AGA	AGG	Renal carnitine transport defect (CDSP);	0.91	-0.14
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.9576C>T (p.Ser3192=)	TCC	TCT	Autosomal recessive polycystic kidney disease (ARPKD)	0.98	-0.03
PLCB1	ENSG00000182621	NM_015192.4(PLCB1):c.627A>G (p.Pro209=)	CCA	CCG	Early infantile epileptic encephalopathy 12 (DEE12);Seizures	0.33	-1.61
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.3324C>T (p.Asn1108=)	AAC	AAT	Wilson disease (WND);	1.01	0.02
ASS1	ENSG00000130707	NM_054012.4(ASS1):c.333C>T (p.Ala111=)	GCC	GCT	Citrullinemia type I (CTNL1);	0.74	-0.44
FLNA	ENSG00000196924	NM_001110556.2(FLNA):c.6993C>T (p.Asp2331=)	GAC	GAT	Periventricular nodular heterotopia 1 (PVNH1);Melnick-Needles syndrome (MNS);Oto-palato-digital syndrome, type II (OPD2);Frontometaphyseal dysplasia (FMD1)	0.99	-0.01
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.2442T>C (p.Thr814=)	ACT	ACC	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD);	1.24	0.31
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.1164G>A (p.Pro388=)	CCG	CCA	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS);	3.05	1.61
LYST	ENSG00000143669	NM_001301365.1(LYST):c.2754G>A (p.Glu918=)	GAG	GAA	Chédiak-Higashi syndrome (CHS);	0.86	-0.22
LAMC2	ENSG00000058085	NM_005562.3(LAMC2):c.1899G>C (p.Leu633=)	CTG	CTC	Junctional epidermolysis bullosa	0.49	-1.02
LRBA	ENSG00000198589	NM_001364905.1(LRBA):c.1713C>T (p.His571=)	CAC	CAT	Common variable immunodeficiency 8, with autoimmunity (CVID8)	0.81	-0.3
SPG11	ENSG00000104133	NM_025137.4(SPG11):c.2887A>C (p.Arg963=)	AGA	CGA	Spastic paraplegia 11, autosomal recessive (SPG11);	0.48	-1.06
PFKM	ENSG00000152556	NM_000289.6(PFKM):c.453G>A (p.Thr151=)	ACG	ACA	Glycogen storage disease, type VII (GSD7);	2.96	1.57
NTRK1	ENSG00000198400	NM_001007792.1(NTRK1):c.1414C>A (p.Arg472=)	CGG	AGG	Hereditary insensitivity to pain with anhidrosis (CIPA);	1.15	0.2
ATP2A1	ENSG00000196296	NM_173201.4(ATP2A1):c.1560C>T (p.Gly520=)	GGC	GGT	Brody myopathy;	0.55	-0.87
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.1431G>A (p.Ala477=)	GCG	GCA	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS);	2.88	1.52
CHM	ENSG00000188419	NM_000390.4(CHM):c.957A>G (p.Thr319=)	ACA	ACG	Choroideremia (CHM)	0.34	-1.57
RELN	ENSG00000189056	NM_005045.4(RELN):c.7644G>A (p.Ser2548=)	TCG	TCA	Norman-Roberts syndrome (LIS2);Epilepsy, familial temporal lobe, 7 (ETL7)	3.5	1.81
DSP	ENSG00000096696	NM_004415.4(DSP):c.7848G>A (p.Ser2616=)	TCG	TCA	Cardiomyopathy (CMYO);Dilated cardiomyopathy with woolly hair and keratoderma (DCWHK);Arrhythmogenic right ventricular dysplasia 8 (ARVD8)	3.5	1.81
PKP2	ENSG00000057294	NM_004572.3(PKP2):c.2151G>A (p.Pro717=)	CCG	CCA	Arrhythmogenic right ventricular dysplasia 9 (ARVD9);Cardiomyopathy (CMYO)	3.05	1.61
SLC22A5	ENSG00000197375	NM_003060.4(SLC22A5):c.1380C>T (p.Asn460=)	AAC	AAT	Renal carnitine transport defect (CDSP);	1.01	0.02

PLEC	ENSG00000178209	NM_201384.3(PLEC):c.1002C>T (p.Ala334=)	GCC	GCT	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.74	-0.44
ATP2A1	ENSG00000196296	NM_173201.4(ATP2A1):c.1329A>G (p.Thr443=)	ACA	ACG	Brody myopathy;	0.34	-1.57
RYR2	ENSG00000198626	NM_001035.3(RYR2):c.4875G>A (p.Leu1625=)	CTG	CTA	Cardiomyopathy (CMYO);Catecholaminergic polymorphic ventricular tachycardia (CPVT1)	0.21	-2.27
FLNA	ENSG00000196924	NM_001110556.2(FLNA):c.7362G>A (p.Thr2454=)	ACG	ACA	Cardiovascular phenotype	2.96	1.57
SLC1A3	ENSG00000079215	NM_004172.5(SLC1A3):c.279G>A (p.Gln93=)	CAG	CAA	Episodic ataxia, type 6 (EA6)	0.4	-1.32
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.1008C>T (p.Ser336=)	AGC	AGT	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD);	0.72	-0.48
PLOD1	ENSG00000083444	NM_000302.4(PLOD1):c.1818C>A (p.Ile606=)	ATC	ATA	Ehlers-Danlos syndrome, hydroxylysine-deficient (EDSKSCL1);	0.44	-1.2
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.6426C>T (p.Ala2142=)	GCC	GCT	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.74	-0.44
POMGNT2	ENSG00000144647	NM_032806.6(POMGNT2):c.561C>T (p.His187=)	CAC	CAT	Muscular dystrophy-dystroglycanopathy (congenital with brain and eye anomalies), type a, 8 (MDDGA8)	0.81	-0.3
NLGN3	ENSG00000196338	NM_181303.2(NLGN3):c.282G>A (p.Ser94=)	TCG	TCA	History of neurodevelopmental disorder	3.5	1.81
PAH	ENSG00000171759	NM_000277.3(PAH):c.1161C>T (p.Tyr387=)	TAC	TAT	Phenylketonuria (PKU);	0.9	-0.15
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.9294C>T (p.Ala3098=)	GCC	GCT	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.74	-0.44
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.2550C>G (p.Ala850=)	GCC	GCG	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.23	-2.11
COL6A1	ENSG00000142156	NM_001848.2(COL6A1):c.1602C>T (p.Pro534=)	CCC	CCT	Bethlem myopathy 1 (BTHLM1)	1.02	0.02
SBF2	ENSG00000133812	NM_030962.3(SBF2):c.777G>A (p.Pro259=)	CCG	CCA	Charcot-Marie-Tooth disease type 4;Charcot-Marie-Tooth disease	3.05	1.61
GLDC	ENSG00000178445	NM_000170.3(GLDC):c.2874C>T (p.Ser958=)	TCC	TCT	Non-ketotic hyperglycinemia (GCE);	0.98	-0.03
CBS	ENSG00000160200	NM_000071.2(CBS):c.894G>A (p.Gln298=)	CAG	CAA	Classic homocystinuria;Cardiovascular phenotype	0.4	-1.32
NF2	ENSG00000186575	NM_000268.4(NF2):c.879T>C (p.Asn293=)	AAT	AAC	Neurofibromatosis, type 2 (NF2);Hereditary cancer-predisposing syndrome	0.99	-0.02
NOTCH3	ENSG00000074181	NM_000435.3(NOTCH3):c.831G>A (p.Glu277=)	GAG	GAA	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy type 1 (CADASIL1)	0.86	-0.22
SYNE2	ENSG00000054654	NM_182914.2(SYNE2):c.14088G>A (p.Gly4696=)	GGG	GGA	Emery-Dreifuss muscular dystrophy 5, autosomal dominant (EDMD5)	1.13	0.17
KMT2D	ENSG00000167548	NM_003482.3(KMT2D):c.8382C>A (p.Gly2794=)	GGC	GGA	Kabuki syndrome 1 (KABUK1)	0.87	-0.2
TUBB4A	ENSG00000104833	NM_006087.4(TUBB4A):c.1311G>A (p.Glu437=)	GAG	GAA	Leukodystrophy, hypomyelinating, 6 (HLD6)	0.86	-0.22

SLC19A3	ENSG00000135917	NM_025243.4(SLC19A3):c.390G>T (p.Val130=)	GTG	GTT	Biotin-responsive basal ganglia disease (THMD2);	0.46	-1.13
SBF1	ENSG00000100241	NM_002972.4(SBF1):c.3765C>T (p.Tyr1255=)	TAC	TAT	Charcot-Marie-Tooth disease, type 4B3 (CMT4B3)	0.9	-0.15
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.1605C>T (p.Pro535=)	CCC	CCT	Bethlem myopathy 1 (BTHLM1)	1.02	0.02
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.2439C>T (p.His813=)	CAC	CAT	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS);	0.81	-0.3
NF2	ENSG00000186575	NM_000268.4(NF2):c.255T>C (p.Asp85=)	GAT	GAC	Neurofibromatosis, type 2 (NF2);Hereditary cancer-predisposing syndrome	1.01	0.01
MYOT	ENSG00000120729	NM_006790.2(MYOT):c.594G>A (p.Val198=)	GTG	GTA	Myofibrillar myopathy 3 (MFM3)	0.3	-1.74
WRN	ENSG00000165392	NM_000553.6(WRN):c.3900C>A (p.Pro1300=)	CCC	CCA	Werner syndrome (WRN);	1	-0.01
TTN	ENSG00000155657	NM_001267550.2(TTN):c.42672G>T (p.Leu14224=)	CTG	CTT	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.39	-1.35
TRPM4	ENSG00000130529	NM_017636.4(TRPM4):c.1242T>C (p.Phe414=)	TTT	TTC	Progressive familial heart block type IB (PFHB1B);	1.02	0.02
GLDC	ENSG00000178445	NM_000170.2(GLDC):c.2730G>A (p.Ser910=)	TCG	TCA	Non-ketotic hyperglycinemia (GCE);	3.5	1.81
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.1869C>T (p.Arg623=)	CGC	CGT	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS)	0.52	-0.93
NDUFAF6	ENSG00000156170	NM_152416.4(NDUFAF6):c.738T>C (p.Phe246=)	TTT	TTC		1.02	0.02
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.3342C>T (p.Asn1114=)	AAC	AAT	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS);	1.01	0.02
PRPF8	ENSG00000174231	NM_006445.4(PRPF8):c.5352C>T (p.Asn1784=)	AAC	AAT	Retinitis pigmentosa (RP)	1.01	0.02
COL4A4	ENSG00000081052	NM_000092.4(COL4A4):c.1776T>C (p.Ala592=)	GCT	GCC	Alport syndrome	1.36	0.44
PTCHD1	ENSG00000165186	NM_173495.3(PTCHD1):c.1311T>C (p.His437=)	CAT	CAC	History of neurodevelopmental disorder	1.23	0.3
CPS1	ENSG00000021826	NM_001875.5(CPS1):c.783C>T (p.Ile261=)	AAC	AAT	Congenital hyperammonemia, type I;	1.01	0.02
CACNA2D4	ENSG00000151062	NM_172364.5(CACNA2D4):c.1239G>A (p.Pro413=)	CCG	CCA	Retinal cone dystrophy 4 (RCD4)	3.05	1.61
SPG21	ENSG00000090487	NM_016630.7(SPG21):c.846G>A (p.Ala282=)	GCG	GCA	Mast syndrome;	2.88	1.52
ABCA3	ENSG00000167972	NM_001089.3(ABCA3):c.3207C>T (p.His1069=)	CAC	CAT	Surfactant metabolism dysfunction, pulmonary, 3 (SMDP3);	0.81	-0.3
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.6189G>A (p.Ala2063=)	GCG	GCA	Cardiovascular phenotype	2.88	1.52
POR	ENSG00000127948	NM_000941.3(POR):c.399C>T (p.Asn133=)	AAC	AAT	Disordered steroidogenesis due to cytochrome p450 oxidoreductase deficiency (ABS1);none provided	1.01	0.02
CPS1	ENSG00000021826	NM_001875.5(CPS1):c.4089G>T (p.Leu1363=)	TCA	TCT	Congenital hyperammonemia, type I;Carbamoyl-phosphate synthase I deficiency	1.2	0.26
TRIOBP	ENSG00000100106	NM_001039141.3(TRIOBP):c.5853G>A (p.Leu1951=)	CTG	CTA		0.21	-2.27
SCN4A	ENSG00000007314	NM_000334.4(SCN4A):c.1902C>T (p.Pro634=)	CCC	CCT	Familial hyperkalemic periodic paralysis	1.02	0.02
NIPBL	ENSG00000164190	NM_133433.4(NIPBL):c.4731A>G (p.Glu1577=)	GAA	GAG	Cornelia de Lange syndrome 1 (CDLS1);	1.16	0.22
SNRNP200	ENSG00000144028	NM_014014.5(SNRNP200):c.3897C>G (p.Thr1299=)	ACC	ACG	Retinitis pigmentosa (RP)	0.31	-1.67
CRTAP	ENSG00000170275	NM_006371.4(CRTAP):c.654C>T (p.Asn218=)	AAC	AAT	Osteogenesis imperfecta type 7 (OI7);	1.01	0.02
CHSY1	ENSG00000131873	NM_014918.5(CHSY1):c.489G>A (p.Lys163=)	AAG	AAA	Temtamy preaxial brachydactyly syndrome (TPBS)	0.87	-0.2
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.2268C>T (p.Thr756=)	ACC	ACT	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.8	-0.31
CAPN3	ENSG00000092529	NM_000070.3(CAPN3):c.1263G>A (p.Leu421=)	CTG	CTA	Limb-girdle muscular dystrophy, type 2A (LGMDR1)	0.21	-2.27
TBCE	ENSG00000116957	NM_003193.5(TBCE):c.585C>T (p.Ser195=)	TCC	TCT	Hypoparathyroidism-retardation-dysmorphism syndrome (HRDS)	0.98	-0.03
BLM	ENSG00000197299	NM_000057.4(BLM):c.807C>T (p.Ser269=)	AGC	AGT	Bloom syndrome (BLM);Hereditary cancer-predisposing syndrome	0.72	-0.48
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.843G>T (p.Val281=)	GTG	GTT	Bethlem myopathy 1 (BTHLM1)	0.46	-1.13
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.1371G>A (p.Ala457=)	GCG	GCA	Qualitative or quantitative defects of dysferlin	2.88	1.52

ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.2109C>T (p.Ile703=)	ATC	ATT	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS);	0.89	-0.17
MLYCD	ENSG00000103150	NM_012213.3(MLYCD):c.1098C>T (p.Ile366=)	ATC	ATT	Deficiency of malonyl-CoA decarboxylase;	0.89	-0.17
TTN	ENSG00000155657	NM_001267550.2(TTN):c.85443A>G (p.Ala28481=)	GCA	GCG	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.35	-1.52
VCL	ENSG00000035403	NM_014000.2(VCL):c.2427C>T (p.Ser809=)	TCC	TCT	Dilated cardiomyopathy 1W (CMD1W);Cardiovascular phenotype	0.98	-0.03
LGI1	ENSG00000108231	NM_005097.4(LGI1):c.1392G>A (p.Ser464=)	TCG	TCA	Familial temporal lobe epilepsy 1 (ETL1);Seizures	3.5	1.81
SMCHD1	ENSG00000101596	NM_015295.2(SMCHD1):c.2838T>C (p.Ala946=)	GCT	GCC	Facioscapulohumeral muscular dystrophy 2 (FSHD2)	1.36	0.44
AGL	ENSG00000162688	NM_000642.3(AGL):c.3345A>T (p.Gly1115=)	GGA	GGT	Glycogen storage disease type III (GSD3);	0.63	-0.67
ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.156G>A (p.Arg52=)	CGG	CGA	Progressive familial intrahepatic cholestasis 2 (PFIC2)	0.6	-0.73
TTN	ENSG00000155657	NM_001267550.2(TTN):c.101037G>A (p.Gln33679=)	CAG	CAA	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.4	-1.32
PKP2	ENSG00000057294	NM_004572.3(PKP2):c.1596C>T (p.Ile532=)	ATC	ATT	Arrhythmogenic right ventricular dysplasia 9 (ARVD9);Cardiomyopathy (CMYO)	0.89	-0.17
TSC2	ENSG00000103197	NM_000548.5(TSC2):c.1308G>T (p.Pro436=)	CCG	CCT	Hereditary cancer-predisposing syndrome	3.11	1.64
ASS1	ENSG00000130707	NM_054012.4(ASS1):c.1101G>A (p.Leu367=)	CTG	CTA	Citrullinemia type I (CTNL1);	0.21	-2.27
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.4461C>T (p.Ile1487=)	ATC	ATT	Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	0.89	-0.17
KMT2D	ENSG00000167548	NM_003482.3(KMT2D):c.3813A>T (p.Leu1271=)	CTA	CTT		1.89	0.92
SMCHD1	ENSG00000101596	NM_015295.2(SMCHD1):c.2151G>A (p.Ala717=)	GCG	GCA	Facioscapulohumeral muscular dystrophy 2 (FSHD2)	2.88	1.52
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.13782G>A (p.Lys4594=)	AAG	AAA	Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);Autosomal dominant cerebellar ataxia	0.87	-0.2
NHLRC1	ENSG00000187566	NM_198586.3(NHLRC1):c.990G>A (p.Gln330=)	CAG	CAA	Lafora disease;Seizures	0.4	-1.32
LDLRAP1	ENSG00000157978	NM_015627.2(LDLRAP1):c.396C>T (p.Ile132=)	ATC	ATT	Familial hypercholesterolemia 4 (FHCL4);	0.89	-0.17
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.13641C>G (p.Ala4547=)	GCC	GCG	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.23	-2.11
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.3885C>T (p.Ala1295=)	GCC	GCT	Wilson disease (WND);	0.74	-0.44
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.1212C>A (p.Pro404=)	CCC	CCA	Aortic aneurysm, familial thoracic 7 (AAT7);	1	-0.01
EIF2B1	ENSG00000111361	NM_001414.4(EIF2B1):c.429G>A (p.Ala143=)	GCG	GCA	Leukoencephalopathy with vanishing white matter (VWM)	2.88	1.52
TSC1	ENSG00000165699	NM_000368.4(TSC1):c.168G>A (p.Pro56=)	CCG	CCA	Tuberous sclerosis 1 (TSC1);Focal cortical dysplasia type II (FCORD2)	3.05	1.61
SLC7A7	ENSG00000155465	NM_001126106.2(SLC7A7):c.234C>T (p.Val78=)	GTC	GTT	Lysinuric protein intolerance (LPI);	0.88	-0.19
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.1305G>A (p.Ala435=)	GCG	GCA	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	2.88	1.52
PROC	ENSG00000115718	NM_000312.3(PROC):c.1299C>T (p.Gly433=)	GGC	GGT	Thrombophilia, hereditary, due to protein C deficiency, autosomal dominant (THPH3);	0.55	-0.87
TTN	ENSG00000155657	NM_001267550.2(TTN):c.1815T>C (p.Thr605=)	ACT	ACC	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	1.24	0.31
FOXN1	ENSG00000109101	NM_001369369.1(FOXN1):c.546C>T (p.Asn182=)	AAC	AAT	T-cell immunodeficiency, congenital alopecia, and nail dystrophy;	1.01	0.02
PRPF6	ENSG00000101161	NM_012469.4(PRPF6):c.891C>T (p.Leu297=)	CTC	CTT	Retinitis pigmentosa (RP)	0.8	-0.33

DICER1	ENSG00000100697	NM_177438.2(DICER1):c.2133T>C (p.His711=)	CAT	CAC	DICER1-related pleuropulmonary blastoma cancer predisposition syndrome (PPBFTDS);Hereditary cancer-predisposing syndrome	1.23	0.3
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.3955C>T (p.Leu1319=)	CTG	TTG	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.37	-1.42
DMD	ENSG00000198947	NM_004006.2(DMD):c.2967G>T (p.Leu989=)	CTG	CTT	Duchenne muscular dystrophy (DMD)	0.39	-1.35
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.10158G>A (p.Ala3386=)	GCG	GCA	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	2.88	1.52
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.7749G>A (p.Thr2583=)	ACG	ACA	Bethlem myopathy 1 (BTHLM1)	2.96	1.57
DICER1	ENSG00000100697	NM_177438.2(DICER1):c.1089C>T (p.Phe363=)	TTC	TTT	DICER1-related pleuropulmonary blastoma cancer predisposition syndrome (PPBFTDS);Hereditary cancer-predisposing syndrome	0.98	-0.02
CUL7	ENSG00000044090	NM_014780.4(CUL7):c.4659G>A (p.Glu1553=)	GGT	GGA	Three M syndrome 1 (3M1)	1.59	0.67
PC	ENSG00000173599	NM_001040716.2(PC):c.3198C>T (p.Ser1066=)	AGC	AGT	Pyruvate carboxylase deficiency;	0.72	-0.48
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.5112C>T (p.Cys1704=)	TGC	TGT	Autosomal recessive polycystic kidney disease (ARPKD);	0.97	-0.05
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.486G>A (p.Val162=)	GTG	GTA	Hereditary cancer-predisposing syndrome	0.3	-1.74
TTN	ENSG00000155657	NM_001267550.2(TTN):c.99840T>C (p.Asp33280=)	GAT	GAC	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	1.01	0.01
NIPBL	ENSG00000164190	NM_133433.4(NIPBL):c.3423A>G (p.Ser1141=)	TCA	TCG	Cornelia de Lange syndrome 1 (CDLS1);	0.29	-1.81
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.11007C>T (p.Asn3669=)	AAC	AAT	Cohen syndrome (COH1);History of neurodevelopmental disorder	1.01	0.02
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.12585G>A (p.Lys4195=)	AAG	AAA	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	0.87	-0.2
PCCA	ENSG00000175198	NM_000282.4(PCCA):c.2172C>T (p.Leu724=)	CTC	CTT	Propionic acidemia (PROP);	0.8	-0.33
PCDH19	ENSG00000165194	NM_001184880.2(PCDH19):c.942G>A (p.Leu314=)	CTG	CTA	Early infantile epileptic encephalopathy 9 (DEE9)	0.21	-2.27
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.9444C>T (p.Cys3148=)	TGC	TGT	Cohen syndrome (COH1);History of neurodevelopmental disorder	0.97	-0.05
NF2	ENSG00000186575	NM_000268.4(NF2):c.903C>T (p.Ile301=)	ATC	ATT	Neurofibromatosis, type 2 (NF2);Hereditary cancer-predisposing syndrome	0.89	-0.17
UBE3A	ENSG00000114062	NM_130839.5(UBE3A):c.1620C>T (p.Ile540=)	ATC	ATT	Angelman syndrome (AS)	0.89	-0.17
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.3804C>T (p.Ala1268=)	GCC	GCT	Autosomal recessive polycystic kidney disease (ARPKD);	0.74	-0.44
CBS	ENSG00000160200	NM_000071.2(CBS):c.1065G>A (p.Ala355=)	GCG	GCA	Classic homocystinuria;	2.88	1.52
PCCB	ENSG00000114054	NM_000532.5(PCCB):c.1452A>G (p.Ala484=)	GCA	GCG	Propionic acidemia (PROP);	0.35	-1.52
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.7194C>T (p.Arg2398=)	CGC	CGT	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.52	-0.93
CACNA1C	ENSG00000151067	NM_000719.7(CACNA1C):c.666C>T (p.Asn222=)	AAC	AAT	Cardiovascular phenotype	1.01	0.02
AGRN	ENSG00000188157	NM_198576.4(AGRN):c.3732C>T (p.His1244=)	CAC	CAT	Myasthenic syndrome, congenital, 8 (CMS8)	0.81	-0.3
LAMA2	ENSG00000196569	NM_000426.3(LAMA2):c.8692A>C (p.Arg2898=)	AGA	CGA	Laminin alpha 2-related dystrophy (LAMA2-RD)	0.48	-1.06

TTN	ENSG00000155657	NM_001267550.2(TTN):c.95961C>T (p.Ala31987=)	GCC	GCT	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.74	-0.44
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.8697C>T (p.Ser2899=)	TCC	TCT	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.98	-0.03
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.11607C>T (p.Ala3869=)	GCC	GCT	Autosomal recessive polycystic kidney disease (ARPKD)	0.74	-0.44
STK11	ENSG00000118046	NM_000455.5(STK11):c.69C>T (p.Asp23=)	GAC	GAT	Peutz-Jeghers syndrome (PJS);Hereditary cancer-predisposing syndrome	0.99	-0.01
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.14727G>A (p.Gly4909=)	GGG	GGA	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	1.13	0.17
RNASEH2B	ENSG00000136104	NM_001142279.2(RNASEH2B):c.741+4414A>G	TCA	TCG	Aicardi Goutieres syndrome 2 (AGS2);	0.29	-1.81
MET	ENSG00000105976	NM_000245.4(MET):c.789G>A (p.Thr263=)	ACG	ACA	Renal cell carcinoma, papillary, 1 (RCCP1);	2.96	1.57
RTTN	ENSG00000176225	NM_173630.4(RTTN):c.2355T>C (p.Ser785=)	AGT	AGC		1.4	0.48
LDLR	ENSG00000130164	NM_000527.5(LDLR):c.1279A>C (p.Arg427=)	AGG	CGG	Familial hypercholesterolemia 1 (FHCL1);Familial hypercholesterolemia (FH)	0.87	-0.2
BLM	ENSG00000197299	NM_000057.4(BLM):c.114A>G (p.Lys38=)	AAA	AAG	Bloom syndrome (BLM);Hereditary cancer-predisposing syndrome	1.15	0.2
MET	ENSG00000105976	NM_000245.4(MET):c.4074C>T (p.Asn1358=)	AAC	AAT	Renal cell carcinoma, papillary, 1 (RCCP1);	1.01	0.02
SLC7A7	ENSG00000155465	NM_001126106.2(SLC7A7):c.339A>C (p.Gly113=)	GGA	GGC	Lysinuric protein intolerance (LPI);	1.15	0.2
ATM	ENSG00000149311	NM_000051.3(ATM):c.3417G>A (p.Glu1139=)	GAG	GAA	Hereditary cancer-predisposing syndrome	0.86	-0.22
SLC2A10	ENSG00000197496	NM_030777.4(SLC2A10):c.810G>C (p.Val270=)	GTG	GTC	Arterial tortuosity syndrome (ATORS);	0.52	-0.94
GRIN1	ENSG00000176884	NM_007327.4(GRIN1):c.2499C>T (p.Ile833=)	ATC	ATT	Neurodevelopmental disorder with or without hyperkinetic movements and seizures, autosomal dominant (NDHMSD)	0.89	-0.17
RB1	ENSG00000139687	NM_000321.2(RB1):c.462G>A (p.Lys154=)	AAG	AAA	Retinoblastoma (RB1);Hereditary cancer-predisposing syndrome	0.87	-0.2
LRPPRC	ENSG00000138095	NM_133259.4(LRPPRC):c.135C>T (p.Ala45=)	GCC	GCT	Congenital lactic acidosis, Saguenay-Lac-Saint-Jean type (MC4DN5);	0.74	-0.44
KMT2D	ENSG00000167548	NM_003482.3(KMT2D):c.6435G>A (p.Pro2145=)	CCG	CCA	Kabuki syndrome	3.05	1.61
FGD1	ENSG00000102302	NM_004463.3(FGD1):c.1563C>T (p.Pro521=)	CCC	CCT	History of neurodevelopmental disorder	1.02	0.02
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.13209G>A (p.Pro4403=)	CCG	CCA	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	3.05	1.61
FGD1	ENSG00000102302	NM_004463.3(FGD1):c.2289G>A (p.Lys763=)	AAG	AAA	History of neurodevelopmental disorder	0.87	-0.2
ATM	ENSG00000149311	NM_000051.3(ATM):c.1905C>T (p.His635=)	CAC	CAT	Hereditary cancer-predisposing syndrome	0.81	-0.3
SLC26A4	ENSG00000091137	NM_000441.2(SLC26A4):c.2283A>G (p.Thr761=)	ACA	ACG	Pendred syndrome (PDS)	0.34	-1.57
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.11836T>C (p.Leu3946=)	TTG	CTG	Autosomal recessive polycystic kidney disease (ARPKD)	2.67	1.42
ALMS1	ENSG00000116127	NM_015120.4(ALMS1):c.2106A>C (p.Pro702=)	GGA	GGC	Alstrom syndrome (ALMS);	1.15	0.2
SLC2A10	ENSG00000197496	NM_030777.4(SLC2A10):c.1605C>T (p.Ile535=)	ATC	ATT	Arterial tortuosity syndrome (ATORS);	0.89	-0.17
DBT	ENSG00000137992	NM_001918.4(DBT):c.291C>T (p.Ser97=)	AGC	AGT	Maple syrup urine disease (MSUD);	0.72	-0.48
SCN4A	ENSG00000007314	NM_000334.4(SCN4A):c.5367G>A (p.Ser1789=)	TCG	TCA	Familial hyperkalemic periodic paralysis	3.5	1.81
BCKDHA	ENSG00000248098	NM_000709.4(BCKDHA):c.63C>T (p.Ala21=)	GCC	GCT	Maple syrup urine disease (MSUD);Maple syrup urine disease type 1A (MSUD1A)	0.74	-0.44

PLEC	ENSG00000178209	NM_201384.3(PLEC):c.12837C>T (p.Pro4279=)	CCC	CCT	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	1.02	0.02
ATM	ENSG00000149311	NM_000051.3(ATM):c.8518T>C (p.Leu2840=)	TTG	CTG	Hereditary cancer-predisposing syndrome	2.67	1.42
SGCD	ENSG00000170624	NM_000337.5(SGCD):c.768G>A (p.Thr256=)	ACG	ACA	Autosomal recessive limb-girdle muscular dystrophy type 2F (LGMD2F)	2.96	1.57
PROP1	ENSG00000175325	NM_006261.4(PROP1):c.456T>C (p.Ala152=)	GCT	GCC	Pituitary hormone deficiency, combined 2 (CPHD2)	1.36	0.44
SMARCA4	ENSG00000127616	NM_001128849.2(SMARCA4):c.4284G>T (p.Thr1428=)	ACG	ACT	Hereditary cancer-predisposing syndrome	2.56	1.36
MPV17	ENSG00000115204	NM_002437.5(MPV17):c.156G>A (p.Leu52=)	CTG	CTA	Navajo neurohepatopathy (MTDPS6)	0.21	-2.27
POLG	ENSG00000140521	NM_002693.2(POLG):c.3564C>T (p.Cys1188=)	TGC	TGT	Progressive sclerosing poliodystrophy (MTDPS4A)	0.97	-0.05
RBM20	ENSG00000203867	NM_001134363.3(RBM20):c.2145C>T (p.Pro715=)	CCC	CCT	Dilated cardiomyopathy 1DD (CMD1DD);Cardiovascular phenotype	1.02	0.02
NEB	ENSG00000183091	NM_001271208.2(NEB):c.5301G>A (p.Pro1767=)	CCG	CCA	Nemaline myopathy 2 (NEM2);	3.05	1.61
LDLR	ENSG00000130164	NM_000527.5(LDLR):c.1911C>T (p.Ser637=)	TCC	TCT	Familial hypercholesterolemia 1 (FHCL1);Familial hypercholesterolemia (FH)	0.98	-0.03
COL3A1	ENSG00000168542	NM_000090.3(COL3A1):c.4020C>T (p.Tyr1340=)	TAC	TAT	Ehlers-Danlos syndrome, type 4 (EDSVASC);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.9	-0.15
ACADVL	ENSG00000072778	NM_000018.4(ACADVL):c.1824C>T (p.Ile608=)	ATC	ATT	Very long chain acyl-CoA dehydrogenase deficiency (VLCAD);	0.89	-0.17
DES	ENSG00000175084	NM_001927.4(DES):c.708C>T (p.Ile236=)	ATC	ATT	Cardiovascular phenotype	0.89	-0.17
LAMB1	ENSG00000091136	NM_002291.3(LAMB1):c.1422C>G (p.Ser474=)	TCC	TCG		0.23	-2.09
AXIN2	ENSG00000168646	NM_004655.4(AXIN2):c.2196G>A (p.Thr732=)	ACG	ACA	Oligodontia-colorectal cancer syndrome (ODCRCS);	2.96	1.57
SLC26A4	ENSG00000091137	NM_000441.2(SLC26A4):c.1233C>T (p.Ala411=)	GCC	GCT	Pendred syndrome (PDS)	0.74	-0.44
PMS2	ENSG00000122512	NM_000535.7(PMS2):c.852A>G (p.Ser284=)	TCA	TCG	Hereditary cancer-predisposing syndrome;Hereditary nonpolyposis colorectal neoplasms	0.29	-1.81
GRIN2B	ENSG00000273079	NM_000834.4(GRIN2B):c.189C>T (p.Ser63=)	TCC	TCT		0.98	-0.03
BSND	ENSG00000162399	NM_057176.3(BSND):c.744G>A (p.Thr248=)	ACG	ACA	Bartter syndrome	2.96	1.57
MYBPC3	ENSG00000134571	NM_000256.3(MYBPC3):c.2034T>C (p.Ala678=)	GCT	GCC	Cardiomyopathy (CMYO);Hypertrophic cardiomyopathy	1.36	0.44
LAMA2	ENSG00000196569	NM_000426.3(LAMA2):c.2037G>C (p.Ala679=)	GCG	GCC	Merosin deficient congenital muscular dystrophy (MDC1A)	4.32	2.11
PTPN11	ENSG00000179295	NM_002834.4(PTPN11):c.132C>T (p.Ser44=)	TCC	TCT		0.98	-0.03
GALT	ENSG00000213930	NM_000155.4(GALT):c.450T>A (p.Val150=)	GTT	GTA	Deficiency of UDPglucose-hexose-1-phosphate uridylyltransferase (GALAC1);	0.65	-0.62
IQSEC2	ENSG00000124313	NM_001111125.3(IQSEC2):c.618C>T (p.Ser206=)	AGC	AGT	Mental retardation, X-linked 1 (MRX1)	0.72	-0.48
BAP1	ENSG00000163930	NM_004656.4(BAP1):c.2118C>A (p.Ile706=)	ATC	ATA	Hereditary cancer-predisposing syndrome	0.44	-1.2
BRIP1	ENSG00000136492	NM_032043.2(BRIP1):c.636C>A (p.Gly212=)	GGC	GGA	Hereditary cancer-predisposing syndrome	0.87	-0.2
IDUA	ENSG00000127415	NM_000203.5(IDUA):c.1479C>A (p.Pro493=)	CCC	CCA	Mucopolysaccharidosis type 1 (MPS1);	1	-0.01
FLNA	ENSG00000196924	NM_001110556.2(FLNA):c.66C>T (p.Asp22=)	GAC	GAT	History of neurodevelopmental disorder	0.99	-0.01
SGCB	ENSG00000163069	NM_000232.4(SGCB):c.498C>T (p.Ile166=)	ATC	ATT	Autosomal recessive limb-girdle muscular dystrophy type 2E (LGMD2E)	0.89	-0.17
IFT140	ENSG00000187535	NM_014714.4(IFT140):c.546C>T (p.Asp182=)	GAC	GAT	Saldino-Mainzer syndrome (SRTD9);	0.99	-0.01
CNGB3	ENSG00000170289	NM_019098.4(CNGB3):c.474C>T (p.Pro158=)	CCC	CCT	Achromatopsia	1.02	0.02
ATM	ENSG00000149311	NM_000051.3(ATM):c.6318T>C (p.Asn2106=)	AAT	AAC	Ataxia-telangiectasia syndrome (AT);Hereditary cancer-predisposing syndrome	0.99	-0.02

BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.5667T>C (p.Ile1889=)	ATT	ATC	Hereditary cancer-predisposing syndrome	1.13	0.17
TTN	ENSG00000155657	NM_001267550.2(TTN):c.2916G>A (p.Pro972=)	CCG	CCA	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	3.05	1.61
TSC2	ENSG00000103197	NM_000548.5(TSC2):c.4260A>G (p.Ser1420=)	TCA	TCG	Tuberous sclerosis 2 (TSC2)	0.29	-1.81
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.325C>T (p.Leu109=)	CTG	TTG	Wilson disease (WND);	0.37	-1.42
TTN	ENSG00000155657	NM_001267550.2(TTN):c.81123G>A (p.Thr27041=)	ACG	ACA	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	2.96	1.57
NTRK1	ENSG00000198400	NM_001007792.1(NTRK1):c.2061C>T (p.Tyr687=)	TAC	TAT	Hereditary insensitivity to pain with anhidrosis (CIPA);	0.9	-0.15
RYR2	ENSG00000198626	NM_001035.3(RYR2):c.13449A>G (p.Lys4483=)	AAA	AAG	Cardiomyopathy (CMYO)	1.15	0.2
BRIP1	ENSG00000136492	NM_032043.2(BRIP1):c.504G>A (p.Gln168=)	CAG	CAA	Hereditary cancer-predisposing syndrome	0.4	-1.32
TTN	ENSG00000155657	NM_001267550.2(TTN):c.23616C>T (p.Asn7872=)	AAC	AAT	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	1.01	0.02
FLNB	ENSG00000136068	NM_001457.4(FLNB):c.7254C>T (p.Ser2418=)	TCC	TCT	FLNB-Related Spectrum Disorders	0.98	-0.03
NF1	ENSG00000196712	NM_000267.3(NF1):c.7263A>G (p.Leu2421=)	TTA	TTG	Neurofibromatosis, type 1 (NF1);Hereditary cancer-predisposing syndrome	1.53	0.61
ACADVL	ENSG00000072778	NM_000018.4(ACADVL):c.1284G>A (p.Lys428=)	AAG	AAA	Very long chain acyl-CoA dehydrogenase deficiency (VLCAD);	0.87	-0.2
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.3699C>T (p.Asp1233=)	GAC	GAT	Bethlem myopathy 1 (BTHLM1)	0.99	-0.01
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.22035T>G (p.Thr7345=)	ACT	ACG	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	0.39	-1.36
TGFBR2	ENSG00000163513	NM_003242.6(TGFBR2):c.1668G>A (p.Lys556=)	AAG	AAA	Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.87	-0.2
ARSB	ENSG00000113273	NM_000046.5(ARSB):c.82C>T (p.Leu28=)	CTG	TTG	Mucopolysaccharidosis type 6 (MPS6);	0.37	-1.42
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.1359C>T (p.Pro453=)	CCC	CCT	Aortic aneurysm, familial thoracic 7 (AAT7);Cardiovascular phenotype	1.02	0.02
SLC22A5	ENSG00000197375	NM_003060.4(SLC22A5):c.279G>C (p.Ser93=)	TCG	TCC	Renal carnitine transport defect (CDSP);	4.26	2.09
TTN	ENSG00000155657	NM_001267550.2(TTN):c.58008T>C (p.Asn19336=)	AAT	AAC	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.99	-0.02
SCN1A	ENSG00000144285	NM_001165963.4(SCN1A):c.4887C>T (p.Phe1629=)	TTC	TTT		0.98	-0.02
USH2A	ENSG00000042781	NM_206933.3(USH2A):c.8028G>A (p.Pro2676=)	CCG	CCA	Usher syndrome, type 2A (USH2A)	3.05	1.61
MSH2	ENSG00000095002	NM_000251.2(MSH2):c.1294T>C (p.Leu432=)	TTG	CTG	Hereditary nonpolyposis colorectal neoplasms	2.67	1.42
ALK	ENSG00000171094	NM_004304.5(ALK):c.615C>G (p.Ser205=)	TCC	TCG	Neuroblastoma 3 (NBLST3);Hereditary cancer-predisposing syndrome	0.23	-2.09
USH2A	ENSG00000042781	NM_206933.3(USH2A):c.5802G>A (p.Ser1934=)	TCG	TCA	Usher syndrome, type 2A (USH2A)	3.5	1.81
TTN	ENSG00000155657	NM_001267550.2(TTN):c.83733C>T (p.Ser27911=)	AGC	AGT	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.72	-0.48
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.3771G>A (p.Glu1257=)	GAG	GAA	Hereditary cancer-predisposing syndrome	0.86	-0.22
CHD8	ENSG00000100888	NM_001170629.2(CHD8):c.456A>G (p.Pro152=)	CCA	CCG	History of neurodevelopmental disorder	0.33	-1.61
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.2820A>G (p.Val940=)	GTA	GTG		3.34	1.74
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.10548C>T (p.Tyr3516=)	TAC	TAT	Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O)	0.9	-0.15
BAP1	ENSG00000163930	NM_004656.4(BAP1):c.1749G>A (p.Ser583=)	TCG	TCA	Tumor susceptibility linked to germline BAP1 mutations (TPDS);Hereditary cancer-predisposing syndrome	3.5	1.81
MSH6	ENSG00000116062	NM_000179.2(MSH6):c.3537C>G (p.Ala1179=)	GCC	GCG	Hereditary cancer-predisposing syndrome;Hereditary nonpolyposis colorectal neoplasms	0.23	-2.11
MEFV	ENSG00000103313	NM_000243.2(MEFV):c.2049G>A (p.Ser683=)	TCG	TCA	Familial Mediterranean fever (FMF);	3.5	1.81
MAGI2	ENSG00000187391	NM_012301.4(MAGI2):c.219C>T (p.Pro73=)	CCC	CCT		1.02	0.02
STK11	ENSG00000118046	NM_000455.4(STK11):c.840C>T (p.Pro280=)	CCC	CCT	Hereditary cancer-predisposing syndrome	1.02	0.02

PYGM	ENSG00000068976	NM_005609.4(PYGM):c.2268C>T (p.Pro756=)	CCC	CCT	Glycogen storage disease, type V (GSD5);	1.02	0.02
CDKN1B	ENSG00000111276	NM_004064.4(CDKN1B):c.279G>A (p.Arg93=)	CGG	CGA	Multiple endocrine neoplasia, type 4 (MEN4);Hereditary cancer-predisposing syndrome	0.6	-0.73
IQSEC2	ENSG00000124313	NM_001111125.3(IQSEC2):c.3735C>T (p.His1245=)	CAC	CAT	Mental retardation, X-linked 1 (MRX1)	0.81	-0.3
ACADVL	ENSG00000072778	NM_000018.4(ACADVL):c.1581G>A (p.Pro527=)	CCG	CCA	Very long chain acyl-CoA dehydrogenase deficiency (VLCAD);	3.05	1.61
DNMT1	ENSG00000130816	NM_001130823.3(DNMT1):c.483T>C (p.Thr161=)	ACT	ACC	Hereditary sensory neuropathy type IE (HSN1E);	1.24	0.31
TTN	ENSG00000155657	NM_001267550.2(TTN):c.93129C>T (p.Asp31043=)	GAC	GAT	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.99	-0.01
BIN1	ENSG00000136717	NM_139343.3(BIN1):c.1143G>A (p.Pro381=)	CCG	CCA	Myopathy, centronuclear, 2 (CNM2);	3.05	1.61
CPT2	ENSG00000157184	NM_000098.3(CPT2):c.1602G>A (p.Glu534=)	GAG	GAA	Carnitine palmitoyltransferase II deficiency (CPT2)	0.86	-0.22
ARG1	ENSG00000118520	NM_000045.4(ARG1):c.75A>G (p.Glu25=)	GAA	GAG	Arginase deficiency;	1.16	0.22
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.285G>A (p.Thr95=)	ACG	ACA	Collagen VI-related myopathy (COL6-RM)	2.96	1.57
TNFRSF1A	ENSG00000067182	NM_001065.4(TNFRSF1A):c.369C>T (p.Thr123=)	ACC	ACT	TNF receptor-associated periodic fever syndrome (TRAPS) (FPF);	0.8	-0.31
PIGO	ENSG00000165282	NM_032634.4(PIGO):c.1758C>T (p.Val586=)	GTC	GTT	Hyperphosphatasia with mental retardation syndrome 2 (HPMRS2);	0.88	-0.19
TTN	ENSG00000155657	NM_001267550.2(TTN):c.29397C>T (p.Gly9799=)	GGC	GGT		0.55	-0.87
BCKDHB	ENSG00000083123	NM_183050.4(BCKDHB):c.51A>G (p.Ala17=)	GCA	GCG	Maple syrup urine disease (MSUD);	0.35	-1.52
ACTC1	ENSG00000159251	NM_005159.5(ACTC1):c.1038C>T (p.Ser346=)	TCC	TCT	Cardiomyopathy (CMYO);	0.98	-0.03
BAP1	ENSG00000163930	NM_004656.4(BAP1):c.2175G>A (p.Lys725=)	AAG	AAA	Tumor susceptibility linked to germline BAP1 mutations (TPDS);Hereditary cancer-predisposing syndrome	0.87	-0.2
AGXT	ENSG00000172482	NM_000030.3(AGXT):c.27C>A (p.Thr9=)	ACC	ACA	Primary hyperoxaluria, type I (HP1);	0.93	-0.1
TRMU	ENSG00000100416	NM_018006.5(TRMU):c.351T>C (p.Asn117=)	AAT	AAC	Acute infantile liver failure due to synthesis defect of mtDNA-encoded proteins	0.99	-0.02
GNPTG	ENSG00000090581	NM_032520.5(GNPTG):c.264C>T (p.Asn88=)	AAC	AAT	Mucolipidosis type III gamma;	1.01	0.02
DOLK	ENSG00000175283	NM_014908.3(DOLK):c.1446G>A (p.Ala482=)	GCG	GCA	Congenital disorder of glycosylation type 1M (CDG1M);	2.88	1.52
DOLK	ENSG00000175283	NM_014908.3(DOLK):c.873C>T (p.Leu291=)	CTC	CTT	Congenital disorder of glycosylation type 1M (CDG1M);	0.8	-0.33
CHD8	ENSG00000100888	NM_001170629.2(CHD8):c.5346A>G (p.Ala1782=)	GCA	GCG	History of neurodevelopmental disorder	0.35	-1.52
PMS2	ENSG00000122512	NM_000535.7(PMS2):c.321G>C (p.Arg107=)	CGG	CGC	Hereditary cancer-predisposing syndrome	0.82	-0.29
NAGS	ENSG00000161653	NM_153006.3(NAGS):c.1302C>T (p.Pro434=)	CCC	CCT	Hyperammonemia, type III (NAGSD);	1.02	0.02
PGAM2	ENSG00000164708	NM_000290.4(PGAM2):c.726C>T (p.Ala242=)	GCC	GCT	Glycogen storage disease type X (GSD10);	0.74	-0.44
SLC3A1	ENSG00000138079	NM_000341.4(SLC3A1):c.1473C>T (p.Ala491=)	GCC	GCT	Cystinuria (CSNU);	0.74	-0.44
PSMB8	ENSG00000204264	NM_148919.4(PSMB8):c.804G>A (p.Leu268=)	CTG	CTA	Proteasome-associated autoinflammatory syndrome 1 (PRAAS1);	0.21	-2.27
ROGDI	ENSG00000067836	NM_024589.2(ROGDI):c.567G>A (p.Leu189=)	CTG	CTA	s syndrome (KTZS)", '	0.21	-2.27
POLD1	ENSG00000062822	NM_002691.4(POLD1):c.2433C>T (p.Gly811=)	GGC	GGT	Colorectal cancer 10 (CRCS10);	0.55	-0.87
MYH7	ENSG00000092054	NM_000257.4(MYH7):c.4992C>T (p.Asn1664=)	AAC	AAT	Cardiomyopathy (CMYO);	1.01	0.02
ROM1	ENSG00000149489	NM_000327.3(ROM1):c.81G>T (p.Leu27=)	CTG	CTT	Retinitis pigmentosa (RP)	0.39	-1.35
MYOT	ENSG00000120729	NM_006790.2(MYOT):c.342C>T (p.Ser114=)	TCC	TCT	Myofibrillar myopathy 3 (MFM3)	0.98	-0.03
BAP1	ENSG00000163930	NM_004656.4(BAP1):c.177G>A (p.Arg59=)	CGG	CGA	Tumor susceptibility linked to germline BAP1 mutations (TPDS);Hereditary cancer-predisposing syndrome	0.6	-0.73
MED12	ENSG00000184634	NM_005120.3(MED12):c.6285A>G (p.Gln2095=)	CAA	CAG	Cardiovascular phenotype	2.49	1.32
ROGDI	ENSG00000067836	NM_024589.2(ROGDI):c.555G>C (p.Pro185=)	CCG	CCC	s syndrome (KTZS)", '	3.07	1.62
WDR62	ENSG00000075702	NM_001083961.2(WDR62):c.1359C>T (p.Asn453=)	AAC	AAT	Primary autosomal recessive microcephaly 2 (MCPH2);	1.01	0.02
MYH6	ENSG00000197616	NM_002471.3(MYH6):c.210T>C (p.Thr70=)	ACT	ACC	Cardiovascular phenotype;Familial hypertrophic cardiomyopathy 14 (CMH14)	1.24	0.31

ATM	ENSG00000149311	NM_000051.3(ATM):c.3150T>C (p.Leu1050=)	CTT	CTC	Ataxia-telangiectasia syndrome (AT);Hereditary cancer-predisposing syndrome;	1.26	0.33
SPRED1	ENSG00000166068	NM_152594.3(SPRED1):c.963G>A (p.Lys321=)	AAG	AAA	Legius syndrome (LGSS);	0.87	-0.2
MTTP	ENSG00000138823	NM_000253.3(MTTP):c.2673C>T (p.Ser891=)	AGC	AGT	Abetalipoproteinaemia (ABL)	0.72	-0.48
SIX1	ENSG00000126778	NM_005982.4(SIX1):c.330G>A (p.Arg110=)	CGG	CGA	Deafness, autosomal dominant 23 (DFNA23);Branchiootic syndrome 3 (BOS3)	0.6	-0.73
MECP2	ENSG00000169057	NM_001110792.2(MECP2):c.1224C>T (p.Ser408=)	TCC	TCT	Severe neonatal-onset encephalopathy with microcephaly	0.98	-0.03
MEFV	ENSG00000103313	NM_000243.2(MEFV):c.372C>T (p.Pro124=)	CCC	CCT	Familial Mediterranean fever (FMF); none provided	1.02	0.02
ATP1A2	ENSG00000018625	NM_000702.4(ATP1A2):c.2412C>T (p.Ile804=)	ATC	ATT	Familial hemiplegic migraine type 2 (FHM2);Alternating hemiplegia of childhood 1 (AHC1)	0.89	-0.17
MED12	ENSG00000184634	NM_005120.3(MED12):c.4488C>T (p.Arg1496=)	CGC	CGT	Cardiovascular phenotype;FG syndrome 1 (OKS)	0.52	-0.93
MSH6	ENSG00000116062	NM_000179.2(MSH6):c.3675G>A (p.Thr1225=)	ACG	ACA	Hereditary cancer-predisposing syndrome;Hereditary nonpolyposis colorectal neoplasms	2.96	1.57
FH	ENSG00000091483	NM_000143.3(FH):c.1482A>G (p.Ala494=)	GCA	GCG	Fumarase deficiency (FMRD);Hereditary cancer-predisposing syndrome;Hereditary leiomyomatosis and renal cell cancer (HLRCC)	0.35	-1.52
KIFBP	ENSG00000198954	NM_015634.4(KIFBP):c.78A>G (p.Lys26=)	AAA	AAG	Goldberg-Shprintzen megacolon syndrome (GOSHS);	1.15	0.2
HRAS	ENSG00000174775	NM_005343.4(HRAS):c.36C>T (p.Gly12=)	GGC	GGT	Costello syndrome (CSTLO);Rasopathy;	0.55	-0.87
KIF1A	ENSG00000130294	NM_004321.7(KIF1A):c.2448C>T (p.Tyr816=)	TAC	TAT	Spastic paraplegia 30, autosomal recessive (SPG30);Spastic paraplegia 30, autosomal recessive (SPG30);Hereditary sensory and autonomic neuropathy type IIC (HSN2C);Intellectual disability, autosomal dominant 9 (NESCAVS);History of neurodevelopmental disorder	0.9	-0.15
SACS	ENSG00000151835	NM_014363.6(SACS):c.3129A>G (p.Ser1043=)	TCA	TCG	Charlevoix-Saguenay spastic ataxia (SACS); Spastic paraplegia	0.29	-1.81
SMARCB1	ENSG00000099956	NM_003073.5(SMARCB1):c.1032C>T (p.Gly344=)	GGC	GGT	Hereditary cancer-predisposing syndrome;Schwannomatosis 1 (SWNTS1);Rhabdoid tumor predisposition syndrome 1 (RTPS1)	0.55	-0.87
KCNH2	ENSG00000055118	NM_000238.4(KCNH2):c.1563C>T (p.Ile521=)	ATC	ATT	Cardiovascular phenotype;Arrhythmia;Long QT syndrome (LQTS);Long QT syndrome 2 (LQT2); none provided	0.89	-0.17
APOB	ENSG00000084674	NM_000384.3(APOB):c.10701G>A (p.Thr3567=)	ACG	ACA	Familial hypercholesterolemia 1 (FHCL1);Hypobetalipoproteinemia, familial, 1 (FHBL1); Familial hypercholesterolemia (FH);Familial hypercholesterolemia 2 (FCHL2);Hypobetalipoproteinemia, familial, 1 (FHBL1);Familial hypercholesterolemia 2 (FCHL2)	2.96	1.57
SCN1A	ENSG00000144285	NM_001165963.4(SCN1A):c.1131A>C (p.Arg377=)	CGA	CGC	Epilepsy;Familial hemiplegic migraine type 3 (FHM3); History of neurodevelopmental disorder;Early infantile epileptic encephalopathy with suppression bursts (EIEE);Generalized epilepsy with febrile seizures plus, type 2 (GEFSP2)	1.36	0.44
SMAD4	ENSG00000141646	NM_005359.6(SMAD4):c.1653A>G (p.Leu551=)	TTA	TTG	Generalized juvenile polyposis/juvenile polyposis coli (JPS);Hereditary cancer-predisposing syndrome; Myhre syndrome (MYHRS);Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (JPHT)	1.53	0.61
ATM	ENSG00000149311	NM_000051.3(ATM):c.1986T>C (p.Phe662=)	TTT	TTC	Ataxia-telangiectasia syndrome (AT);Hereditary cancer-predisposing syndrome; none provided	1.02	0.02
CEP152	ENSG00000103995	NM_001194998.2(CEP152):c.5115A>G (p.Pro1705=)	CCA	CCG	Primary autosomal recessive microcephaly 9 (MCPH9); Seckel syndrome 5 (SCKL5)	0.33	-1.61
SMC3	ENSG00000108055	NM_005445.3(SMC3):c.2329T>C (p.Leu777=)	TTG	CTG	Cornelia de Lange syndrome 3 (CDLS3); History of neurodevelopmental disorder	2.67	1.42
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.2049C>T (p.His683=)	CAC	CAT	Aortic aneurysm, familial thoracic 4 (AAT4);Cardiovascular phenotype; Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.81	-0.3

CDK4	ENSG00000135446	NM_000075.4(CDK4):c.660C>T (p.Ala220=)	GCC	GCT	Hereditary cancer-predisposing syndrome; Cutaneous malignant melanoma 3 (CMM3);Hereditary melanoma	0.74	-0.44
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.17640C>T (p.Arg5880=)	CGC	CGT	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Spinocerebellar ataxia, autosomal recessive 8 (SCAR8)	0.52	-0.93
LDLR	ENSG00000130164	NM_000527.5(LDLR):c.507C>T (p.Asn169=)	AAC	AAT	Familial hypercholesterolemia 1 (FHCL1); Familial hypercholesterolemia (FH)	1.01	0.02
LDLR	ENSG00000130164	NM_000527.4(LDLR):c.1056C>T (p.Cys352=)	TGC	TGT	Familial hypercholesterolemia 1 (FHCL1); Familial hypercholesterolemia (FH)	0.97	-0.05
ATM	ENSG00000149311	NM_000051.3(ATM):c.2805G>C (p.Thr935=)	ACG	ACC	Ataxia-telangiectasia syndrome (AT);Hereditary cancer-predisposing syndrome;	3.18	1.67
STK11	ENSG00000118046	NM_000455.4(STK11):c.1185A>G (p.Thr395=)	ACA	ACG	Peutz-Jeghers syndrome (PJS);Hereditary cancer-predisposing syndrome;	0.34	-1.57
SCN2A	ENSG00000136531	NM_001040142.2(SCN2A):c.5397T>C (p.Tyr1799=)	TAT	TAC	Seizures, benign familial infantile, 3 (BFIS3); Seizures, benign familial infantile, 3 (BFIS3);Early infantile epileptic encephalopathy 11 (DEE11)	1.11	0.15
ATM	ENSG00000149311	NM_000051.3(ATM):c.1272T>C (p.Pro424=)	CCT	CCC	Ataxia-telangiectasia syndrome (AT);Hereditary cancer-predisposing syndrome;	0.98	-0.02
ATM	ENSG00000149311	NM_000051.4(ATM):c.6795C>T	TTC	TTT	Ataxia-telangiectasia syndrome (AT);Hereditary cancer-predisposing syndrome; none provided	0.98	-0.02
DYNC2H1	ENSG00000187240	NM_001377.3(DYNC2H1):c.9939T>C (p.Ala3313=)	GCT	GCC	Jeune thoracic dystrophy (ATD1);Short-rib thoracic dysplasia 3 with or without polydactyly (SRTD3);	1.36	0.44
HBB	ENSG00000244734	NM_000518.5(HBB):c.402G>C (p.Val134=)	GTG	GTC	beta Thalassemia (BTHAL); Fetal hemoglobin quantitative trait locus 1 (HBFQTL1);Hemoglobin E;Hb SS disease (SCD)	0.52	-0.94
ACADM	ENSG00000117054	NM_000016.5(ACADM):c.994C>T (p.Leu332=)	CTA	TTA	Medium-chain acyl-coenzyme A dehydrogenase deficiency (ACADMD);	1.18	0.24
BIN1	ENSG00000136717	NM_139343.3(BIN1):c.30G>A (p.Thr10=)	ACG	ACA	Myopathy, centronuclear, 2 (CNM2);	2.96	1.57
CPLANE1	ENSG00000197603	NM_023073.3(CPLANE1):c.3828T>C (p.Leu1276=)	CTT	CTC	Joubert syndrome 17 (JBTS17); Orofaciodigital syndrome type 6 (OFD6);Joubert syndrome 17 (JBTS17)	1.26	0.33
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.105C>A (p.Gly35=)	GGC	GGA	History of neurodevelopmental disorder; Pitt-Hopkins-like syndrome 2 (PTHSL2)	0.87	-0.2
SCN8A	ENSG00000196876	NM_001330260.2(SCN8A):c.4764C>T (p.Phe1588=)	TTC	TTT	History of neurodevelopmental disorder; Early infantile epileptic encephalopathy with suppression bursts (EIEE)	0.98	-0.02
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.978A>T (p.Thr326=)	ACA	ACT	Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	0.86	-0.21
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.4167C>G (p.Pro1389=)	CCC	CCG	Pitt-Hopkins-like syndrome 2 (PTHSL2);History of neurodevelopmental disorder	0.33	-1.62
KCNH2	ENSG00000055118	NM_172056.2(KCNH2):c.1641G>A (p.Ala547=)	GCG	GCA	Long QT syndrome (LQTS); Arrhythmia	2.88	1.52
PRKAG2	ENSG00000106617	NM_016203.4(PRKAG2):c.1644G>A (p.Ser548=)	TCG	TCA	Glycogen storage disease of heart, lethal congenital;Cardiomyopathy (CMYO)	3.5	1.81
CBS	ENSG00000160200	NM_000071.2(CBS):c.1425G>A (p.Pro475=)	CCG	CCA	Classic homocystinuria; Cardiovascular phenotype	3.05	1.61
FBXO7	ENSG00000100225	NM_012179.4(FBXO7):c.693C>T (p.Ser231=)	AGC	AGT	Parkinson disease 15 (PARK15);	0.72	-0.48
LAMA3	ENSG00000053747	NM_000227.5(LAMA3):c.3201C>T (p.Asn1067=)	AAC	AAT	Junctional epidermolysis bullosa gravis of Herlitz;Laryngo-onycho-cutaneous syndrome	1.01	0.02
PLOD1	ENSG00000083444	NM_000302.4(PLOD1):c.897G>A (p.Pro299=)	CCG	CCA	Ehlers-Danlos syndrome, hydroxylysine-deficient (EDSKSCL1); Cardiovascular phenotype	3.05	1.61

BICD2	ENSG00000185963	NM_001003800.2(BICD2):c.1893C>T (p.Ile631=)	ATC	ATT	Spinal muscular atrophy, lower extremity-predominant, 2A, autosomal dominant (SMALED2A);none provided	0.89	-0.17
PLOD1	ENSG00000083444	NM_000302.4(PLOD1):c.1428G>A (p.Lys476=)	AAG	AAA	Ehlers-Danlos syndrome, hydroxylysine-deficient (EDSKSCL1); Cardiovascular phenotype	0.87	-0.2
MEFV	ENSG00000103313	NM_000243.2(MEFV):c.1245C>T (p.Val415=)	GTC	GTT	Familial Mediterranean fever (FMF);	0.88	-0.19
SMC3	ENSG00000108055	NM_005445.3(SMC3):c.2934G>A (p.Lys978=)	AAG	AAA	Cornelia de Lange syndrome 3 (CDLS3); History of neurodevelopmental disorder	0.87	-0.2
GNE	ENSG00000159921	NM_005476.7(GNE):c.1242T>C (p.Leu414=)	CTT	CTC	GNE myopathy (NM);Sialuria;GNE myopathy (NM)	1.26	0.33
SLC2A10	ENSG00000197496	NM_030777.4(SLC2A10):c.330C>T (p.Phe110=)	TTC	TTT	Arterial tortuosity syndrome (ATORS); Cardiovascular phenotype	0.98	-0.02
GRIN2B	ENSG00000273079	NM_000834.4(GRIN2B):c.291G>A (p.Val97=)	GTG	GTA	Mental retardation, autosomal dominant 6 (MRD6);Epileptic encephalopathy, early infantile, 27 (DEE27);History of neurodevelopmental disorder	0.3	-1.74
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.21612C>T (p.Pro7204=)	CCC	CCT	Emery-Dreifuss muscular dystrophy (EDMD);Cerebellar ataxia	1.02	0.02
USH2A	ENSG00000042781	NM_206933.3(USH2A):c.10341C>T (p.Ala3447=)	GCC	GCT	Usher syndrome, type 2A (USH2A)	0.74	-0.44
TGFBR1	ENSG00000106799	NM_004612.4(TGFBR1):c.207C>T (p.Ser69=)	AGC	AGT	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Cardiovascular phenotype	0.72	-0.48
AARS1	ENSG00000090861	NM_001605.2(AARS1):c.600C>T (p.Ala200=)	GCC	GCT	Charcot-Marie-Tooth disease, type 2;Charcot-Marie-Tooth disease, type 2N (CMT2N)	0.74	-0.44
DNM2	ENSG00000079805	NM_001005360.2(DNM2):c.2592C>T (p.Ala864=)	GCC	GCT	Charcot-Marie-Tooth disease, dominant intermediate B (CMTDIB)	0.74	-0.44
BLM	ENSG00000197299	NM_000057.4(BLM):c.2739C>T (p.Leu913=)	CTC	CTT	Bloom syndrome (BLM);Hereditary cancer-predisposing syndrome;	0.8	-0.33
APC	ENSG00000134982	NM_000038.6(APC):c.4413A>G (p.Ala1471=)	GCA	GCG	Familial adenomatous polyposis 1 (FAP1);Hereditary cancer-predisposing syndrome	0.35	-1.52
KCNQ2	ENSG00000075043	NM_172107.4(KCNQ2):c.1842C>T (p.Pro614=)	CCC	CCT	Seizures;Early infantile epileptic encephalopathy with suppression bursts (EIEE)	1.02	0.02
GLE1	ENSG00000119392	NM_001499.2(GLE1):c.1641T>C (p.Tyr547=)	TAT	TAC	Lethal congenital contracture syndrome 1 (LCCS1);Lethal arthrogryposis with anterior horn cell disease (CAAHD)	1.11	0.15
LDLR	ENSG00000130164	NM_000527.4(LDLR):c.564C>T (p.Tyr188=)	TAC	TAT	Familial hypercholesterolemia 1 (FHCL1); Familial hypercholesterolemia (FH)	0.9	-0.15
BLM	ENSG00000197299	NM_000057.4(BLM):c.1785A>T (p.Ser595=)	TCA	TCT	Bloom syndrome (BLM);Hereditary cancer-predisposing syndrome;	1.2	0.26
FKRP	ENSG00000181027	NM_024301.5(FKRP):c.885C>T (p.Arg295=)	CGC	CGT	Walker-Warburg congenital muscular dystrophy (MDDGA1);Limb-girdle muscular dystrophy-dystroglycanopathy, type C5 (MDDGC5)	0.52	-0.93
APC	ENSG00000134982	NM_000038.6(APC):c.7533C>T (p.Leu2511=)	CTC	CTT	Hereditary cancer-predisposing syndrome;Familial adenomatous polyposis 1 (FAP1)	0.8	-0.33
PYGM	ENSG00000068976	NM_005609.4(PYGM):c.330C>T (p.Asp110=)	GAC	GAT	Glycogen storage disease, type V (GSD5);	0.99	-0.01
AXIN2	ENSG00000168646	NM_004655.4(AXIN2):c.897C>T (p.Asp299=)	GAC	GAT	Oligodontia-colorectal cancer syndrome (ODCRCS); Hereditary cancer-predisposing syndrome	0.99	-0.01
BRIP1	ENSG00000136492	NM_032043.2(BRIP1):c.387T>C (p.Pro129=)	CCT	CCC	Familial cancer of breast;Fanconi anemia, complementation group J (FANCJ);Hereditary cancer-predisposing syndrome	0.98	-0.02
ATM	ENSG00000149311	NM_000051.3(ATM):c.3300G>A (p.Thr1100=)	ACG	ACA	Ataxia-telangiectasia syndrome (AT);Hereditary cancer-predisposing syndrome;	2.96	1.57
NAGLU	ENSG00000108784	NM_000263.4(NAGLU):c.1446G>A (p.Arg482=)	CGG	CGA	Mucopolysaccharidosis, MPS-III-B (MPS3B); Mucopolysaccharidosis, MPS-III-B (MPS3B);Charcot-Marie-Tooth disease, axonal type 2V (CMT2V)	0.6	-0.73
SPTAN1	ENSG00000197694	NM_001130438.3(SPTAN1):c.3042T>G (p.Gly1014=)	GGT	GGG	Seizures;Early infantile epileptic encephalopathy with suppression bursts (EIEE)	1.41	0.5
POLE	ENSG00000177084	NM_006231.3(POLE):c.3763T>C (p.Leu1255=)	TTG	CTG	Colorectal cancer, susceptibility to, 12 (CRCS12);Hereditary cancer-predisposing syndrome	2.67	1.42

POLG	ENSG00000140521	NM_002693.2(POLG):c.3700C>A (p.Arg1234=)	CGA	AGA	Progressive sclerosing poliodystrophy (MTDPS4A);	2.09	1.06
ATM	ENSG00000149311	NM_000051.3(ATM):c.5002C>T (p.Leu1668=)	CTA	TTA	Ataxia-telangiectasia syndrome (AT); Hereditary cancer-predisposing syndrome	1.18	0.24
RYR2	ENSG00000198626	NM_001035.3(RYR2):c.1527C>T (p.Ser509=)	AGC	AGT	Cardiovascular phenotype;Cardiomyopathy (CMYO)	0.72	-0.48
SAMHD1	ENSG00000101347	NM_015474.4(SAMHD1):c.993C>T (p.Tyr331=)	TAC	TAT	Aicardi Goutieres syndrome 5 (AGS5);Chilblain lupus 2 (CHBL2);Aicardi Goutieres syndrome (AGS)	0.9	-0.15
STK11	ENSG00000118046	NM_000455.4(STK11):c.120C>T (p.Arg40=)	CGC	CGT	Peutz-Jeghers syndrome (PJS); Hereditary cancer-predisposing syndrome	0.52	-0.93
ASS1	ENSG00000130707	NM_054012.4(ASS1):c.240C>T (p.Ser80=)	AGC	AGT	Citrullinemia type I (CTNL1); Citrullinemia (CTNL1)	0.72	-0.48
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.8355T>C (p.Pro2785=)	CCT	CCC	Hereditary cancer-predisposing syndrome;	0.98	-0.02
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.3216C>T (p.Asp1072=)	GAC	GAT	Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.99	-0.01
NBN	ENSG00000104320	NM_002485.4(NBN):c.1383G>A (p.Pro461=)	CCG	CCA	Microcephaly, normal intelligence and immunodeficiency (NBS); Hereditary cancer-predisposing syndrome	3.05	1.61
AIP	ENSG00000110711	NM_003977.4(AIP):c.807C>T (p.Phe269=)	TTC	TTT	Somatotroph adenoma (PITA1);Hereditary cancer-predisposing syndrome;	0.98	-0.02
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.1122C>G (p.Val374=)	GTC	GTG	Wilson disease (WND);	1.92	0.94
LMNA	ENSG00000160789	NM_170707.4(LMNA):c.1773C>T (p.Cys591=)	TGC	TGT	Charcot-Marie-Tooth disease, type 2;Cardiomyopathy (CMYO)	0.97	-0.05
STK11	ENSG00000118046	NM_000455.4(STK11):c.957A>G (p.Pro319=)	CCA	CCG	Peutz-Jeghers syndrome (PJS); Hereditary cancer-predisposing syndrome	0.33	-1.61
SLC25A22	ENSG00000177542	NM_001191061.2(SLC25A22):c.885C>T (p.Ile295=)	ATC	ATT	Early infantile epileptic encephalopathy with suppression bursts (EIEE);Seizures	0.89	-0.17
ATM	ENSG00000149311	NM_000051.3(ATM):c.8391T>C (p.Ser2797=)	AGT	AGC	Ataxia-telangiectasia syndrome (AT); Hereditary cancer-predisposing syndrome	1.4	0.48
ENPP1	ENSG00000197594	NM_006208.3(ENPP1):c.1791T>C (p.Asn597=)	AAT	AAC	Arterial calcification, generalized, of infancy, 1 (GACI1);Hypophosphatemic rickets, autosomal recessive, 2 (ARHR2)	0.99	-0.02
MYH7	ENSG00000092054	NM_000257.4(MYH7):c.5139G>A (p.Val1713=)	GTG	GTA	Cardiovascular phenotype;Cardiomyopathy (CMYO)	0.3	-1.74
MEFV	ENSG00000103313	NM_000243.2(MEFV):c.564C>T (p.Pro188=)	CCC	CCT	Familial Mediterranean fever (FMF); none provided	1.02	0.02
BARD1	ENSG00000138376	NM_000465.4(BARD1):c.93C>G (p.Arg31=)	CGC	CGG	Familial cancer of breast;Hereditary cancer-predisposing syndrome;	1.22	0.29
MSH2	ENSG00000095002	NM_000251.2(MSH2):c.51C>A (p.Val17=)	GTC	GTA	Hereditary cancer-predisposing syndrome; Hereditary nonpolyposis colorectal neoplasms	0.57	-0.8
POLD1	ENSG00000062822	NM_002691.4(POLD1):c.3231C>T (p.Pro1077=)	CCC	CCT	Hereditary cancer-predisposing syndrome;Colorectal cancer 10 (CRCS10)	1.02	0.02
POLD1	ENSG00000062822	NM_002691.4(POLD1):c.3258G>C (p.Arg1086=)	CGG	CGC	Colorectal cancer 10 (CRCS10);Hereditary cancer-predisposing syndrome	0.82	-0.29
MYH7	ENSG00000092054	NM_000257.4(MYH7):c.4668C>A (p.Gly1556=)	GGC	GGA	Cardiomyopathy (CMYO);Hypertrophic cardiomyopathy;	0.87	-0.2
FOXG1	ENSG00000176165	NM_005249.5(FOXG1):c.672C>G (p.Gly224=)	GGC	GGG	Rett syndrome, congenital variant; History of neurodevelopmental disorder	0.77	-0.37
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.1575A>G (p.Arg525=)	AGA	AGG	History of neurodevelopmental disorder;Pitt-Hopkins-like syndrome 2 (PTHSL2)	0.91	-0.14
ARHGEF9	ENSG00000131089	NM_001353921.2(ARHGEF9):c.675G>A (p.Gln225=)	CAG	CAA	History of neurodevelopmental disorder;Early infantile epileptic encephalopathy 8 (DEE8)	0.4	-1.32
POLD1	ENSG00000062822	NM_002691.4(POLD1):c.2100A>G (p.Val700=)	GTA	GTG	Hereditary cancer-predisposing syndrome; Colorectal cancer 10 (CRCS10)	3.34	1.74
HSPG2	ENSG00000142798	NM_005529.7(HSPG2):c.11475C>T (p.Ile3825=)	ATC	ATT	Schwartz-Jampel syndrome;Lethal Kniest-like syndrome (DDSH);	0.89	-0.17

FBN1	ENSG00000166147	NM_000138.4(FBN1):c.783T>C (p.Asn261=)	AAT	AAC	Familial thoracic aortic aneurysm and aortic dissection (TAAD); Marfan syndrome (MFS);Ectopia lentis, isolated, autosomal dominant (ECTOL1);Stiff skin syndrome (SSKS);Acromicric dysplasia (ACMICD);Weill-Marchesani syndrome;Geleophysic dysplasia;Cardiovascular phenotype; Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.99	-0.02
LMNA	ENSG00000160789	NM_170707.4(LMNA):c.1017G>A (p.Ala339=)	GCG	GCA	Cardiovascular phenotype; Cardiomyopathy (CMYO);Charcot-Marie-Tooth disease, type 2;Charcot-Marie-Tooth disease	2.88	1.52
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.9234C>T (p.Val3078=)	GTC	GTT	Hereditary cancer-predisposing syndrome;Breast-ovarian cancer, familial 2 (BROVCA2); Hereditary breast and ovarian cancer syndrome (HBOC)	0.88	-0.19
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.2802G>A (p.Glu934=)	GAG	GAA	Familial thoracic aortic aneurysm and aortic dissection (TAAD); Aortic aneurysm, familial thoracic 4 (AAT4);Cardiovascular phenotype	0.86	-0.22
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.8502A>G (p.Gln2834=)	CAA	CAG	Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);History of neurodevelopmental disorder;	2.49	1.32
BRIP1	ENSG00000136492	NM_032043.2(BRIP1):c.408A>C (p.Ala136=)	GCA	GCC	Familial cancer of breast;Fanconi anemia, complementation group J (FANCJ);Hereditary cancer-predisposing syndrome;Familial cancer of breast	1.5	0.59
GYS1	ENSG00000104812	NM_002103.5(GYS1):c.1848C>T (p.Ala616=)	GCC	GCT	Glycogen storage disease 0, muscle (GSD0B);Neuroferritinopathy (NBIA3);Hereditary hyperferritinemia with congenital cataracts (HRFTC);	0.74	-0.44
DSC2	ENSG00000134755	NM_024422.6(DSC2):c.2430G>A (p.Arg810=)	AGG	AGA	Arrhythmogenic right ventricular cardiomyopathy, type 11 (ARVD11); Cardiovascular phenotype;Cardiomyopathy (CMYO)	1.1	0.14
FLNA	ENSG00000196924	NM_001110556.2(FLNA):c.1029C>T (p.Ser343=)	TCC	TCT	Cardiovascular phenotype;History of neurodevelopmental disorder; Periventricular nodular heterotopia 1 (PVNH1);Melnick-Needles syndrome (MNS);Oto-palato-digital syndrome, type II (OPD2);Frontometaphyseal dysplasia (FMD1)	0.98	-0.03
MSH6	ENSG00000116062	NM_000179.2(MSH6):c.240A>G (p.Val80=)	GTA	GTG	Hereditary nonpolyposis colorectal cancer type 5 (HNPCC5);Hereditary cancer-predisposing syndrome; Hereditary nonpolyposis colorectal neoplasms	3.34	1.74
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.12588C>T (p.Ile4196=)	ATC	ATT	Central core myopathy (CCD);Neuromuscular disease, congenital, with uniform type 1 fiber (CNMDU1);Multiminicore Disease (MmD);Malignant hyperthermia susceptibility (MHS);RYR1-Related Disorders	0.89	-0.17
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.14505G>A (p.Gly4835=)	GGG	GGA	Malignant hyperthermia, susceptibility to, 1 (MHS1);Minicore myopathy with external ophthalmoplegia;Central core myopathy (CCD);Neuromuscular disease, congenital, with uniform type 1 fiber (CNMDU1); RYR1-Related Disorders	1.13	0.17

LMNA	ENSG00000160789	NM_170707.4(LMNA):c.1551G>A (p.Gln517=)	CAG	CAA	Charcot-Marie-Tooth disease, type 2;Mandibuloacral dysplasia with type A lipodystrophy (MADA);Limb-Girdle Muscular Dystrophy, Recessive;Hutchinson-Gilford syndrome (HGPS);Dilated cardiomyopathy 1A (CMD1A);Lethal tight skin contracture syndrome;Familial partial lipodystrophy 2 (FPLD2);Emery-Dreifuss muscular dystrophy (EDMD);Congenital muscular dystrophy, LMNA-related (MDCL);Lipoatrophy with Diabetes, Hepatic Steatosis, Hypertrophic Cardiomyopathy, and Leukomelanodermic Papules; Cardiovascular phenotype;Cardiomyopathy (CMYO);Charcot-Marie-Tooth disease type 2B1 (CMT2B1);Emery-Dreifuss muscular dystrophy 2, autosomal dominant (EDMD2);Charcot-Marie-Tooth disease	0.4	-1.32
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.7056C>T (p.Ser2352=)	TCC	TCT	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Weill-Marchesani syndrome;Acromicric dysplasia (ACMICD);Stiff skin syndrome (SSKS);Ectopia lentis, isolated, autosomal dominant (ECTOL1);Marfan syndrome (MFS);Geleophysic dysplasia; Cardiovascular phenotype;Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.98	-0.03
SMAD4	ENSG00000141646	NM_005359.6(SMAD4):c.1545A>G (p.Arg515=)	AGA	AGG	Generalized juvenile polyposis/juvenile polyposis coli (JPS);Hereditary cancer-predisposing syndrome; Cardiovascular phenotype;Myhre syndrome (MYHRS);Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (JPHT)	0.91	-0.14
MYH7	ENSG00000092054	NM_000257.4(MYH7):c.2334C>T (p.Asp778=)	GAC	GAT	Cardiovascular phenotype;Hypertrophic cardiomyopathy;Cardiomyopathy (CMYO);Myosin storage myopathy (MSMA);Dilated cardiomyopathy 1S (CMD1S);Myopathy, distal, 1 (MPD1);Familial hypertrophic cardiomyopathy 1 (CMH1)	0.99	-0.01
SMAD4	ENSG00000141646	NM_005359.6(SMAD4):c.1632G>A (p.Pro544=)	CCG	CCA	Generalized juvenile polyposis/juvenile polyposis coli (JPS);Hereditary cancer-predisposing syndrome; Cardiovascular phenotype;Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (JPHT);Myhre syndrome (MYHRS);	3.05	1.61
PTCH1	ENSG00000185920	NM_000264.5(PTCH1):c.801G>A (p.Glu267=)	GAG	GAA	Gorlin syndrome (BCNS);Hereditary cancer-predisposing syndrome; Holoprosencephaly 7 (HPE7)	0.86	-0.22
KIT	ENSG00000157404	NM_000222.2(KIT):c.2349C>T (p.Leu783=)	CTC	CTT	Gastrointestinal stromal tumor (GIST);Hereditary cancer-predisposing syndrome;Mastocytosis (MASTC);Partial albinism (PBT)	0.8	-0.33
TBC1D24	ENSG00000162065	NM_001199107.2(TBC1D24):c.1026G>A (p.Ser342=)	TCG	TCA	Epileptic encephalopathy, early infantile, 1 (DEE1);Deafness, autosomal dominant 65 (DFNA65);Caused by mutation in the TBC1 domain family, member 24;Myoclonic epilepsy, familial infantile (FIME)	3.5	1.81
CFTR	ENSG00000001626	NM_000492.3(CFTR):c.3429G>A (p.Leu1143=)	TTG	TTA	Cystic fibrosis (CF);Inborn genetic diseases;CFTR-related disorders (CFTR-RD)	0.65	-0.61
PTCH1	ENSG00000185920	NM_000264.5(PTCH1):c.3372A>T (p.Ala1124=)	GCA	GCT	Gorlin syndrome (BCNS); Hereditary cancer-predisposing syndrome;Holoprosencephaly 7 (HPE7)	1.11	0.14
TSC1	ENSG00000165699	NM_000368.4(TSC1):c.519G>A (p.Ala173=)	GCG	GCA	Tuberous sclerosis 1 (TSC1); Hereditary cancer-predisposing syndrome;Focal cortical dysplasia type II (FCORD2)	2.88	1.52
CFTR	ENSG00000001626	NM_000492.3(CFTR):c.360G>A (p.Ala120=)	GCG	GCA	Cystic fibrosis (CF);CFTR-related disorders (CFTR-RD)	2.88	1.52

SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.22038A>G (p.Ser7346=)	TCA	TCG	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Spinocerebellar ataxia, autosomal recessive 8 (SCAR8)	0.29	-1.81
SMAD4	ENSG00000141646	NM_005359.6(SMAD4):c.342T>C (p.Tyr114=)	TAT	TAC	Generalized juvenile polyposis/juvenile polyposis coli (JPS); Hereditary cancer-predisposing syndrome;Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (JPHT);Myhre syndrome (MYHRS)	1.11	0.15
NF1	ENSG00000196712	NM_000267.3(NF1):c.1866T>C (p.Cys622=)	TGT	TGC	Neurofibromatosis, type 1 (NF1);Hereditary cancer-predisposing syndrome; Neurofibromatosis-Noonan syndrome (NFNS);Neurofibromatosis, familial spinal (FSNF);Café-au-lait macules with pulmonary stenosis (WTSN)	1.03	0.05
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.5106A>G (p.Lys1702=)	AAA	AAG	Hereditary cancer-predisposing syndrome;Breast-ovarian cancer, familial 1 (BROVCA1)	1.15	0.2
HNF4A	ENSG00000101076	NM_175914.4(HNF4A):c.381G>A (p.Leu127=)	CTG	CTA	Maturity-onset diabetes of the young, type 1 (MODY1); Familial hyperinsulinism	0.21	-2.27
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.1278C>T (p.Val426=)	GTC	GTT	Wilson disease (WND);	0.88	-0.19
TPO	ENSG00000115705	NM_001206744.2(TPO):c.660C>T (p.Val220=)	GTC	GTT	Deficiency of iodide peroxidase (TDH2A)	0.88	-0.19
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.4254C>T (p.Pro1418=)	CCC	CCT	Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	1.02	0.02
FLNB	ENSG00000136068	NM_001457.4(FLNB):c.3594G>A (p.Thr1198=)	ACG	ACA	FLNB-Related Spectrum Disorders	2.96	1.57
BLM	ENSG00000197299	NM_000057.4(BLM):c.1467G>A (p.Arg489=)	AGG	AGA	Bloom syndrome (BLM);Hereditary cancer-predisposing syndrome;	1.1	0.14
RELN	ENSG00000189056	NM_005045.4(RELN):c.5643G>A (p.Leu1881=)	CTG	CTA	Norman-Roberts syndrome (LIS2);Epilepsy, familial temporal lobe, 7 (ETL7);Norman-Roberts syndrome (LIS2)	0.21	-2.27
PCNT	ENSG00000160299	NM_006031.6(PCNT):c.7803G>A (p.Ala2601=)	GCG	GCA	Microcephalic osteodysplastic primordial dwarfism type II (MOPD2)	2.88	1.52
HMGCS2	ENSG00000134240	NM_001166107.1(HMGCS2):c.174C>T (p.Ala58=)	GCC	GCT	mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency (HMGCS2D);	0.74	-0.44
CAVIN1	ENSG00000177469	NM_012232.6(CAVIN1):c.540G>A (p.Glu180=)	GAG	GAA	Lipodystrophy, congenital generalized, type 4 (CGL4)	0.86	-0.22
PYGM	ENSG00000068976	NM_005609.4(PYGM):c.1083C>T (p.Asp361=)	GAC	GAT	Glycogen storage disease, type V (GSD5);	0.99	-0.01
RP1	ENSG00000104237	NM_006269.2(RP1):c.228C>T (p.Leu76=)	CTC	CTT	Retinitis pigmentosa 1 (RP1);Retinitis pigmentosa (RP)	0.8	-0.33
GNE	ENSG00000159921	NM_005476.7(GNE):c.1509C>G (p.Pro503=)	CCC	CCG	GNE myopathy (NM);Sialuria;GNE myopathy (NM)	0.33	-1.62
PTCH1	ENSG00000185920	NM_000264.5(PTCH1):c.777C>T (p.Phe259=)	TTC	TTT	Gorlin syndrome (BCNS);Hereditary cancer-predisposing syndrome;Holoprosencephaly 7 (HPE7)	0.98	-0.02
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.17016G>T (p.Arg5672=)	CGG	CGT	Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Spinocerebellar ataxia, autosomal recessive 8 (SCAR8)	0.43	-1.22
CHD7	ENSG00000171316	NM_017780.4(CHD7):c.7848G>A (p.Leu2616=)	CTG	CTA	CHARGE association (CHARGE);	0.21	-2.27
ATP13A2	ENSG00000159363	NM_022089.4(ATP13A2):c.3258G>A (p.Ala1086=)	GCG	GCA	Kufor-Rakeb syndrome (KRS);Spastic paraplegia 78, autosomal recessive (SPG78);Kufor-Rakeb syndrome (KRS)	2.88	1.52
PTCH1	ENSG00000185920	NM_000264.5(PTCH1):c.3066C>T (p.Ile1022=)	ATC	ATT	Gorlin syndrome (BCNS);Hereditary cancer-predisposing syndrome;Holoprosencephaly 7 (HPE7)	0.89	-0.17
MEN1	ENSG00000133895	NM_000244.3(MEN1):c.585G>A (p.Gly195=)	GGG	GGA	Multiple endocrine neoplasia, type 1 (MEN1);Hereditary cancer-predisposing syndrome;Hyperparathyroidism	1.13	0.17
ZEB2	ENSG00000169554	NM_014795.4(ZEB2):c.9G>A (p.Gln3=)	CAG	CAA	Mowat-Wilson syndrome (MOWS);	0.4	-1.32
NBN	ENSG00000104320	NM_002485.4(NBN):c.207A>G (p.Lys69=)	AAA	AAG	Hereditary cancer-predisposing syndrome;Microcephaly, normal intelligence and immunodeficiency (NBS)	1.15	0.2
CDKN2A	ENSG00000147889	NM_000077.4(CDKN2A):c.246G>C (p.Val82=)	GTG	GTC	Hereditary cancer-predisposing syndrome;Hereditary melanoma	0.52	-0.94

ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.10149C>T (p.Ser3383=)	TCC	TCT	Usher syndrome, type 2C (USH2C)	0.98	-0.03
SLC2A1	ENSG00000117394	NM_006516.3(SLC2A1):c.1395C>T (p.Ser465=)	TCC	TCT	GLUT1 deficiency syndrome 1, autosomal recessive;Stomatin-deficient cryohydrocytosis with neurologic defects (SDCHCN);Dystonia 9 (DYT9);GLUT1 deficiency syndrome 1 (GLUT1DS1);GLUT1 deficiency syndrome 2 (GLUT1DS2);Epilepsy, idiopathic generalized, susceptibility to, 12 (EIG12)	0.98	-0.03
FOXG1	ENSG00000176165	NM_005249.5(FOXG1):c.456G>T (p.Gly152=)	GGG	GGT	Rett syndrome, congenital variant;	0.71	-0.5
CFTR	ENSG00000001626	NM_000492.3(CFTR):c.1365G>T (p.Ala455=)	GCG	GCT	CFTR-related disorders (CFTR-RD)	3.18	1.67
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.2772C>T (p.Tyr924=)	TAC	TAT	History of neurodevelopmental disorder; Pitt-Hopkins-like syndrome 2 (PTHSL2)	0.9	-0.15
KIF1A	ENSG00000130294	NM_004321.7(KIF1A):c.3042C>G (p.Ala1014=)	GCC	GCG	History of neurodevelopmental disorder; Spastic paraplegia 30, autosomal recessive (SPG30);Hereditary sensory and autonomic neuropathy type IIC (HSN2C);Intellectual disability, autosomal dominant 9 (NESCAVS);Spastic paraplegia 30, autosomal recessive (SPG30)	0.23	-2.11
PALB2	ENSG00000083093	NM_024675.3(PALB2):c.2100A>T (p.Ser700=)	TCA	TCT	Hereditary cancer-predisposing syndrome;Familial cancer of breast;Fanconi anemia, complementation group N (FANCN);	1.2	0.26
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.5319G>A (p.Glu1773=)	GAG	GAA	Hereditary breast and ovarian cancer syndrome (HBOC);Hereditary cancer-predisposing syndrome;Fanconi anemia (FA); Breast-ovarian cancer, familial 2 (BROVCA2)	0.86	-0.22
KCTD7	ENSG00000243335	NM_153033.4(KCTD7):c.273C>T (p.Ser91=)	TCC	TCT	Seizures; Epilepsy, progressive myoclonic 3 (EPM3)	0.98	-0.03
SMAD3	ENSG00000166949	NM_005902.4(SMAD3):c.984G>A (p.Pro328=)	CCG	CCA	Familial thoracic aortic aneurysm and aortic dissection (TAAD); Loeys-Dietz syndrome (LDS);Cardiovascular phenotype	3.05	1.61
PCSK9	ENSG00000169174	NM_174936.3(PCSK9):c.1227C>T (p.Ala409=)	GCC	GCT	Familial hypercholesterolemia 3 (FHCL3);Familial hypercholesterolemia 1 (FHCL1);Hypobetalipoproteinemia;Familial hypercholesterolemia (FH)	0.74	-0.44
AGXT	ENSG00000172482	NM_000030.3(AGXT):c.489G>A (p.Leu163=)	CTG	CTA	Primary hyperoxaluria, type I (HP1); Primary hyperoxaluria;	0.21	-2.27
KIT	ENSG00000157404	NM_000222.2(KIT):c.1674G>A (p.Lys558=)	AAG	AAA	Gastrointestinal stromal tumor (GIST);Hereditary cancer-predisposing syndrome;Partial albinism (PBT);Mastocytosis (MASTC)	0.87	-0.2
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.6339T>C (p.Thr2113=)	ACT	ACC	Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	1.24	0.31
CASR	ENSG00000036828	NM_000388.4(CASR):c.60C>T (p.Tyr20=)	TAC	TAT	Familial hypocalciuric hypercalcemia (FHH);Hypocalcemia, autosomal dominant 1 (HYPOC1);Hypocalcemia, autosomal dominant 1 (HYPOC1);Familial isolated hypoparathyroidism (FIH);Hypocalciuric hypercalcemia, familial, type 1 (HHC1);Neonatal severe hyperparathyroidism (NSHPT)	0.9	-0.15
TTN	ENSG00000155657	NM_001267550.2(TTN):c.56535G>A (p.Thr18845=)	ACG	ACA	Cardiovascular phenotype; Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Dilated cardiomyopathy 1G (CMD1G);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Tibial muscular dystrophy (TMD);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9)	2.96	1.57

RYR1	ENSG00000196218	NM_000540.2(RYR1):c.4911G>A (p.Ala1637=)	GCG	GCA	RYR1-Related Disorders;Minicore myopathy with external ophthalmoplegia;Malignant hyperthermia, susceptibility to, 1 (MHS1)	2.88	1.52
CDC73	ENSG00000134371	NM_024529.4(CDC73):c.1011C>T (p.Ala337=)	GCC	GCT	Parathyroid carcinoma (PRTC);Hereditary cancer-predisposing syndrome;Hyperparathyroidism 1 (HRPT1);Hyperparathyroidism 2 (HRPT2)	0.74	-0.44
GBE1	ENSG00000114480	NM_000158.4(GBE1):c.1521T>C (p.Thr507=)	ACT	ACC	Glycogen storage disease, type IV (GSD4);Glycogen storage disease IV, classic hepatic;Adult polyglucosan body disease (APBN);Glycogen storage disease, type IV (GSD4)	1.24	0.31
KIT	ENSG00000157404	NM_000222.2(KIT):c.2118T>G (p.Leu706=)	CTT	CTG	Gastrointestinal stromal tumor (GIST);Hereditary cancer-predisposing syndrome;Mastocytosis (MASTC);Partial albinism (PBT)	2.54	1.35
KIT	ENSG00000157404	NM_000222.2(KIT):c.978C>T (p.Asn326=)	AAC	AAT	Gastrointestinal stromal tumor (GIST);Hereditary cancer-predisposing syndrome;Partial albinism (PBT);Mastocytosis (MASTC)	1.01	0.02
CYP1B1	ENSG00000138061	NM_000104.3(CYP1B1):c.1590T>C (p.Asp530=)	GAT	GAC	Congenital glaucoma;Glaucoma 3, primary congenital, A (GLC3A);Irido-corneo-trabecular dysgenesis (ASGD5)	1.01	0.01
TTN	ENSG00000155657	NM_001267550.2(TTN):c.43161G>A (p.Glu14387=)	GAG	GAA	Tibial muscular dystrophy (TMD);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Dilated cardiomyopathy 1G (CMD1G)	0.86	-0.22
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.4980C>T (p.Arg1660=)	CGC	CGT	RYR1-Related Disorders;Central core myopathy (CCD);Malignant hyperthermia, susceptibility to, 1 (MHS1);Minicore myopathy with external ophthalmoplegia	0.52	-0.93
NF1	ENSG00000196712	NM_000267.3(NF1):c.7047C>T (p.His2349=)	CAC	CAT	Neurofibromatosis, type 1 (NF1);Hereditary cancer-predisposing syndrome;Neurofibromatosis-Noonan syndrome (NFNS);Café-au-lait macules with pulmonary stenosis (WTSN);Neurofibromatosis, familial spinal (FSNF)	0.81	-0.3
TTN	ENSG00000155657	NM_001267550.2(TTN):c.80553C>T (p.Phe26851=)	TTC	TTT	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Tibial muscular dystrophy (TMD)	0.98	-0.02
MYO7A	ENSG00000137474	NM_000260.4(MYO7A):c.3297C>T (p.Pro1099=)	CCC	CCT	Deafness, autosomal dominant 11 (DFNA11);Deafness, autosomal recessive 2 (DFNB2);Usher syndrome type 1 (USH1);Usher syndrome, type 1B (USH1B)	1.02	0.02
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.2091C>T (p.Ala697=)	GCC	GCT	Central core myopathy (CCD);Minicore myopathy with external ophthalmoplegia;Neuromuscular disease, congenital, with uniform type 1 fiber (CNMDU1);Malignant hyperthermia, susceptibility to, 1 (MHS1);RYR1-Related Disorders	0.74	-0.44
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.5211A>G (p.Arg1737=)	AGA	AGG	Hereditary breast and ovarian cancer syndrome (HBOC);Breast-ovarian cancer, familial 1 (BROVCA1);Hereditary cancer-predisposing syndrome	0.91	-0.14
SERPINA1	ENSG00000197249	NM_000295.5(SERPINA1):c.171C>T (p.Phe57=)	TTC	TTT	Alpha-1-antitrypsin deficiency (A1ATD);	0.98	-0.02
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.2937C>T (p.Pro979=)	CCC	CCT	Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	1.02	0.02
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.4341G>A (p.Leu1447=)	CTG	CTA	Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	0.21	-2.27
TRAPPC9	ENSG00000167632	NM_001160372.4(TRAPPC9):c.1809G>A (p.Leu603=)	ACC	ACA	Intellectual Disability, Recessive	0.93	-0.1
MCPH1	ENSG00000147316	NM_024596.5(MCPH1):c.1752A>G (p.Pro584=)	CCA	CCG	Primary autosomal recessive microcephaly 1 (MCPH1)	0.33	-1.61

ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.2544C>T (p.Gly848=)	GGC	GGT	Wilson disease (WND);	0.55	-0.87
ADGRG1	ENSG00000205336	NM_201525.4(ADGRG1):c.1188C>T (p.Asp396=)	GAC	GAT	Polymicrogyria, bilateral frontoparietal (BFPP)	0.99	-0.01
DYNC2H1	ENSG00000187240	NM_001377.3(DYNC2H1):c.4959T>C (p.Tyr1653=)	TAT	TAC	Jeune thoracic dystrophy (ATD1);Short-rib thoracic dysplasia 3 with or without polydactyly (SRTD3)	1.11	0.15
MMP2	ENSG00000087245	NM_004530.6(MMP2):c.759C>T (p.Ser253=)	AGC	AGT	Multicentric osteolysis, nodulosis and arthropathy (MONA)	0.72	-0.48
POU1F1	ENSG00000064835	NM_000306.4(POU1F1):c.252C>T (p.His84=)	CAC	CAT	Pituitary hormone deficiency, combined, 1 (CPHD1)	0.81	-0.3
ARSB	ENSG00000113273	NM_000046.5(ARSB):c.1078C>T (p.Leu360=)	CTG	TTG	Mucopolysaccharidosis type 6 (MPS6);	0.37	-1.42
CDH3	ENSG00000062038	NM_001793.6(CDH3):c.918C>T (p.Asp306=)	GAC	GAT	EEM syndrome (EEMS)	0.99	-0.01
USH1C	ENSG00000006611	NM_153676.4(USH1C):c.669C>A (p.Gly223=)	GGC	GGA	Usher syndrome, type 1C (USH1C)	0.87	-0.2
P3H1	ENSG00000117385	NM_022356.3(P3H1):c.1428C>T (p.Gly476=)	GGC	GGT	Osteogenesis imperfecta type 8 (OI8);Osteogenesis Imperfecta, Recessive	0.55	-0.87
FRAS1	ENSG00000138759	NM_025074.7(FRAS1):c.969G>A (p.Val323=)	GTG	GTA	Fraser syndrome 1 (FRASRS1)	0.3	-1.74
FLNA	ENSG00000196924	NM_001110556.2(FLNA):c.7389G>A (p.Ser2463=)	TCG	TCA	Periventricular nodular heterotopia 1 (PVNH1);Melnick-Needles syndrome (MNS);Oto-palato-digital syndrome, type II (OPD2);Frontometaphyseal dysplasia 1 (FMD1)	3.5	1.81
PCNT	ENSG00000160299	NM_006031.6(PCNT):c.7332C>T (p.Thr2444=)	ACC	ACT	Microcephalic osteodysplastic primordial dwarfism type II (MOPD2)	0.8	-0.31
SLC25A19	ENSG00000125454	NM_001126121.2(SLC25A19):c.93G>A (p.Ala31=)	GCG	GCA	Amish lethal microcephaly (MCPHA)	2.88	1.52
KCNT1	ENSG00000107147	NM_020822.3(KCNT1):c.1110G>A (p.Thr370=)	ACG	ACA	Early infantile epileptic encephalopathy 14 (DEE14);Epilepsy, nocturnal frontal lobe, 5 (ENFL5)	2.96	1.57
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.7533A>G (p.Ser2511=)	TCA	TCG	Autosomal recessive polycystic kidney disease (ARPKD);	0.29	-1.81
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.2781A>G (p.Gln927=)	CAA	CAG	Autosomal recessive polycystic kidney disease (ARPKD);	2.49	1.32
USH1C	ENSG00000006611	NM_153676.4(USH1C):c.513C>T (p.Pro171=)	CCC	CCT	Usher syndrome, type 1C (USH1C)	1.02	0.02
LARGE1	ENSG00000133424	NM_004737.6(LARGE1):c.99C>T (p.Ser33=)	AGC	AGT	Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B6 (MDDGB6);Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, type A6 (MDDGA6)	0.72	-0.48
SIM1	ENSG00000112246	NM_005068.2(SIM1):c.279C>T (p.Phe93=)	TTC	TTT	Obesity due to SIM1 deficiency	0.98	-0.02
LRP2	ENSG00000081479	NM_004525.3(LRP2):c.4831C>T (p.Leu1611=)	CTG	TTG	Donnai-Barrow syndrome	0.37	-1.42
PROP1	ENSG00000175325	NM_006261.4(PROP1):c.96G>A (p.Pro32=)	CCG	CCA	Pituitary hormone deficiency, combined 2 (CPHD2)	3.05	1.61
ELP1	ENSG00000070061	NM_003640.5(ELP1):c.2217A>G (p.Lys739=)	AAA	AAG	Familial dysautonomia (HSAN3)	1.15	0.2
USH1C	ENSG00000006611	NM_153676.4(USH1C):c.360C>T (p.Gly120=)	GGC	GGT	Usher syndrome, type 1C (USH1C)	0.55	-0.87
FLNB	ENSG00000136068	NM_001457.4(FLNB):c.3288C>T (p.Ser1096=)	TCC	TCT	FLNB-Related Spectrum Disorders	0.98	-0.03
SNRNP200	ENSG00000144028	NM_014014.5(SNRNP200):c.2928G>A (p.Thr976=)	ACG	ACA	Retinitis pigmentosa (RP)	2.96	1.57
CYP27A1	ENSG00000135929	NM_000784.4(CYP27A1):c.276C>T (p.Tyr92=)	TAC	TAT	Cholestanol storage disease (CTX);	0.9	-0.15
CDH3	ENSG00000062038	NM_001793.6(CDH3):c.1785C>T (p.Val595=)	GTC	GTT	EEM syndrome (EEMS)	0.88	-0.19
FREM2	ENSG00000150893	NM_207361.6(FREM2):c.7062G>A (p.Thr2354=)	ACG	ACA	Fraser syndrome 2	2.96	1.57
PEX3	ENSG00000034693	NM_003630.3(PEX3):c.165A>G (p.Gln55=)	CAA	CAG	Peroxisome biogenesis disorder 10A (PBD10A)	2.49	1.32
ABCC2	ENSG00000023839	NM_000392.5(ABCC2):c.2955G>A (p.Ala985=)	GCG	GCA	Dubin-Johnson syndrome (DJS)	2.88	1.52
ABCG8	ENSG00000143921	NM_022437.3(ABCG8):c.1839T>C (p.Tyr613=)	TAT	TAC	Sitosterolemia 1 (STSL1)	1.11	0.15
ABCG8	ENSG00000143921	NM_022437.3(ABCG8):c.1386C>T (p.Asn462=)	AAC	AAT	Sitosterolemia 1 (STSL1)	1.01	0.02
CYP27A1	ENSG00000135929	NM_000784.4(CYP27A1):c.789C>T (p.Pro263=)	CCC	CCT	Cholestanol storage disease (CTX);	1.02	0.02
DDR2	ENSG00000162733	NM_006182.4(DDR2):c.720C>T (p.Asp240=)	GAC	GAT	Spondyloepimetaphyseal dysplasia-short limb-abnormal calcification syndrome (SMED-SL)	0.99	-0.01
TARDBP	ENSG00000120948	NM_007375.3(TARDBP):c.669C>G (p.Pro223=)	CCC	CCG	Amyotrophic lateral sclerosis type 10 (ALS10)	0.33	-1.62

TYK2	ENSG00000105397	NM_003331.5(TYK2):c.648G>A (p.Pro216=)	CCG	CCA	Tyrosine kinase 2 deficiency (IMD35);Immunodeficiency;Recurrent skin infections	3.05	1.61
CHRNA1	ENSG00000138435	NM_001039523.3(CHRNA1):c.987C>T (p.Phe329=)	TTC	TTT	Lethal multiple pterygium syndrome (LMPS);Congenital myasthenic syndrome (CMS)	0.98	-0.02
GH1	ENSG00000259384	NM_000515.5(GH1):c.15C>T (p.Ser5=)	TCC	TCT	Growth hormone deficiency	0.98	-0.03
PCARE	ENSG00000179270	NM_001029883.3(PCARE):c.2418C>T (p.Pro806=)	CCC	CCT	Retinitis pigmentosa (RP)	1.02	0.02
VSX2	ENSG00000119614	NM_182894.3(VSX2):c.699C>T (p.Pro233=)	CCC	CCT	Microphthalmia, isolated 2 (MCOP2);Microphthalmia, isolated, with coloboma 3 (MCOPCB3)	1.02	0.02
MTTP	ENSG00000138823	NM_000253.3(MTTP):c.2025C>T (p.Ile675=)	ATC	ATT	Abetalipoproteinaemia (ABL)	0.89	-0.17
ABCA4	ENSG00000198691	NM_000350.3(ABCA4):c.1932C>T (p.Asp644=)	GAC	GAT	ABCA4-Related Disorders	0.99	-0.01
FAM161A	ENSG00000170264	NM_001201543.2(FAM161A):c.1929A>G (p.Ser643=)	TCA	TCG	Retinitis pigmentosa (RP)	0.29	-1.81
LHX3	ENSG00000107187	NM_178138.6(LHX3):c.198C>G (p.Ala66=)	GCC	GCG	Non-acquired combined pituitary hormone deficiency with spine abnormalities (CPHD3)	0.23	-2.11
CDH3	ENSG00000062038	NM_001793.6(CDH3):c.1443C>T (p.Asp481=)	GAC	GAT	EEM syndrome (EEMS)	0.99	-0.01
MUTYH	ENSG00000132781	NM_001128425.1(MUTYH):c.1600C>A (p.Arg534=)	CGG	AGG	Hereditary cancer-predisposing syndrome;MYH-associated polyposis (FAP2)	1.15	0.2
ABCG8	ENSG00000143921	NM_022437.3(ABCG8):c.1941C>G (p.Val647=)	GTC	GTG	Sitosterolemia 1 (STSL1)	1.92	0.94
USH2A	ENSG00000042781	NM_206933.3(USH2A):c.15306C>T (p.Ala5102=)	GCC	GCT	Usher syndrome, type 2A (USH2A)	0.74	-0.44
ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.2811A>T (p.Gly937=)	GGA	GGT	Progressive familial intrahepatic cholestasis 2 (PFIC2)	0.63	-0.67
SLC17A5	ENSG00000119899	NM_012434.5(SLC17A5):c.957C>A (p.Ile319=)	ATC	ATA	Salla disease (SD);Sialic acid storage disease, severe infantile type (ISSD)	0.44	-1.2
MYO7A	ENSG00000137474	NM_000260.4(MYO7A):c.2025C>T (p.Arg675=)	CGC	CGT	Usher syndrome, type 1B (USH1B)	0.52	-0.93
CUL7	ENSG00000044090	NM_014780.4(CUL7):c.3747G>A (p.Leu1249=)	CCC	CCA	Three M syndrome 1 (3M1)	1	-0.01
ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.1254T>C (p.Gly418=)	GGT	GGC	Progressive familial intrahepatic cholestasis 2 (PFIC2)	1.82	0.87
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.1926C>T (p.Phe642=)	TTC	TTT	Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	0.98	-0.02
NEK1	ENSG00000137601	NM_012224.3(NEK1):c.2805G>A (p.Ser935=)	TCG	TCA	none provided	3.5	1.81
ATP1A3	ENSG00000105409	NM_152296.5(ATP1A3):c.1011C>T (p.Thr337=)	ACC	ACT	Dystonia 12 (DYT12);Alternating hemiplegia of childhood 2 (AHC2)	0.8	-0.31
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.4236C>T (p.Gly1412=)	GGC	GGT	Pitt-Hopkins-like syndrome 2 (PTHSL2)	0.55	-0.87
AIPL1	ENSG00000129221	NM_014336.5(AIPL1):c.33G>C (p.Gly11=)	GGG	GGC	Leber congenital amaurosis 4 (LCA4);Retinitis pigmentosa (RP)	1.29	0.37
TSC1	ENSG00000165699	NM_000368.5(TSC1):c.1734C>T (p.Thr578=)	ACC	ACT	Tuberous sclerosis 1 (TSC1);Focal cortical dysplasia type II (FCORD2)	0.8	-0.31
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.9198C>T (p.Val3066=)	GTC	GTT	Collagen VI-related myopathy (COL6-RM)	0.88	-0.19
ABCC8	ENSG00000006071	NM_000352.6(ABCC8):c.279C>A (p.Ile93=)	ATC	ATA	Hereditary hyperinsulinism	0.44	-1.2
GJB6	ENSG00000121742	NM_001110219.3(GJB6):c.672A>G (p.Arg224=)	AGA	AGG	Hidrotic ectodermal dysplasia syndrome (GJB6)	0.91	-0.14
FREM2	ENSG00000150893	NM_207361.6(FREM2):c.2823C>T (p.Pro941=)	CCC	CCT	Fraser syndrome 2	1.02	0.02
LOXHD1	ENSG00000167210	NM_144612.6(LOXHD1):c.6330C>T (p.Ala2110=)	GCC	GCT	Deafness, autosomal recessive 77 (DFNB77)	0.74	-0.44
ABHD12	ENSG00000100997	NM_001042472.3(ABHD12):c.1041C>T (p.Ile347=)	ATC	ATT	Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (PHARC)	0.89	-0.17
SPATA7	ENSG00000042317	NM_018418.5(SPATA7):c.57G>A (p.Pro19=)	CCG	CCA	Leber congenital amaurosis 3 (LCA3);Retinitis pigmentosa (RP)	3.05	1.61
SACS	ENSG00000151835	NM_014363.6(SACS):c.3915T>C (p.His1305=)	CAT	CAC	Charlevoix-Saguenay spastic ataxia (SACS)	1.23	0.3
CNGA1	ENSG00000198515	NM_000087.4(CNGA1):c.372C>T (p.Asn124=)	CTA	CTT	Retinitis pigmentosa (RP)	1.89	0.92
TSC1	ENSG00000165699	NM_000368.5(TSC1):c.2994C>T (p.Asp998=)	GAC	GAT	Tuberous sclerosis 1 (TSC1);Focal cortical dysplasia type II (FCORD2)	0.99	-0.01

SH3PXD2B	ENSG00000174705	NM_001017995.3(SH3PXD2B):c.1602G>A (p.Gly534=)	GGG	GGA	Frank-Ter Haar syndrome	1.13	0.17
FREM2	ENSG00000150893	NM_207361.6(FREM2):c.2367G>A (p.Pro789=)	CCG	CCA	Fraser syndrome 2	3.05	1.61
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.1359C>T (p.Arg453=)	CGC	CGT	Collagen VI-related myopathy (COL6-RM)	0.52	-0.93
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.4074C>T (p.Ala1358=)	GCC	GCT	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Lissencephaly, Recessive	0.74	-0.44
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.2079G>T (p.Leu693=)	CTG	CTT	Autosomal recessive polycystic kidney disease (ARPKD);	0.39	-1.35
FLNC	ENSG00000128591	NM_001458.4(FLNC):c.3054C>T (p.Gly1018=)	GGC	GGT	Myofibrillar myopathy, filamin C-related (MFM5);Myopathy, distal, 4 (MPD4);Cardiomyopathy, familial hypertrophic, 26 (CMH26);Dilated Cardiomyopathy, Dominant	0.55	-0.87
CYP7B1	ENSG00000172817	NM_004820.5(CYP7B1):c.90C>T (p.Leu30=)	CTC	CTT	Hereditary spastic paraplegia 5A (SPG5A)	0.8	-0.33
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.15987C>T (p.Tyr5329=)	TAC	TAT	Retinal dystrophy	0.9	-0.15
SLC17A5	ENSG00000119899	NM_012434.5(SLC17A5):c.1272C>A (p.Ile424=)	ATC	ATA	Salla disease (SD);Sialic acid storage disease, severe infantile type (ISSD)	0.44	-1.2
MYO7A	ENSG00000137474	NM_000260.4(MYO7A):c.5494C>A (p.Arg1832=)	CGG	AGG	Usher syndrome, type 1B (USH1B)	1.15	0.2
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.7221T>C (p.Phe2407=)	TTT	TTC	Autosomal recessive polycystic kidney disease (ARPKD);	1.02	0.02
ADSL	ENSG00000239900	NM_000026.4(ADSL):c.579G>C (p.Leu193=)	CTG	CTC	Adenylosuccinate lyase deficiency (ADSLD)	0.49	-1.02
IGF1R	ENSG00000140443	NM_000875.5(IGF1R):c.84G>A (p.Thr28=)	ACG	ACA	Growth delay due to insulin-like growth factor I resistance	2.96	1.57
NODAL	ENSG00000156574	NM_018055.5(NODAL):c.972G>A (p.Leu324=)	CTG	CTA	Visceral heterotaxy 5, autosomal (HTX5);Holoprosencephaly sequence (HPE)	0.21	-2.27
VSX2	ENSG00000119614	NM_182894.3(VSX2):c.504C>T (p.Asn168=)	AAC	AAT	Microphthalmia, isolated 2 (MCOP2);Microphthalmia, isolated, with coloboma 3 (MCOPCB3)	1.01	0.02
GAA	ENSG00000171298	NM_000152.5(GAA):c.705G>A (p.Thr235=)	ACG	ACA	Glycogen storage disease, type II (GSD2);	2.96	1.57
ITPR1	ENSG00000150995	NM_002222.6(ITPR1):c.3801C>T (p.Phe1267=)	TTC	TTT	Autosomal dominant cerebellar ataxia	0.98	-0.02
ALDH7A1	ENSG00000164904	NM_001182.5(ALDH7A1):c.201G>T (p.Thr67=)	ACG	ACT	Pyridoxine-dependent epilepsy (EPD)	2.56	1.36
RARS2	ENSG00000146282	NM_020320.5(RARS2):c.78A>C (p.Thr26=)	ACA	ACC	Pontocerebellar hypoplasia type 6 (PCH6)	1.07	0.1
CNTNAP2	ENSG00000174469	NM_014141.6(CNTNAP2):c.645C>T (p.Asn215=)	AAC	AAT	Pitt-Hopkins-like syndrome 1 (PTHSL1);Pitt-Hopkins-like syndrome	1.01	0.02
BBS2	ENSG00000125124	NM_031885.5(BBS2):c.327G>A	TCG	TCA	Bardet-Biedl syndrome 2 (BBS2);Bardet-Biedl syndrome (BBS)	3.5	1.81
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.1296A>G (p.Val432=)	GTA	GTG	Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);Autosomal dominant cerebellar ataxia	3.34	1.74
FRAS1	ENSG00000138759	NM_025074.7(FRAS1):c.9627C>T (p.Tyr3209=)	TAC	TAT	Fraser syndrome 1 (FRASRS1)	0.9	-0.15
TCIRG1	ENSG00000110719	NM_006019.4(TCIRG1):c.2397C>T (p.His799=)	CAC	CAT	Autosomal recessive osteopetrosis 1	0.81	-0.3
FOXI1	ENSG00000168269	NM_012188.5(FOXI1):c.825C>T (p.Ala275=)	GCC	GCT	Deafness, autosomal recessive 4, with enlarged vestibular aqueduct (DFNB4)	0.74	-0.44
MAK	ENSG00000111837	NM_001242957.3(MAK):c.975G>A (p.Pro325=)	CCG	CCA	Retinitis Pigmentosa, Recessive	3.05	1.61
FBN2	ENSG00000138829	NM_001999.4(FBN2):c.3690A>G (p.Gly1230=)	GGA	GGG	Congenital contractural arachnodactyly (CCA)	0.89	-0.17
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.7422A>G (p.Glu2474=)	GAA	GAG	Hereditary cancer-predisposing syndrome	1.16	0.22
UBE3A	ENSG00000114062	NM_130839.5(UBE3A):c.582A>G (p.Ala194=)	GCA	GCG	Angelman syndrome (AS)	0.35	-1.52
FREM2	ENSG00000150893	NM_207361.6(FREM2):c.177T>C (p.Gly59=)	GGT	GGC	Fraser syndrome 2	1.82	0.87
NOTCH3	ENSG00000074181	NM_000435.3(NOTCH3):c.351C>T (p.Cys117=)	TGC	TGT	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy type 1 (CADASIL1)	0.97	-0.05
ERCC2	ENSG00000104884	NM_000400.4(ERCC2):c.1789C>T (p.Leu597=)	CTG	TTG	Xeroderma pigmentosum, group D (XPD)	0.37	-1.42
PEX1	ENSG00000127980	NM_000466.3(PEX1):c.147G>A (p.Val49=)	GTG	GTA	Peroxisome biogenesis disorder 1A (Zellweger) (PBD1A);Zellweger syndrome (ZS)	0.3	-1.74
TCIRG1	ENSG00000110719	NM_006019.4(TCIRG1):c.2445C>T (p.Gly815=)	GGC	GGT	Autosomal recessive osteopetrosis 1	0.55	-0.87

ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.2298G>A (p.Gly766=)	GGG	GGA	Progressive familial intrahepatic cholestasis 2 (PFIC2)	1.13	0.17
ADGRG1	ENSG00000205336	NM_201525.4(ADGRG1):c.1287-6G>A	CCG	CCA	Polymicrogyria, bilateral frontoparietal (BFPP)	3.05	1.61
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.5829C>T (p.Gly1943=)	GGC	GGT	Autosomal recessive polycystic kidney disease (ARPKD);	0.55	-0.87
USH2A	ENSG00000042781	NM_206933.3(USH2A):c.5265C>T (p.Phe1755=)	TTC	TTT	Usher syndrome, type 2A (USH2A)	0.98	-0.02
CHRND	ENSG00000135902	NM_000751.3(CHRND):c.45G>A (p.Ala15=)	GCG	GCA	Lethal multiple pterygium syndrome (LMPS);Congenital myasthenic syndrome (CMS)	2.88	1.52
CDHR1	ENSG00000148600	NM_033100.4(CDHR1):c.2229G>A (p.Arg743=)	CGG	CGA	Cone-rod dystrophy 15 (CORD15)	0.6	-0.73
HBB	ENSG00000244734	NM_000518.5(HBB):c.33C>A (p.Ala11=)	GCC	GCA	none provided	0.67	-0.59
DGUOK	ENSG00000114956	NM_080916.3(DGUOK):c.630G>A (p.Glu210=)	GAG	GAA	Mitochondrial DNA-depletion syndrome 3, hepatocerebral (MTDPS3)	0.86	-0.22
TCIRG1	ENSG00000110719	NM_006019.4(TCIRG1):c.2163C>T (p.Ile721=)	ATC	ATT	Autosomal recessive osteopetrosis 1	0.89	-0.17
CAPN3	ENSG00000092529	NM_000070.3(CAPN3):c.2088C>T (p.Ser696=)	TCC	TCT	Limb-girdle muscular dystrophy, type 2A (LGMDR1);Limb-Girdle Muscular Dystrophy, Recessive	0.98	-0.03
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.267C>T (p.Ala89=)	GCC	GCT	Usher syndrome, type 2C (USH2C)	0.74	-0.44
USH2A	ENSG00000042781	NM_206933.3(USH2A):c.14073C>T (p.Asn4691=)	AAC	AAT	Usher syndrome, type 2A (USH2A)	1.01	0.02
CHRND	ENSG00000135902	NM_000751.3(CHRND):c.1455A>G (p.Thr485=)	ACA	ACG	Lethal multiple pterygium syndrome (LMPS);Congenital myasthenic syndrome (CMS)	0.34	-1.57
ABCA4	ENSG00000198691	NM_000350.3(ABCA4):c.3576C>T (p.Val1192=)	GTC	GTT	ABCA4-Related Disorders	0.88	-0.19
CAPN3	ENSG00000092529	NM_000070.3(CAPN3):c.1818G>A (p.Ser606=)	TCG	TCA	Limb-girdle muscular dystrophy, type 2A (LGMDR1);	3.5	1.81
CDKN2A	ENSG00000147889	NM_000077.4(CDKN2A):c.168C>T (p.Ser56=)	AGC	AGT	Hereditary cancer-predisposing syndrome;Hereditary melanoma	0.72	-0.48
CHRND	ENSG00000135902	NM_000751.3(CHRND):c.480C>T (p.Phe160=)	TTC	TTT	Lethal multiple pterygium syndrome (LMPS);Congenital myasthenic syndrome (CMS)	0.98	-0.02
TCIRG1	ENSG00000110719	NM_006019.4(TCIRG1):c.90C>T (p.Gly30=)	GGC	GGT	Autosomal recessive osteopetrosis 1	0.55	-0.87
PHOX2B	ENSG00000109132	NM_003924.3(PHOX2B):c.729A>G (p.Ala243=)	GCA	GCG	Congenital central hypoventilation (CCHS);Neuroblastoma 2 (NBLST2)	0.35	-1.52
PDE6A	ENSG00000132915	NM_000440.3(PDE6A):c.594G>A (p.Val198=)	GTG	GTA	Retinitis pigmentosa (RP)	0.3	-1.74
ZNF513	ENSG00000163795	NM_144631.6(ZNF513):c.519C>T (p.Ser173=)	AGC	AGT	Retinitis pigmentosa (RP)	0.72	-0.48
CDKN2A	ENSG00000147889	NM_000077.4(CDKN2A):c.225C>G (p.Pro75=)	CCC	CCG	Hereditary cancer-predisposing syndrome;Hereditary melanoma	0.33	-1.62
PTCH1	ENSG00000185920	NM_000264.5(PTCH1):c.63C>T (p.Ile21=)	ATC	ATT	Gorlin syndrome (BCNS);Holoprosencephaly 7 (HPE7)	0.89	-0.17
AAAS	ENSG00000094914	NM_015665.6(AAAS):c.679T>C (p.Leu227=)	TTG	CTG	Glucocorticoid deficiency with achalasia (AAA);	2.67	1.42
RARS2	ENSG00000146282	NM_020320.5(RARS2):c.888G>C (p.Thr296=)	ACG	ACC	Pontocerebellar hypoplasia type 6 (PCH6);	3.18	1.67
NAGLU	ENSG00000108784	NM_000263.4(NAGLU):c.1515C>T (p.Ser505=)	TCC	TCT	Mucopolysaccharidosis, MPS-III-B (MPS3B); Mucopolysaccharidosis, MPS-III-B (MPS3B);Charcot-Marie-Tooth disease, axonal type 2V (CMT2V)	0.98	-0.03
SCN2A	ENSG00000136531	NM_001040142.2(SCN2A):c.2673C>T (p.Ile891=)	ATC	ATT	Seizures, benign familial infantile, 3 (BFIS3)	0.89	-0.17
CHD7	ENSG00000171316	NM_017780.4(CHD7):c.6822T>C (p.Ala2274=)	GCT	GCC	CHARGE association (CHARGE)	1.36	0.44
TP63	ENSG00000073282	NM_003722.5(TP63):c.678C>T (p.Arg226=)	CGC	CGT	Orofacial cleft 8;Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome 3 (EEC3);TP63-Related Spectrum Disorders	0.52	-0.93
ZFYVE26	ENSG00000072121	NM_015346.4(ZFYVE26):c.4197C>T (p.Thr1399=)	ACC	ACT	Hereditary spastic paraplegia 15 (SPG15); Spastic paraplegia	0.8	-0.31
TPP1	ENSG00000166340	NM_000391.4(TPP1):c.840G>C (p.Leu280=)	CTG	CTC	Ceroid lipofuscinosis neuronal 2 (CLN2); Seizures;Neuronal ceroid lipofuscinosis	0.49	-1.02
PSAP	ENSG00000197746	NM_002778.4(PSAP):c.1146C>T (p.Cys382=)	TGC	TGT	Sphingolipid activator protein 1 deficiency;Combined saposin deficiency;Gaucher disease, atypical, due to saposin C deficiency;Krabbe disease, atypical, due to saposin A deficiency;Metachromatic leukodystrophy (MLD)	0.97	-0.05
CNTNAP2	ENSG00000174469	NM_014141.6(CNTNAP2):c.3600G>A (p.Ser1200=)	TCG	TCA	Pitt-Hopkins-like syndrome 1 (PTHSL1)	3.5	1.81

ASPM	ENSG00000066279	NM_018136.5(ASPM):c.7620A>G (p.Ala2540=)	GCA	GCG	Primary autosomal recessive microcephaly 5 (MCPH5);	0.35	-1.52
POMT2	ENSG00000009830	NM_013382.5(POMT2):c.1701C>G (p.Pro567=)	CCC	CCG	Limb-girdle muscular dystrophy-dystroglycanopathy, type C2 (MDDGC2); Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, type A2 (MDDGA2);Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B2 (MDDGB2);Limb-girdle muscular dystrophy-dystroglycanopathy, type C2 (MDDGC2)	0.33	-1.62
RYR2	ENSG00000198626	NM_001035.3(RYR2):c.14703G>C (p.Val4901=)	GTG	GTC	Arrhythmogenic right ventricular cardiomyopathy (ARVD);Catecholaminergic polymorphic ventricular tachycardia (CPVT1);Cardiovascular phenotype;Cardiomyopathy (CMYO);	0.52	-0.94
RELN	ENSG00000189056	NM_005045.4(RELN):c.6939T>C (p.Ile2313=)	ATT	ATC	Norman-Roberts syndrome (LIS2);Epilepsy, familial temporal lobe, 7 (ETL7)	1.13	0.17
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.9402G>A (p.Lys3134=)	AAG	AAA	Autosomal recessive polycystic kidney disease (ARPKD);	0.87	-0.2
CERKL	ENSG00000188452	NM_201548.5(CERKL):c.27G>A (p.Arg9=)	CGG	CGA	Retinitis pigmentosa (RP);Retinitis pigmentosa 26 (RP26)	0.6	-0.73
PGM1	ENSG00000079739	NM_002633.3(PGM1):c.420A>G (p.Pro140=)	CCA	CCG	Congenital disorder of glycosylation type 1t (CDG1T);Congenital disorder of glycosylation (CDG);	0.33	-1.61
HPS1	ENSG00000107521	NM_000195.5(HPS1):c.198G>A (p.Ser66=)	TCG	TCA	Hermansky-Pudlak syndrome 1 (HPS1);Hermansky-Pudlak syndrome (HPS)	3.5	1.81
GCH1	ENSG00000131979	NM_000161.3(GCH1):c.195G>A (p.Glu65=)	GAG	GAA	GTP cyclohydrolase I deficiency (HPABH4B);Dystonia 5 (DRD)	0.86	-0.22
PTCH1	ENSG00000185920	NM_000264.5(PTCH1):c.1653G>A (p.Thr551=)	ACG	ACA	Gorlin syndrome (BCNS);Holoprosencephaly 7 (HPE7);Hereditary cancer-predisposing syndrome	2.96	1.57
POMT1	ENSG00000130714	NM_001077365.2(POMT1):c.129C>T (p.Asp43=)	GAC	GAT	Limb-girdle muscular dystrophy-dystroglycanopathy, type C1 (MDDGC1);Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B1 (MDDGB1);Walker-Warburg congenital muscular dystrophy (MDDGA1)	0.99	-0.01
CNTNAP2	ENSG00000174469	NM_014141.6(CNTNAP2):c.2460C>T (p.Ser820=)	AGC	AGT	Pitt-Hopkins-like syndrome 1 (PTHSL1);Pitt-Hopkins-like syndrome;History of neurodevelopmental disorder	0.72	-0.48
PTCH1	ENSG00000185920	NM_000264.5(PTCH1):c.2460C>T (p.Tyr820=)	TAC	TAT	Gorlin syndrome (BCNS);Holoprosencephaly sequence (HPE);Hereditary cancer-predisposing syndrome	0.9	-0.15
ALMS1	ENSG00000116127	NM_015120.4(ALMS1):c.6540C>T (p.Thr2180=)	ATT	ATT	Alstrom syndrome (ALMS)	1	0
VSX2	ENSG00000119614	NM_182894.3(VSX2):c.564G>A (p.Pro188=)	CCG	CCA	Microphthalmia, isolated 2 (MCOP2);Microphthalmia, isolated, with coloboma 3 (MCOPCB3);Microphthalmia	3.05	1.61
SCN1A	ENSG00000144285	NM_001165963.4(SCN1A):c.3039A>G (p.Gln1013=)	CAA	CAG	History of neurodevelopmental disorder	2.49	1.32
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.5772C>G (p.Leu1924=)	CTC	CTG	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Lissencephaly, Recessive;	2.02	1.02
APOB	ENSG00000084674	NM_000384.3(APOB):c.4929G>A (p.Ala1643=)	GCG	GCA	Familial hypercholesterolemia 1 (FHCL1);Familial hypobetalipoproteinemia (FHBL);Familial hypercholesterolemia (FH)	2.88	1.52
VSX2	ENSG00000119614	NM_182894.3(VSX2):c.171C>G (p.Ala57=)	GCC	GCG	Microphthalmia, isolated 2 (MCOP2);Microphthalmia, isolated, with coloboma 3 (MCOPCB3);Microphthalmia	0.23	-2.11
MARVELD2	ENSG00000152939	NM_001038603.3(MARVELD2):c.30G>A (p.Arg10=)	CGG	CGA	Deafness, autosomal recessive 49 (DFNB49);	0.6	-0.73
KIF1A	ENSG00000130294	NM_004321.7(KIF1A):c.4740G>A (p.Gly1580=)	GGG	GGA	Spastic paraplegia 30, autosomal recessive (SPG30);History of neurodevelopmental disorder;Spastic paraplegia 30, autosomal recessive (SPG30);Hereditary sensory and autonomic neuropathy type IIC (HSN2C);Intellectual disability, autosomal dominant 9 (NESCAVS)	1.13	0.17
SYN1	ENSG00000008056	NM_006950.3(SYN1):c.1107C>T (p.Ile369=)	ATC	ATT	History of neurodevelopmental disorder;Epilepsy, X-linked, with variable learning disabilities and behavior disorders (EPILX)	0.89	-0.17

MYH11	ENSG00000133392	NM_002474.3(MYH11):c.5247G>A (p.Gln1749=)	CAG	CAA	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Lissencephaly, Recessive; Aortic aneurysm, familial thoracic 4 (AAT4)	0.4	-1.32
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.6237G>A (p.Val2079=)	GTG	GTA	Hereditary breast and ovarian cancer syndrome (HBOC);Fanconi anemia (FA);Breast-ovarian cancer, familial 2 (BROVCA2);Hereditary cancer-predisposing syndrome	0.3	-1.74
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.963A>G (p.Gln321=)	CAA	CAG	Hereditary breast and ovarian cancer syndrome (HBOC);Fanconi anemia (FA);Breast-ovarian cancer, familial 2 (BROVCA2);Hereditary cancer-predisposing syndrome;	2.49	1.32
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.3936C>T (p.Ser1312=)	TCC	TCT	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Marfan syndrome (MFS);Geleophysic dysplasia;Stiff skin syndrome (SSKS);Weill-Marchesani syndrome;Acromicric dysplasia (ACMICD);Ectopia lentis, isolated, autosomal dominant (ECTOL1); Cardiovascular phenotype;Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.98	-0.03
POMT2	ENSG00000009830	NM_013382.5(POMT2):c.1404A>G (p.Lys468=)	AAA	AAG	Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, type A2 (MDDGA2);Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B2 (MDDGB2);Limb-girdle muscular dystrophy-dystroglycanopathy, type C2 (MDDGC2);Limb-girdle muscular dystrophy-dystroglycanopathy, type C2 (MDDGC2)	1.15	0.2
NPHP1	ENSG00000144061	NM_000272.4(NPHP1):c.1035A>G (p.Gln345=)	CAA	CAG	Joubert syndrome 4 (JBTS4);Nephronophthisis;Senior-Loken syndrome 1 (SLSN1);Nephronophthisis 1 (NPHP1)	2.49	1.32
PRPH2	ENSG00000112619	NM_000322.5(PRPH2):c.888C>T (p.Pro296=)	CCC	CCT	Pigmentary retinal dystrophy;Macular dystrophy, vitelliform, adult-onset;Macular dystrophy, patterned, 1 (MDPT1);Retinitis pigmentosa (RP);Cone-rod dystrophy;Choroidal dystrophy, central areolar 2 (CACD2)	1.02	0.02
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.5454C>T (p.Asp1818=)	GAC	GAT	Hereditary cancer-predisposing syndrome; Breast-ovarian cancer, familial 1 (BROVCA1);	0.99	-0.01
LDLR	ENSG00000130164	NM_000527.5(LDLR):c.1503G>A (p.Ala501=)	GCG	GCA	Familial hypercholesterolemia 1 (FHCL1);Familial hypercholesterolemia (FH);	2.88	1.52
SCN2A	ENSG00000136531	NM_001040142.2(SCN2A):c.5319G>A (p.Ala1773=)	GCG	GCA	Seizures, benign familial infantile, 3 (BFIS3);Early infantile epileptic encephalopathy 11 (DEE11);	2.88	1.52
ABCB4	ENSG00000005471	NM_000443.4(ABCB4):c.3402C>T (p.Asp1134=)	GAC	GAT	Cholestasis, intrahepatic, of pregnancy 3 (ICP3);Progressive familial intrahepatic cholestasis 3 (PFIC3)	0.99	-0.01
HSPG2	ENSG00000142798	NM_005529.7(HSPG2):c.732A>G (p.Thr244=)	ACA	ACG	Lethal Kniest-like syndrome (DDSH);Schwartz-Jampel syndrome	0.34	-1.57
KIF1B	ENSG00000054523	NM_015074.3(KIF1B):c.315T>C (p.Tyr105=)	TAT	TAC	Charcot-Marie-Tooth disease, type 2;Pheochromocytoma;Neuroblastoma (NB)	1.11	0.15
CHRNG	ENSG00000196811	NM_005199.5(CHRNG):c.663G>A (p.Ala221=)	GCG	GCA	Lethal multiple pterygium syndrome (LMPS);Autosomal recessive multiple pterygium syndrome	2.88	1.52
SAG	ENSG00000130561	NM_000541.5(SAG):c.468C>T (p.Phe156=)	TTC	TTT	s disease", 'Retinitis pigmentosa (RP)	0.98	-0.02
SCN1A	ENSG00000144285	NM_001165963.4(SCN1A):c.3732G>A (p.Gln1244=)	CAG	CAA	Familial hemiplegic migraine type 3 (FHM3);Generalized epilepsy with febrile seizures plus, type 2 (GEFSP2)	0.4	-1.32
HPS1	ENSG00000107521	NM_000195.5(HPS1):c.700C>T (p.Leu234=)	CTG	TTG	Hermansky-Pudlak syndrome 1 (HPS1);Hermansky-Pudlak syndrome (HPS)	0.37	-1.42
DLD	ENSG00000091140	NM_000108.5(DLD):c.375G>A (p.Glu125=)	GAG	GAA	Maple syrup urine disease, type 3 (MSUD3);Pyruvate dehydrogenase complex deficiency (PDHC);Leigh syndrome (LS)	0.86	-0.22

LARGE1	ENSG00000133424	NM_004737.6(LARGE1):c.909T>G (p.Leu303=)	CTT	CTG	Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B6 (MDDGB6);Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, type A6 (MDDGA6)	2.54	1.35
TGFBR2	ENSG00000163513	NM_003242.6(TGFBR2):c.696C>T (p.Ala232=)	GCC	GCT	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Marfan syndrome (MFS);Loeys-Dietz syndrome (LDS)	0.74	-0.44
KIT	ENSG00000157404	NM_000222.2(KIT):c.2562C>G (p.Ser854=)	TCC	TCG	Gastrointestinal stromal tumor (GIST);Mastocytosis (MASTC);Partial albinism (PBT)	0.23	-2.09
CAPN3	ENSG00000092529	NM_000070.3(CAPN3):c.2409A>G (p.Gly803=)	GGA	GGG	Limb-girdle muscular dystrophy, type 2A (LGMDR1);Limb-Girdle Muscular Dystrophy, Recessive;	0.89	-0.17
MMADHC	ENSG00000168288	NM_015702.3(MMADHC):c.735T>G (p.Thr245=)	ACT	ACG	Methylmalonic acidemia with homocystinuria cblD (MAHCD);Disorders of Intracellular Cobalamin Metabolism;Methylmalonic aciduria with homocystinuria cblD type	0.39	-1.36
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.6423T>G (p.Gly2141=)	GGT	GGG	Hereditary breast and ovarian cancer syndrome (HBOC);	1.41	0.5
TNFRSF11A	ENSG00000141655	NM_003839.4(TNFRSF11A):c.1254T>G (p.Ser418=)	TCT	TCG	Autosomal recessive osteopetrosis 7;Paget disease of bone 2, early-onset (PDB2)	0.24	-2.06
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.2679A>G (p.Gln893=)	CAA	CAG	Hereditary cancer-predisposing syndrome; Hereditary breast and ovarian cancer syndrome (HBOC)	2.49	1.32
BRIP1	ENSG00000136492	NM_032043.2(BRIP1):c.537A>G (p.Glu179=)	GAA	GAG	Hereditary cancer-predisposing syndrome;Familial cancer of breast;Fanconi anemia, complementation group J (FANCJ);	1.16	0.22
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.1125C>T (p.Asp375=)	GAC	GAT	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	0.99	-0.01
VSX2	ENSG00000119614	NM_182894.3(VSX2):c.249G>A (p.Gly83=)	GGG	GGA	Microphthalmia, isolated 2 (MCOP2);Microphthalmia, isolated, with coloboma 3 (MCOPCB3);Microphthalmia	1.13	0.17
KIT	ENSG00000157404	NM_000222.2(KIT):c.252G>A (p.Thr84=)	ACG	ACA	Gastrointestinal stromal tumor (GIST);Mastocytosis (MASTC);Partial albinism (PBT)	2.96	1.57
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.4821C>T (p.Asp1607=)	GAC	GAT	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Lissencephaly, Recessive;Aortic aneurysm, familial thoracic 4 (AAT4)	0.99	-0.01
CDKN2A	ENSG00000147889	NM_000077.4(CDKN2A):c.339G>A (p.Leu113=)	CTG	CTA	Hereditary cancer-predisposing syndrome; Hereditary melanoma	0.21	-2.27
KIT	ENSG00000157404	NM_000222.2(KIT):c.1185C>A (p.Ser395=)	TCC	TCA	Gastrointestinal stromal tumor (GIST);Mastocytosis (MASTC);Partial albinism (PBT)	0.82	-0.29
WFS1	ENSG00000109501	NM_006005.3(WFS1):c.2424C>T (p.Ser808=)	AGC	AGT	WFS1-Related Spectrum Disorders;Autosomal dominant nonsyndromic deafness 6 (DFNA6);	0.72	-0.48
MUTYH	ENSG00000132781	NM_001048174.2(MUTYH):c.954G>A (p.Ser318=)	TCG	TCA	Hereditary cancer-predisposing syndrome; MYH-associated polyposis (FAP2);	3.5	1.81
LARGE1	ENSG00000133424	NM_004737.6(LARGE1):c.1092C>T (p.Thr364=)	ACC	ACT	Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, type A6 (MDDGA6); Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B6 (MDDGB6)	0.8	-0.31
WHRN	ENSG00000095397	NM_015404.4(WHRN):c.1455G>A (p.Pro485=)	CCG	CCA	Usher syndrome, type 2D (USH2D);Deafness, autosomal recessive 31 (DFNB31);	3.05	1.61
CNGB3	ENSG00000170289	NM_019098.4(CNGB3):c.1833C>T (p.His611=)	CAC	CAT	Achromatopsia 3 (ACHM3);Stargardt disease 1 (STGD1);Achromatopsia	0.81	-0.3
CDH23	ENSG00000107736	NM_022124.6(CDH23):c.10044C>G (p.Pro3348=)	CCC	CCG	Usher syndrome type 1D (USH1D);Deafness, autosomal recessive 12 (DFNB12);Usher syndrome type 1 (USH1)	0.33	-1.62
KIT	ENSG00000157404	NM_000222.2(KIT):c.2670C>T (p.Leu890=)	CTC	CTT	Gastrointestinal stromal tumor (GIST);Partial albinism (PBT);Mastocytosis (MASTC);Hereditary cancer-predisposing syndrome	0.8	-0.33

SMAD4	ENSG00000141646	NM_005359.6(SMAD4):c.1644A>G (p.Pro548=)	CCA	CCG	Generalized juvenile polyposis/juvenile polyposis coli (JPS);Myhre syndrome (MYHRS);Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (JPHT);Hereditary cancer-predisposing syndrome;	0.33	-1.61
TGFBR2	ENSG00000163513	NM_003242.6(TGFBR2):c.690G>A (p.Thr230=)	ACG	ACA	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Loeys-Dietz syndrome (LDS);Marfan syndrome (MFS);	2.96	1.57
FH	ENSG00000091483	NM_000143.3(FH):c.12A>G (p.Ala4=)	GCA	GCG	Fumarase deficiency (FMRD);Hereditary leiomyomatosis and renal cell cancer (HLRCC);Multiple Cutaneous and Uterine Leiomyomas;Hereditary cancer-predisposing syndrome;	0.35	-1.52
RLBP1	ENSG00000140522	NM_000326.5(RLBP1):c.303C>T (p.Arg101=)	CGC	CGT	Pigmentary retinal dystrophy;Retinitis pigmentosa (RP);Newfoundland rod-cone dystrophy (NFRCD)	0.52	-0.93
ABCA4	ENSG00000198691	NM_000350.3(ABCA4):c.4611G>A (p.Thr1537=)	ACG	ACA	Stargardt disease 1 (STGD1);Retinal dystrophy;ABCA4-Related Disorders	2.96	1.57
ABCA4	ENSG00000198691	NM_000350.3(ABCA4):c.1029T>C (p.Asn343=)	AAT	AAC	Stargardt disease 1 (STGD1);Retinal dystrophy;ABCA4-Related Disorders	0.99	-0.02
UGT1A6	ENSG00000242366	NM_001072.4(UGT1A6):c.862-6558C>T	GAC	GAT	s syndrome", 'Crigler-Najjar syndrome;Lucey-Driscoll syndrome (HBLRTFN)	0.99	-0.01
CC2D2A	ENSG00000048342	NM_001080522.2(CC2D2A):c.4296T>C (p.Cys1432=)	TGT	TGC	CC2D2A-Related Disorders;Joubert syndrome 9 (JBTS9);Meckel syndrome type 6 (MKS6);	1.03	0.05
F5	ENSG00000198734	NM_000130.4(F5):c.5490G>A (p.Leu1830=)	CTG	CTA	Factor V deficiency;Budd-Chiari syndrome (BDCHS);Thrombophilia due to thrombin defect (THPH1);Thrombophilia due to factor V Leiden (THPH2);	0.21	-2.27
SCN4A	ENSG00000007314	NM_000334.4(SCN4A):c.2220G>A (p.Pro740=)	CCG	CCA	Familial hyperkalemic periodic paralysis;Congenital myasthenic syndrome, acetazolamide-responsive (CMS16);Potassium-aggravated myotonia;Hypokalemic periodic paralysis, type 2 (HOKPP2);Paramyotonia congenita of von Eulenburg (PMC)	3.05	1.61
SCN4A	ENSG00000007314	NM_000334.4(SCN4A):c.5148G>A (p.Glu1716=)	GAG	GAA	Familial hyperkalemic periodic paralysis;Potassium-aggravated myotonia;Congenital myasthenic syndrome, acetazolamide-responsive (CMS16);Paramyotonia congenita of von Eulenburg (PMC);Hypokalemic periodic paralysis, type 2 (HOKPP2)	0.86	-0.22
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.5637C>T (p.Asp1879=)	GAC	GAT	Central core myopathy (CCD);Malignant hyperthermia, susceptibility to, 1 (MHS1);Neuromuscular disease, congenital, with uniform type 1 fiber (CNMDU1);Minicore myopathy with external ophthalmoplegia;RYR1-Related Disorders	0.99	-0.01
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.6801C>T (p.Asn2267=)	AAC	AAT	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Acromicric dysplasia (ACMICD);Ectopia lentis, isolated, autosomal dominant (ECTOL1);Geleophysic dysplasia;Weill-Marchesani syndrome;Marfan syndrome (MFS);Stiff skin syndrome (SSKS)	1.01	0.02
STK11	ENSG00000118046	NM_000455.4(STK11):c.1296G>A (p.Gln432=)	CAG	CAA	Hereditary cancer-predisposing syndrome; Peutz-Jeghers syndrome (PJS);none provided	0.4	-1.32
SH3TC2	ENSG00000169247	NM_024577.3(SH3TC2):c.3795G>C (p.Leu1265=)	CTG	CTC	Mononeuropathy of the median nerve, mild (MNMN); Charcot-Marie-Tooth disease type 4; Charcot-Marie-Tooth disease, type 4C (CMT4C);Charcot-Marie-Tooth disease	0.49	-1.02
PTPN11	ENSG00000179295	NM_002834.5(PTPN11):c.48A>G (p.Ala16=)	GCA	GCG	LEOPARD syndrome 1 (LPRD1);Metachondromatosis (METCDS);Noonan syndrome 1 (NS1);Rasopathy;	0.35	-1.52
GLDC	ENSG00000178445	NM_000170.2(GLDC):c.498T>C (p.Pro166=)	CCT	CCC	Non-ketotic hyperglycinemia (GCE)	0.98	-0.02
BARD1	ENSG00000138376	NM_000465.4(BARD1):c.2082C>T (p.Leu694=)	CTC	CTT	Hereditary cancer-predisposing syndrome; Familial cancer of breast	0.8	-0.33
NPC1	ENSG00000141458	NM_000271.5(NPC1):c.66A>G (p.Ser22=)	TCA	TCG	Niemann-Pick disease type C1 (NPC1)	0.29	-1.81

DHCR7	ENSG00000172893	NM_001360.2(DHCR7):c.987C>T (p.Pro329=)	CCC	CCT	History of neurodevelopmental disorder; Smith-Lemli-Opitz syndrome (SLOS)	1.02	0.02
ATM	ENSG00000149311	NM_000051.3(ATM):c.6108T>C (p.Tyr2036=)	TAT	TAC	Hereditary cancer-predisposing syndrome; Ataxia-telangiectasia syndrome (AT)	1.11	0.15
MRE11	ENSG00000020922	NM_005590.4(MRE11):c.120C>T (p.Leu40=)	CTC	CTT	Hereditary cancer-predisposing syndrome; Ataxia-telangiectasia-like disorder 1 (ATLD1); Ataxia-telangiectasia-like disorder (ATLD)	0.8	-0.33
MSH6	ENSG00000116062	NM_000179.2(MSH6):c.1449G>T (p.Val483=)	GTG	GTT	Hereditary cancer-predisposing syndrome; Hereditary nonpolyposis colorectal cancer type 5 (HNPCC5); Hereditary nonpolyposis colorectal neoplasms	0.46	-1.13
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.7902C>T (p.Pro2634=)	CCC	CCT	Cardiovascular phenotype; Familial thoracic aortic aneurysm and aortic dissection (TAAD);Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	1.02	0.02
BRIP1	ENSG00000136492	NM_032043.2(BRIP1):c.36G>T (p.Gly12=)	GGG	GGT	Hereditary cancer-predisposing syndrome; Fanconi anemia, complementation group J (FANCJ);Neoplasm of ovary; Familial cancer of breast;Fanconi anemia, complementation group J (FANCJ)	0.71	-0.5
BARD1	ENSG00000138376	NM_000465.4(BARD1):c.1473G>A (p.Gly491=)	GGG	GGA	Hereditary cancer-predisposing syndrome; Familial cancer of breast	1.13	0.17
ACTA2	ENSG00000107796	NM_001613.4(ACTA2):c.420G>A (p.Ala140=)	GCG	GCA	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Multisystemic smooth muscle dysfunction syndrome (MSMDS);Cardiovascular phenotype;Aortic aneurysm, familial thoracic 6 (AAT6)	2.88	1.52
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.13101C>T (p.Ile4367=)	ATC	ATT	Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	0.89	-0.17
BRCA2	ENSG00000139618	NM_000059.4(BRCA2):c.6513G>T (p.Val2171=)	GTG	GTT	Hereditary cancer-predisposing syndrome; Breast-ovarian cancer, familial 2 (BROVCA2); Hereditary breast and ovarian cancer syndrome (HBOC)	0.46	-1.13
MLH1	ENSG00000076242	NM_000249.3(MLH1):c.1269G>A (p.Arg423=)	AGG	AGA	Hereditary cancer-predisposing syndrome; Lynch syndrome II (HNPCC2);Hereditary nonpolyposis colorectal neoplasms	1.1	0.14
MSH6	ENSG00000116062	NM_000179.2(MSH6):c.3513T>C (p.Asp1171=)	GAT	GAC	Hereditary cancer-predisposing syndrome; Hereditary nonpolyposis colorectal cancer type 5 (HNPCC5);Hereditary nonpolyposis colorectal neoplasms	1.01	0.01
ATM	ENSG00000149311	NM_000051.3(ATM):c.6234C>T (p.Ser2078=)	TCC	TCT	Hereditary cancer-predisposing syndrome; Ataxia-telangiectasia syndrome (AT)	0.98	-0.03
APC	ENSG00000134982	NM_000038.6(APC):c.6526T>C (p.Leu2176=)	TTG	CTG	Hereditary cancer-predisposing syndrome; APC-Associated Polyposis Disorders; Familial adenomatous polyposis 1 (FAP1)	2.67	1.42
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.7458A>G (p.Gln2486=)	CAA	CAG	Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	2.49	1.32
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.13572C>T (p.Val4524=)	GTC	GTT	Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	0.88	-0.19
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.12564C>T (p.Ser4188=)	TCC	TCT	Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	0.98	-0.03

SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.16296G>A (p.Arg5432=)	CGG	CGA	Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	0.6	-0.73
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.22068C>T (p.Thr7356=)	ACC	ACT	Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	0.8	-0.31
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.8973G>A (p.Thr2991=)	ACG	ACA	Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	2.96	1.57
TTN	ENSG00000155657	NM_001267550.2(TTN):c.78855T>C (p.Asp26285=)	GAT	GAC	Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Dilated cardiomyopathy 1G (CMD1G);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Tibial muscular dystrophy (TMD);Limb-girdle muscular dystrophy, type 2J (LGMDR10); Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	1.01	0.01
MSH2	ENSG00000095002	NM_000251.2(MSH2):c.1680T>C (p.Asn560=)	AAT	AAC	Lynch syndrome;Hereditary cancer-predisposing syndrome; Lynch syndrome I (COCA1);Hereditary nonpolyposis colorectal neoplasms	0.99	-0.02
MSH2	ENSG00000095002	NM_000251.2(MSH2):c.1560A>G (p.Gly520=)	GGA	GGG	Hereditary cancer-predisposing syndrome; Hereditary nonpolyposis colorectal neoplasms;Lynch syndrome I (COCA1)	0.89	-0.17
STK11	ENSG00000118046	NM_000455.4(STK11):c.795G>A (p.Glu265=)	GAG	GAA	Hereditary cancer-predisposing syndrome;Peutz-Jeghers syndrome (PJS);	0.86	-0.22
MSH6	ENSG00000116062	NM_000179.2(MSH6):c.1665A>G (p.Ala555=)	GCA	GCG	Hereditary cancer-predisposing syndrome; Hereditary nonpolyposis colorectal cancer type 5 (HNPCC5);Hereditary nonpolyposis colorectal neoplasms	0.35	-1.52
MSH2	ENSG00000095002	NM_000251.2(MSH2):c.2154A>G (p.Gln718=)	CAA	CAG	Lynch syndrome;Hereditary cancer-predisposing syndrome; Lynch syndrome I (COCA1);Hereditary nonpolyposis colorectal neoplasms	2.49	1.32
ATM	ENSG00000149311	NM_000051.3(ATM):c.8532T>C (p.Ile2844=)	ATT	ATC	Hereditary cancer-predisposing syndrome; Ataxia-telangiectasia syndrome (AT)	1.13	0.17
MRE11	ENSG00000020922	NM_005591.3(MRE11):c.822T>C (p.Leu274=)	CTT	CTC	Hereditary cancer-predisposing syndrome; Ataxia-telangiectasia-like disorder 1 (ATLD1);Ataxia-telangiectasia-like disorder (ATLD)	1.26	0.33
MRE11	ENSG00000020922	NM_005591.3(MRE11):c.426C>T (p.Asp142=)	GAC	GAT	Hereditary cancer-predisposing syndrome; Ataxia-telangiectasia-like disorder 1 (ATLD1); Ataxia-telangiectasia-like disorder (ATLD)	0.99	-0.01
PMS2	ENSG00000122512	NM_000535.7(PMS2):c.384G>A (p.Ser128=)	TCG	TCA	Lynch syndrome;Hereditary cancer-predisposing syndrome;Hereditary nonpolyposis colorectal cancer type 4 (HNPCC4); Hereditary nonpolyposis colorectal neoplasms;Breast neoplasm	3.5	1.81
MSH2	ENSG00000095002	NM_000251.2(MSH2):c.972G>A (p.Gln324=)	CAG	CAA	Lynch syndrome;Hereditary cancer-predisposing syndrome;Lynch syndrome I (COCA1); Hereditary nonpolyposis colorectal neoplasms	0.4	-1.32
LDLRAP1	ENSG00000157978	NM_015627.2(LDLRAP1):c.672C>T (p.Ser224=)	TCC	TCT	Familial hypercholesterolemia 4 (FHCL4);Familial hypercholesterolemia (FH)	0.98	-0.03
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.2253C>T (p.Thr751=)	ACC	ACT	Familial thoracic aortic aneurysm and aortic dissection (TAAD); Aortic aneurysm, familial thoracic 7 (AAT7);Cardiovascular phenotype;Connective tissue disease	0.8	-0.31
MSH2	ENSG00000095002	NM_000251.2(MSH2):c.2400A>G (p.Leu800=)	CTA	CTG	Hereditary cancer-predisposing syndrome; Lynch syndrome I (COCA1); Hereditary nonpolyposis colorectal neoplasms	4.81	2.27

APC	ENSG00000134982	NM_000038.6(APC):c.2232T>G (p.Ser744=)	TCT	TCG	Hereditary cancer-predisposing syndrome; Familial adenomatous polyposis 1 (FAP1);	0.24	-2.06
MUTYH	ENSG00000132781	NM_001048171.1(MUTYH):c.1506G>A (p.Pro502=)	CCG	CCA	Hereditary cancer-predisposing syndrome; MYH-associated polyposis (FAP2)	3.05	1.61
STK11	ENSG00000118046	NM_000455.4(STK11):c.615G>A (p.Ala205=)	GCG	GCA	Hereditary cancer-predisposing syndrome; Peutz-Jeghers syndrome (PJS);	2.88	1.52
BRIP1	ENSG00000136492	NM_032043.2(BRIP1):c.3459T>C (p.Asp1153=)	GAT	GAC	Hereditary cancer-predisposing syndrome; Neoplasm of ovary;Fanconi anemia, complementation group J (FANCJ); Familial cancer of breast;Familial cancer of breast;Fanconi anemia, complementation group J (FANCJ)	1.01	0.01
MSH2	ENSG00000095002	NM_000251.2(MSH2):c.336C>A (p.Ser112=)	TCC	TCA	Hereditary cancer-predisposing syndrome; Lynch syndrome I (COCA1);Hereditary nonpolyposis colorectal neoplasms	0.82	-0.29
FBN1	ENSG00000166147	NM_000138.5(FBN1):c.510C>T (p.Tyr170=)	TAC	TAT	Marfan syndrome (MFS); Geleophysic dysplasia;Weill-Marchesani syndrome;Familial thoracic aortic aneurysm and aortic dissection (TAAD);Ectopia lentis, isolated, autosomal dominant (ECTOL1);Stiff skin syndrome (SSKS);Acromicric dysplasia (ACMICD);Cardiovascular phenotype; Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.9	-0.15
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.429G>A (p.Lys143=)	AAG	AAA	Familial thoracic aortic aneurysm and aortic dissection (TAAD); Cardiovascular phenotype;Connective tissue disease;Aortic aneurysm, familial thoracic 4 (AAT4)	0.87	-0.2
NBN	ENSG00000104320	NM_002485.4(NBN):c.1089C>T (p.Tyr363=)	TAC	TAT	Hereditary cancer-predisposing syndrome; Microcephaly, normal intelligence and immunodeficiency (NBS)	0.9	-0.15
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.3069T>C (p.Thr1023=)	ACT	ACC	Wilson disease (WND)	1.24	0.31
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.6168C>T (p.Phe2056=)	TTC	TTT		0.98	-0.02
GHR	ENSG00000112964	NM_000163.5(GHR):c.195A>G (p.Ser65=)	TCA	TCG		0.29	-1.81
PCDH15	ENSG00000150275	NM_033056.4(PCDH15):c.330C>T (p.Asn110=)	AAC	AAT		1.01	0.02
OTOF	ENSG00000115155	NM_194248.3(OTOF):c.4548C>T (p.Tyr1516=)	TAC	TAT		0.9	-0.15
ITGB2	ENSG00000160255	NM_000211.5(ITGB2):c.2145C>T (p.Ile715=)	ATC	ATT	Leukocyte adhesion deficiency 1	0.89	-0.17
COLQ	ENSG00000206561	NM_005677.4(COLQ):c.561C>T (p.Ser187=)	TCC	TCT	Endplate acetylcholinesterase deficiency (CMS5)	0.98	-0.03
NEK1	ENSG00000137601	NM_012224.3(NEK1):c.2337C>T (p.Phe779=)	TTC	TTT	Short rib-polydactyly syndrome, Majewski type (SRTD6)	0.98	-0.02
HGF	ENSG00000019991	NM_000601.6(HGF):c.270T>C (p.Asp90=)	GAT	GAC		1.01	0.01
ALPL	ENSG00000162551	NM_000478.6(ALPL):c.1002C>T (p.Gly334=)	GGC	GGT	Hypophosphatasia;	0.55	-0.87
NEB	ENSG00000183091	NM_001271208.2(NEB):c.3444G>A (p.Ala1148=)	GCG	GCA	Nemaline myopathy 2 (NEM2)	2.88	1.52
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.1500G>A (p.Gln500=)	CAG	CAA	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD)	0.4	-1.32
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.3160A>C (p.Arg1054=)	AGG	CGG	Wilson disease (WND)	0.87	-0.2
GSS	ENSG00000100983	NM_000178.4(GSS):c.816T>G (p.Pro272=)	CCT	CCG	Gluthathione synthetase deficiency (GSSD)	0.32	-1.64
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.3003C>T (p.Ser1001=)	AGC	AGT	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD)	0.72	-0.48
TCF4	ENSG00000196628	NM_001083962.2(TCF4):c.1113G>A (p.Ser371=)	TCG	TCA	Pitt-Hopkins syndrome (PTHS)	3.5	1.81
PLCB1	ENSG00000182621	NM_015192.4(PLCB1):c.288G>T (p.Gly96=)	GGG	GGT	Seizures;Early infantile epileptic encephalopathy 12 (DEE12)	0.71	-0.5
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.1083T>C (p.Asp361=)	GAT	GAC	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS)	1.01	0.01
PAX6	ENSG00000007372	NM_000280.4(PAX6):c.423C>G (p.Gly141=)	GGC	GGG		0.77	-0.37
OPA1	ENSG00000198836	NM_015560.2(OPA1):c.756C>T (p.Asp252=)	GAC	GAT		0.99	-0.01
NEB	ENSG00000183091	NM_001271208.2(NEB):c.22752G>A (p.Glu7584=)	GAG	GAA	Nemaline myopathy 2 (NEM2)	0.86	-0.22

NEB	ENSG00000183091	NM_001271208.2(NEB):c.22110G>A (p.Thr7370=)	ACG	ACA	Nemaline myopathy 2 (NEM2)	2.96	1.57
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.2124C>T (p.Ala708=)	GCC	GCT	Aortic aneurysm, familial thoracic 7 (AAT7)	0.74	-0.44
CACNA1A	ENSG00000141837	NM_001127222.2(CACNA1A):c.5451C>T (p.Thr1817=)	ACC	ACT		0.8	-0.31
LYST	ENSG00000143669	NM_001301365.1(LYST):c.7506A>G (p.Gln2502=)	CAA	CAG	Chédiak-Higashi syndrome (CHS)	2.49	1.32
WFS1	ENSG00000109501	NM_006005.3(WFS1):c.975C>T (p.Asn325=)	AAC	AAT		1.01	0.02
COG5	ENSG00000164597	NM_006348.5(COG5):c.2271C>T (p.Pro757=)	CTC	CTT	Congenital disorder of glycosylation type 2i (CDG2I)	0.8	-0.33
PNPLA6	ENSG00000032444	NM_001166114.2(PNPLA6):c.3954C>T (p.Ala1318=)	GCC	GCT	Hereditary spastic paraplegia 39 (SPG39)	0.74	-0.44
SLC35C1	ENSG00000181830	NM_018389.4(SLC35C1):c.522C>T (p.Cys174=)	TGC	TGT	Leukocyte adhesion deficiency type II	0.97	-0.05
MFN2	ENSG00000116688	NM_014874.3(MFN2):c.1818C>T (p.Gly606=)	GGC	GGT	Hereditary motor and sensory neuropathy with optic atrophy (HMSN6A);Charcot-Marie-Tooth disease, type 2	0.55	-0.87
COG5	ENSG00000164597	NM_006348.5(COG5):c.264A>G (p.Ala88=)	GCA	GCG	Congenital disorder of glycosylation type 2i (CDG2I)	0.35	-1.52
RTTN	ENSG00000176225	NM_173630.4(RTTN):c.3048G>A (p.Pro1016=)	CCG	CCA		3.05	1.61
PHKB	ENSG00000102893	NM_000293.3(PHKB):c.1746A>G (p.Leu582=)	CTA	CTG	Glycogen storage disease IXb (GSD9B)	4.81	2.27
BLM	ENSG00000197299	NM_000057.4(BLM):c.2898C>G (p.Leu966=)	CTC	CTG	Hereditary cancer-predisposing syndrome;Bloom syndrome (BLM)	2.02	1.02
NEB	ENSG00000183091	NM_001271208.2(NEB):c.18870C>T (p.Asn6290=)	AAC	AAT	Nemaline myopathy 2 (NEM2)	1.01	0.02
CACNA1D	ENSG00000157388	NM_001128840.3(CACNA1D):c.2805G>C (p.Leu935=)	CTG	CTC		0.49	-1.02
NEB	ENSG00000183091	NM_001271208.2(NEB):c.21966G>A (p.Arg7322=)	CGG	CGA	Nemaline myopathy 2 (NEM2)	0.6	-0.73
SPINK5	ENSG00000133710	NM_006846.3(SPINK5):c.2124T>C (p.Ala708=)	GCT	GCC	Netherton syndrome (NETH)	1.36	0.44
NEB	ENSG00000183091	NM_001271208.2(NEB):c.8490G>A (p.Arg2830=)	AGG	AGA	Nemaline myopathy 2 (NEM2)	1.1	0.14
USH2A	ENSG00000042781	NM_206933.4(USH2A):c.1581C>T (p.Cys527=)	TGC	TGT		0.97	-0.05
COL2A1	ENSG00000139219	NM_001844.5(COL2A1):c.1176C>T (p.Arg392=)	CGC	CGT		0.52	-0.93
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.3303A>G (p.Thr1101=)	ACA	ACG	Autosomal recessive polycystic kidney disease (ARPKD)	0.34	-1.57
NEB	ENSG00000183091	NM_001271208.2(NEB):c.5181C>T (p.Tyr1727=)	TAC	TAT	Nemaline myopathy 2 (NEM2)	0.9	-0.15
WDR62	ENSG00000075702	NM_001083961.2(WDR62):c.477G>A (p.Ala159=)	GCG	GCA		2.88	1.52
WFS1	ENSG00000109501	NM_006005.3(WFS1):c.1743C>T (p.Gly581=)	GGC	GGT		0.55	-0.87
PYGM	ENSG00000068976	NM_005609.4(PYGM):c.540C>T (p.Ala180=)	GCC	GCT	Glycogen storage disease, type V (GSD5)	0.74	-0.44
SERPINF2	ENSG00000167711	NM_000934.3(SERPINF2):c.1107C>T (p.Ser369=)	TCC	TCT		0.98	-0.03
GALNS	ENSG00000141012	NM_000512.5(GALNS):c.858G>A (p.Thr286=)	ACG	ACA	Mucopolysaccharidosis, MPS-IV-A (MPS4A)	2.96	1.57
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.3537T>C (p.Asn1179=)	AAT	AAC	Autosomal recessive polycystic kidney disease (ARPKD)	0.99	-0.02
PEX1	ENSG00000127980	NM_000466.3(PEX1):c.1011G>A (p.Lys337=)	AAG	AAA	Peroxisome biogenesis disorder 1A (Zellweger) (PBD1A)	0.87	-0.2
PCCA	ENSG00000175198	NM_000282.4(PCCA):c.828T>C (p.Gly276=)	GGT	GGC	Propionic acidemia (PROP)	1.82	0.87
LRP5	ENSG00000162337	NM_002335.4(LRP5):c.3990G>A (p.Ala1330=)	GCG	GCA		2.88	1.52
PHEX	ENSG00000102174	NM_000444.6(PHEX):c.1344C>T (p.Asp448=)	GAC	GAT		0.99	-0.01
CREBBP	ENSG00000005339	NM_004380.3(CREBBP):c.6090G>A (p.Gln2030=)	CAG	CAA		0.4	-1.32
NTRK1	ENSG00000198400	NM_001007792.1(NTRK1):c.540C>T (p.Asp180=)	GAC	GAT	Hereditary insensitivity to pain with anhidrosis (CIPA)	0.99	-0.01
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.3204A>G (p.Thr1068=)	ACA	ACG	History of neurodevelopmental disorder;Cohen syndrome (COH1)	0.34	-1.57
WDR62	ENSG00000075702	NM_001083961.2(WDR62):c.2766C>T (p.Arg922=)	CGC	CGT		0.52	-0.93
TMEM237	ENSG00000155755	NM_001044385.3(TMEM237):c.348G>A (p.Ala116=)	GCG	GCA	Joubert syndrome 14 (JBTS14)	2.88	1.52
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.5064C>A (p.Pro1688=)	CCC	CCA	History of neurodevelopmental disorder;Cohen syndrome (COH1)	1	-0.01
COG7	ENSG00000168434	NM_153603.4(COG7):c.2052G>A (p.Ser684=)	TCG	TCA	COG7 congenital disorder of glycosylation (CDG2E)	3.5	1.81

KCNQ1	ENSG00000053918	NM_181798.1(KCNQ1):c.498C>A (p.Arg166=)	CGC	CGA		0.74	-0.44
USH2A	ENSG00000042781	NM_206933.4(USH2A):c.1590A>T (p.Thr530=)	ACA	ACT		0.86	-0.21
WFS1	ENSG00000109501	NM_006005.3(WFS1):c.1632C>T (p.Ser544=)	TCC	TCT		0.98	-0.03
NEB	ENSG00000183091	NM_001271208.2(NEB):c.984C>T (p.Thr328=)	ACC	ACT	Nemaline myopathy 2 (NEM2)	0.8	-0.31
RSPH4A	ENSG00000111834	NM_001010892.3(RSPH4A):c.675G>T (p.Ser225=)	TCG	TCT	Primary ciliary dyskinesia (PCD)	4.18	2.06
ASPM	ENSG00000066279	NM_018136.5(ASPM):c.9276T>C (p.Gly3092=)	GGT	GGC		1.82	0.87
PYGM	ENSG00000068976	NM_005609.4(PYGM):c.1692C>T (p.Phe564=)	TTC	TTT	Glycogen storage disease, type V (GSD5)	0.98	-0.02
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.2157T>C (p.His719=)	CAT	CAC	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD)	1.23	0.3
LIM2	ENSG00000105370	NM_001161748.2(LIM2):c.231C>T (p.Ser77=)	TCC	TCT	Cataract 19, multiple types (CTRCT19)	0.98	-0.03
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.7926G>A (p.Pro2642=)	CCG	CCA		3.05	1.61
KIF1C	ENSG00000129250	NM_006612.6(KIF1C):c.996C>T (p.Tyr332=)	TAC	TAT		0.9	-0.15
SLC2A10	ENSG00000197496	NM_030777.4(SLC2A10):c.432C>T (p.Thr144=)	ACC	ACT	Cardiovascular phenotype;Arterial tortuosity syndrome (ATORS)	0.8	-0.31
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.9528C>T (p.Ala3176=)	GCC	GCT		0.74	-0.44
NEB	ENSG00000183091	NM_001271208.2(NEB):c.10608C>T (p.Gly3536=)	GGC	GGT	Nemaline myopathy 2 (NEM2)	0.55	-0.87
SPTBN2	ENSG00000173898	NM_006946.3(SPTBN2):c.2526C>T (p.Gly842=)	GGC	GGT	Autosomal dominant cerebellar ataxia;	0.55	-0.87
GRHL2	ENSG00000083307	NM_024915.4(GRHL2):c.804C>T (p.Thr268=)	ACC	ACT		0.8	-0.31
ARFGEF2	ENSG00000124198	NM_006420.3(ARFGEF2):c.4812G>A (p.Lys1604=)	AAG	AAA		0.87	-0.2
GLDC	ENSG00000178445	NM_000170.2(GLDC):c.2964G>A (p.Arg988=)	CGG	CGA	Non-ketotic hyperglycinemia (GCE)	0.6	-0.73
COL6A1	ENSG00000142156	NM_001848.2(COL6A1):c.2709C>T (p.Ala903=)	GCC	GCT		0.74	-0.44
FAH	ENSG00000103876	NM_000137.3(FAH):c.150T>C (p.Phe50=)	TTT	TTC	Tyrosinemia type I (TYRSN1)	1.02	0.02
RFT1	ENSG00000163933	NM_052859.4(RFT1):c.303C>G (p.Gly101=)	GGC	GGG	Congenital disorder of glycosylation type 1N (CDG1N)	0.77	-0.37
TYK2	ENSG00000105397	NM_003331.5(TYK2):c.2250C>T (p.Gly750=)	GGC	GGT	Tyrosine kinase 2 deficiency (IMD35)	0.55	-0.87
SUCLA2	ENSG00000136143	NM_003850.2(SUCLA2):c.1350G>A (p.Ala450=)	GCG	GCA	Mitochondrial DNA depletion syndrome 5 (encephalomyopathic with or without methylmalonic aciduria) (MTDPS5)	2.88	1.52
BBS9	ENSG00000122507	NM_198428.3(BBS9):c.771A>G (p.Ala257=)	GCA	GCG		0.35	-1.52
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.4743C>T (p.Ile1581=)	ATC	ATT	Connective tissue disease;Aortic aneurysm, familial thoracic 7 (AAT7)	0.89	-0.17
HADHB	ENSG00000138029	NM_000183.3(HADHB):c.900C>T (p.Tyr300=)	TAC	TAT	Mitochondrial trifunctional protein deficiency (MTPD)	0.9	-0.15
CCBE1	ENSG00000183287	NM_133459.4(CCBE1):c.843A>T (p.Pro281=)	CCA	CCT	Hennekam lymphangiectasia-lymphedema syndrome 1 (HKLLS1)	1.02	0.03
PCCB	ENSG00000114054	NM_000532.5(PCCB):c.561C>T (p.Ser187=)	TCC	TCT	Propionic acidemia (PROP)	0.98	-0.03
CBS	ENSG00000160200	NM_000071.2(CBS):c.924C>T (p.Tyr308=)	TAC	TAT	Classic homocystinuria	0.9	-0.15
CYP27A1	ENSG00000135929	NM_000784.4(CYP27A1):c.702C>T (p.Pro234=)	CCC	CCT	Cholestanol storage disease (CTX)	1.02	0.02
SUCLG1	ENSG00000163541	NM_003849.4(SUCLG1):c.384C>T (p.Ala128=)	GCC	GCT	Mitochondrial DNA depletion syndrome 9 (encephalomyopathic with methylmalonic aciduria) (MTDPS9)	0.74	-0.44
PIGO	ENSG00000165282	NM_032634.4(PIGO):c.969T>G (p.Leu323=)	CTT	CTG	Hyperphosphatasia with mental retardation syndrome 2 (HPMRS2)	2.54	1.35
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.303C>T (p.Ser101=)	AGC	AGT	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD)	0.72	-0.48
COG5	ENSG00000164597	NM_006348.5(COG5):c.2124A>G (p.Arg708=)	TTG	TTG	Congenital disorder of glycosylation type 2i (CDG2I)	1	0
RBM20	ENSG00000203867	NM_001134363.3(RBM20):c.1659G>A (p.Ser553=)	TCG	TCA	Dilated cardiomyopathy 1DD (CMD1DD)	3.5	1.81
LMBRD1	ENSG00000168216	NM_018368.4(LMBRD1):c.384T>C (p.Asp128=)	GAT	GAC	Methylmalonic aciduria and homocystinuria type cblF (MAHCF)	1.01	0.01
MYH7	ENSG00000092054	NM_000257.4(MYH7):c.2859C>T (p.Asp953=)	GAC	GAT	Hypertrophic cardiomyopathy;Cardiomyopathy (CMYO)	0.99	-0.01
ABCC6	ENSG00000091262	NM_001171.5(ABCC6):c.1263C>T (p.Thr421=)	ACC	ACT		0.8	-0.31

COG7	ENSG00000168434	NM_153603.4(COG7):c.2283C>T (p.Thr761=)	ACC	ACT	COG7 congenital disorder of glycosylation (CDG2E)	0.8	-0.31
SLC22A5	ENSG00000197375	NM_003060.4(SLC22A5):c.852C>T (p.Leu284=)	CTC	CTT	Renal carnitine transport defect (CDSP)	0.8	-0.33
KMT2D	ENSG00000167548	NM_003482.3(KMT2D):c.1149C>T (p.Asp383=)	GAC	GAT		0.99	-0.01
USH2A	ENSG00000042781	NM_206933.4(USH2A):c.10470G>T (p.Val3490=)	GTG	GTT		0.46	-1.13
DNM2	ENSG00000079805	NM_001005360.2(DNM2):c.1773G>A (p.Thr591=)	ACG	ACA	Myopathy, centronuclear, 1 (CNM1);Charcot-Marie-Tooth disease, dominant intermediate B (CMTDIB)	2.96	1.57
DOCK8	ENSG00000107099	NM_203447.3(DOCK8):c.1881T>C (p.Phe627=)	TTT	TTC	Hyperimmunoglobulin E recurrent infection syndrome, autosomal recessive (HIES2)	1.02	0.02
PRF1	ENSG00000180644	NM_001083116.3(PRF1):c.807C>T (p.His269=)	CAC	CAT	Familial hemophagocytic lymphohistiocytosis 2 (FHL2)	0.81	-0.3
KCNMA1	ENSG00000156113	NM_001161352.2(KCNMA1):c.2547C>T (p.Asp849=)	GAC	GAT	Paroxysmal nonkinesigenic dyskinesia, 3, with or without generalized epilepsy (PNKD3)	0.99	-0.01
WDR62	ENSG00000075702	NM_001083961.2(WDR62):c.3087C>T (p.Cys1029=)	TGC	TGT		0.97	-0.05
PAFAH1B1	ENSG00000007168	NM_000430.4(PAFAH1B1):c.387T>C (p.Asp129=)	GAT	GAC		1.01	0.01
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.3018C>T (p.Asp1006=)	GAC	GAT	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS)	0.99	-0.01
PHKB	ENSG00000102893	NM_000293.3(PHKB):c.270C>T (p.Cys90=)	TGC	TGT	Glycogen storage disease IXb (GSD9B)	0.97	-0.05
IGHMBP2	ENSG00000132740	NM_002180.2(IGHMBP2):c.1737C>T (p.Phe579=)	TTC	TTT		0.98	-0.02
CRTAP	ENSG00000170275	NM_006371.4(CRTAP):c.732C>T (p.Leu244=)	CTC	CTT	Osteogenesis imperfecta type 7 (OI7)	0.8	-0.33
TYK2	ENSG00000105397	NM_003331.5(TYK2):c.2670G>C (p.Thr890=)	ACG	ACC	Tyrosine kinase 2 deficiency (IMD35)	3.18	1.67
SMARCB1	ENSG00000099956	NM_003073.5(SMARCB1):c.444C>T (p.Ser148=)	TCC	TCT	Hereditary cancer-predisposing syndrome;	0.98	-0.03
TTN	ENSG00000155657	NM_001267550.2(TTN):c.58191G>A (p.Thr19397=)	ACG	ACA		2.96	1.57
CPS1	ENSG00000021826	NM_001875.5(CPS1):c.1116C>T (p.Phe372=)	CCA	CCT	Congenital hyperammonemia, type I	1.02	0.03
PEX1	ENSG00000127980	NM_000466.3(PEX1):c.468A>G (p.Gln156=)	CAA	CAG	Peroxisome biogenesis disorder 1A (Zellweger) (PBD1A)	2.49	1.32
GYS1	ENSG00000104812	NM_002103.5(GYS1):c.1332C>T (p.Cys444=)	TGC	TGT	Glycogen storage disease 0, muscle (GSD0B)	0.97	-0.05
SCN1A	ENSG00000144285	NM_001165963.4(SCN1A):c.3591A>G (p.Glu1197=)	GAA	GAG		1.16	0.22
TTN	ENSG00000155657	NM_001267550.2(TTN):c.14049C>T (p.Ser4683=)	AGC	AGT	Cardiovascular phenotype;	0.72	-0.48
TRIOBP	ENSG00000100106	NM_001039141.3(TRIOBP):c.6771G>A (p.Gln2257=)	CAG	CAA		0.4	-1.32
JAK3	ENSG00000105639	NM_000215.3(JAK3):c.1929G>A (p.Leu643=)	CTG	CTA	Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-negative	0.21	-2.27
VCL	ENSG00000035403	NM_014000.3(VCL):c.3066C>T (p.Ile1022=)	ATC	ATT	Dilated cardiomyopathy 1W (CMD1W)	0.89	-0.17
ATL1	ENSG00000198513	NM_001127713.1(ATL1):c.1152A>G (p.Pro384=)	CCA	CCG	Hereditary spastic paraplegia 3A (SPG3A)	0.33	-1.61
CACNA1D	ENSG00000157388	NM_001128840.3(CACNA1D):c.6417C>T (p.Asp2139=)	GAC	GAT		0.99	-0.01
MLYCD	ENSG00000103150	NM_012213.3(MLYCD):c.1074G>A (p.Ser358=)	TCG	TCA	Deficiency of malonyl-CoA decarboxylase	3.5	1.81
PCNT	ENSG00000160299	NM_006031.6(PCNT):c.8889G>A (p.Ser2963=)	TCG	TCA		3.5	1.81
PC	ENSG00000173599	NM_001040716.2(PC):c.1446C>T (p.Asp482=)	GAC	GAT	Pyruvate carboxylase deficiency	0.99	-0.01
PCCA	ENSG00000175198	NM_000282.4(PCCA):c.42C>T (p.Ala14=)	GCC	GCT	Propionic acidemia (PROP)	0.74	-0.44
ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.279C>T (p.Tyr93=)	TAC	TAT		0.9	-0.15
TCTN1	ENSG00000204852	NM_001082538.3(TCTN1):c.1563C>T (p.Tyr521=)	TAC	TAT		0.9	-0.15
CDH1	ENSG00000039068	NM_004360.5(CDH1):c.2505T>C (p.Tyr835=)	TAT	TAC	Hereditary cancer-predisposing syndrome;Hereditary diffuse gastric cancer (HDGC)	1.11	0.15
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.3852C>T (p.Phe1284=)	TTC	TTT		0.98	-0.02
SLC25A19	ENSG00000125454	NM_001126121.2(SLC25A19):c.750G>A (p.Glu250=)	GAG	GAA		0.86	-0.22

AP3B1	ENSG00000132842	NM_003664.4(AP3B1):c.822C>T (p.Tyr274=)	TAC	TAT	Hermansky-Pudlak syndrome 2 (HPS2)	0.9	-0.15
CAPN3	ENSG00000092529	NM_000070.3(CAPN3):c.1350C>T (p.Phe450=)	TTC	TTT	Limb-girdle muscular dystrophy, type 2A (LGMDR1)	0.98	-0.02
MECP2	ENSG00000169057	NM_001110792.2(MECP2):c.90C>G (p.Leu30=)	CTC	CTG		2.02	1.02
MYH9	ENSG00000100345	NM_002473.6(MYH9):c.591G>A (p.Ser197=)	TCG	TCA		3.5	1.81
VWF	ENSG00000110799	NM_000552.4(VWF):c.546G>A (p.Ser182=)	TCG	TCA		3.5	1.81
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.3303C>T (p.Tyr1101=)	TAC	TAT	Qualitative or quantitative defects of dysferlin	0.9	-0.15
TTBK2	ENSG00000128881	NM_173500.4(TTBK2):c.3543G>A (p.Ser1181=)	TCG	TCA	Spinocerebellar ataxia type 11 (SCA11);	3.5	1.81
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.2484C>T (p.Gly828=)	GGC	GGT	Wilson disease (WND)	0.55	-0.87
PYGM	ENSG00000068976	NM_005609.4(PYGM):c.612C>T (p.Tyr204=)	TAC	TAT	Glycogen storage disease, type V (GSD5)	0.9	-0.15
LAMC3	ENSG00000050555	NM_006059.4(LAMC3):c.4092C>T (p.Ser1364=)	TCC	TCT		0.98	-0.03
USH1C	ENSG00000006611	NM_153676.4(USH1C):c.2443C>T (p.Leu815=)	CTG	TTG		0.37	-1.42
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.12207C>T (p.Thr4069=)	ACC	ACT		0.8	-0.31
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.1752A>G (p.Leu584=)	CTA	CTG	Cardiovascular phenotype;Aortic aneurysm, familial thoracic 7 (AAT7)	4.81	2.27
ACADM	ENSG00000117054	NM_000016.5(ACADM):c.645T>A (p.Ala215=)	GCT	GCA	Medium-chain acyl-coenzyme A dehydrogenase deficiency (ACADMD)	0.9	-0.14
ATM	ENSG00000149311	NM_000051.3(ATM):c.2778A>G (p.Lys926=)	AAA	AAG	Hereditary cancer-predisposing syndrome;Ataxia-telangiectasia syndrome (AT)	1.15	0.2
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.522G>A (p.Arg174=)	CGG	CGA	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD)	0.6	-0.73
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.798C>T (p.Tyr266=)	TAC	TAT	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS)	0.9	-0.15
NEB	ENSG00000183091	NM_001271208.2(NEB):c.17415C>T (p.Tyr5805=)	TAC	TAT	Nemaline myopathy 2 (NEM2)	0.9	-0.15
MYO15A	ENSG00000091536	NM_016239.4(MYO15A):c.858C>G (p.Pro286=)	CCC	CCG		0.33	-1.62
ASL	ENSG00000126522	NM_000048.4(ASL):c.399G>A (p.Ser133=)	TCG	TCA	Argininosuccinate lyase deficiency	3.5	1.81
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.3897C>T (p.Ala1299=)	GCC	GCT	Aortic aneurysm, familial thoracic 7 (AAT7)	0.74	-0.44
ALG13	ENSG00000101901	NM_001099922.3(ALG13):c.2607G>A (p.Ala869=)	GCG	GCA		2.88	1.52
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.14373T>A (p.Ala4791=)	GCT	GCA		0.9	-0.14
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.2529C>T (p.Asp843=)	GAC	GAT	Collagen VI-related myopathy (COL6-RM);	0.99	-0.01
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.3402C>T (p.Pro1134=)	CCC	CCT	Wilson disease (WND)	1.02	0.02
HLCS	ENSG00000159267	NM_001352514.2(HLCS):c.1278G>A (p.Glu426=)	GAG	GAA	Holocarboxylase synthetase deficiency	0.86	-0.22
NEB	ENSG00000183091	NM_001271208.2(NEB):c.11025G>A (p.Thr3675=)	ACG	ACA	Nemaline myopathy 2 (NEM2)	2.96	1.57
SCN2A	ENSG00000136531	NM_001040142.2(SCN2A):c.5574A>G (p.Leu1858=)	TTA	TTG		1.53	0.61
SCN1A	ENSG00000144285	NM_001165963.4(SCN1A):c.144C>T (p.Gly48=)	GGC	GGT		0.55	-0.87
NEB	ENSG00000183091	NM_001271208.2(NEB):c.11133T>C (p.Asp3711=)	GAT	GAC	Nemaline myopathy 2 (NEM2)	1.01	0.01
TRIOBP	ENSG00000100106	NM_001039141.3(TRIOBP):c.483G>A (p.Glu161=)	GAG	GAA		0.86	-0.22
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.4251A>G (p.Thr1417=)	ACA	ACG	Wilson disease (WND)	0.34	-1.57
DMD	ENSG00000198947	NM_004006.2(DMD):c.5530C>A (p.Arg1844=)	CGA	AGA		2.09	1.06
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.7702C>T (p.Leu2568=)	CTG	TTG		0.37	-1.42
CACNA1A	ENSG00000141837	NM_001127222.2(CACNA1A):c.5868C>T (p.Tyr1956=)	TAC	TAT		0.9	-0.15
VIPAS39	ENSG00000151445	NM_022067.4(VIPAS39):c.1254T>C (p.Asn418=)	AAT	AAC		0.99	-0.02
MCPH1	ENSG00000147316	NM_024596.5(MCPH1):c.297C>T (p.His99=)	CAC	CAT		0.81	-0.3
ABCB4	ENSG00000005471	NM_000443.4(ABCB4):c.2325G>A (p.Thr775=)	ACG	ACA		2.96	1.57

CIB2	ENSG00000136425	NM_006383.4(CIB2):c.192G>A (p.Glu64=)	GAG	GAA		0.86	-0.22
DNAAF11	ENSG00000129295	NM_012472.6(DNAAF11):c.1245A>G (p.Lys415=)	AAA	AAG	Ciliary dyskinesia, primary, 19 (CILD19)	1.15	0.2
DSP	ENSG00000096696	NM_004415.4(DSP):c.1065G>A (p.Gln355=)	CAG	CAA		0.4	-1.32
GAA	ENSG00000171298	NM_000152.5(GAA):c.1758G>A (p.Ala586=)	GCG	GCA	Glycogen storage disease, type II (GSD2)	2.88	1.52
VCL	ENSG00000035403	NM_014000.3(VCL):c.808T>C (p.Leu270=)	TTG	CTG	Dilated cardiomyopathy 1W (CMD1W)	2.67	1.42
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.567C>T (p.Ala189=)	GCC	GCT		0.74	-0.44
DOCK8	ENSG00000107099	NM_203447.4(DOCK8):c.3543A>G (p.Val1181=)	GTA	GTG	Hyperimmunoglobulin E recurrent infection syndrome, autosomal recessive (HIES2)	3.34	1.74
NEB	ENSG00000183091	NM_001271208.2(NEB):c.7953C>T (p.Ser2651=)	AGC	AGT	Nemaline myopathy 2 (NEM2)	0.72	-0.48
OTOF	ENSG00000115155	NM_194248.3(OTOF):c.1530C>T (p.Ile510=)	ATC	ATT		0.89	-0.17
COG7	ENSG00000168434	NM_153603.4(COG7):c.75C>G (p.Ser25=)	TCC	TCG	COG7 congenital disorder of glycosylation (CDG2E)	0.23	-2.09
COG7	ENSG00000168434	NM_153603.4(COG7):c.1455C>T (p.Phe485=)	TTC	TTT	COG7 congenital disorder of glycosylation (CDG2E)	0.98	-0.02
ASPM	ENSG00000066279	NM_018136.5(ASPM):c.9657T>G (p.Ser3219=)	TCT	TCG		0.24	-2.06
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.10563T>C (p.Leu3521=)	CTT	CTC		1.26	0.33
SPTBN2	ENSG00000173898	NM_006946.3(SPTBN2):c.1161C>T (p.Arg387=)	CGC	CGT	Autosomal dominant cerebellar ataxia;	0.52	-0.93
DSC2	ENSG00000134755	NM_024422.6(DSC2):c.669A>G (p.Pro223=)	CCA	CCG	Cardiovascular phenotype;Cardiomyopathy (CMYO)	0.33	-1.61
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.8319G>A (p.Ser2773=)	TCG	TCA	Cohen syndrome (COH1)	3.5	1.81
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.7806C>G (p.Pro2602=)	CCC	CCG		0.33	-1.62
KCNT1	ENSG00000107147	NM_020822.3(KCNT1):c.285C>T (p.Asn95=)	AAC	AAT		1.01	0.02
KCNQ1	ENSG00000053918	NM_181798.1(KCNQ1):c.378C>T (p.Ser126=)	TCC	TCT		0.98	-0.03
COL2A1	ENSG00000139219	NM_001844.5(COL2A1):c.1077C>T (p.Val359=)	GTC	GTT		0.88	-0.19
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.8403C>T (p.Tyr2801=)	TAC	TAT		0.9	-0.15
TTN	ENSG00000155657	NM_001267550.2(TTN):c.47598A>G (p.Leu15866=)	CTA	CTG		4.81	2.27
CHD7	ENSG00000171316	NM_017780.4(CHD7):c.8580C>T (p.Ser2860=)	AGC	AGT	Hypogonadotropic hypogonadism 5 with or without anosmia (KAL5);	0.72	-0.48
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.7569A>G (p.Thr2523=)	ACA	ACG		0.34	-1.57
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.1290C>T (p.Thr430=)	ACC	ACT	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);	0.8	-0.31
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.3180A>G (p.Pro1060=)	CCA	CCG	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD)	0.33	-1.61
SCN1A	ENSG00000144285	NM_001165963.4(SCN1A):c.5532A>G (p.Pro1844=)	CCA	CCG		0.33	-1.61
DNAI1	ENSG00000122735	NM_012144.4(DNAI1):c.1929C>A (p.Ile643=)	ATC	ATA	Primary ciliary dyskinesia (PCD);Kartagener syndrome (CILD1)	0.44	-1.2
LPIN2	ENSG00000101577	NM_014646.2(LPIN2):c.2535A>C (p.Gly845=)	GGA	GGC	Majeed syndrome (MJDS)	1.15	0.2
CDH1	ENSG00000039068	NM_004360.5(CDH1):c.1716T>C (p.Ser572=)	TCT	TCC	Hereditary cancer-predisposing syndrome;Hereditary diffuse gastric cancer (HDGC)	1.02	0.03
TTN	ENSG00000155657	NM_001267550.2(TTN):c.69984G>A (p.Ala23328=)	GCG	GCA		2.88	1.52
SCN8A	ENSG00000196876	NM_001330260.2(SCN8A):c.3327C>T (p.Asn1109=)	AAC	AAT	History of neurodevelopmental disorder;	1.01	0.02
KCNQ2	ENSG00000075043	NM_172107.4(KCNQ2):c.1209C>T (p.Leu403=)	CTC	CTT		0.8	-0.33
DNAJB6	ENSG00000105993	NM_058246.4(DNAJB6):c.831T>G (p.Ser277=)	TCT	TCG		0.24	-2.06
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.1056G>A (p.Pro352=)	CCG	CCA		3.05	1.61
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.5488T>C (p.Leu1830=)	TTG	CTG		2.67	1.42
ACADM	ENSG00000117054	NM_000016.5(ACADM):c.210T>G (p.Thr70=)	ACT	ACG	Medium-chain acyl-coenzyme A dehydrogenase deficiency (ACADMD)	0.39	-1.36
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.19815T>A (p.Gly6605=)	GGT	GGA		1.59	0.67

PLEC	ENSG00000178209	NM_201384.3(PLEC):c.10791C>T (p.Pro3597=)	CCC	CCT		1.02	0.02
WFS1	ENSG00000109501	NM_006005.3(WFS1):c.726C>T (p.Ile242=)	ATC	ATT		0.89	-0.17
PSTPIP1	ENSG00000140368	NM_003978.5(PSTPIP1):c.657A>G (p.Gln219=)	CAA	CAG	Pyogenic arthritis-pyoderma gangrenosum-acne syndrome	2.49	1.32
PHKG2	ENSG00000156873	NM_000294.3(PHKG2):c.360A>G (p.Thr120=)	ACA	ACG	Glycogen storage disease IXc (GSD9C)	0.34	-1.57
MYO7A	ENSG00000137474	NM_000260.4(MYO7A):c.5227C>A (p.Arg1743=)	CGG	AGG		1.15	0.2
NF1	ENSG00000196712	NM_000267.3(NF1):c.5556C>G (p.Ala1852=)	GCC	GCG	Hereditary cancer-predisposing syndrome;Neurofibromatosis, type 1 (NF1)	0.23	-2.11
MYH9	ENSG00000100345	NM_002473.5(MYH9):c.2871C>T (p.Ser957=)	AGC	AGT		0.72	-0.48
PNPLA2	ENSG00000177666	NM_020376.4(PNPLA2):c.369C>T (p.Asp123=)	GAC	GAT	Neutral lipid storage myopathy (NLSDM)	0.99	-0.01
TTN	ENSG00000155657	NM_001267550.2(TTN):c.89295T>C (p.Ala29765=)	GCT	GCC		1.36	0.44
COL11A1	ENSG00000060718	NM_001854.4(COL11A1):c.2115A>G (p.Gln705=)	CAA	CAG		2.49	1.32
COG5	ENSG00000164597	NM_006348.5(COG5):c.795C>T (p.Asp265=)	CGT	CGT	Congenital disorder of glycosylation type 2i (CDG2I)	1	0
MBD5	ENSG00000204406	NM_018328.4(MBD5):c.4032C>T (p.Ser1344=)	AGC	AGT		0.72	-0.48
RYR2	ENSG00000198626	NM_001035.3(RYR2):c.8736G>A (p.Leu2912=)	CTG	CTA	Cardiomyopathy (CMYO)	0.21	-2.27
ATM	ENSG00000149311	NM_000051.3(ATM):c.3982T>C (p.Leu1328=)	TTG	CTG	Hereditary cancer-predisposing syndrome;Ataxia-telangiectasia syndrome (AT)	2.67	1.42
ACTG1	ENSG00000184009	NM_001614.5(ACTG1):c.825C>T (p.His275=)	CAC	CAT		0.81	-0.3
SKI	ENSG00000157933	NM_003036.4(SKI):c.2058C>T (p.Ala686=)	GCC	GCT	Cardiovascular phenotype;Shprintzen-Goldberg syndrome (SGS)	0.74	-0.44
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.13287C>A (p.Gly4429=)	GGC	GGA		0.87	-0.2
HMGCS2	ENSG00000134240	NM_001166107.1(HMGCS2):c.560-697C>T	GCC	GCT	mitochondrial 3-hydroxy-3-methylglutaryl-CoA synthase deficiency (HMGCS2D)	0.74	-0.44
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.4935G>A (p.Val1645=)	GTG	GTA	Cardiovascular phenotype;	0.3	-1.74
MBD5	ENSG00000204406	NM_018328.4(MBD5):c.4188G>A (p.Leu1396=)	CTG	CTA		0.21	-2.27
COL6A1	ENSG00000142156	NM_001848.2(COL6A1):c.2220G>T (p.Pro740=)	CCG	CCT		3.11	1.64
MCCC2	ENSG00000131844	NM_022132.5(MCCC2):c.330C>T (p.Asp110=)	GAC	GAT	3-methylcrotonyl CoA carboxylase 2 deficiency (MCC2D)	0.99	-0.01
SLC35C1	ENSG00000181830	NM_018389.4(SLC35C1):c.747C>T (p.Leu249=)	CTC	CTT	Leukocyte adhesion deficiency type II	0.8	-0.33
G6PC1	ENSG00000131482	NM_000151.4(G6PC1):c.909C>T (p.Leu303=)	CTC	CTT	Glycogen storage disease due to glucose-6-phosphatase deficiency type IA (GSD1A)	0.8	-0.33
TTN	ENSG00000155657	NM_001267550.2(TTN):c.26928G>A (p.Leu8976=)	CTG	CTA		0.21	-2.27
PHF6	ENSG00000156531	NM_001015877.2(PHF6):c.414C>T (p.Ser138=)	TCC	TCT		0.98	-0.03
STIL	ENSG00000123473	NM_001048166.1(STIL):c.2070A>T (p.Ser690=)	TCA	TCT		1.2	0.26
MATN3	ENSG00000132031	NM_002381.5(MATN3):c.330C>T (p.Ile110=)	ATC	ATT	Multiple epiphyseal dysplasia type 5 (EDM5);	0.89	-0.17
CTC1	ENSG00000178971	NM_025099.6(CTC1):c.147C>T (p.Val49=)	GTC	GTT	Dyskeratosis congenita	0.88	-0.19
CACNA1A	ENSG00000141837	NM_001127222.2(CACNA1A):c.6372A>G (p.Ser2124=)	TCA	TCG		0.29	-1.81
RTTN	ENSG00000176225	NM_173630.4(RTTN):c.1221A>G (p.Glu407=)	GAA	GAG		1.16	0.22
COL5A2	ENSG00000204262	NM_000393.5(COL5A2):c.2103C>T (p.Pro701=)	CCC	CCT		1.02	0.02
POMT2	ENSG00000009830	NM_013382.5(POMT2):c.1017C>T (p.Tyr339=)	TAC	TAT		0.9	-0.15
MMUT	ENSG00000146085	NM_000255.4(MMUT):c.1515T>C (p.Ile505=)	ATT	ATC	Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency	1.13	0.17
FLNC	ENSG00000128591	NM_001458.4(FLNC):c.6441C>T (p.Ile2147=)	ATC	ATT		0.89	-0.17
NHS	ENSG00000188158	NM_001291867.2(NHS):c.513C>T (p.Leu171=)	CTC	CTT		0.8	-0.33
TRIP11	ENSG00000100815	NM_004239.4(TRIP11):c.492T>C (p.Phe164=)	TTT	TTC	Achondrogenesis, type IA (ACG1A)	1.02	0.02
AP5Z1	ENSG00000242802	NM_014855.3(AP5Z1):c.1563G>A (p.Leu521=)	CTG	CTA	Spastic paraplegia 48, autosomal recessive (SPG48)	0.21	-2.27

RXYLT1	ENSG00000118600	NM_014254.3(RXYLT1):c.252C>T (p.Ser84=)	AGC	AGT		0.72	-0.48
NTRK1	ENSG00000198400	NM_001007792.1(NTRK1):c.621G>A (p.Thr207=)	ACG	ACA	Hereditary insensitivity to pain with anhidrosis (CIPA)	2.96	1.57
PEX19	ENSG00000162735	NM_002857.3(PEX19):c.261C>T (p.Phe87=)	TTC	TTT	Peroxisome biogenesis disorder 12A (PBD12A)	0.98	-0.02
ADAMTS2	ENSG00000087116	NM_014244.5(ADAMTS2):c.2892C>T (p.Pro964=)	CCC	CCT	Ehlers-Danlos syndrome dermatosparaxis type (EDSDERMS)	1.02	0.02
LMNA	ENSG00000160789	NM_170707.4(LMNA):c.1749G>A (p.Ser583=)	TCG	TCA	Charcot-Marie-Tooth disease, type 2;Cardiomyopathy (CMYO)	3.5	1.81
MYBPC3	ENSG00000134571	NM_000256.3(MYBPC3):c.1038C>T (p.Arg346=)	CGC	CGT	Cardiomyopathy (CMYO)	0.52	-0.93
PMM2	ENSG00000140650	NM_000303.3(PMM2):c.93C>T (p.Phe31=)	TTC	TTT	Congenital disorder of glycosylation, type Ia (CDG1A)	0.98	-0.02
PHKG2	ENSG00000156873	NM_000294.3(PHKG2):c.585G>A (p.Ala195=)	GCG	GCA	Glycogen storage disease IXc (GSD9C)	2.88	1.52
GALC	ENSG00000054983	NM_000153.4(GALC):c.18C>G (p.Leu6=)	CTC	CTG	Galactosylceramide beta-galactosidase deficiency	2.02	1.02
NAGS	ENSG00000161653	NM_153006.3(NAGS):c.612A>G (p.Val204=)	GTA	GTG	Hyperammonemia, type III (NAGSD)	3.34	1.74
GLI3	ENSG00000106571	NM_000168.6(GLI3):c.1182A>G (p.Pro394=)	CCA	CCG		0.33	-1.61
AP5Z1	ENSG00000242802	NM_014855.3(AP5Z1):c.1557A>G (p.Gln519=)	CAA	CAG	Spastic paraplegia 48, autosomal recessive (SPG48)	2.49	1.32
CHMP1A	ENSG00000131165	NM_002768.5(CHMP1A):c.198G>A (p.Ala66=)	GCG	GCA		2.88	1.52
GCDH	ENSG00000105607	NM_000159.4(GCDH):c.738G>A (p.Ser246=)	TCG	TCA	Glutaric aciduria, type 1 (GA1)	3.5	1.81
ACADVL	ENSG00000072778	NM_000018.4(ACADVL):c.1839G>A (p.Arg613=)	CGG	CGA	Very long chain acyl-CoA dehydrogenase deficiency (VLCAD)	0.6	-0.73
ASS1	ENSG00000130707	NM_054012.4(ASS1):c.930A>G (p.Lys310=)	AAA	AAG	Citrullinemia type I (CTNL1)	1.15	0.2
TTN	ENSG00000155657	NM_001267550.2(TTN):c.86085C>T (p.Asp28695=)	GAC	GAT		0.99	-0.01
TTN	ENSG00000155657	NM_001267550.2(TTN):c.102024A>G (p.Leu34008=)	CTA	CTG		4.81	2.27
UNC13D	ENSG00000092929	NM_199242.2(UNC13D):c.99G>A (p.Pro33=)	CCG	CCA	Familial hemophagocytic lymphohistiocytosis 3 (FHL3)	3.05	1.61
UNC13D	ENSG00000092929	NM_199242.2(UNC13D):c.24G>A (p.Pro8=)	CCG	CCA	Familial hemophagocytic lymphohistiocytosis 3 (FHL3)	3.05	1.61
POMT1	ENSG00000130714	NM_001077365.2(POMT1):c.1443C>T (p.His481=)	CAC	CAT		0.81	-0.3
TTN	ENSG00000155657	NM_001267550.2(TTN):c.58653T>C (p.Ile19551=)	ATT	ATC		1.13	0.17
MCCC1	ENSG00000078070	NM_020166.5(MCCC1):c.231G>A (p.Ala77=)	GCG	GCA	3 Methylcrotonyl-CoA carboxylase 1 deficiency (MCC1D)	2.88	1.52
TTN	ENSG00000155657	NM_001267550.2(TTN):c.55290C>T (p.Pro18430=)	CCC	CCT		1.02	0.02
TMEM165	ENSG00000134851	NM_018475.5(TMEM165):c.294C>T (p.Val98=)	GTC	GTT	Congenital disorder of glycosylation type 2k (CDG2K)	0.88	-0.19
TTC21B	ENSG00000123607	NM_024753.5(TTC21B):c.549T>C (p.Gly183=)	GGT	GGC		1.82	0.87
PMM2	ENSG00000140650	NM_000303.3(PMM2):c.597C>T (p.Asp199=)	GAC	GAT	Congenital disorder of glycosylation, type Ia (CDG1A)	0.99	-0.01
ACADM	ENSG00000117054	NM_000016.5(ACADM):c.582C>T (p.Asn194=)	AAC	AAT	Medium-chain acyl-coenzyme A dehydrogenase deficiency (ACADMD)	1.01	0.02
TTN	ENSG00000155657	NM_001267550.2(TTN):c.24045A>T (p.Ser8015=)	TCA	TCT		1.2	0.26
TNFRSF13C	ENSG00000159958	NM_052945.3(TNFRSF13C):c.60C>T (p.Val20=)	GTC	GTT	Common variable immunodeficiency 4 (CVID4)	0.88	-0.19
GCDH	ENSG00000105607	NM_000159.4(GCDH):c.642G>A (p.Thr214=)	ACG	ACA	Glutaric aciduria, type 1 (GA1)	2.96	1.57
TTN	ENSG00000155657	NM_001267550.2(TTN):c.52374T>C (p.Val17458=)	GTT	GTC		1.14	0.19
SKI	ENSG00000157933	NM_003036.4(SKI):c.1890C>T (p.Ala630=)	GCC	GCT		0.74	-0.44
PNPLA6	ENSG00000032444	NM_001166114.2(PNPLA6):c.225A>G (p.Arg75=)	CGA	CGG	Hereditary spastic paraplegia 39 (SPG39)	1.65	0.73
TTN	ENSG00000155657	NM_001267550.2(TTN):c.97294C>T (p.Leu32432=)	CTG	TTG		0.37	-1.42
AARS1	ENSG00000090861	NM_001605.2(AARS1):c.1275T>C (p.Thr425=)	ACT	ACC		1.24	0.31
ASS1	ENSG00000130707	NM_054012.4(ASS1):c.786C>T (p.Gly262=)	GGC	GGT	Citrullinemia type I (CTNL1)	0.55	-0.87
KMT2D	ENSG00000167548	NM_003482.3(KMT2D):c.2232A>C (p.Ser744=)	TCA	TCC		1.22	0.29
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.1140A>G (p.Gln380=)	CAA	CAG		2.49	1.32
POR	ENSG00000127948	NM_000941.3(POR):c.984C>T (p.Ala328=)	GCC	GCT	Disordered steroidogenesis due to cytochrome p450 oxidoreductase deficiency (ABS1)	0.74	-0.44

SGSH	ENSG00000181523	NM_000199.5(SGSH):c.1002C>T (p.Ala334=)	GCC	GCT	Mucopolysaccharidosis, MPS-III-A (MPS3A)	0.74	-0.44
CC2D2A	ENSG00000048342	NM_001080522.2(CC2D2A):c.3145C>A (p.Arg1049=)	CGA	AGA		2.09	1.06
SLC25A15	ENSG00000102743	NM_014252.4(SLC25A15):c.564C>T (p.Phe188=)	TTC	TTT	Hyperornithinemia-hyperammonemia-homocitrullinuria syndrome (HHHS)	0.98	-0.02
EFEMP2	ENSG00000172638	NM_016938.5(EFEMP2):c.885C>T (p.Ser295=)	TCC	TCT	Autosomal recessive cutis laxa type 1B (ARCL1B)	0.98	-0.03
MMAB	ENSG00000139428	NM_052845.4(MMAB):c.732G>A (p.Ser244=)	TCG	TCA	Vitamin B12-responsive methylmalonic acidemia type cblB	3.5	1.81
ATP1A2	ENSG00000018625	NM_000702.4(ATP1A2):c.1710G>A (p.Thr570=)	ACG	ACA	Familial hemiplegic migraine	2.96	1.57
RBM20	ENSG00000203867	NM_001134363.3(RBM20):c.2244T>G (p.Ser748=)	TCT	TCG	Dilated cardiomyopathy 1DD (CMD1DD)	0.24	-2.06
ALG6	ENSG00000088035	NM_013339.4(ALG6):c.1398A>T (p.Leu466=)	CTA	CTT	Congenital disorder of glycosylation type 1C (CDG1C)	1.89	0.92
OFD1	ENSG00000046651	NM_003611.3(OFD1):c.54A>G (p.Glu18=)	GAA	GAG		1.16	0.22
MMAB	ENSG00000139428	NM_052845.4(MMAB):c.387G>A (p.Ala129=)	GCG	GCA	Vitamin B12-responsive methylmalonic acidemia type cblB	2.88	1.52
SGSH	ENSG00000181523	NM_000199.5(SGSH):c.1317C>T (p.Tyr439=)	TAC	TAT	Mucopolysaccharidosis, MPS-III-A (MPS3A)	0.9	-0.15
MCOLN1	ENSG00000090674	NM_020533.3(MCOLN1):c.1272C>T (p.Ser424=)	AGC	AGT	Mucolipidosis type IV (ML4)	0.72	-0.48
TTN	ENSG00000155657	NM_001267550.2(TTN):c.64683C>G (p.Gly21561=)	GGC	GGG		0.77	-0.37
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.576G>T (p.Pro192=)	CCG	CCT		3.11	1.64
TJP2	ENSG00000119139	NM_004817.4(TJP2):c.3372G>A (p.Thr1124=)	ACG	ACA		2.96	1.57
GNPTG	ENSG00000090581	NM_032520.5(GNPTG):c.255G>A (p.Pro85=)	CCG	CCA	Mucolipidosis type III gamma;	3.05	1.61
PIGO	ENSG00000165282	NM_032634.4(PIGO):c.2166G>C (p.Ala722=)	GCG	GCC	Hyperphosphatasia with mental retardation syndrome 2 (HPMRS2)	4.32	2.11
MMAB	ENSG00000139428	NM_052845.4(MMAB):c.333C>T (p.Ala111=)	GCC	GCT	Vitamin B12-responsive methylmalonic acidemia type cblB	0.74	-0.44
MMUT	ENSG00000146085	NM_000255.4(MMUT):c.189C>A (p.Thr63=)	ACC	ACA	Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency	0.93	-0.1
MGAT2	ENSG00000168282	NM_002408.4(MGAT2):c.63C>T (p.Gly21=)	GGC	GGT	Congenital disorder of glycosylation, type IIa (CDG2A)	0.55	-0.87
NAGS	ENSG00000161653	NM_153006.3(NAGS):c.246G>A (p.Pro82=)	CCG	CCA	Hyperammonemia, type III (NAGSD)	3.05	1.61
PHKG2	ENSG00000156873	NM_000294.3(PHKG2):c.921G>T (p.Arg307=)	CGG	CGT	Glycogen storage disease IXc (GSD9C)	0.43	-1.22
ALG3	ENSG00000214160	NM_005787.6(ALG3):c.222C>T (p.Tyr74=)	TAC	TAT	ALG3-CDG (CDG1D)	0.9	-0.15
DOLK	ENSG00000175283	NM_014908.4(DOLK):c.525T>G (p.Val175=)	GTT	GTG	Congenital disorder of glycosylation type 1M (CDG1M)	2.18	1.13
COL6A3	ENSG00000163359	NM_004369.3(COL6A3):c.543T>C (p.Asp181=)	GAT	GAC		1.01	0.01
COG8	ENSG00000213380	NM_032382.4(COG8):c.903C>G (p.Pro301=)	CCC	CCG	Congenital disorder of glycosylation type 2H (CDG2H)	0.33	-1.62
GARS1	ENSG00000106105	NM_002047.4(GARS1):c.69G>A (p.Arg23=)	CGG	CGA		0.6	-0.73
DOLK	ENSG00000175283	NM_014908.4(DOLK):c.1314C>T (p.Leu438=)	CTC	CTT	Congenital disorder of glycosylation type 1M (CDG1M)	0.8	-0.33
ATP8B1	ENSG00000081923	NM_005603.6(ATP8B1):c.2928G>A (p.Ala976=)	GCG	GCA		2.88	1.52
THPO	ENSG00000090534	NM_000460.4(THPO):c.579C>T (p.Asn193=)	AAC	AAT	Thrombocythemia 1 (THCYT1)	1.01	0.02
GCDH	ENSG00000105607	NM_000159.4(GCDH):c.1299G>A (p.Ala433=)	GCG	GCA	Glutaric aciduria, type 1 (GA1)	2.88	1.52
TMEM70	ENSG00000175606	NM_017866.6(TMEM70):c.97C>A (p.Arg33=)	CGG	AGG	Nuclearly-encoded mitochondrial complex V (ATP synthase) deficiency 2 (MC5DN2)	1.15	0.2
NPHP3	ENSG00000113971	NM_153240.5(NPHP3):c.306C>T (p.Arg102=)	CGC	CGT		0.52	-0.93
PHKG2	ENSG00000156873	NM_000294.3(PHKG2):c.1137T>C (p.Pro379=)	CCT	CCC	Glycogen storage disease IXc (GSD9C)	0.98	-0.02
MUTYH	ENSG00000132781	NM_001048171.1(MUTYH):c.158-8C>T	GCC	GCT	Hereditary cancer-predisposing syndrome;MYH-associated polyposis (FAP2)	0.74	-0.44
SOX10	ENSG00000100146	NM_006941.4(SOX10):c.72C>T (p.Ser24=)	TCC	TCT		0.98	-0.03
CHKB	ENSG00000100288	NM_005198.4(CHKB):c.708C>T (p.Val236=)	GTC	GTT	Megaconial type congenital muscular dystrophy (MDCMC)	0.88	-0.19
IDUA	ENSG00000127415	NM_000203.5(IDUA):c.234C>T (p.Gly78=)	GGC	GGT	Mucopolysaccharidosis type 1 (MPS1)	0.55	-0.87

POLE	ENSG00000177084	NM_006231.3(POLE):c.6777G>C (p.Arg2259=)	CGG	CGC	Hereditary cancer-predisposing syndrome;	0.82	-0.29
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.2565C>T (p.Phe855=)	TTC	TTT		0.98	-0.02
GP1BB	ENSG00000203618	NM_000407.4(GP1BB):c.399C>T (p.Ala133=)	GCC	GCT		0.74	-0.44
MPDU1	ENSG00000129255	NM_004870.4(MPDU1):c.393C>T (p.Val131=)	GTC	GTT	MPDU1-CDG	0.88	-0.19
DOLK	ENSG00000175283	NM_014908.3(DOLK):c.579G>A (p.Glu193=)	GAG	GAA	Congenital disorder of glycosylation type 1M (CDG1M)	0.86	-0.22
DPM3	ENSG00000179085	NM_153741.2(DPM3):c.249C>A (p.Ala83=)	GCC	GCA	Congenital disorder of glycosylation type 1O (MDDGC15)	0.67	-0.59
PRRT2	ENSG00000167371	NM_145239.3(PRRT2):c.912C>T (p.Asp304=)	GAC	GAT		0.99	-0.01
OPA1	ENSG00000198836	NM_015560.2(OPA1):c.1923G>A (p.Ala641=)	GCG	GCA	Autosomal dominant optic atrophy classic form (OPA1)	2.88	1.52
LARGE1	ENSG00000133424	NM_004737.6(LARGE1):c.210C>T (p.Arg70=)	CGC	CGT	Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B6 (MDDGB6)	0.52	-0.93
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.9333G>A (p.Gly3111=)	GGG	GGA	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	1.13	0.17
SRPX2	ENSG00000102359	NM_014467.3(SRPX2):c.840G>A (p.Ala280=)	GCG	GCA	Rolandic epilepsy with mental retardation and speech dyspraxia, X-linked (RESDX)	2.88	1.52
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.7830G>A (p.Ala2610=)	GCG	GCA	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	2.88	1.52
CACNA1A	ENSG00000141837	NM_001127222.2(CACNA1A):c.3531C>G (p.Pro1177=)	CCC	CCG	Episodic ataxia type 2 (EA2);Epileptic encephalopathy, early infantile, 42 (DEE42)	0.33	-1.62
BARD1	ENSG00000138376	NM_000465.4(BARD1):c.279A>G (p.Gln93=)	CAA	CAG	Hereditary cancer-predisposing syndrome;Familial cancer of breast;	2.49	1.32
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.12216C>T (p.Phe4072=)	TTC	TTT	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.98	-0.02
PKP2	ENSG00000057294	NM_001005242.3(PKP2):c.2037A>G (p.Thr679=)	ACA	ACG	Arrhythmogenic right ventricular dysplasia 9 (ARVD9);Cardiomyopathy (CMYO)	0.34	-1.57
MRE11	ENSG00000020922	NM_005591.3(MRE11):c.1491C>T (p.Ile497=)	ATC	ATT	Hereditary cancer-predisposing syndrome;Ataxia-telangiectasia-like disorder 1 (ATLD1);Ataxia-telangiectasia-like disorder (ATLD)	0.89	-0.17
POMT1	ENSG00000130714	NM_001077365.2(POMT1):c.1149C>T (p.His383=)	CAC	CAT	Limb-girdle muscular dystrophy-dystroglycanopathy, type C1 (MDDGC1);Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B1 (MDDGB1);Walker-Warburg congenital muscular dystrophy (MDDGA1)	0.81	-0.3
VCL	ENSG00000035403	NM_014000.3(VCL):c.378C>T (p.Phe126=)	TTC	TTT	Dilated cardiomyopathy 1W (CMD1W);Cardiomyopathy (CMYO)	0.98	-0.02
AP5Z1	ENSG00000242802	NM_014855.3(AP5Z1):c.999C>T (p.Asp333=)	GAC	GAT	Spastic paraplegia 48, autosomal recessive (SPG48);	0.99	-0.01
SGCA	ENSG00000108823	NM_000023.4(SGCA):c.366G>A (p.Leu122=)	CTG	CTA	Autosomal recessive limb-girdle muscular dystrophy type 2D (LGMD2D)	0.21	-2.27
PDX1	ENSG00000139515	NM_000209.4(PDX1):c.543C>T (p.Val181=)	GTC	GTT	Maturity-onset diabetes of the young type 4 (MODY4);	0.88	-0.19

POMT1	ENSG00000130714	NM_001077365.2(POMT1):c.1986C>T (p.Ile662=)	ATC	ATT	Limb-girdle muscular dystrophy-dystroglycanopathy, type C1 (MDDGC1);Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B1 (MDDGB1);Walker-Warburg congenital muscular dystrophy (MDDGA1)	0.89	-0.17
SHH	ENSG00000164690	NM_000193.4(SHH):c.1078C>T (p.Leu360=)	CTG	TTG	Holoprosencephaly 3 (HPE3)	0.37	-1.42
VCL	ENSG00000035403	NM_014000.3(VCL):c.492T>G (p.Leu164=)	CTT	CTG	Dilated cardiomyopathy 1W (CMD1W);Cardiovascular phenotype;none provided	2.54	1.35
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.396T>C (p.Asp132=)	GAT	GAC	Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD);Geleophysic dysplasia;Ectopia lentis, isolated, autosomal dominant (ECTOL1);Acromicric dysplasia (ACMICD);Stiff skin syndrome (SSKS);Weill-Marchesani syndrome;Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	1.01	0.01
TP53	ENSG00000141510	NM_000546.5(TP53):c.63C>T (p.Asp21=)	GAC	GAT	Hereditary cancer-predisposing syndrome;Li-Fraumeni syndrome (LFS); Familial cancer of breast	0.99	-0.01
COL1A2	ENSG00000164692	NM_000089.3(COL1A2):c.2904C>T (p.Pro968=)	CCC	CCT	Ehlers-Danlos syndrome, classic type (cEDS);Osteogenesis imperfecta type I (OI1);Ehlers-danlos syndrome, arthrochalasia type, 2;Osteogenesis imperfecta (OI);none provided	1.02	0.02
STK11	ENSG00000118046	NM_000455.4(STK11):c.357C>T (p.Asn119=)	AAC	AAT	Hereditary cancer-predisposing syndrome;Peutz-Jeghers syndrome (PJS); none provided	1.01	0.02
KRIT1	ENSG00000001631	NM_194456.1(KRIT1):c.1326C>G (p.Thr442=)	ACC	ACG	Cerebral cavernous malformation (CCM);Angiokeratoma corporis diffusum with arteriovenous fistulas;	0.31	-1.67
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.189G>A (p.Thr63=)	ACG	ACA	Myosclerosis, autosomal recessive; Collagen VI-related myopathy (COL6-RM);Bethlem myopathy 1 (BTHLM1)	2.96	1.57
SH3TC2	ENSG00000169247	NM_024577.3(SH3TC2):c.1482C>T (p.Leu494=)	CTC	CTT	Charcot-Marie-Tooth disease type 4;Charcot-Marie-Tooth disease	0.8	-0.33
VRK1	ENSG00000100749	NM_003384.3(VRK1):c.1020C>T (p.Asp340=)	GAC	GAT	Pontocerebellar hypoplasia type 1 (PCH1A);Pontocerebellar hypoplasia type 1A (PCH1A)	0.99	-0.01
SMAD4	ENSG00000141646	NM_005359.6(SMAD4):c.21G>A (p.Thr7=)	ACG	ACA	Hereditary cancer-predisposing syndrome;Generalized juvenile polyposis/juvenile polyposis coli (JPS); Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (JPHT);Myhre syndrome (MYHRS)	2.96	1.57
ATM	ENSG00000149311	NM_000051.3(ATM):c.7044G>A (p.Thr2348=)	ACG	ACA	Hereditary cancer-predisposing syndrome;Ataxia-telangiectasia syndrome (AT);	2.96	1.57
ATM	ENSG00000149311	NM_000051.3(ATM):c.6382T>C (p.Leu2128=)	TTG	CTG	Hereditary cancer-predisposing syndrome;Ataxia-telangiectasia syndrome (AT);	2.67	1.42
PIGO	ENSG00000165282	NM_032634.4(PIGO):c.2268G>A (p.Ala756=)	GCG	GCA	Hyperphosphatasia with mental retardation syndrome 2 (HPMRS2)	2.88	1.52
MUTYH	ENSG00000132781	NM_001048171.1(MUTYH):c.42C>T (p.Ile14=)	ATC	ATT	Hereditary cancer-predisposing syndrome;MYH-associated polyposis (FAP2);	0.89	-0.17
STK11	ENSG00000118046	NM_000455.4(STK11):c.1284G>A (p.Ser428=)	TCG	TCA	Hereditary cancer-predisposing syndrome;Peutz-Jeghers syndrome (PJS);	3.5	1.81
TRPV4	ENSG00000111199	NM_021625.4(TRPV4):c.2304G>C (p.Ser768=)	TCG	TCC	Charcot-Marie-Tooth disease axonal type 2C (HMSN2C);Scapuloperoneal spinal muscular atrophy (SPSMA);Spondylometaphyseal dysplasia, Kozlowski type (SMDK);Metatrophic dysplasia;Distal spinal muscular atrophy, congenital nonprogressive (HMN8);Brachyrachia (short spine dysplasia) (BCYM3);Charcot-Marie-Tooth disease	4.26	2.09
MUTYH	ENSG00000132781	NM_001048171.1(MUTYH):c.771C>T (p.Asp257=)	GAC	GAT	Hereditary cancer-predisposing syndrome;MYH-associated polyposis (FAP2);	0.99	-0.01

NEB	ENSG00000183091	NM_001271208.2(NEB):c.22983C>A (p.Ala7661=)	GCC	GCA	Nemaline myopathy 2 (NEM2)	0.67	-0.59
AGL	ENSG00000162688	NM_000642.3(AGL):c.1875G>T (p.Thr625=)	ACG	ACT	Glycogen storage disease type III (GSD3)	2.56	1.36
LOXHD1	ENSG00000167210	NM_144612.6(LOXHD1):c.5127C>T (p.Gly1709=)	GGC	GGT	Deafness, autosomal recessive 77 (DFNB77);	0.55	-0.87
NEB	ENSG00000183091	NM_001271208.2(NEB):c.177G>A (p.Gln59=)	CAG	CAA	Nemaline myopathy 2 (NEM2)	0.4	-1.32
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.2955C>T (p.Cys985=)	TGC	TGT	Wilson disease (WND)	0.97	-0.05
SIL1	ENSG00000120725	NM_022464.5(SIL1):c.1167C>T (p.Pro389=)	CCC	CCT	Marinesco-Sjögren syndrome (MSS)	1.02	0.02
PCNT	ENSG00000160299	NM_006031.6(PCNT):c.4140G>A (p.Ala1380=)	GCG	GCA	Microcephalic osteodysplastic primordial dwarfism type II (MOPD2);	2.88	1.52
CAPN3	ENSG00000092529	NM_000070.3(CAPN3):c.552G>A (p.Thr184=)	ACG	ACA	Limb-girdle muscular dystrophy, type 2A (LGMDR1)	2.96	1.57
RBM20	ENSG00000203867	NM_001134363.3(RBM20):c.849C>T (p.Tyr283=)	TAC	TAT	Dilated cardiomyopathy 1DD (CMD1DD)	0.9	-0.15
STK11	ENSG00000118046	NM_000455.4(STK11):c.618G>A (p.Ala206=)	GCG	GCA	Hereditary cancer-predisposing syndrome; Peutz-Jeghers syndrome (PJS)	2.88	1.52
ALMS1	ENSG00000116127	NM_015120.4(ALMS1):c.8448A>G (p.Ser2816=)	AGA	AGG	Alstrom syndrome (ALMS)	0.91	-0.14
GAA	ENSG00000171298	NM_000152.5(GAA):c.1920T>G (p.Pro640=)	CCT	CCG	Glycogen storage disease, type II (GSD2)	0.32	-1.64
STK11	ENSG00000118046	NM_000455.5(STK11):c.1038C>T (p.Gly346=)	GGC	GGT	Hereditary cancer-predisposing syndrome;Peutz-Jeghers syndrome (PJS);	0.55	-0.87
BLM	ENSG00000197299	NM_000057.4(BLM):c.3849G>A (p.Gln1283=)	CAG	CAA	Hereditary cancer-predisposing syndrome; Bloom syndrome (BLM);	0.4	-1.32
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.3588C>T (p.Asp1196=)	GAC	GAT	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.99	-0.01
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.8613C>T (p.Cys2871=)	TGC	TGT	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.97	-0.05
LOXHD1	ENSG00000167210	NM_144612.6(LOXHD1):c.6057T>C (p.Cys2019=)	TGT	TGC	Deafness, autosomal recessive 77 (DFNB77);	1.03	0.05
DMD	ENSG00000198947	NM_004006.2(DMD):c.8322G>A (p.Leu2774=)	CTG	CTA	Duchenne muscular dystrophy (DMD)	0.21	-2.27
GAA	ENSG00000171298	NM_000152.5(GAA):c.1830C>T (p.Ala610=)	GCC	GCT	Glycogen storage disease, type II (GSD2);	0.74	-0.44
KCNT1	ENSG00000107147	NM_020822.3(KCNT1):c.1899G>A (p.Ser633=)	TCG	TCA	Early infantile epileptic encephalopathy 14 (DEE14);Epilepsy, nocturnal frontal lobe, 5 (ENFL5)	3.5	1.81
AUH	ENSG00000148090	NM_001698.2(AUH):c.936T>C (p.Tyr312=)	TAT	TAC	3-Methylglutaconic aciduria type 1 (MGCA1);	1.11	0.15
NTRK1	ENSG00000198400	NM_001007792.1(NTRK1):c.189G>A (p.Leu63=)	CTG	CTA	Hereditary insensitivity to pain with anhidrosis (CIPA);	0.21	-2.27
POMGNT1	ENSG00000085998	NM_017739.3(POMGNT1):c.453G>A (p.Thr151=)	ACG	ACA	Limb-girdle muscular dystrophy-dystroglycanopathy, type C3 (MDDGC3);Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B3 (MDDGB3)	2.96	1.57
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.8073C>T (p.Tyr2691=)	TAC	TAT	RYR1-Related Disorders	0.9	-0.15
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.19927T>C (p.Leu6643=)	TTG	CTG	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	2.67	1.42
GAA	ENSG00000171298	NM_000152.5(GAA):c.1593C>T (p.Asp531=)	GAC	GAT	Glycogen storage disease, type II (GSD2)	0.99	-0.01
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.5364T>G (p.Ala1788=)	GCT	GCG	RYR1-Related Disorders	0.31	-1.67
MSH2	ENSG00000095002	NM_000251.2(MSH2):c.1638G>A (p.Lys546=)	AAG	AAA	Hereditary cancer-predisposing syndrome; Hereditary nonpolyposis colorectal neoplasms	0.87	-0.2

PLOD1	ENSG00000083444	NM_000302.4(PLOD1):c.804C>T (p.Thr268=)	ACC	ACT	Cardiovascular phenotype;Ehlers-Danlos syndrome, hydroxylysine-deficient (EDSKSCL1);	0.8	-0.31
MYO7A	ENSG00000137474	NM_000260.4(MYO7A):c.5253G>T (p.Pro1751=)	CCG	CCT	Usher syndrome, type 1B (USH1B)	3.11	1.64
CACNA1A	ENSG00000141837	NM_001127222.2(CACNA1A):c.3618A>G (p.Glu1206=)	GAA	GAG	Episodic ataxia type 2 (EA2);Epileptic encephalopathy, early infantile, 42 (DEE42)	1.16	0.22
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.7647C>T (p.His2549=)	CAC	CAT	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	0.81	-0.3
PKP2	ENSG00000057294	NM_001005242.3(PKP2):c.795G>T (p.Gly265=)	GGG	GGT	Arrhythmogenic right ventricular dysplasia 9 (ARVD9);Cardiomyopathy (CMYO)	0.71	-0.5
KCNT1	ENSG00000107147	NM_020822.3(KCNT1):c.942C>T (p.Thr314=)	ACC	ACT	Early infantile epileptic encephalopathy 14 (DEE14);Epilepsy, nocturnal frontal lobe, 5 (ENFL5)	0.8	-0.31
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.11634G>A (p.Ser3878=)	TCG	TCA	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	3.5	1.81
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.2478C>T (p.Asp826=)	GAC	GAT	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.99	-0.01
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.5811G>A (p.Ala1937=)	GCG	GCA	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	2.88	1.52
ELN	ENSG00000049540	NM_000501.4(ELN):c.861G>A (p.Gly287=)	GGG	GGA	Cutis laxa, autosomal dominant 1 (ADCL1);Supravalvar aortic stenosis (SVAS);	1.13	0.17
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.10302C>A (p.Thr3434=)	ACC	ACA	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.93	-0.1
LINS1	ENSG00000140471	NM_001040616.3(LINS1):c.1479T>C (p.Cys493=)	TGT	TGC	History of neurodevelopmental disorder	1.03	0.05
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.9324A>G (p.Glu3108=)	GAA	GAG	Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);Autosomal dominant cerebellar ataxia	1.16	0.22
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.540C>T (p.Cys180=)	TGC	TGT	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	0.97	-0.05
MEGF10	ENSG00000145794	NM_001256545.2(MEGF10):c.1626C>T (p.Cys542=)	TGC	TGT	Myopathy, areflexia, respiratory distress, and dysphagia, early-onset (EMARDD);	0.97	-0.05

PLEC	ENSG00000178209	NM_201384.3(PLEC):c.6786G>A (p.Thr2262=)	ACG	ACA	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	2.96	1.57
COL4A4	ENSG00000081052	NM_000092.4(COL4A4):c.4185G>A (p.Gly1395=)	GGG	GGA	Alport syndrome	1.13	0.17
ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.408C>T (p.Ser136=)	AGC	AGT	Progressive familial intrahepatic cholestasis 2 (PFIC2)	0.72	-0.48
BRIP1	ENSG00000136492	NM_032043.2(BRIP1):c.249A>G (p.Gln83=)	CAA	CAG	Hereditary cancer-predisposing syndrome; Familial cancer of breast;Fanconi anemia, complementation group J (FANCJ)	2.49	1.32
COL6A1	ENSG00000142156	NM_001848.2(COL6A1):c.666C>T (p.Arg222=)	CGC	CGT	Bethlem myopathy 1 (BTHLM1)	0.52	-0.93
FAT4	ENSG00000196159	NM_024582.4(FAT4):c.1128G>A (p.Val376=)	GTG	GTA	none provided	0.3	-1.74
USH2A	ENSG00000042781	NM_206933.4(USH2A):c.7038C>T (p.His2346=)	CAC	CAT	Usher syndrome, type 2A (USH2A)	0.81	-0.3
KCNJ11	ENSG00000187486	NM_000525.3(KCNJ11):c.678C>T (p.Pro226=)	CCC	CCT	Permanent neonatal diabetes mellitus (PNDM)	1.02	0.02
DSC2	ENSG00000134755	NM_024422.6(DSC2):c.2139G>A (p.Thr713=)	ACG	ACA	Arrhythmogenic right ventricular cardiomyopathy, type 11 (ARVD11);Cardiomyopathy (CMYO)	2.96	1.57
EMD	ENSG00000102119	NM_000117.2(EMD):c.537G>A (p.Leu179=)	CTG	CTA	Emery-Dreifuss muscular dystrophy 1, X-linked (EDMD1)	0.21	-2.27
KCNT1	ENSG00000107147	NM_020822.3(KCNT1):c.2214G>A (p.Pro738=)	CCG	CCA	Early infantile epileptic encephalopathy 14 (DEE14);Epilepsy, nocturnal frontal lobe, 5 (ENFL5)	3.05	1.61
IGHMBP2	ENSG00000132740	NM_002180.2(IGHMBP2):c.2619G>A (p.Pro873=)	CCG	CCA	Charcot-Marie-Tooth disease	3.05	1.61
TTN	ENSG00000155657	NM_001267550.2(TTN):c.104364C>T (p.Ser34788=)	AGC	AGT	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.72	-0.48
PKP2	ENSG00000057294	NM_001005242.3(PKP2):c.306C>A (p.Ser102=)	TCC	TCA	Arrhythmogenic right ventricular dysplasia 9 (ARVD9);Cardiomyopathy (CMYO)	0.82	-0.29
SCN5A	ENSG00000183873	NM_000335.5(SCN5A):c.3904C>A (p.Arg1302=)	CGG	AGG	Arrhythmia	1.15	0.2
COL6A2	ENSG00000142173	NM_001849.3(COL6A2):c.459C>T (p.Thr153=)	ACC	ACT	Collagen VI-related myopathy (COL6-RM)	0.8	-0.31
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.708C>T (p.Asn236=)	AAC	AAT	Aortic aneurysm, familial thoracic 4 (AAT4);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	1.01	0.02
CAPN3	ENSG00000092529	NM_000070.3(CAPN3):c.1668C>T (p.Ile556=)	ATC	ATT	Limb-girdle muscular dystrophy, type 2A (LGMDR1)	0.89	-0.17
TTN	ENSG00000155657	NM_001267550.2(TTN):c.267G>A (p.Ala89=)	GCG	GCA	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	2.88	1.52
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.5454G>A (p.Ala1818=)	GCG	GCA	Aortic aneurysm, familial thoracic 4 (AAT4);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	2.88	1.52
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.13479G>A (p.Ser4493=)	TCG	TCA	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	3.5	1.81
TTN	ENSG00000155657	NM_001267550.2(TTN):c.47196G>C (p.Val15732=)	GTG	GTC	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.52	-0.94
SCN5A	ENSG00000183873	NM_000335.5(SCN5A):c.1734C>T (p.Pro578=)	CCC	CCT	Arrhythmia	1.02	0.02
HSD17B4	ENSG00000133835	NM_000414.4(HSD17B4):c.1317A>G (p.Val439=)	GTA	GTG	Bifunctional peroxisomal enzyme deficiency (DBIF);Perrault syndrome	3.34	1.74
LPIN2	ENSG00000101577	NM_014646.2(LPIN2):c.2625G>A (p.Pro875=)	CCG	CCA	Majeed syndrome (MJDS);	3.05	1.61
TTN	ENSG00000155657	NM_001267550.2(TTN):c.87495C>T (p.Asp29165=)	GAC	GAT	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.99	-0.01

PTCH1	ENSG00000185920	NM_000264.5(PTCH1):c.2634C>T (p.Asp878=)	GAC	GAT	Hereditary cancer-predisposing syndrome; Gorlin syndrome (BCNS)	0.99	-0.01
FKRP	ENSG00000181027	NM_024301.5(FKRP):c.969C>T (p.Arg323=)	CGC	CGT	Walker-Warburg congenital muscular dystrophy (MDDGA1)	0.52	-0.93
MECP2	ENSG00000169057	NM_001110792.2(MECP2):c.429C>G (p.Ala143=)	GCC	GCG	History of neurodevelopmental disorder	0.23	-2.11
MYO7A	ENSG00000137474	NM_000260.4(MYO7A):c.6165C>T (p.Ser2055=)	AGC	AGT	Usher syndrome, type 1B (USH1B)	0.72	-0.48
MUTYH	ENSG00000132781	NM_001048171.1(MUTYH):c.1149G>T (p.Leu383=)	CTG	CTT	Hereditary cancer-predisposing syndrome;MYH-associated polyposis (FAP2);none provided	0.39	-1.35
FKRP	ENSG00000181027	NM_024301.5(FKRP):c.531G>A (p.Glu177=)	GAG	GAA	Walker-Warburg congenital muscular dystrophy (MDDGA1)	0.86	-0.22
ATM	ENSG00000149311	NM_000051.3(ATM):c.411C>T (p.Tyr137=)	TAC	TAT	Hereditary cancer-predisposing syndrome;Ataxia-telangiectasia syndrome (AT);	0.9	-0.15
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.6915G>A (p.Lys2305=)	AAG	AAA	Hereditary cancer-predisposing syndrome	0.87	-0.2
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.2127A>C (p.Ala709=)	GCA	GCC	Cardiovascular phenotype; Familial thoracic aortic aneurysm and aortic dissection (TAAD)	1.5	0.59
PLEC	ENSG00000178209	NM_201384.3(PLEC):c.4446G>A (p.Ala1482=)	GCG	GCA	Epidermolysis bullosa simplex with muscular dystrophy (EBSMD);Epidermolysis bullosa simplex, Ogna type (EBSOG);Epidermolysis bullosa simplex with pyloric atresia (EBSPA);Limb-girdle muscular dystrophy, type 2Q (LGMDR17);Epidermolysis bullosa simplex with nail dystrophy (EBSND)	2.88	1.52
TTN	ENSG00000155657	NM_001267550.2(TTN):c.14535C>T (p.Asp4845=)	GAC	GAT	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.99	-0.01
KIF7	ENSG00000166813	NM_198525.3(KIF7):c.612C>T (p.His204=)	CAC	CAT	Acrocallosal syndrome (ACLS)	0.81	-0.3
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.2190C>T (p.Asp730=)	GAC	GAT	Wilson disease (WND);	0.99	-0.01
GRIN2B	ENSG00000273079	NM_000834.4(GRIN2B):c.3981G>A (p.Lys1327=)	AAG	AAA	Mental retardation, autosomal dominant 6 (MRD6);Epileptic encephalopathy, early infantile, 27 (DEE27);	0.87	-0.2
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.1413C>T (p.Phe471=)	TTC	TTT	Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.98	-0.02
MESP2	ENSG00000188095	NM_001039958.2(MESP2):c.957G>A (p.Ser319=)	TCG	TCA	Spondylocostal dysostosis 2, autosomal recessive;	3.5	1.81
TTN	ENSG00000155657	NM_001267550.2(TTN):c.34845C>T (p.Pro11615=)	CCC	CCT	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	1.02	0.02
VCL	ENSG00000035403	NM_014000.2(VCL):c.2802C>T (p.Ala934=)	GCC	GCT	Dilated cardiomyopathy 1W (CMD1W);	0.74	-0.44
LDLRAP1	ENSG00000157978	NM_015627.2(LDLRAP1):c.75T>A (p.Gly25=)	GGT	GGA	Familial hypercholesterolemia 4 (FHCL4);Familial hypercholesterolemia (FH)	1.59	0.67
DSG2	ENSG00000046604	NM_001943.5(DSG2):c.147C>T (p.Arg49=)	CGC	CGT	Arrhythmogenic right ventricular cardiomyopathy, type 10 (ARVD10);Cardiomyopathy (CMYO)	0.52	-0.93
POLG	ENSG00000140521	NM_002693.2(POLG):c.1905G>T (p.Pro635=)	CCG	CCT	Progressive sclerosing poliodystrophy (MTDPS4A)	3.11	1.64
STK11	ENSG00000118046	NM_000455.4(STK11):c.612C>T (p.Phe204=)	TTC	TTT	Hereditary cancer-predisposing syndrome; Peutz-Jeghers syndrome (PJS)	0.98	-0.02
ATM	ENSG00000149311	NM_000051.3(ATM):c.2220A>G (p.Ala740=)	GCA	GCG	Hereditary cancer-predisposing syndrome;Ataxia-telangiectasia syndrome (AT);	0.35	-1.52
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.1008A>G (p.Thr336=)	ACA	ACG	Hereditary breast and ovarian cancer syndrome (HBOC); Hereditary cancer-predisposing syndrome	0.34	-1.57
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.993G>A (p.Thr331=)	ACG	ACA	Cardiovascular phenotype;Aortic aneurysm, familial thoracic 7 (AAT7);	2.96	1.57
CAPN3	ENSG00000092529	NM_000070.3(CAPN3):c.1302C>T (p.Asn434=)	AAC	AAT	Limb-girdle muscular dystrophy, type 2A (LGMDR1);	1.01	0.02
IQSEC2	ENSG00000124313	NM_001111125.3(IQSEC2):c.4293C>T (p.Ile1431=)	ATC	ATT	Mental retardation, X-linked 1 (MRX1)	0.89	-0.17
POLG	ENSG00000140521	NM_002693.2(POLG):c.3444C>T (p.Arg1148=)	CGC	CGT	Progressive sclerosing poliodystrophy (MTDPS4A)	0.52	-0.93
CPT2	ENSG00000157184	NM_000098.3(CPT2):c.1422C>A (p.Ala474=)	GCC	GCA	Carnitine palmitoyltransferase II deficiency (CPT2)	0.67	-0.59

TTN	ENSG00000155657	NM_001267550.2(TTN):c.17082G>T (p.Leu5694=)	CTG	CTT	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.39	-1.35
SCN9A	ENSG00000169432	NM_001365536.1(SCN9A):c.2964C>T (p.Leu988=)	CTC	CTT	Hereditary sensory and autonomic neuropathy type IIA (HSAN2A);Generalized epilepsy with febrile seizures plus, type 7 (GEFSP7)	0.8	-0.33
GALT	ENSG00000213930	NM_000155.4(GALT):c.1128A>T (p.Ala376=)	GCA	GCT	Deficiency of UDPglucose-hexose-1-phosphate uridylyltransferase (GALAC1);Galactosemia	1.11	0.14
MSH6	ENSG00000116062	NM_000179.2(MSH6):c.249T>G (p.Ala83=)	GCT	GCG	Hereditary cancer-predisposing syndrome;Hereditary nonpolyposis colorectal cancer type 5 (HNPCC5);Hereditary nonpolyposis colorectal neoplasms	0.31	-1.67
PCSK9	ENSG00000169174	NM_174936.3(PCSK9):c.1560C>T (p.Val520=)	GTC	GTT	Familial hypercholesterolemia (FH);Familial hypercholesterolemia 3 (FHCL3);Hypobetalipoproteinemia	0.88	-0.19
ABCB4	ENSG00000005471	NM_000443.4(ABCB4):c.696C>T (p.Ala232=)	GCC	GCT	Progressive familial intrahepatic cholestasis 3 (PFIC3);Cholestasis, intrahepatic, of pregnancy 3 (ICP3);	0.74	-0.44
TSC2	ENSG00000103197	NM_000548.5(TSC2):c.3489C>T (p.Ala1163=)	GCC	GCT	Hereditary cancer-predisposing syndrome;Tuberous sclerosis 2 (TSC2)	0.74	-0.44
TSC2	ENSG00000103197	NM_000548.5(TSC2):c.4911G>A (p.Lys1637=)	AAG	AAA	Tuberous sclerosis syndrome (TSC); Hereditary cancer-predisposing syndrome;Tuberous sclerosis 2 (TSC2)	0.87	-0.2
PKP2	ENSG00000057294	NM_001005242.3(PKP2):c.2001C>T (p.Ala667=)	GCC	GCT	Arrhythmogenic right ventricular dysplasia 9 (ARVD9);Cardiovascular phenotype;Cardiomyopathy (CMYO)	0.74	-0.44
CFTR	ENSG00000001626	NM_000492.3(CFTR):c.1365G>A (p.Ala455=)	GCG	GCA	Inborn genetic diseases;Cystic fibrosis (CF);CFTR-related disorders (CFTR-RD)	2.88	1.52
TTN	ENSG00000155657	NM_001267550.2(TTN):c.16716A>G (p.Pro5572=)	CCA	CCG	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Tibial muscular dystrophy (TMD);Dilated cardiomyopathy 1G (CMD1G);Myopathy, early-onset, with fatal cardiomyopathy (SALMY)	0.33	-1.61
TTN	ENSG00000155657	NM_001267550.2(TTN):c.31518C>T (p.Pro10506=)	CCC	CCT	Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Tibial muscular dystrophy (TMD);Dilated cardiomyopathy 1G (CMD1G);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	1.02	0.02
DSG2	ENSG00000046604	NM_001943.5(DSG2):c.1851C>T (p.Leu617=)	CTC	CTT	Arrhythmogenic right ventricular cardiomyopathy, type 10 (ARVD10);Cardiovascular phenotype;Cardiomyopathy (CMYO)	0.8	-0.33
PCSK9	ENSG00000169174	NM_174936.3(PCSK9):c.753C>T (p.Arg251=)	CGC	CGT	Familial hypercholesterolemia 1 (FHCL1);Hypobetalipoproteinemia;Familial hypercholesterolemia 3 (FHCL3);	0.52	-0.93
COL3A1	ENSG00000168542	NM_000090.3(COL3A1):c.1188C>T (p.Gly396=)	GGC	GGT	Cardiovascular phenotype; Familial thoracic aortic aneurysm and aortic dissection (TAAD);Ehlers-Danlos syndrome, type 4 (EDSVASC)	0.55	-0.87
MLH1	ENSG00000076242	NM_000249.3(MLH1):c.438A>G (p.Gln146=)	CAA	CAG	Hereditary nonpolyposis colorectal neoplasms; Hereditary cancer-predisposing syndrome;Lynch syndrome II (HNPCC2);Lynch syndrome	2.49	1.32
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.690C>T (p.Pro230=)	CCC	CCT	Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	1.02	0.02
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.18789G>A (p.Ser6263=)	TCG	TCA	Emery-Dreifuss muscular dystrophy (EDMD); Cerebellar ataxia;Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	3.5	1.81
SPINK1	ENSG00000164266	NM_003122.4(SPINK1):c.33C>T (p.Ala11=)	GCC	GCT	Hereditary pancreatitis (PCTT);Inborn genetic diseases;none provided	0.74	-0.44

LDLR	ENSG00000130164	NM_000527.5(LDLR):c.1875C>T (p.Asn625=)	AAC	AAT	Familial hypercholesterolemia 1 (FHCL1); Familial hypercholesterolemia (FH)	1.01	0.02
POLE	ENSG00000177084	NM_006231.3(POLE):c.5769C>T (p.Gly1923=)	GGC	GGT	Hereditary cancer-predisposing syndrome;Colorectal cancer, susceptibility to, 12 (CRCS12)	0.55	-0.87
ACTA2	ENSG00000107796	NM_001613.4(ACTA2):c.174C>T (p.Asp58=)	GAC	GAT	Aortic aneurysm, familial thoracic 6 (AAT6);Multisystemic smooth muscle dysfunction syndrome (MSMDS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.99	-0.01
TTN	ENSG00000155657	NM_001267550.2(TTN):c.79863G>A (p.Thr26621=)	ACG	ACA	Cardiovascular phenotype;Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	2.96	1.57
PALB2	ENSG00000083093	NM_024675.3(PALB2):c.2442G>A (p.Glu814=)	GAG	GAA	Hereditary cancer-predisposing syndrome; Familial cancer of breast	0.86	-0.22
PMS2	ENSG00000122512	NM_000535.7(PMS2):c.2127C>T (p.Phe709=)	TTC	TTT	Hereditary cancer-predisposing syndrome; Hereditary nonpolyposis colorectal neoplasms	0.98	-0.02
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.2820C>T (p.Ala940=)	GCC	GCT	Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	0.74	-0.44
LMNA	ENSG00000160789	NM_170707.4(LMNA):c.1051A>C (p.Arg351=)	AGG	CGG	Charcot-Marie-Tooth disease, type 2;Cardiomyopathy (CMYO)	0.87	-0.2
SCN5A	ENSG00000183873	NM_198056.2(SCN5A):c.5337G>A (p.Thr1779=)	ACG	ACA	Arrhythmia;Brugada syndrome	2.96	1.57
TSC1	ENSG00000165699	NM_000368.4(TSC1):c.2922C>T (p.Leu974=)	CTC	CTT	Hereditary cancer-predisposing syndrome;Tuberous sclerosis 1 (TSC1); Focal cortical dysplasia type II (FCORD2)	0.8	-0.33
CLCN1	ENSG00000188037	NM_000083.3(CLCN1):c.1392C>T (p.Phe464=)	TTC	TTT	Congenital myotonia, autosomal recessive form;Congenital myotonia, autosomal dominant form (THD);Myotonia congenita	0.98	-0.02
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.1467G>A (p.Glu489=)	GAG	GAA	Breast-ovarian cancer, familial 1 (BROVCA1); Hereditary cancer-predisposing syndrome	0.86	-0.22
TTN	ENSG00000155657	NM_001267550.2(TTN):c.63960T>A (p.Val21320=)	GTT	GTA	Cardiomyopathy (CMYO);Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.65	-0.62
TTN	ENSG00000155657	NM_001267550.2(TTN):c.21642C>T (p.Asn7214=)	AAC	AAT	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Cardiomyopathy (CMYO)	1.01	0.02
MLH1	ENSG00000076242	NM_000249.3(MLH1):c.222T>C (p.Asp74=)	GAT	GAC	Hereditary cancer-predisposing syndrome;Hereditary nonpolyposis colorectal neoplasms	1.01	0.01
CDH1	ENSG00000039068	NM_004360.5(CDH1):c.1170C>T (p.Asn390=)	AAC	AAT	Hereditary cancer-predisposing syndrome;Hereditary diffuse gastric cancer (HDGC);	1.01	0.02
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.9396A>G (p.Lys3132=)	AAA	AAG	Hereditary cancer-predisposing syndrome; Breast-ovarian cancer, familial 2 (BROVCA2); Hereditary breast and ovarian cancer syndrome (HBOC)	1.15	0.2
LMNA	ENSG00000160789	NM_170707.4(LMNA):c.471G>A (p.Thr157=)	ACG	ACA	Cardiomyopathy (CMYO);Charcot-Marie-Tooth disease, type 2;Hutchinson-Gilford syndrome (HGPS);Dilated cardiomyopathy 1A (CMD1A);Lipoatrophy with Diabetes, Hepatic Steatosis, Hypertrophic Cardiomyopathy, and Leukomelanodermic Papules;Emery-Dreifuss muscular dystrophy 2, autosomal dominant (EDMD2);Mandibuloacral dysplasia with type A lipodystrophy (MADA);Lethal tight skin contracture syndrome;Familial partial lipodystrophy 2 (FPLD2);Emery-Dreifuss muscular dystrophy (EDMD);Charcot-Marie-Tooth disease type 2B1 (CMT2B1);Congenital muscular dystrophy, LMNA-related (MDCL)	2.96	1.57
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.10941G>A (p.Pro3647=)	CCG	CCA	Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);Autosomal dominant cerebellar ataxia;Charcot-Marie-Tooth disease;none provided	3.05	1.61

BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.564A>G (p.Glu188=)	GAA	GAG	Hereditary cancer-predisposing syndrome; Breast-ovarian cancer, familial 1 (BROVCA1); Hereditary breast and ovarian cancer syndrome (HBOC)	1.16	0.22
BRIP1	ENSG00000136492	NM_032043.2(BRIP1):c.612C>G (p.Ser204=)	TCC	TCG	Familial cancer of breast;Fanconi anemia, complementation group J (FANCJ);Fanconi anemia, complementation group J (FANCJ);Neoplasm of ovary; Hereditary cancer-predisposing syndrome	0.23	-2.09
DNAAF3	ENSG00000167646	NM_001256715.2(DNAAF3):c.531C>T (p.Gly177=)	GGC	GGT	Dilated Cardiomyopathy, Recessive;Primary ciliary dyskinesia (PCD);Familial restrictive cardiomyopathy (RCM);Familial Hypertrophic Cardiomyopathy with Wolff-Parkinson-White Syndrome;Hypertrophic cardiomyopathy	0.55	-0.87
CFTR	ENSG00000001626	NM_000492.3(CFTR):c.4296C>T (p.Asn1432=)	AAC	AAT	Cystic fibrosis (CF); Inborn genetic diseases;CFTR-related disorders (CFTR-RD)	1.01	0.02
CFTR	ENSG00000001626	NM_000492.3(CFTR):c.2245C>T (p.Leu749=)	CTG	TTG	Inborn genetic diseases;Cystic fibrosis (CF);CFTR-related disorders (CFTR-RD);none provided	0.37	-1.42
TTN	ENSG00000155657	NM_001267550.2(TTN):c.16551G>A (p.Ser5517=)	TCG	TCA	Cardiomyopathy (CMYO);Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Tibial muscular dystrophy (TMD);Dilated cardiomyopathy 1G (CMD1G)	3.5	1.81
TTN	ENSG00000155657	NM_001267550.2(TTN):c.78774A>G (p.Arg26258=)	AGA	AGG	Tibial muscular dystrophy (TMD);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Dilated cardiomyopathy 1G (CMD1G)	0.91	-0.14
TTN	ENSG00000155657	NM_001267550.2(TTN):c.49395C>T (p.Asp16465=)	GAC	GAT	Cardiovascular phenotype; Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Tibial muscular dystrophy (TMD)	0.99	-0.01
DHCR7	ENSG00000172893	NM_001360.2(DHCR7):c.1368C>T (p.Gly456=)	GGC	GGT	Smith-Lemli-Opitz syndrome (SLOS);History of neurodevelopmental disorder;	0.55	-0.87
WFS1	ENSG00000109501	NM_006005.3(WFS1):c.1152C>T (p.Phe384=)	TTC	TTT	Autosomal dominant nonsyndromic deafness 6 (DFNA6);WFS1-Related Spectrum Disorders	0.98	-0.02
BRCA2	ENSG00000139618	NM_000059.4(BRCA2):c.8007A>G (p.Arg2669=)	AGA	AGG	Hereditary breast and ovarian cancer syndrome (HBOC);Hereditary cancer-predisposing syndrome; Breast-ovarian cancer, familial 2 (BROVCA2)	0.91	-0.14
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.4320A>G (p.Lys1440=)	AAA	AAG	Breast-ovarian cancer, familial 2 (BROVCA2); Hereditary cancer-predisposing syndrome;	1.15	0.2
SGCA	ENSG00000108823	NM_000023.4(SGCA):c.690G>C (p.Leu230=)	CTG	CTC	Autosomal recessive limb-girdle muscular dystrophy type 2D (LGMD2D);Sarcoglycanopathy	0.49	-1.02
MYO7A	ENSG00000137474	NM_000260.4(MYO7A):c.486C>T (p.Ala162=)	GCC	GCT	Deafness, autosomal dominant 11 (DFNA11);Usher syndrome type 1 (USH1);Deafness, autosomal recessive 2 (DFNB2)	0.74	-0.44

DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.2376C>T (p.Cys792=)	TGC	TGT	Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);History of neurodevelopmental disorder;Spinal muscular atrophy, lower extremity predominant 1, autosomal dominant (SMALED1);Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);Mental retardation, autosomal dominant 13 (MRD13);Autosomal dominant cerebellar ataxia	0.97	-0.05
MYH7	ENSG00000092054	NM_000257.4(MYH7):c.4557C>T (p.Ser1519=)	AGC	AGT	Cardiomyopathy (CMYO); Myosin storage myopathy (MSMA);Familial hypertrophic cardiomyopathy 1 (CMH1);Myopathy, distal, 1 (MPD1)	0.72	-0.48
TTN	ENSG00000155657	NM_001267550.2(TTN):c.86526T>G (p.Val28842=)	GTT	GTG	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Dilated cardiomyopathy 1G (CMD1G);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Tibial muscular dystrophy (TMD)	2.18	1.13
NF1	ENSG00000196712	NM_000267.3(NF1):c.4686A>G (p.Glu1562=)	GAA	GAG	Hereditary cancer-predisposing syndrome;Neurofibromatosis, type 1 (NF1);Neurofibromatosis-Noonan syndrome (NFNS);Neurofibromatosis, familial spinal (FSNF);Café-au-lait macules with pulmonary stenosis (WTSN);	1.16	0.22
GAA	ENSG00000171298	NM_000152.5(GAA):c.2415G>A (p.Val805=)	GTG	GTA	Glycogen storage disease, type II (GSD2);	0.3	-1.74
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.3783C>T (p.Gly1261=)	GGC	GGT	Autosomal recessive polycystic kidney disease (ARPKD);	0.55	-0.87
LIG4	ENSG00000174405	NM_206937.2(LIG4):c.285G>A (p.Glu95=)	GAG	GAA	Lig4 syndrome;Severe combined immunodeficiency due to DCLRE1C deficiency (RS-SCID)	0.86	-0.22
ELP1	ENSG00000070061	NM_003640.5(ELP1):c.1704A>G (p.Ser568=)	TCA	TCG	Familial dysautonomia (HSAN3)	0.29	-1.81
ADGRG1	ENSG00000205336	NM_201525.4(ADGRG1):c.1810C>T (p.Leu604=)	CTG	TTG	Polymicrogyria, bilateral frontoparietal (BFPP)	0.37	-1.42
OPA1	ENSG00000198836	NM_015560.2(OPA1):c.2427T>C (p.Leu809=)	CTT	CTC	Autosomal dominant optic atrophy classic form (OPA1)	1.26	0.33
GAA	ENSG00000171298	NM_000152.5(GAA):c.726G>A (p.Ala242=)	GCG	GCA	Glycogen storage disease, type II (GSD2);	2.88	1.52
MYO15A	ENSG00000091536	NM_016239.4(MYO15A):c.54G>A (p.Lys18=)	AAG	AAA	Deafness, autosomal recessive 3 (DFNB3)	0.87	-0.2
NDUFAF5	ENSG00000101247	NM_024120.5(NDUFAF5):c.585T>C (p.Tyr195=)	TAT	TAC	Mitochondrial complex I deficiency	1.11	0.15
ABCC9	ENSG00000069431	NM_005691.3(ABCC9):c.3339T>G (p.Ser1113=)	TCT	TCG	Dilated cardiomyopathy 1O (CMD1O);Hypertrichotic osteochondrodysplasia Cantu type	0.24	-2.06
PYGM	ENSG00000068976	NM_005609.4(PYGM):c.924C>T (p.Ile308=)	ATC	ATT	Glycogen storage disease, type V (GSD5);	0.89	-0.17
CDH23	ENSG00000107736	NM_022124.6(CDH23):c.8886C>T (p.Asn2962=)	AAC	AAT	Usher syndrome type 1 (USH1)	1.01	0.02
CLDN14	ENSG00000159261	NM_001146079.2(CLDN14):c.690C>T (p.His230=)	CAC	CAT	Deafness, autosomal recessive 29 (DFNB29)	0.81	-0.3
MEF2C	ENSG00000081189	NM_002397.5(MEF2C):c.585C>T (p.Asn195=)	AAC	AAT	Mental retardation, stereotypic movements, epilepsy, and/or cerebral malformations (MRD20);	1.01	0.02
SLC25A19	ENSG00000125454	NM_001126121.2(SLC25A19):c.504C>T (p.Ser168=)	AGC	AGT	Amish lethal microcephaly (MCPHA)	0.72	-0.48
ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.1281C>T (p.Phe427=)	TTC	TTT	Progressive familial intrahepatic cholestasis 2 (PFIC2)	0.98	-0.02
ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.2886A>G (p.Ala962=)	GCA	GCG	Progressive familial intrahepatic cholestasis 2 (PFIC2)	0.35	-1.52
ABCB11	ENSG00000073734	NM_003742.4(ABCB11):c.2907G>A (p.Lys969=)	AAG	AAA	Progressive familial intrahepatic cholestasis 2 (PFIC2)	0.87	-0.2
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.4032C>T (p.Tyr1344=)	TAC	TAT	Usher syndrome, type 2C (USH2C)	0.9	-0.15
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.5221T>C (p.Leu1741=)	TTA	CTA	Usher syndrome, type 2C (USH2C)	0.85	-0.24
ATP8B1	ENSG00000081923	NM_005603.6(ATP8B1):c.1014C>T (p.Asn338=)	AAC	AAT	Cholestasis, progressive familial intrahepatic 1 (PFIC1)	1.01	0.02
CDH1	ENSG00000039068	NM_004360.5(CDH1):c.2343A>G (p.Glu781=)	GAA	GAG	Hereditary cancer-predisposing syndrome; Hereditary diffuse gastric cancer (HDGC)	1.16	0.22

CHRND	ENSG00000135902	NM_000751.3(CHRND):c.414C>T (p.Phe138=)	TTC	TTT	Lethal multiple pterygium syndrome (LMPS);Congenital myasthenic syndrome (CMS)	0.98	-0.02
LOXHD1	ENSG00000167210	NM_144612.6(LOXHD1):c.6276C>G (p.Val2092=)	GTC	GTG	Deafness, autosomal recessive 77 (DFNB77)	1.92	0.94
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.10260C>T (p.Phe3420=)	TTC	TTT	Usher syndrome, type 2C (USH2C)	0.98	-0.02
CLRN1	ENSG00000163646	NM_174878.3(CLRN1):c.226T>C (p.Leu76=)	TTG	CTG	Usher Syndrome, Type III (USH3)	2.67	1.42
RARS2	ENSG00000146282	NM_020320.5(RARS2):c.888G>A (p.Thr296=)	ACG	ACA	Pontocerebellar hypoplasia type 6 (PCH6)	2.96	1.57
MYBPC3	ENSG00000134571	NM_000256.3(MYBPC3):c.2877G>A (p.Thr959=)	ACG	ACA	Cardiomyopathy (CMYO);Hypertrophic cardiomyopathy	2.96	1.57
WDR62	ENSG00000075702	NM_001083961.2(WDR62):c.2976G>A (p.Ser992=)	TCG	TCA	Primary autosomal recessive microcephaly 2 (MCPH2)	3.5	1.81
KIF7	ENSG00000166813	NM_198525.3(KIF7):c.3514C>A (p.Arg1172=)	CGA	AGA	Acrocallosal syndrome (ACLS);	2.09	1.06
PCSK9	ENSG00000169174	NM_174936.3(PCSK9):c.1944C>T (p.Tyr648=)	TAC	TAT	Familial hypercholesterolemia (FH);Familial hypercholesterolemia 3 (FHCL3);Hypobetalipoproteinemia	0.9	-0.15
KIF7	ENSG00000166813	NM_198525.3(KIF7):c.3960T>A (p.Pro1320=)	CCT	CCA	Acrocallosal syndrome (ACLS);	0.98	-0.03
TTN	ENSG00000155657	NM_001267550.2(TTN):c.95130C>A (p.Gly31710=)	GGC	GGA	Cardiomyopathy (CMYO)	0.87	-0.2
NPC1	ENSG00000141458	NM_000271.5(NPC1):c.3198C>T (p.Thr1066=)	ACC	ACT	Niemann-Pick disease type C1 (NPC1);	0.8	-0.31
USH2A	ENSG00000042781	NM_206933.4(USH2A):c.14664G>A (p.Thr4888=)	ACG	ACA	Usher syndrome, type 2A (USH2A);none provided	2.96	1.57
CNTNAP2	ENSG00000174469	NM_014141.6(CNTNAP2):c.1311C>T (p.Ile437=)	ATC	ATT	Pitt-Hopkins-like syndrome 1 (PTHSL1);Pitt-Hopkins-like syndrome; History of neurodevelopmental disorder	0.89	-0.17
TTN	ENSG00000155657	NM_001267550.2(TTN):c.204C>T (p.Pro68=)	CCC	CCT	Cardiovascular phenotype; Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	1.02	0.02
RAD51C	ENSG00000108384	NM_058216.3(RAD51C):c.87T>C (p.Ser29=)	TCT	TCC	Hereditary cancer-predisposing syndrome;Fanconi anemia, complementation group O (FANCO);Breast-ovarian cancer, familial 3 (BROVCA3);	1.02	0.03
SMAD3	ENSG00000166949	NM_005902.4(SMAD3):c.885G>A (p.Arg295=)	CGG	CGA	Familial thoracic aortic aneurysm and aortic dissection (TAAD);Loeys-Dietz syndrome (LDS);Cardiovascular phenotype;	0.6	-0.73
DLD	ENSG00000091140	NM_000108.5(DLD):c.321A>G (p.Ala107=)	GCA	GCG	Maple syrup urine disease, type 3 (MSUD3);Leigh syndrome (LS);Pyruvate dehydrogenase complex deficiency (PDHC)	0.35	-1.52
APOB	ENSG00000084674	NM_000384.3(APOB):c.4299G>A (p.Ser1433=)	TCG	TCA	Familial hypercholesterolemia (FH); Hypobetalipoproteinemia, familial, 1 (FHBL1);Familial hypercholesterolemia 2 (FCHL2)	3.5	1.81
RYR2	ENSG00000198626	NM_001035.3(RYR2):c.13665C>T (p.Ile4555=)	ATC	ATT	Catecholaminergic polymorphic ventricular tachycardia (CPVT1); Arrhythmogenic right ventricular dysplasia, familial, 2 (ARVD2);Catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1);Cardiomyopathy (CMYO)	0.89	-0.17
PRKAG2	ENSG00000106617	NM_016203.4(PRKAG2):c.912G>A (p.Ala304=)	GCG	GCA	Glycogen storage disease of heart, lethal congenital;Wolff-Parkinson-White syndrome;Familial Hypertrophic Cardiomyopathy with Wolff-Parkinson-White Syndrome;Cardiovascular phenotype; Cardiomyopathy (CMYO)	2.88	1.52
NF1	ENSG00000196712	NM_000267.3(NF1):c.864G>C (p.Val288=)	GTG	GTC	Hereditary cancer-predisposing syndrome;Neurofibromatosis, type 1 (NF1);Neurofibromatosis, familial spinal (FSNF);Café-au-lait macules with pulmonary stenosis (WTSN);Neurofibromatosis-Noonan syndrome (NFNS)	0.52	-0.94
MYO7A	ENSG00000137474	NM_000260.4(MYO7A):c.3978C>T (p.Cys1326=)	TGC	TGT	Deafness, autosomal recessive 2 (DFNB2);Deafness, autosomal dominant 11 (DFNA11);Usher syndrome type 1 (USH1)	0.97	-0.05
NF1	ENSG00000196712	NM_000267.3(NF1):c.3213A>G (p.Ala1071=)	GCA	GCG	Hereditary cancer-predisposing syndrome;Neurofibromatosis, type 1 (NF1);Café-au-lait macules with pulmonary stenosis (WTSN);Neurofibromatosis, familial spinal (FSNF);Neurofibromatosis-Noonan syndrome (NFNS)	0.35	-1.52

NF1	ENSG00000196712	NM_000267.3(NF1):c.7183C>T (p.Leu2395=)	CTA	TTA	Hereditary cancer-predisposing syndrome;Neurofibromatosis, type 1 (NF1);Café-au-lait macules with pulmonary stenosis (WTSN);Neurofibromatosis-Noonan syndrome (NFNS);Neurofibromatosis, familial spinal (FSNF)	1.18	0.24
NF1	ENSG00000196712	NM_000267.3(NF1):c.3303G>A (p.Gln1101=)	CAG	CAA	Hereditary cancer-predisposing syndrome;Neurofibromatosis, type 1 (NF1);Neurofibromatosis-Noonan syndrome (NFNS);Café-au-lait macules with pulmonary stenosis (WTSN);Neurofibromatosis, familial spinal (FSNF)	0.4	-1.32
MYO7A	ENSG00000137474	NM_000260.4(MYO7A):c.5688G>A (p.Gln1896=)	CAG	CAA	Usher syndrome type 1 (USH1);Deafness, autosomal dominant 11 (DFNA11);Deafness, autosomal recessive 2 (DFNB2)	0.4	-1.32
UGT1A6	ENSG00000242366	NM_001072.4(UGT1A6):c.862-6207A>G	GAA	GAG	s syndrome", 'Crigler-Najjar syndrome;Lucey-Driscoll syndrome (HBLRTFN)	1.16	0.22
MYO7A	ENSG00000137474	NM_000260.4(MYO7A):c.448C>A (p.Arg150=)	CGA	AGA	Deafness, autosomal recessive 2 (DFNB2);Usher syndrome type 1 (USH1);Deafness, autosomal dominant 11 (DFNA11);Usher syndrome, type 1B (USH1B)	2.09	1.06
LDB3	ENSG00000122367	NM_007078.3(LDB3):c.690-4716G>A	GCG	GCA	Myofibrillar myopathy, ZASP-related (MFM4);Myofibrillar Myopathy, Dominant;Cardiomyopathy, left ventricular noncompaction;Dilated Cardiomyopathy, Dominant;Dilated cardiomyopathy 1C (CMD1C)	2.88	1.52
HBB	ENSG00000244734	NM_000518.5(HBB):c.294C>T (p.His98=)	CAC	CAT	beta Thalassemia (BTHAL);Fetal hemoglobin quantitative trait locus 1 (HBFQTL1);Hemoglobin E;Hb SS disease (SCD)	0.81	-0.3
HBB	ENSG00000244734	NM_000518.5(HBB):c.246C>A (p.Leu82=)	CTC	CTA	beta Thalassemia (BTHAL);Hemoglobin E;Hb SS disease (SCD);Fetal hemoglobin quantitative trait locus 1 (HBFQTL1)	0.42	-1.25
TTN	ENSG00000155657	NM_001267550.2(TTN):c.732C>T (p.Ala244=)	GCC	GCT	Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Tibial muscular dystrophy (TMD)	0.74	-0.44
MYH9	ENSG00000100345	NM_002473.6(MYH9):c.3192C>T (p.Ile1064=)	ATC	ATT	Autosomal dominant nonsyndromic deafness 17 (DFNA17);MYH9-related disorder;	0.89	-0.17
MYH9	ENSG00000100345	NM_002473.6(MYH9):c.4878C>T (p.Ile1626=)	ATC	ATT	Autosomal dominant nonsyndromic deafness 17 (DFNA17);MYH9-related disorder;	0.89	-0.17
VHL	ENSG00000134086	NM_000551.3(VHL):c.183C>G (p.Pro61=)	CCC	CCG	Von Hippel-Lindau syndrome (VHLS);Hereditary cancer-predisposing syndrome; Erythrocytosis, familial, 2 (ECYT2);Von Hippel-Lindau syndrome (VHLS)	0.33	-1.62
RYR2	ENSG00000198626	NM_001035.3(RYR2):c.12159G>A (p.Glu4053=)	GAG	GAA	Cardiovascular phenotype;Catecholaminergic polymorphic ventricular tachycardia (CPVT1);Arrhythmogenic right ventricular dysplasia, familial, 2 (ARVD2); Cardiomyopathy (CMYO);Catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1)	0.86	-0.22
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.1821T>C (p.Asp607=)	GAT	GAC	Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD);Geleophysic dysplasia;Familial thoracic aortic aneurysm and aortic dissection (TAAD);Marfan syndrome (MFS);Weill-Marchesani syndrome;Ectopia lentis, isolated, autosomal dominant (ECTOL1);Acromicric dysplasia (ACMICD);Stiff skin syndrome (SSKS);none provided	1.01	0.01
MLH1	ENSG00000076242	NM_000249.3(MLH1):c.702G>A (p.Glu234=)	GAG	GAA	Lynch syndrome;Hereditary cancer-predisposing syndrome; Lynch syndrome II (HNPCC2);Hereditary nonpolyposis colorectal neoplasms	0.86	-0.22
BRCA2	ENSG00000139618	NM_000059.4(BRCA2):c.1011C>T (p.Asn337=)	AAC	AAT	Breast-ovarian cancer, familial 2 (BROVCA2);Hereditary cancer-predisposing syndrome; Familial cancer of breast; Hereditary breast and ovarian cancer syndrome (HBOC)	1.01	0.02

MUTYH	ENSG00000132781	NM_012222.2(MUTYH):c.129C>T (p.Asn43=)	AAC	AAT	Hereditary cancer-predisposing syndrome;MYH-associated polyposis (FAP2);	1.01	0.02
ATM	ENSG00000149311	NM_000051.3(ATM):c.7494T>C (p.Ser2498=)	TCT	TCC	Hereditary cancer-predisposing syndrome;Ataxia-telangiectasia syndrome (AT);	1.02	0.03
TSC2	ENSG00000103197	NM_000548.5(TSC2):c.5028G>A (p.Leu1676=)	CTG	CTA	Tuberous sclerosis syndrome (TSC);Hereditary cancer-predisposing syndrome; Tuberous sclerosis 2 (TSC2)	0.21	-2.27
BARD1	ENSG00000138376	NM_000465.4(BARD1):c.2280G>A (p.Ser760=)	TCG	TCA	Hereditary cancer-predisposing syndrome; Familial cancer of breast	3.5	1.81
MSH2	ENSG00000095002	NM_000251.2(MSH2):c.198C>T (p.Tyr66=)	TAC	TAT	Hereditary cancer-predisposing syndrome;Hereditary nonpolyposis colorectal neoplasms; Lynch syndrome I (COCA1);	0.9	-0.15
MSH2	ENSG00000095002	NM_000251.2(MSH2):c.1488A>G (p.Leu496=)	TTA	TTG	Lynch syndrome;Hereditary cancer-predisposing syndrome; Lynch syndrome I (COCA1); Hereditary nonpolyposis colorectal neoplasms	1.53	0.61
NF1	ENSG00000196712	NM_000267.3(NF1):c.4986C>T (p.Asn1662=)	AAC	AAT	Hereditary cancer-predisposing syndrome; Neurofibromatosis, type 1 (NF1);Café-au-lait macules with pulmonary stenosis (WTSN);Neurofibromatosis, familial spinal (FSNF);Neurofibromatosis-Noonan syndrome (NFNS)	1.01	0.02
CBS	ENSG00000160200	NM_000071.2(CBS):c.1161C>T (p.Ser387=)	AGC	AGT	Cardiovascular phenotype; Classic homocystinuria	0.72	-0.48
PNPLA6	ENSG00000032444	NM_001166114.2(PNPLA6):c.1935C>G (p.Arg645=)	CGC	CGG	Hereditary spastic paraplegia 39 (SPG39)	1.22	0.29
SCN2A	ENSG00000136531	NM_001040142.2(SCN2A):c.3210C>T (p.Asp1070=)	GAC	GAT	History of neurodevelopmental disorder;	0.99	-0.01
NEB	ENSG00000183091	NM_001271208.2(NEB):c.7581C>T (p.Tyr2527=)	TAC	TAT	Nemaline myopathy 2 (NEM2)	0.9	-0.15
EYA1	ENSG00000104313	NM_000503.6(EYA1):c.630T>C (p.Ser210=)	AGT	AGC	Branchiootic syndrome 1 (BOS1);Otofaciocervical syndrome 1 (OTFCS);	1.4	0.48
NEB	ENSG00000183091	NM_001271208.2(NEB):c.19746T>C (p.Ala6582=)	GCT	GCC	Nemaline myopathy 2 (NEM2)	1.36	0.44
GSDME	ENSG00000105928	NM_001127453.2(GSDME):c.1122C>T (p.Pro374=)	CCC	CCT	Deafness, autosomal dominant 5 (DFNA5);	1.02	0.02
KCNT1	ENSG00000107147	NM_020822.3(KCNT1):c.2052G>A (p.Thr684=)	ACG	ACA	Seizures;	2.96	1.57
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.207C>T (p.Asn69=)	AAC	AAT	Cardiovascular phenotype;Aortic aneurysm, familial thoracic 7 (AAT7)	1.01	0.02
COL4A4	ENSG00000081052	NM_000092.5(COL4A4):c.2241C>T (p.Pro747=)	CCC	CCT	Alport syndrome	1.02	0.02
RHO	ENSG00000163914	NM_000539.3(RHO):c.480C>A (p.Thr160=)	ACC	ACA	Retinitis pigmentosa (RP);Congenital stationary night blindness, autosomal dominant 1 (CSNBAD1);	0.93	-0.1
FRMPD4	ENSG00000169933	NM_001368397.1(FRMPD4):c.3937C>A (p.Arg1313=)	CGG	AGG	Autism, susceptibility to, X-linked 4 (AUTSX4);	1.15	0.2
AGPS	ENSG00000018510	NM_003659.4(AGPS):c.1380A>C (p.Pro460=)	CCA	CCC	Rhizomelic chondrodysplasia punctata type 3 (RCDP3)	1	0.01
COL9A2	ENSG00000049089	NM_001852.4(COL9A2):c.1041C>T (p.Gly347=)	GGC	GGT	Epiphyseal dysplasia, multiple, 2 (EDM2);	0.55	-0.87
ENPP1	ENSG00000197594	NM_006208.3(ENPP1):c.2757A>T (p.Pro919=)	CCA	CCT	Arterial calcification, generalized, of infancy, 1 (GACI1);Hypophosphatemic rickets, autosomal recessive, 2 (ARHR2);	1.02	0.03
LRMDA	ENSG00000148655	NM_001305581.2(LRMDA):c.193C>T (p.Leu65=)	CTG	TTG	Albinism, oculocutaneous, type VII (OCA7);	0.37	-1.42
PHKG2	ENSG00000156873	NM_000294.3(PHKG2):c.288C>T (p.Ser96=)	TCC	TCT	Glycogen storage disease IXc (GSD9C)	0.98	-0.03
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.4725C>T (p.Tyr1575=)	TAC	TAT	Cardiovascular phenotype;Aortic aneurysm, familial thoracic 7 (AAT7)	0.9	-0.15
APC	ENSG00000134982	NM_000038.6(APC):c.564A>G (p.Gln188=)	CAA	CAG	Hereditary cancer-predisposing syndrome; Familial adenomatous polyposis 1 (FAP1)	2.49	1.32
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.2016C>T (p.Asn672=)	AAC	AAT	Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B);Qualitative or quantitative defects of dysferlin	1.01	0.02
ATP8B1	ENSG00000081923	NM_005603.6(ATP8B1):c.150A>G (p.Glu50=)	GAA	GAG	Cholestasis, progressive familial intrahepatic 1 (PFIC1);	1.16	0.22

LOXHD1	ENSG00000167210	NM_144612.6(LOXHD1):c.3936C>G (p.Leu1312=)	CTC	CTG	Deafness, autosomal recessive 77 (DFNB77);	2.02	1.02
BMPR1A	ENSG00000107779	NM_004329.2(BMPR1A):c.1068C>T (p.Pro356=)	CCC	CCT	Hereditary cancer-predisposing syndrome; Generalized juvenile polyposis/juvenile polyposis coli (JPS)	1.02	0.02
RBM20	ENSG00000203867	NM_001134363.3(RBM20):c.3648C>T (p.Ser1216=)	AGC	AGT	Cardiovascular phenotype; Dilated cardiomyopathy 1DD (CMD1DD)	0.72	-0.48
PALB2	ENSG00000083093	NM_024675.3(PALB2):c.1227T>C (p.Tyr409=)	TAT	TAC	Hereditary cancer-predisposing syndrome;	1.11	0.15
RYR2	ENSG00000198626	NM_001035.3(RYR2):c.7443A>G (p.Gln2481=)	CAA	CAG	Cardiovascular phenotype;Catecholaminergic polymorphic ventricular tachycardia (CPVT1);Cardiomyopathy (CMYO)	2.49	1.32
ACTC1	ENSG00000159251	NM_005159.5(ACTC1):c.903A>G (p.Leu301=)	TTA	TTG	Familial hypertrophic cardiomyopathy 11 (CMH11);Dilated cardiomyopathy 1R (CMD1R);Atrial septal defect 5 (ASD5);Cardiomyopathy (CMYO)	1.53	0.61
NTRK1	ENSG00000198400	NM_001007792.1(NTRK1):c.978C>T (p.Asn326=)	AAC	AAT	Hereditary insensitivity to pain with anhidrosis (CIPA)	1.01	0.02
GCDH	ENSG00000105607	NM_000159.4(GCDH):c.1143C>T (p.Ile381=)	ATC	ATT	Glutaric aciduria, type 1 (GA1);	0.89	-0.17
ATM	ENSG00000149311	NM_000051.3(ATM):c.7542T>C (p.Tyr2514=)	TAT	TAC	Hereditary cancer-predisposing syndrome; Ataxia-telangiectasia syndrome (AT)	1.11	0.15
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.6648C>T (p.Cys2216=)	TGC	TGT	Emery-Dreifuss muscular dystrophy (EDMD);Cerebellar ataxia;	0.97	-0.05
CREBBP	ENSG00000005339	NM_004380.3(CREBBP):c.5829G>A (p.Pro1943=)	CCG	CCA	History of neurodevelopmental disorder;	3.05	1.61
CDH1	ENSG00000039068	NM_004360.5(CDH1):c.462A>G (p.Arg154=)	AGA	AGG	Hereditary cancer-predisposing syndrome;Hereditary diffuse gastric cancer (HDGC)	0.91	-0.14
MAN1B1	ENSG00000177239	NM_016219.5(MAN1B1):c.1173C>T (p.Ser391=)	TCC	TCT	History of neurodevelopmental disorder;Mental retardation, autosomal recessive 15 (RAFQS)	0.98	-0.03
USH1C	ENSG00000006611	NM_153676.4(USH1C):c.2124T>C (p.Ser708=)	TCT	TCC	Usher syndrome, type 1C (USH1C);Deafness, autosomal recessive 18 (DFNB18A);	1.02	0.03
DSG2	ENSG00000046604	NM_001943.5(DSG2):c.1920C>T (p.Gly640=)	GGC	GGT	Arrhythmogenic right ventricular cardiomyopathy, type 10 (ARVD10); Cardiomyopathy (CMYO)	0.55	-0.87
BARD1	ENSG00000138376	NM_000465.4(BARD1):c.735A>G (p.Gln245=)	CAA	CAG	Hereditary cancer-predisposing syndrome; Familial cancer of breast	2.49	1.32
BAP1	ENSG00000163930	NM_004656.4(BAP1):c.1227G>C (p.Val409=)	GTG	GTC	Hereditary cancer-predisposing syndrome;Tumor susceptibility linked to germline BAP1 mutations (TPDS);	0.52	-0.94
CHKB	ENSG00000100288	NM_005198.4(CHKB):c.457T>C (p.Leu153=)	TTG	CTG	Megaconial type congenital muscular dystrophy (MDCMC)	2.67	1.42
FLNA	ENSG00000196924	NM_001110556.2(FLNA):c.3285C>T (p.Ala1095=)	GCC	GCT	History of neurodevelopmental disorder; Periventricular nodular heterotopia 1 (PVNH1);Melnick-Needles syndrome (MNS);Oto-palato-digital syndrome, type II (OPD2);Frontometaphyseal dysplasia (FMD1)	0.74	-0.44
TRPM4	ENSG00000130529	NM_017636.4(TRPM4):c.1368C>G (p.Thr456=)	ACC	ACG	Cardiovascular phenotype;Progressive familial heart block type IB (PFHB1B);none provided	0.31	-1.67
KCNT1	ENSG00000107147	NM_020822.3(KCNT1):c.474G>A (p.Ser158=)	TCG	TCA	Seizures; Early infantile epileptic encephalopathy 14 (DEE14);Epilepsy, nocturnal frontal lobe, 5 (ENFL5)	3.5	1.81
TRPM4	ENSG00000130529	NM_017636.4(TRPM4):c.870C>T (p.Asn290=)	AAC	AAT	Cardiovascular phenotype;Progressive familial heart block type IB (PFHB1B);none provided	1.01	0.02
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.10887C>T (p.Phe3629=)	TTC	TTT	History of neurodevelopmental disorder; Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O)	0.98	-0.02
PKP2	ENSG00000057294	NM_004572.3(PKP2):c.1323G>T (p.Arg441=)	CGG	CGT	Cardiovascular phenotype;Arrhythmogenic right ventricular dysplasia 9 (ARVD9);Cardiomyopathy (CMYO)	0.43	-1.22
CAV3	ENSG00000182533	NM_033337.3(CAV3):c.234G>A (p.Thr78=)	ACG	ACA	Cardiovascular phenotype; Long QT syndrome (LQTS)	2.96	1.57
POLE	ENSG00000177084	NM_006231.3(POLE):c.6453C>T (p.Tyr2151=)	TAC	TAT	Hereditary cancer-predisposing syndrome; Colorectal cancer, susceptibility to, 12 (CRCS12)	0.9	-0.15

TSC2	ENSG00000103197	NM_000548.5(TSC2):c.2031C>T (p.Pro677=)	CCC	CCT	Tuberous sclerosis syndrome (TSC);Hereditary cancer-predisposing syndrome; Tuberous sclerosis 2 (TSC2); none provided	1.02	0.02
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.1884C>T (p.Cys628=)	TGC	TGT	Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD);Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD);Stiff skin syndrome (SSKS);Acromicric dysplasia (ACMICD);Weill-Marchesani syndrome;Geleophysic dysplasia;Ectopia lentis, isolated, autosomal dominant (ECTOL1)	0.97	-0.05
RYR2	ENSG00000198626	NM_001035.3(RYR2):c.3888C>T (p.Asn1296=)	AAC	AAT	Cardiovascular phenotype; Cardiomyopathy (CMYO);Catecholaminergic polymorphic ventricular tachycardia (CPVT1)	1.01	0.02
ATM	ENSG00000149311	NM_000051.3(ATM):c.6465G>A (p.Val2155=)	GTG	GTA	Hereditary cancer-predisposing syndrome; Ataxia-telangiectasia syndrome (AT)	0.3	-1.74
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.693G>A (p.Thr231=)	ACG	ACA	Hereditary cancer-predisposing syndrome;Breast-ovarian cancer, familial 1 (BROVCA1); Hereditary breast and ovarian cancer syndrome (HBOC)	2.96	1.57
TTN	ENSG00000155657	NM_001267550.2(TTN):c.7957T>C (p.Leu2653=)	TTG	CTG	Cardiovascular phenotype; Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	2.67	1.42
POLE	ENSG00000177084	NM_006231.3(POLE):c.1188G>A (p.Glu396=)	GAG	GAA	Hereditary cancer-predisposing syndrome; Colorectal cancer, susceptibility to, 12 (CRCS12)	0.86	-0.22
ATM	ENSG00000149311	NM_000051.3(ATM):c.5352C>T (p.Asn1784=)	AAC	AAT	Hereditary cancer-predisposing syndrome; Ataxia-telangiectasia syndrome (AT)	1.01	0.02
MMAA	ENSG00000151611	NM_172250.3(MMAA):c.630A>G (p.Pro210=)	CCA	CCG	Vitamin B12-responsive methylmalonic acidemia type cblA;Methylmalonic acidemia (MMA)	0.33	-1.61
MUTYH	ENSG00000132781	NM_001048171.1(MUTYH):c.654C>T (p.Thr218=)	ACC	ACT	Hereditary cancer-predisposing syndrome;MYH-associated polyposis (FAP2);	0.8	-0.31
STK11	ENSG00000118046	NM_000455.4(STK11):c.846C>G (p.Leu282=)	CTC	CTG	Hereditary cancer-predisposing syndrome; Peutz-Jeghers syndrome (PJS);	2.02	1.02
COL3A1	ENSG00000168542	NM_000090.3(COL3A1):c.4086C>T (p.Ser1362=)	AGC	AGT	Cardiovascular phenotype; Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.72	-0.48
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.441A>G (p.Gln147=)	CAA	CAG	Hereditary breast and ovarian cancer syndrome (HBOC);Breast-ovarian cancer, familial 2 (BROVCA2); Hereditary cancer-predisposing syndrome	2.49	1.32
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.7308G>A (p.Ala2436=)	GCG	GCA	Autosomal dominant cerebellar ataxia; Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);Charcot-Marie-Tooth disease	2.88	1.52
GYS1	ENSG00000104812	NM_002103.5(GYS1):c.2013C>T (p.Asp671=)	GAC	GAT	Hereditary hyperferritinemia with congenital cataracts (HRFTC);Neuroferritinopathy (NBIA3);Glycogen storage disease 0, muscle (GSD0B);	0.99	-0.01
PMS2	ENSG00000122512	NM_000535.7(PMS2):c.795T>C (p.Asn265=)	AAT	AAC	Hereditary cancer-predisposing syndrome; Hereditary nonpolyposis colorectal neoplasms	0.99	-0.02
HCN4	ENSG00000138622	NM_005477.3(HCN4):c.621C>G (p.Arg207=)	CGC	CGG	Cardiovascular phenotype; Brugada syndrome 8 (BRGDA8)	1.22	0.29
PKP2	ENSG00000057294	NM_004572.3(PKP2):c.1449T>C (p.Thr483=)	ACT	ACC	Cardiomyopathy (CMYO);Arrhythmogenic right ventricular dysplasia 9 (ARVD9);	1.24	0.31
TTN	ENSG00000155657	NM_001267550.2(TTN):c.93972A>G (p.Glu31324=)	GAA	GAG	Cardiovascular phenotype; Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	1.16	0.22
BARD1	ENSG00000138376	NM_000465.4(BARD1):c.1194A>G (p.Thr398=)	ACA	ACG	Hereditary cancer-predisposing syndrome; Familial cancer of breast	0.34	-1.57
MLH1	ENSG00000076242	NM_000249.3(MLH1):c.69A>G (p.Glu23=)	GAA	GAG	Hereditary nonpolyposis colorectal neoplasms;Hereditary cancer-predisposing syndrome; Lynch syndrome II (HNPCC2)	1.16	0.22

RAD51C	ENSG00000108384	NM_058216.3(RAD51C):c.435A>G (p.Pro145=)	CCA	CCG	Hereditary cancer-predisposing syndrome; Fanconi anemia, complementation group O (FANCO);Breast-ovarian cancer, familial 3 (BROVCA3)	0.33	-1.61
TNNI3	ENSG00000129991	NM_000363.5(TNNI3):c.384G>A (p.Leu128=)	CTG	CTA	Cardiomyopathy (CMYO);Hypertrophic cardiomyopathy	0.21	-2.27
MLH1	ENSG00000076242	NM_000249.3(MLH1):c.1743G>A (p.Pro581=)	CCG	CCA	Hereditary cancer-predisposing syndrome; Lynch syndrome II (HNPCC2); Hereditary nonpolyposis colorectal neoplasms	3.05	1.61
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.1056G>A (p.Ser352=)	TCG	TCA	Cardiovascular phenotype; Aortic aneurysm, familial thoracic 4 (AAT4); Familial thoracic aortic aneurysm and aortic dissection (TAAD)	3.5	1.81
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.2211T>A (p.Val737=)	GTT	GTA	Autosomal dominant cerebellar ataxia; Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);History of neurodevelopmental disorder;Charcot-Marie-Tooth disease	0.65	-0.62
FGD4	ENSG00000139132	NM_139241.3(FGD4):c.255A>T (p.Ala85=)	GCA	GCT	Charcot-Marie-Tooth disease type 4; Charcot-Marie-Tooth disease, type 4H (CMT4H);Charcot-Marie-Tooth disease;	1.11	0.14
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.378A>G (p.Gln126=)	CAA	CAG	Hereditary cancer-predisposing syndrome;Breast-ovarian cancer, familial 1 (BROVCA1); Hereditary breast and ovarian cancer syndrome (HBOC)	2.49	1.32
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.5157G>T (p.Val1719=)	GTG	GTT	Hereditary cancer-predisposing syndrome;Breast-ovarian cancer, familial 1 (BROVCA1); Hereditary breast and ovarian cancer syndrome (HBOC)	0.46	-1.13
MYBPC3	ENSG00000134571	NM_000256.3(MYBPC3):c.1566G>A (p.Ala522=)	GCG	GCA	Familial hypertrophic cardiomyopathy 4 (CMH4);Cardiomyopathy (CMYO);Hypertrophic cardiomyopathy;Left ventricular noncompaction 10 (LVNC10)	2.88	1.52
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.5022C>T (p.Ile1674=)	ATC	ATT	Hereditary cancer-predisposing syndrome;Breast-ovarian cancer, familial 1 (BROVCA1); Hereditary breast and ovarian cancer syndrome (HBOC);Breast-ovarian cancer, familial 1 (BROVCA1);Hereditary breast and ovarian cancer syndrome (HBOC)	0.89	-0.17
TTN	ENSG00000155657	NM_001267550.2(TTN):c.62424C>T (p.Asp20808=)	GAC	GAT	Cardiovascular phenotype; Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Cardiomyopathy (CMYO)	0.99	-0.01
ABCC9	ENSG00000069431	NM_005691.3(ABCC9):c.3357G>A (p.Leu1119=)	CTG	CTA	Cardiovascular phenotype;Dilated cardiomyopathy 1O (CMD1O);Cardiomyopathy (CMYO);Hypertrichotic osteochondrodysplasia Cantu type	0.21	-2.27
TTN	ENSG00000155657	NM_001267550.2(TTN):c.101925A>G (p.Leu33975=)	CTA	CTG	Cardiovascular phenotype; Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Dilated cardiomyopathy 1G (CMD1G);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Tibial muscular dystrophy (TMD);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, early-onset, with fatal cardiomyopathy (SALMY)	4.81	2.27
CFTR	ENSG00000001626	NM_000492.3(CFTR):c.3558A>G (p.Gln1186=)	CAA	CAG	Cystic fibrosis (CF); Inborn genetic diseases;CFTR-related disorders (CFTR-RD);none provided	2.49	1.32
TTN	ENSG00000155657	NM_001267550.2(TTN):c.77073T>C (p.Asp25691=)	GAT	GAC	Cardiovascular phenotype; Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Dilated cardiomyopathy 1G (CMD1G);Tibial muscular dystrophy (TMD)	1.01	0.01

INVS	ENSG00000119509	NM_014425.5(INVS):c.2310C>T (p.His770=)	CAC	CAT	Nephronophthisis; Infantile nephronophthisis (NPHP2);	0.81	-0.3
BMPR1A	ENSG00000107779	NM_004329.2(BMPR1A):c.1059A>G (p.Gln353=)	CAA	CAG	Generalized juvenile polyposis/juvenile polyposis coli (JPS);Hereditary cancer-predisposing syndrome; Juvenile polyposis syndrome (JPS)	2.49	1.32
COL2A1	ENSG00000139219	NM_001844.5(COL2A1):c.195C>T (p.Asp65=)	GAC	GAT	Connective tissue disease; Stickler syndrome type 1 (STL1);Type II Collagenopathies;none provided	0.99	-0.01
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.15015G>A (p.Thr5005=)	ACG	ACA	Malignant hyperthermia, susceptibility to, 1 (MHS1);Central core myopathy (CCD);Minicore myopathy with external ophthalmoplegia;Neuromuscular disease, congenital, with uniform type 1 fiber (CNMDU1); RYR1-Related Disorders	2.96	1.57
NF1	ENSG00000196712	NM_000267.3(NF1):c.681T>C (p.Tyr227=)	TAT	TAC	Hereditary cancer-predisposing syndrome;Neurofibromatosis, type 1 (NF1);Café-au-lait macules with pulmonary stenosis (WTSN);Neurofibromatosis-Noonan syndrome (NFNS);Neurofibromatosis, familial spinal (FSNF)	1.11	0.15
NF1	ENSG00000196712	NM_000267.3(NF1):c.2178G>C (p.Val726=)	GTG	GTC	Hereditary cancer-predisposing syndrome; Neurofibromatosis, type 1 (NF1);Neurofibromatosis, familial spinal (FSNF);Café-au-lait macules with pulmonary stenosis (WTSN);Neurofibromatosis-Noonan syndrome (NFNS)	0.52	-0.94
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.7560G>A (p.Thr2520=)	ACG	ACA	Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD); Familial thoracic aortic aneurysm and aortic dissection (TAAD);Stiff skin syndrome (SSKS);Marfan syndrome (MFS);Ectopia lentis, isolated, autosomal dominant (ECTOL1);Weill-Marchesani syndrome;Acromicric dysplasia (ACMICD)	2.96	1.57
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.546C>T (p.Ala182=)	GCC	GCT	Familial thoracic aortic aneurysm and aortic dissection (TAAD); Cardiovascular phenotype;Aortic aneurysm, familial thoracic 4 (AAT4)	0.74	-0.44
MSH2	ENSG00000095002	NM_000251.2(MSH2):c.843A>T (p.Ser281=)	TCA	TCT	Hereditary nonpolyposis colorectal neoplasms; Hereditary cancer-predisposing syndrome;Lynch syndrome I (COCA1)	1.2	0.26
DSC2	ENSG00000134755	NM_024422.6(DSC2):c.348A>G (p.Gln116=)	CAA	CAG	Cardiovascular phenotype;Arrhythmogenic right ventricular cardiomyopathy, type 11 (ARVD11);Cardiomyopathy (CMYO)	2.49	1.32
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.4809G>A (p.Thr1603=)	ACG	ACA	Familial thoracic aortic aneurysm and aortic dissection (TAAD); Cardiovascular phenotype;Aortic aneurysm, familial thoracic 4 (AAT4)	2.96	1.57
SMAD3	ENSG00000166949	NM_005902.4(SMAD3):c.798G>A (p.Ser266=)	TCG	TCA	Cardiovascular phenotype;Familial thoracic aortic aneurysm and aortic dissection (TAAD)	3.5	1.81
GYS1	ENSG00000104812	NM_002103.5(GYS1):c.2043C>T (p.Ala681=)	GCC	GCT	Neuroferritinopathy (NBIA3);Hereditary hyperferritinemia with congenital cataracts (HRFTC); Glycogen storage disease 0, muscle (GSD0B)	0.74	-0.44
BMPR1A	ENSG00000107779	NM_004329.2(BMPR1A):c.33G>A (p.Leu11=)	TTG	TTA	Hereditary cancer-predisposing syndrome; Generalized juvenile polyposis/juvenile polyposis coli (JPS)	0.65	-0.61
TSC2	ENSG00000103197	NM_000548.5(TSC2):c.300G>A (p.Ala100=)	GCG	GCA	Tuberous sclerosis syndrome (TSC);Hereditary cancer-predisposing syndrome; Tuberous sclerosis 2 (TSC2)	2.88	1.52
BARD1	ENSG00000138376	NM_000465.4(BARD1):c.1152C>T (p.Ser384=)	TCC	TCT	Hereditary cancer-predisposing syndrome; Triple-Negative Breast Cancer Finding;Familial cancer of breast;	0.98	-0.03

FBN1	ENSG00000166147	NM_000138.4(FBN1):c.2094G>T (p.Pro698=)	CCG	CCT	Cardiovascular phenotype;Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD); Familial thoracic aortic aneurysm and aortic dissection (TAAD);Geleophysic dysplasia;Ectopia lentis, isolated, autosomal dominant (ECTOL1);Marfan syndrome (MFS);Weill-Marchesani syndrome;Stiff skin syndrome (SSKS);Acromicric dysplasia (ACMICD)	3.11	1.64
MYBPC3	ENSG00000134571	NM_000256.3(MYBPC3):c.1608T>A (p.Ala536=)	GCT	GCA	Cardiovascular phenotype;Familial hypertrophic cardiomyopathy 4 (CMH4);Cardiomyopathy (CMYO);Hypertrophic cardiomyopathy;Left ventricular noncompaction 10 (LVNC10)	0.9	-0.14
FBN1	ENSG00000166147	NM_000138.5(FBN1):c.3423G>A (p.Pro1141=)	CCG	CCA	Geleophysic dysplasia;Weill-Marchesani syndrome;Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD);Acromicric dysplasia (ACMICD);Ectopia lentis, isolated, autosomal dominant (ECTOL1);Stiff skin syndrome (SSKS);Cardiovascular phenotype;Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	3.05	1.61
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.522A>G (p.Gln174=)	CAA	CAG	Hereditary cancer-predisposing syndrome; Breast-ovarian cancer, familial 1 (BROVCA1); Hereditary breast and ovarian cancer syndrome (HBOC)	2.49	1.32
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.4209C>T (p.Asn1403=)	AAC	AAT	Hereditary cancer-predisposing syndrome; Breast-ovarian cancer, familial 1 (BROVCA1); Hereditary breast and ovarian cancer syndrome (HBOC)	1.01	0.02
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.3880T>C (p.Leu1294=)	TTA	CTA	Hereditary cancer-predisposing syndrome; Breast-ovarian cancer, familial 2 (BROVCA2); Hereditary breast and ovarian cancer syndrome (HBOC)	0.85	-0.24
MSH6	ENSG00000116062	NM_000179.2(MSH6):c.1170T>C (p.Asp390=)	GAT	GAC	Hereditary cancer-predisposing syndrome;Hereditary nonpolyposis colorectal neoplasms; Hereditary nonpolyposis colorectal cancer type 5 (HNPCC5);	1.01	0.01
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.4047G>A (p.Thr1349=)	ACG	ACA	Hereditary cancer-predisposing syndrome; Breast-ovarian cancer, familial 1 (BROVCA1); Hereditary breast and ovarian cancer syndrome (HBOC)	2.96	1.57
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.3012G>A (p.Glu1004=)	GAG	GAA	Hereditary cancer-predisposing syndrome;Hereditary breast and ovarian cancer syndrome (HBOC);Breast-ovarian cancer, familial 1 (BROVCA1);	0.86	-0.22
GJB2	ENSG00000165474	NM_004004.6(GJB2):c.120A>C (p.Ala40=)	GCA	GCC	Deafness, autosomal recessive 1A (DFNB1A);Hystrix-like ichthyosis with deafness;Deafness, autosomal dominant 3a (DFNA3A);	1.5	0.59
NF1	ENSG00000196712	NM_000267.3(NF1):c.5694G>A (p.Glu1898=)	GAG	GAA	Hereditary cancer-predisposing syndrome; Neurofibromatosis, type 1 (NF1);Neurofibromatosis, familial spinal (FSNF);Neurofibromatosis-Noonan syndrome (NFNS);Café-au-lait macules with pulmonary stenosis (WTSN);none provided	0.86	-0.22
SMAD4	ENSG00000141646	NM_005359.6(SMAD4):c.1492T>C (p.Leu498=)	TTA	CTA	Hereditary cancer-predisposing syndrome; Generalized juvenile polyposis/juvenile polyposis coli (JPS);Myhre syndrome (MYHRS);Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome (JPHT)	0.85	-0.24
NF1	ENSG00000196712	NM_000267.3(NF1):c.1032A>G (p.Leu344=)	CTA	CTG	Hereditary cancer-predisposing syndrome; Neurofibromatosis, type 1 (NF1);Neurofibromatosis-Noonan syndrome (NFNS);Café-au-lait macules with pulmonary stenosis (WTSN);Neurofibromatosis, familial spinal (FSNF)	4.81	2.27

GARS1	ENSG00000106105	NM_002047.4(GARS1):c.1716G>A (p.Pro572=)	CCG	CCA	Distal hereditary motor neuronopathy type 5 (HMN5);Charcot-Marie-Tooth disease type 2D (CMT2D);Distal spinal muscular atrophy; Charcot-Marie-Tooth disease	3.05	1.61
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.4293G>A (p.Pro1431=)	CCG	CCA	Cardiovascular phenotype; Connective tissue disease;Aortic aneurysm, familial thoracic 7 (AAT7);none provided	3.05	1.61
PSAP	ENSG00000197746	NM_002778.4(PSAP):c.1056C>T (p.Ser352=)	TCC	TCT	Metachromatic leukodystrophy (MLD);Combined saposin deficiency;Galactosylceramide beta-galactosidase deficiency;Atypical Gaucher Disease;Sphingolipid activator protein 1 deficiency;Krabbe disease, atypical, due to saposin A deficiency;Gaucher disease, atypical, due to saposin C deficiency	0.98	-0.03
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.5724A>G (p.Thr1908=)	ACA	ACG	Geleophysic dysplasia;Acromicric dysplasia (ACMICD);Weill-Marchesani syndrome;Ectopia lentis, isolated, autosomal dominant (ECTOL1);Familial thoracic aortic aneurysm and aortic dissection (TAAD);Stiff skin syndrome (SSKS);Marfan syndrome (MFS);Cardiovascular phenotype	0.34	-1.57
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.7923C>G (p.Leu2641=)	CTC	CTG	Malignant hyperthermia, susceptibility to, 1 (MHS1);Minicore myopathy with external ophthalmoplegia;Central core myopathy (CCD);Neuromuscular disease, congenital, with uniform type 1 fiber (CNMDU1); RYR1-Related Disorders	2.02	1.02
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.2979C>T (p.Cys993=)	TGC	TGT	Geleophysic dysplasia;Weill-Marchesani syndrome;Stiff skin syndrome (SSKS);Acromicric dysplasia (ACMICD);Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD);Ectopia lentis, isolated, autosomal dominant (ECTOL1);Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.97	-0.05
RET	ENSG00000165731	NM_020975.6(RET):c.2673G>A (p.Ser891=)	TCG	TCA	Hereditary cancer-predisposing syndrome; Multiple endocrine neoplasia, type 2 (MEN2); Multiple endocrine neoplasia, type 2 (MEN2)	3.5	1.81
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.10980T>C (p.Pro3660=)	CCT	CCC	History of neurodevelopmental disorder; Cohen syndrome (COH1)	0.98	-0.02
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.8478A>G (p.Ala2826=)	GCA	GCG	Autosomal dominant cerebellar ataxia; Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);Charcot-Marie-Tooth disease	0.35	-1.52
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.9285C>T (p.Asp3095=)	GAC	GAT	Hereditary cancer-predisposing syndrome;Hereditary breast and ovarian cancer syndrome (HBOC);Breast neoplasm; Breast-ovarian cancer, familial 2 (BROVCA2);	0.99	-0.01
RYR2	ENSG00000198626	NM_001035.3(RYR2):c.3153C>T (p.Arg1051=)	CGC	CGT	Cardiovascular phenotype;Catecholaminergic polymorphic ventricular tachycardia (CPVT1);Cardiomyopathy (CMYO);Arrhythmogenic right ventricular dysplasia, familial, 2 (ARVD2);Catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1)	0.52	-0.93
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.1017C>T (p.Ser339=)	AGC	AGT	Cardiovascular phenotype; Familial thoracic aortic aneurysm and aortic dissection (TAAD);Aortic aneurysm, familial thoracic 4 (AAT4)	0.72	-0.48
RYR2	ENSG00000198626	NM_001035.3(RYR2):c.8913T>C (p.Ile2971=)	ATT	ATC	Catecholaminergic polymorphic ventricular tachycardia (CPVT1);Arrhythmogenic right ventricular dysplasia, familial, 2 (ARVD2);Cardiomyopathy (CMYO); Catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1)	1.13	0.17
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.3111C>T (p.Ser1037=)	AGC	AGT	Neuromuscular disease, congenital, with uniform type 1 fiber (CNMDU1);Minicore myopathy with external ophthalmoplegia;Malignant hyperthermia, susceptibility to, 1 (MHS1);Central core myopathy (CCD); RYR1-Related Disorders	0.72	-0.48

RYR1	ENSG00000196218	NM_000540.2(RYR1):c.10119G>A (p.Val3373=)	GTG	GTA	Central core myopathy (CCD);Minicore myopathy with external ophthalmoplegia;Malignant hyperthermia, susceptibility to, 1 (MHS1);Neuromuscular disease, congenital, with uniform type 1 fiber (CNMDU1); RYR1-Related Disorders	0.3	-1.74
COL11A2	ENSG00000204248	NM_080680.3(COL11A2):c.3616C>T (p.Leu1206=)	CTG	TTG	Otospondylomegaepiphyseal dysplasia, autosomal dominant (OSMEDA);Otospondylomegaepiphyseal dysplasia, autosomal recessive (OSMEDB);Stickler Syndrome, Dominant;Fibrochondrogenesis 2 (FBCG2);	0.37	-1.42
CDKL5	ENSG00000008086	NM_001323289.2(CDKL5):c.291C>T (p.Leu97=)	CTC	CTT	Early infantile epileptic encephalopathy 2 (DEE2);Angelman syndrome-like;Early infantile epileptic encephalopathy 2 (DEE2)	0.8	-0.33
PAH	ENSG00000171759	NM_000277.3(PAH):c.1101G>A (p.Leu367=)	CTG	CTA	Phenylketonuria (PKU)	0.21	-2.27
LDLR	ENSG00000130164	NM_000527.4(LDLR):c.1167G>A (p.Thr389=)	ACG	ACA	Familial hypercholesterolemia 1 (FHCL1);Familial hypercholesterolemia (FH)	2.96	1.57
SLC34A1	ENSG00000131183	NM_003052.5(SLC34A1):c.654G>A (p.Ala218=)	GCG	GCA	Nephrolithiasis/osteoporosis, hypophosphatemic, 1 (NPHLOP1);Hypercalcemia, infantile, 2 (HCINF2)	2.88	1.52
SPARC	ENSG00000113140	NM_003118.4(SPARC):c.891C>T (p.Ile297=)	ATC	ATT	Osteogenesis imperfecta, type xvii (OI17)	0.89	-0.17
LMF1	ENSG00000103227	NM_022773.4(LMF1):c.1431C>T (p.Asn477=)	AAC	AAT	Lipase deficiency, combined	1.01	0.02
TTN	ENSG00000155657	NM_001267550.2(TTN):c.70131A>G (p.Thr23377=)	ACA	ACG	Limb-girdle muscular dystrophy, type 2J (LGMDR10);Tibial muscular dystrophy (TMD);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Dilated cardiomyopathy 1G (CMD1G);Myopathy, early-onset, with fatal cardiomyopathy (SALMY); Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.34	-1.57
TTN	ENSG00000155657	NM_001267550.2(TTN):c.62994C>T (p.Tyr20998=)	TAC	TAT	Limb-girdle muscular dystrophy, type 2J (LGMDR10);Tibial muscular dystrophy (TMD);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Dilated cardiomyopathy 1G (CMD1G);Cardiovascular phenotype; Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.9	-0.15
SCNN1G	ENSG00000166828	NM_001039.4(SCNN1G):c.1575G>A (p.Glu525=)	GAG	GAA	Autosomal recessive pseudohypoaldosteronism type 1;Liddle syndrome 2;	0.86	-0.22
SGCD	ENSG00000170624	NM_000337.5(SGCD):c.510G>A (p.Glu170=)	GAG	GAA	Limb-Girdle Muscular Dystrophy, Recessive;Qualitative or quantitative defects of delta-sarcoglycan; Cardiovascular phenotype; Cardiomyopathy (CMYO);Autosomal recessive limb-girdle muscular dystrophy type 2F (LGMD2F)	0.86	-0.22
BIN1	ENSG00000136717	NM_139343.3(BIN1):c.942C>T (p.His314=)	CAC	CAT	Myopathy, centronuclear, 2 (CNM2)	0.81	-0.3
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.3489C>T (p.Ala1163=)	GCC	GCT	Pitt-Hopkins-like syndrome 2 (PTHSL2)	0.74	-0.44
NEB	ENSG00000183091	NM_001271208.2(NEB):c.23118C>T (p.Ser7706=)	AGC	AGT	Nemaline myopathy 2 (NEM2)	0.72	-0.48
GAA	ENSG00000171298	NM_000152.5(GAA):c.2652G>A (p.Thr884=)	ACG	ACA	Glycogen storage disease, type II (GSD2)	2.96	1.57
IFT122	ENSG00000163913	NM_052989.3(IFT122):c.1026C>T (p.Asp342=)	GAC	GAT	Cranioectodermal dysplasia 1 (CED1)	0.99	-0.01
MCPH1	ENSG00000147316	NM_024596.5(MCPH1):c.433C>T (p.Leu145=)	CTA	TTA	Primary autosomal recessive microcephaly 1 (MCPH1);	1.18	0.24
GAA	ENSG00000171298	NM_000152.5(GAA):c.2736G>A (p.Ala912=)	GCG	GCA	Glycogen storage disease, type II (GSD2)	2.88	1.52
PLCB1	ENSG00000182621	NM_015192.4(PLCB1):c.1491C>T (p.Phe497=)	TTC	TTT	Early infantile epileptic encephalopathy 12 (DEE12)	0.98	-0.02
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.6774A>C (p.Val2258=)	GTA	GTC	Autosomal recessive polycystic kidney disease (ARPKD)	1.74	0.8
GAA	ENSG00000171298	NM_000152.5(GAA):c.915G>A (p.Gly305=)	GGG	GGA	Glycogen storage disease, type II (GSD2)	1.13	0.17
NBN	ENSG00000104320	NM_002485.4(NBN):c.798G>A (p.Pro266=)	CCG	CCA	Microcephaly, normal intelligence and immunodeficiency (NBS);Hereditary cancer-predisposing syndrome	3.05	1.61
WDR62	ENSG00000075702	NM_001083961.2(WDR62):c.3303G>A (p.Thr1101=)	ACG	ACA	Primary autosomal recessive microcephaly 2 (MCPH2);	2.96	1.57

WDR62	ENSG00000075702	NM_001083961.2(WDR62):c.3612C>T (p.Gly1204=)	GGC	GGT	Primary autosomal recessive microcephaly 2 (MCPH2);	0.55	-0.87
DHCR7	ENSG00000172893	NM_001360.2(DHCR7):c.906C>T (p.Phe302=)	TTC	TTT	Smith-Lemli-Opitz syndrome (SLOS)	0.98	-0.02
MPI	ENSG00000178802	NM_002435.3(MPI):c.303C>T (p.Leu101=)	CTC	CTT	MPI-CDG	0.8	-0.33
SLC19A3	ENSG00000135917	NM_025243.4(SLC19A3):c.399C>G (p.Pro133=)	CCC	CCG	Biotin-responsive basal ganglia disease (THMD2)	0.33	-1.62
SLC19A3	ENSG00000135917	NM_025243.4(SLC19A3):c.801A>G (p.Gln267=)	CAA	CAG	Biotin-responsive basal ganglia disease (THMD2)	2.49	1.32
NEB	ENSG00000183091	NM_001271208.2(NEB):c.25140C>T (p.Asp8380=)	GAC	GAT	Nemaline myopathy 2 (NEM2)	0.99	-0.01
ALDOB	ENSG00000136872	NM_000035.4(ALDOB):c.681C>T (p.Thr227=)	ACC	ACT	Hereditary fructosuria (HFI)	0.8	-0.31
ST3GAL5	ENSG00000115525	NM_003896.4(ST3GAL5):c.1212G>A (p.Glu404=)	GAG	GAA	GM3 synthase deficiency (SPDRS)	0.86	-0.22
FAH	ENSG00000103876	NM_000137.3(FAH):c.243G>A (p.Ala81=)	GCG	GCA	Tyrosinemia type I (TYRSN1)	2.88	1.52
SRD5A3	ENSG00000128039	NM_024592.5(SRD5A3):c.43C>T (p.Leu15=)	CTG	TTG	Congenital disorder of glycosylation type 1Q (CDG1Q)	0.37	-1.42
ATP7B	ENSG00000123191	NM_000053.4(ATP7B):c.2976C>A (p.Pro992=)	CCC	CCA	Wilson disease (WND)	1	-0.01
LOXHD1	ENSG00000167210	NM_144612.6(LOXHD1):c.4068G>A (p.Arg1356=)	AGG	AGA	Deafness, autosomal recessive 77 (DFNB77);	1.1	0.14
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.8826G>A (p.Ser2942=)	TCG	TCA	Cohen syndrome (COH1)	3.5	1.81
GCDH	ENSG00000105607	NM_000159.4(GCDH):c.471C>T (p.Ser157=)	AGC	AGT	Glutaric aciduria, type 1 (GA1)	0.72	-0.48
GAA	ENSG00000171298	NM_000152.5(GAA):c.1356C>T (p.Ala452=)	GCC	GCT	Glycogen storage disease, type II (GSD2)	0.74	-0.44
CP	ENSG00000047457	NM_000096.4(CP):c.2571C>T (p.Tyr857=)	TAC	TAT	Deficiency of ferroxidase	0.9	-0.15
FOLR1	ENSG00000110195	NM_016729.3(FOLR1):c.510A>G (p.Ala170=)	GCA	GCG	Cerebral folate transport deficiency (NCFTD);	0.35	-1.52
ALDH7A1	ENSG00000164904	NM_001182.5(ALDH7A1):c.1017T>C (p.His339=)	CAT	CAC	Pyridoxine-dependent epilepsy (EPD)	1.23	0.3
MMAB	ENSG00000139428	NM_052845.4(MMAB):c.444G>A (p.Gly148=)	GGG	GGA	Vitamin B12-responsive methylmalonic acidemia type cblB	1.13	0.17
TSEN54	ENSG00000182173	NM_207346.3(TSEN54):c.984T>C (p.Ala328=)	GCT	GCC	Pontoneocerebellar hypoplasia;	1.36	0.44
ATP6V0A2	ENSG00000185344	NM_012463.4(ATP6V0A2):c.2229T>C (p.Cys743=)	TGT	TGC	Cutis laxa, recessive; ALG9 congenital disorder of glycosylation (CDG1L)	1.03	0.05
SELENON	ENSG00000162430	NM_020451.3(SELENON):c.729G>A (p.Pro243=)	CCG	CCA	SEPN1-Related Disorders; Eichsfeld type congenital muscular dystrophy (RSMD1)	3.05	1.61
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.4542C>T (p.Ile1514=)	ATC	ATT	Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	0.89	-0.17
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.3678C>T (p.Ile1226=)	ATC	ATT	Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	0.89	-0.17
LAMA2	ENSG00000196569	NM_000426.3(LAMA2):c.7395T>C (p.Asp2465=)	GAT	GAC	Congenital muscular dystrophy due to partial LAMA2 deficiency; Laminin alpha 2-related dystrophy (LAMA2-RD)	1.01	0.01
BSND	ENSG00000162399	NM_057176.3(BSND):c.102C>T (p.Tyr34=)	TAC	TAT	Bartter disease type 4a (BARTS4A); Bartter syndrome	0.9	-0.15
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.5625C>T (p.Ser1875=)	AGC	AGT	Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	0.72	-0.48
PTCH1	ENSG00000185920	NM_000264.5(PTCH1):c.2184G>A (p.Thr728=)	ACG	ACA	Holoprosencephaly 7 (HPE7);Gorlin syndrome (BCNS);Hereditary cancer-predisposing syndrome	2.96	1.57
PALB2	ENSG00000083093	NM_024675.3(PALB2):c.2130G>A (p.Thr710=)	ACG	ACA	Hereditary cancer-predisposing syndrome; Familial cancer of breast;	2.96	1.57
MSH2	ENSG00000095002	NM_000251.2(MSH2):c.115C>A (p.Arg39=)	CGG	AGG	Hereditary cancer-predisposing syndrome;Hereditary nonpolyposis colorectal neoplasms; Lynch syndrome I (COCA1)	1.15	0.2
ABCC9	ENSG00000069431	NM_005691.3(ABCC9):c.372T>C (p.Asn124=)	AAT	AAC	Hypertrichotic osteochondrodysplasia Cantu type;Dilated cardiomyopathy 1O (CMD1O);Cardiovascular phenotype;Cardiomyopathy (CMYO)	0.99	-0.02
PROM1	ENSG00000007062	NM_006017.3(PROM1):c.2271C>T (p.Ile757=)	ATC	ATT	Stargardt disease 4 (STGD4);Retinitis pigmentosa (RP); Cone-rod dystrophy 12 (CORD12)	0.89	-0.17

NF1	ENSG00000196712	NM_000267.3(NF1):c.1308G>A (p.Ser436=)	TCG	TCA	Hereditary cancer-predisposing syndrome; Neurofibromatosis, type 1 (NF1);Neurofibromatosis-Noonan syndrome (NFNS);Neurofibromatosis, familial spinal (FSNF);Café-au-lait macules with pulmonary stenosis (WTSN)	3.5	1.81
CAPN3	ENSG00000092529	NM_000070.3(CAPN3):c.525C>T (p.Asp175=)	GAC	GAT	Limb-Girdle Muscular Dystrophy, Recessive;Limb-girdle muscular dystrophy, type 2A (LGMDR1);	0.99	-0.01
MMUT	ENSG00000146085	NM_000255.4(MMUT):c.393G>A (p.Gln131=)	CAG	CAA	Methylmalonic aciduria due to methylmalonyl-CoA mutase deficiency;Methylmalonic aciduria due to complete methylmalonyl-CoA mutase deficiency	0.4	-1.32
NF1	ENSG00000196712	NM_000267.3(NF1):c.6492G>A (p.Arg2164=)	AGG	AGA	Hereditary cancer-predisposing syndrome;Neurofibromatosis, familial spinal (FSNF);Neurofibromatosis, type 1 (NF1);Café-au-lait macules with pulmonary stenosis (WTSN);Neurofibromatosis-Noonan syndrome (NFNS)	1.1	0.14
NSD1	ENSG00000165671	NM_022455.4(NSD1):c.5520A>G (p.Glu1840=)	GAA	GAG	Sotos syndrome 1 (SOTOS1);History of neurodevelopmental disorder;	1.16	0.22
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.3516A>G (p.Thr1172=)	ACA	ACG	History of neurodevelopmental disorder;Cohen syndrome (COH1)	0.34	-1.57
DYNC2H1	ENSG00000187240	NM_001377.3(DYNC2H1):c.8481A>C (p.Thr2827=)	ACA	ACC	Jeune thoracic dystrophy (ATD1);Short-rib thoracic dysplasia 3 with or without polydactyly (SRTD3)	1.07	0.1
FH	ENSG00000091483	NM_000143.3(FH):c.63C>T (p.Ala21=)	GCC	GCT	Hereditary cancer-predisposing syndrome;Hereditary leiomyomatosis and renal cell cancer (HLRCC);Multiple Cutaneous and Uterine Leiomyomas;Fumarase deficiency (FMRD);	0.74	-0.44
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.837T>C (p.His279=)	CAT	CAC	Hereditary cancer-predisposing syndrome;Breast neoplasm;Hereditary breast and ovarian cancer syndrome (HBOC);Breast-ovarian cancer, familial 1 (BROVCA1);	1.23	0.3
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.2319C>T (p.Asp773=)	GAC	GAT	Central core myopathy (CCD);Minicore myopathy with external ophthalmoplegia;Neuromuscular disease, congenital, with uniform type 1 fiber (CNMDU1);Malignant hyperthermia, susceptibility to, 1 (MHS1); RYR1-Related Disorders	0.99	-0.01
NF1	ENSG00000196712	NM_000267.3(NF1):c.6963G>A (p.Leu2321=)	CTG	CTA	Hereditary cancer-predisposing syndrome;Neurofibromatosis, familial spinal (FSNF);Neurofibromatosis-Noonan syndrome (NFNS);Café-au-lait macules with pulmonary stenosis (WTSN);Neurofibromatosis, type 1 (NF1);	0.21	-2.27
TTN	ENSG00000155657	NM_001267550.2(TTN):c.56403A>G (p.Gln18801=)	CAA	CAG	Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Tibial muscular dystrophy (TMD);Dilated cardiomyopathy 1G (CMD1G);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Limb-girdle muscular dystrophy, type 2J (LGMDR10); Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	2.49	1.32
NPHP3	ENSG00000113971	NM_153240.5(NPHP3):c.2154C>T (p.Phe718=)	TTC	TTT	Nephronophthisis	0.98	-0.02
LARGE1	ENSG00000133424	NM_004737.6(LARGE1):c.1962G>A (p.Glu654=)	GAG	GAA	Congenital muscular dystrophy-dystroglycanopathy with brain and eye anomalies, type A6 (MDDGA6); Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B6 (MDDGB6)	0.86	-0.22
SEMA4A	ENSG00000196189	NM_022367.4(SEMA4A):c.84G>A (p.Thr28=)	ACG	ACA	Retinitis Pigmentosa, Recessive;Cone-rod dystrophy 10 (CORD10); Retinitis pigmentosa (RP)	2.96	1.57
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.3111C>T (p.Pro1037=)	CCC	CCT	Limb-Girdle Muscular Dystrophy, Recessive;Miyoshi myopathy;Qualitative or quantitative defects of dysferlin; Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	1.02	0.02

TTN	ENSG00000155657	NM_001267550.2(TTN):c.71373T>G (p.Leu23791=)	CTT	CTG	Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Dilated cardiomyopathy 1G (CMD1G);Tibial muscular dystrophy (TMD); Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	2.54	1.35
TTN	ENSG00000155657	NM_001267550.2(TTN):c.96234C>T (p.Tyr32078=)	TAC	TAT	Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Dilated cardiomyopathy 1G (CMD1G);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Tibial muscular dystrophy (TMD);Cardiovascular phenotype; Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.9	-0.15
TTN	ENSG00000155657	NM_001267550.2(TTN):c.96252A>G (p.Thr32084=)	ACA	ACG	Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Tibial muscular dystrophy (TMD);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Cardiovascular phenotype; Dilated cardiomyopathy 1G (CMD1G);Limb-girdle muscular dystrophy, type 2J (LGMDR10)	0.34	-1.57
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.3852G>A (p.Pro1284=)	CCG	CCA	Limb-Girdle Muscular Dystrophy, Recessive;Miyoshi myopathy; Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	3.05	1.61
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.4878C>T (p.Ala1626=)	GCC	GCT	Malignant hyperthermia, susceptibility to, 1 (MHS1);Neuromuscular disease, congenital, with uniform type 1 fiber (CNMDU1);Central core myopathy (CCD);Minicore myopathy with external ophthalmoplegia; RYR1-Related Disorders	0.74	-0.44
VWA8	ENSG00000102763	NM_015058.2(VWA8):c.2451G>A (p.Thr817=)	ACG	ACA	Nonsyndromic cleft lip palate	2.96	1.57
F9	ENSG00000101981	NM_000133.4(F9):c.459G>A (p.Val153=)	GTG	GTA		0.3	-1.74
LMNA	ENSG00000160789	NM_170707.4(LMNA):c.1146C>A (p.Gly382=)	GGC	GGA		0.87	-0.2
TRPV4	ENSG00000111199	NM_021625.5(TRPV4):c.2400C>G (p.Gly800=)	GGC	GGG		0.77	-0.37
ARSA	ENSG00000100299	NM_000487.6(ARSA):c.1200C>T (p.Phe400=)	TTC	TTT	Metachromatic leukodystrophy (MLD)	0.98	-0.02
INPP4A	ENSG00000040933	NM_001134225.2(INPP4A):c.36C>T (p.Ala12=)	GCC	GCT	Dyskeratosis congenita, autosomal dominant 1 (DKCA1)	0.74	-0.44
GBA	ENSG00000177628	NM_000157.4(GBA):c.1197G>T (p.Gly399=)	GGG	GGT	Gaucher's disease, type 1 (GD1)	0.71	-0.5
NLRP12	ENSG00000142405	NM_001277126.1(NLRP12):c.858C>G (p.Pro286=)	CCC	CCG	Childhood-Onset Schizophrenia	0.33	-1.62
AHI1	ENSG00000135541	NM_001134831.2(AHI1):c.2106G>A (p.Thr702=)	ACG	ACA	Joubert syndrome (JBTS)	2.96	1.57
PAX6	ENSG00000007372	NM_000280.4(PAX6):c.174C>T (p.Gly58=)	GGC	GGT	Aniridia 1 (AN1)	0.55	-0.87
LIPA	ENSG00000107798	NM_000235.4(LIPA):c.600G>A (p.Leu200=)	CTG	CTA	Lysosomal acid lipase deficiency	0.21	-2.27
NF1	ENSG00000196712	NM_000267.3(NF1):c.7027C>A (p.Arg2343=)	CGG	AGG	Neurofibromatosis, type 1 (NF1)	1.15	0.2
KRAS	ENSG00000133703	NM_004985.5(KRAS):c.39C>A (p.Gly13=)	GGC	GGA	Non-small cell lung cancer (NSCLC)	0.87	-0.2
WDR35	ENSG00000118965	NM_020779.4(WDR35):c.3345G>A (p.Leu1115=)	TTG	TTA	Cranioectodermal dysplasia 2 (CED2);Short-rib thoracic dysplasia 7 with or without polydactyly (SRTD7)	0.65	-0.61
PTPN11	ENSG00000179295	NM_002834.5(PTPN11):c.489C>T (p.Gly163=)	GGC	GGT	Rasopathy	0.55	-0.87
KRAS	ENSG00000133703	NM_004985.5(KRAS):c.39C>T (p.Gly13=)	GGC	GGT	Non-small cell lung cancer (NSCLC)	0.55	-0.87
NIPBL	ENSG00000164190	NM_133433.4(NIPBL):c.7623G>A (p.Gln2541=)	CAG	CAA	Cornelia de Lange syndrome 1 (CDLS1)	0.4	-1.32
KNL1	ENSG00000137812	NM_144508.5(KNL1):c.1521A>G (p.Gln507=)	CAA	CAG	Primary autosomal recessive microcephaly 4 (MCPH4)	2.49	1.32
CNGA3	ENSG00000144191	NM_001298.3(CNGA3):c.1611G>A (p.Gln537=)	CAG	CAA	Retinal dystrophy	0.4	-1.32
MAF	ENSG00000178573	NM_005360.5(MAF):c.915C>T (p.Cys305=)	TGC	TGT	Congenital cataract	0.97	-0.05

SCN1A	ENSG00000144285	NM_001165963.4(SCN1A):c.4701A>G (p.Glu1567=)	GAA	GAG		1.16	0.22
NIPBL	ENSG00000164190	NM_133433.4(NIPBL):c.345A>G (p.Arg115=)	AGA	AGG	Cornelia de Lange syndrome 1 (CDLS1)	0.91	-0.14
PAX6	ENSG00000007372	NM_000280.4(PAX6):c.333C>A (p.Val111=)	GTC	GTA	Aniridia 1 (AN1)	0.57	-0.8
DDX3X	ENSG00000215301	NM_001356.4(DDX3X):c.744C>T (p.Gly248=)	GGC	GGT		0.55	-0.87
CSRP3	ENSG00000129170	NM_003476.5(CSRP3):c.96G>A (p.Lys32=)	AAG	AAA	Primary dilated cardiomyopathy (DCM)	0.87	-0.2
VWF	ENSG00000110799	NM_000552.4(VWF):c.3390C>T (p.Cys1130=)	TGC	TGT	von Willebrand disease type 1 (VWD1)	0.97	-0.05
NPHS1	ENSG00000161270	NM_004646.3(NPHS1):c.1905C>T (p.Ser635=)	AGC	AGT	Finnish congenital nephrotic syndrome (NPHS1)	0.72	-0.48
POLR3A	ENSG00000148606	NM_007055.4(POLR3A):c.1800C>T (p.Ile600=)	ATC	ATT	Neonatal pseudo-hydrocephalic progeroid syndrome (WDRTS)	0.89	-0.17
CSRP3	ENSG00000129170	NM_003476.5(CSRP3):c.354G>A (p.Glu118=)	GAG	GAA	Primary dilated cardiomyopathy (DCM)	0.86	-0.22
FGFR3	ENSG00000068078	NM_000142.5(FGFR3):c.2287C>T (p.Leu763=)	CTG	TTG	Camptodactyly-tall stature-scoliosis-hearing loss syndrome	0.37	-1.42
CASQ2	ENSG00000118729	NM_001232.3(CASQ2):c.381C>T (p.Gly127=)	GGC	GGT	Ventricular tachycardia, catecholaminergic polymorphic, 2 (CPVT2)	0.55	-0.87
VWF	ENSG00000110799	NM_000552.4(VWF):c.7464C>T (p.Gly2488=)	GGC	GGT		0.55	-0.87
ATM	ENSG00000149311	NM_000051.3(ATM):c.513C>T (p.Tyr171=)	TAC	TAT	Ataxia-telangiectasia syndrome (AT)	0.9	-0.15
JAK3	ENSG00000105639	NM_000215.4(JAK3):c.2652C>T (p.Val884=)	GTC	GTT	Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-negative	0.88	-0.19
P3H1	ENSG00000117385	NM_022356.3(P3H1):c.2055+18G>A	GCG	GCA	Osteogenesis imperfecta type 8 (OI8)	2.88	1.52
HGD	ENSG00000113924	NM_000187.4(HGD):c.753C>T (p.Gly251=)	GGC	GGT	Alkaptonuria (AKU)	0.55	-0.87
KDM4B	ENSG00000127663	NM_015015.3(KDM4B):c.288C>T (p.Gly96=)	GGC	GGT	Syndromic global developmental delay	0.55	-0.87
F8	ENSG00000185010	NM_000132.3(F8):c.222G>A (p.Thr74=)	ACG	ACA		2.96	1.57
VWF	ENSG00000110799	NM_000552.4(VWF):c.7056C>T (p.Gly2352=)	GGC	GGT	von Willebrand disorder (VWD)	0.55	-0.87
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.7746G>A (p.Gln2582=)	CAG	CAA	Marfan syndrome (MFS)	0.4	-1.32
MSH6	ENSG00000116062	NM_000179.2(MSH6):c.3417C>T (p.Gly1139=)	GGC	GGT	Hereditary cancer-predisposing syndrome	0.55	-0.87
NPC1	ENSG00000141458	NM_000271.5(NPC1):c.2727C>T (p.Cys909=)	TGC	TGT	Niemann-Pick disease type C1 (NPC1)	0.97	-0.05
USP11	ENSG00000102226	NM_004651.3(USP11):c.1599G>A (p.Thr533=)	GGT	GGA	Dynein arm defect of respiratory motile cilia;Absent inner and outer dynein arms;Abnormal ciliary motility;Bronchiectasis	1.59	0.67
HBB	ENSG00000244734	NM_000518.5(HBB):c.51C>T (p.Gly17=)	GGC	GGT		0.55	-0.87
ZMIZ1	ENSG00000108175	NM_020338.4(ZMIZ1):c.2610C>T (p.Ser870=)	TCC	TCT	Syndromic neurodevelopmental disorder	0.98	-0.03
COLQ	ENSG00000206561	NM_005677.4(COLQ):c.1281C>T (p.Cys427=)	TGC	TGT	Endplate acetylcholinesterase deficiency (CMS5)	0.97	-0.05
ABCA3	ENSG00000167972	NM_001089.3(ABCA3):c.2883C>T (p.Gly961=)	GGC	GGT	Idiopathic Pulmonary Fibrosis (IPF)	0.55	-0.87
SEPSECS	ENSG00000109618	NM_016955.4(SEPSECS):c.846G>A (p.Leu282=)	TTG	TTA	Pontocerebellar hypoplasia type 2D (PCH2D)	0.65	-0.61
LRP1	ENSG00000123384	NM_002332.3(LRP1):c.300C>T (p.Asp100=)	GAC	GAT	Keratosis pilaris (KPA)	0.99	-0.01
GLDC	ENSG00000178445	NM_000170.2(GLDC):c.513G>C (p.Gly171=)	GGG	GGC	Non-ketotic hyperglycinemia (GCE)	1.29	0.37
LDLR	ENSG00000130164	NM_000527.4(LDLR):c.528C>T (p.Gly176=)	GGC	GGT	Familial hypercholesterolemia 1 (FHCL1)	0.55	-0.87
ATM	ENSG00000149311	NM_000051.3(ATM):c.3873T>G (p.Leu1291=)	CTT	CTG		2.54	1.35
OCLN	ENSG00000197822	NM_001205254.2(OCLN):c.546G>C (p.Leu182=)	CTG	CTC	Pseudo-TORCH syndrome 1 (PTORCH1)	0.49	-1.02
CHRNA1	ENSG00000138435	NM_001039523.3(CHRNA1):c.762C>T (p.Arg254=)	CGC	CGT	Non-immune hydrops fetalis (NIHF)	0.52	-0.93
MKS1	ENSG00000011143	NM_001165927.1(MKS1):c.1359G>T (p.Arg453=)	CGG	CGT	Joubert syndrome (JBTS)	0.43	-1.22
TTN	ENSG00000155657	NM_001267550.2(TTN):c.66904C>T (p.Leu22302=)	CTA	TTA	Wolff-Parkinson-White pattern	1.18	0.24
CHD2	ENSG00000173575	NM_001271.4(CHD2):c.390C>T (p.Ser130=)	AGC	AGT	Epileptic encephalopathy, childhood-onset (EEOC)	0.72	-0.48
FGF8	ENSG00000107831	NM_001206389.1(FGF8):c.-76C>G	CTC	CTG	Hypogonadotropic hypogonadism 6 with or without anosmia (HH6)	2.02	1.02
DYNC2H1	ENSG00000187240	NM_001377.3(DYNC2H1):c.11049G>A (p.Pro3683=)	CCG	CCA	Jeune thoracic dystrophy (ATD1)	3.05	1.61
POLG	ENSG00000140521	NM_002693.2(POLG):c.3522C>A (p.Pro1174=)	CCC	CCA	Alpers-like hepatocerebral syndrome	1	-0.01

CLCN1	ENSG00000188037	NM_000083.3(CLCN1):c.264G>A (p.Val88=)	GTG	GTA	Congenital myotonia, autosomal recessive form;Congenital myotonia, autosomal dominant form (THD)	0.3	-1.74
SRD5A3	ENSG00000128039	NM_024592.5(SRD5A3):c.921G>C (p.Pro307=)	CCG	CCC	Congenital disorder of glycosylation (CDG)	3.07	1.62
LDLR	ENSG00000130164	NM_000527.4(LDLR):c.2079G>A (p.Lys693=)	AAG	AAA	Familial hypercholesterolemia 1 (FHCL1)	0.87	-0.2
FLVCR1	ENSG00000162769	NM_014053.4(FLVCR1):c.87G>C (p.Ala29=)	GCG	GCC	Jeune thoracic dystrophy (ATD1)	4.32	2.11
BSCL2	ENSG00000168000	NM_032667.6(BSCL2):c.1125C>A (p.Val375=)	GTC	GTA	Familial partial lipodystrophy 3 (FPLD3)	0.57	-0.8
CTNNB1	ENSG00000168036	NM_001904.4(CTNNB1):c.723G>A (p.Val241=)	GTG	GTA		0.3	-1.74
SYN1	ENSG00000008056	NM_006950.3(SYN1):c.2028C>T (p.Ala676=)	GCC	GCT	Epilepsy, X-linked, with variable learning disabilities and behavior disorders (EPILX)	0.74	-0.44
HAND2	ENSG00000164107	NM_021973.3(HAND2):c.390C>A (p.Pro130=)	CCC	CCA		1	-0.01
TOE1	ENSG00000132773	NM_025077.4(TOE1):c.957C>T (p.His319=)	CAC	CAT	Pontocerebellar hypoplasia, type 7 (PCH7)	0.81	-0.3
TMEM216	ENSG00000187049	NM_001173990.3(TMEM216):c.216T>C (p.Ile72=)	ATT	ATC	Joubert syndrome 2 (JBTS2);Joubert syndrome (JBTS)	1.13	0.17
FTL	ENSG00000087086	NM_000146.4(FTL):c.163T>C (p.Leu55=)	TTG	CTG	sporadic abdominal aortic aneurysm; Neuroferritinopathy (NBIA3);Hereditary hyperferritinemia with congenital cataracts (HRFTC);Glycogen storage disease 0, muscle (GSD0B);	2.67	1.42
NF1	ENSG00000196712	NM_000267.3(NF1):c.6801A>G (p.Gln2267=)	CAA	CAG	Neurofibromatosis, type 1 (NF1)	2.49	1.32
MYO15A	ENSG00000091536	NM_016239.4(MYO15A):c.9861C>T (p.Gly3287=)	GGC	GGT	Rare genetic deafness;Deafness, autosomal recessive 3 (DFNB3);	0.55	-0.87
LDLR	ENSG00000130164	NM_000527.4(LDLR):c.1221C>T (p.His407=)	CAC	CAT	Familial hypercholesterolemia 1 (FHCL1);Familial hypercholesterolemia (FH)	0.81	-0.3
ALMS1	ENSG00000116127	NM_015120.4(ALMS1):c.9789G>A (p.Gln3263=)	GGC	GGA	Alstrom syndrome (ALMS)	0.87	-0.2
NFIX	ENSG00000008441	NM_002501.4(NFIX):c.348G>A (p.Arg116=)	CGG	CGA	Marshall-Smith syndrome (MRSHSS);Marfanoid habitus and intellectual disability	0.6	-0.73
MPZ	ENSG00000158887	NM_000530.8(MPZ):c.309G>T (p.Gly103=)	GGG	GGT	Charcot-Marie-Tooth disease, type I (CMT1)	0.71	-0.5
HEXA	ENSG00000213614	NM_000520.6(HEXA):c.1305C>T (p.Tyr435=)	TAC	TAT	Tay-Sachs disease (TSD);Inborn genetic diseases	0.9	-0.15
MLH1	ENSG00000076242	NM_000249.3(MLH1):c.27G>A (p.Arg9=)	CGG	CGA	Hereditary cancer-predisposing syndrome;Hereditary nonpolyposis colorectal neoplasms	0.6	-0.73
KIAA0753	ENSG00000198920	NM_014804.3(KIAA0753):c.810C>T (p.Tyr270=)	TAC	TAT	Jeune thoracic dystrophy (ATD1);Jeune thoracic dystrophy (ATD1);Joubert syndrome (JBTS);	0.9	-0.15
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.2673A>G (p.Gln891=)	CAA	CAG	Cardiovascular phenotype; Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	2.49	1.32
PMS2	ENSG00000122512	NM_000535.7(PMS2):c.825A>G (p.Gln275=)	CAA	CAG	Hereditary cancer-predisposing syndrome; Hereditary nonpolyposis colorectal neoplasms;Turcot syndrome (MMRCS1);Hereditary nonpolyposis colorectal cancer type 4 (HNPCC4);Hereditary nonpolyposis colorectal cancer type 4 (HNPCC4)	2.49	1.32
PDHA1	ENSG00000131828	NM_000284.4(PDHA1):c.738C>T (p.Gly246=)	GGC	GGT	Pyruvate dehydrogenase E1-alpha deficiency (PDHAD)	0.55	-0.87
JAK3	ENSG00000105639	NM_000215.3(JAK3):c.1767C>T (p.Gly589=)	GGC	GGT	Severe combined immunodeficiency disease (SCID);	0.55	-0.87
DOK7	ENSG00000175920	NM_173660.5(DOK7):c.513C>T (p.Gly171=)	GGC	GGT	Myasthenia, limb-girdle, familial (CMS10);Pena-Shokeir syndrome type I (FADS1);Myasthenia, limb-girdle, familial (CMS10)	0.55	-0.87
SPINK5	ENSG00000133710	NM_001127698.2(SPINK5):c.891C>T (p.Cys297=)	TGC	TGT	Erythroderma;Increased IgE level; Netherton syndrome (NETH)	0.97	-0.05
SCN5A	ENSG00000183873	NM_198056.2(SCN5A):c.4719C>T (p.Gly1573=)	GGC	GGT	Cardiovascular phenotype; Cardiac arrhythmia;Brugada syndrome	0.55	-0.87
LMNA	ENSG00000160789	NM_170707.4(LMNA):c.1146C>T (p.Gly382=)	GGC	GGT	Primary dilated cardiomyopathy (DCM);Neuromuscular disease; Charcot-Marie-Tooth disease, type 2;Cardiovascular phenotype	0.55	-0.87
GAA	ENSG00000171298	NM_000152.5(GAA):c.1626C>G (p.Pro542=)	CCC	CCG	Glycogen storage disease, type II (GSD2)	0.33	-1.62
PAX6	ENSG00000007372	NM_000280.4(PAX6):c.255C>T (p.Ser85=)	AGC	AGT	Aniridia 1 (AN1)	0.72	-0.48
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.3291C>T (p.Gly1097=)	GGC	GGT	Central core myopathy (CCD);RYR1-Related Disorders	0.55	-0.87

CFTR	ENSG00000001626	NM_000492.3(CFTR):c.2679G>T (p.Gly893=)	GGG	GGT	Cystic fibrosis (CF)	0.71	-0.5
ATM	ENSG00000149311	NM_000051.4(ATM):c.2149C>A (p.Arg717=)	CGG	AGG	Hereditary cancer-predisposing syndrome;Ataxia-telangiectasia syndrome (AT)	1.15	0.2
AIP	ENSG00000110711	NM_003977.4(AIP):c.249G>T (p.Gly83=)	GGG	GGT	Somatotroph adenoma (PITA1);	0.71	-0.5
PALB2	ENSG00000083093	NM_024675.3(PALB2):c.18G>T (p.Gly6=)	GGG	GGT	Hereditary cancer-predisposing syndrome; Familial cancer of breast;	0.71	-0.5
HSPG2	ENSG00000142798	NM_005529.7(HSPG2):c.4233C>T (p.Tyr1411=)	TAC	TAT	Childhood-Onset Schizophrenia;Lethal Kniest-like syndrome (DDSH);Schwartz-Jampel syndrome	0.9	-0.15
CHRNA4	ENSG00000101204	NM_000744.7(CHRNA4):c.1635G>A (p.Thr545=)	ACG	ACA	Tobacco use disorder; Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	2.96	1.57
AIPL1	ENSG00000129221	NM_014336.5(AIPL1):c.267C>T (p.Cys89=)	TGC	TGT	Retinitis Pigmentosa, Recessive;Retinitis Pigmentosa, Dominant;Leber congenital amaurosis 4 (LCA4);none provided	0.97	-0.05
TSC1	ENSG00000165699	NM_000368.4(TSC1):c.3387C>T (p.Ala1129=)	GCC	GCT	Tuberous sclerosis syndrome (TSC); Tuberous sclerosis 1 (TSC1);Focal cortical dysplasia type II (FCORD2);Hereditary cancer-predisposing syndrome	0.74	-0.44
TNNT1	ENSG00000105048	NM_003283.6(TNNT1):c.279A>G (p.Glu93=)	GAA	GAG	Nemaline myopathy 5 (NEM5)	1.16	0.22
CHRNA4	ENSG00000101204	NM_000744.7(CHRNA4):c.729G>A (p.Pro243=)	CCG	CCA	Tobacco use disorder; Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	3.05	1.61
TSC1	ENSG00000165699	NM_000368.4(TSC1):c.1047A>G (p.Pro349=)	CCA	CCG	Tuberous sclerosis syndrome (TSC); Tuberous sclerosis 1 (TSC1);Hereditary cancer-predisposing syndrome;Focal cortical dysplasia type II (FCORD2)	0.33	-1.61
AIPL1	ENSG00000129221	NM_014336.5(AIPL1):c.234C>T (p.Ser78=)	TCC	TCT	Leber congenital amaurosis 4 (LCA4);Retinitis pigmentosa (RP)	0.98	-0.03
AIPL1	ENSG00000129221	NM_014336.5(AIPL1):c.765T>C (p.Asp255=)	GAT	GAC	Retinitis Pigmentosa, Recessive;Retinitis Pigmentosa, Dominant;Leber congenital amaurosis 4 (LCA4)	1.01	0.01
TSC2	ENSG00000103197	NM_000548.5(TSC2):c.3723C>T (p.Phe1241=)	TTC	TTT	Tuberous sclerosis syndrome (TSC);Hereditary cancer-predisposing syndrome; Tuberous sclerosis 2 (TSC2)	0.98	-0.02
PAH	ENSG00000171759	NM_000277.3(PAH):c.1194A>G (p.Lys398=)	AAA	AAG	Phenylketonuria (PKU)	1.15	0.2
TSC1	ENSG00000165699	NM_000368.5(TSC1):c.2646C>T (p.Ala882=)	GCC	GCT	Tuberous sclerosis syndrome (TSC);Urinary bladder cancer; Hereditary cancer-predisposing syndrome;Tuberous sclerosis 1 (TSC1);Focal cortical dysplasia type II (FCORD2)	0.74	-0.44
LMNA	ENSG00000160789	NM_170707.4(LMNA):c.1908C>T (p.Ser636=)	AGC	AGT	Charcot-Marie-Tooth disease	0.72	-0.48
ASB10	ENSG00000146926	NM_001142459.2(ASB10):c.810C>T (p.Thr270=)	ACC	ACT	Glaucoma 1, open angle, F (GLC1F)	0.8	-0.31
GUSB	ENSG00000169919	NM_000181.4(GUSB):c.1617C>T (p.Ser539=)	AGC	AGT	Mucopolysaccharidosis type 7 (MPS7)	0.72	-0.48
IRGM	ENSG00000237693	NM_001145805.1(IRGM):c.313C>T (p.Leu105=)	CTG	TTG	Inflammatory bowel disease 19 (IBD19)	0.37	-1.42
F10	ENSG00000126218	NM_000504.4(F10):c.921G>A (p.Val307=)	GTG	GTA	Factor X deficiency	0.3	-1.74
GLDC	ENSG00000178445	NM_000170.2(GLDC):c.2607C>A (p.Pro869=)	CCC	CCA	Non-ketotic hyperglycinemia (GCE)	1	-0.01
MYT1L	ENSG00000186487	NM_001303052.2(MYT1L):c.1579C>T (p.Leu527=)	CTG	TTG	Intellectual disability	0.37	-1.42
KIAA0586	ENSG00000100578	NM_001329943.3(KIAA0586):c.831C>T (p.Leu277=)	CTC	CTT	Joubert syndrome 23 (JBTS23);Short-rib thoracic dysplasia 14 with polydactyly (SRTD14)	0.8	-0.33
GHR	ENSG00000112964	NM_000163.5(GHR):c.594A>G (p.Glu198=)	GAA	GAG	Laron-type isolated somatotropin defect	1.16	0.22
MITF	ENSG00000187098	NM_001354604.2(MITF):c.808C>T (p.Leu270=)	CTG	TTG	Waardenburg syndrome type 2A (WS2A)	0.37	-1.42
KCNQ2	ENSG00000075043	NM_172107.4(KCNQ2):c.973A>C (p.Arg325=)	AGG	CGG	Early infantile epileptic encephalopathy 7 (DEE7)	0.87	-0.2
DMD	ENSG00000198947	NM_000109.4(DMD):c.4782A>T (p.Gly1594=)	GGA	GGT		0.63	-0.67
SCN5A	ENSG00000183873	NM_198056.2(SCN5A):c.6048G>A (p.Val2016=)	GTG	GTA	Familial isolated arrhythmogenic right ventricular dysplasia	0.3	-1.74
KCNQ2	ENSG00000075043	NM_172107.4(KCNQ2):c.1203T>C (p.Ser401=)	TCT	TCC	Early infantile epileptic encephalopathy 7 (DEE7)	1.02	0.03
LDLR	ENSG00000130164	NM_000527.4(LDLR):c.2253G>A (p.Arg751=)	CGG	CGA	Familial hypercholesterolemia 1 (FHCL1)	0.6	-0.73

AKR1C2	ENSG00000151632	NM_001354.5(AKR1C2):c.666T>C (p.His222=)	CAT	CAC	CIC-DUX Sarcoma	1.23	0.3
GRHL3	ENSG00000158055	NM_198173.3(GRHL3):c.738C>T (p.Gly246=)	GGC	GGT	nonsyndromic cleft palate	0.55	-0.87
MECP2	ENSG00000169057	NM_001110792.2(MECP2):c.538C>A (p.Arg180=)	CGA	AGA	Rett syndrome (RTT)	2.09	1.06
KAT6B	ENSG00000156650	NM_012330.4(KAT6B):c.2598G>A (p.Arg866=)	AGG	AGA	Blepharophimosis - intellectual disability syndrome, SBBYS type (SBBYSS)	1.1	0.14
CDKL5	ENSG00000008086	NM_001323289.2(CDKL5):c.1099C>T (p.Leu367=)	CTA	TTA	Early infantile epileptic encephalopathy 4 (DEE4)	1.18	0.24
FGFR3	ENSG00000068078	NM_000142.5(FGFR3):c.597C>T (p.His199=)	CAC	CAT	Hypochondroplasia (HCH)	0.81	-0.3
FANCA	ENSG00000187741	NM_000135.4(FANCA):c.820C>T (p.Leu274=)	CTG	TTG	Fanconi anemia, complementation group A (FANCA)	0.37	-1.42
RUNX2	ENSG00000124813	NM_001024630.4(RUNX2):c.738C>T (p.Leu246=)	CTC	CTT	Cleidocranial dysostosis (CCD)	0.8	-0.33
CUL3	ENSG00000036257	NM_003590.5(CUL3):c.1236G>A (p.Leu412=)	TTG	TTA	Pseudohypoaldosteronism type 2A (PHA2A)	0.65	-0.61
GFAP	ENSG00000131095	NM_002055.5(GFAP):c.1074C>G (p.Ala358=)	GCC	GCG	Alexander Disease (ALXDRD)	0.23	-2.11
DNAJC6	ENSG00000116675	NM_001256864.2(DNAJC6):c.2223A>T (p.Thr741=)	ACA	ACT	Parkinson disease 19b, early-onset (PARK19B)	0.86	-0.21
FGFR3	ENSG00000068078	NM_000142.5(FGFR3):c.801G>T (p.Leu267=)	CTG	CTT	Hypochondroplasia (HCH)	0.39	-1.35
SFTPB	ENSG00000168878	NM_000542.5(SFTPB):c.465G>T (p.Gly155=)	CCT	CCT	Surfactant metabolism dysfunction, pulmonary, 1 (SMDP1)	1	0
ALDH5A1	ENSG00000112294	NM_001080.3(ALDH5A1):c.321G>A (p.Glu107=)	GAG	GAA	Succinate-semialdehyde dehydrogenase deficiency (SSADHD)	0.86	-0.22
COL4A5	ENSG00000188153	NM_033380.3(COL4A5):c.876A>T (p.Gly292=)	GGA	GGT	Alport syndrome 1, X-linked recessive (ATS1)	0.63	-0.67
IGF1R	ENSG00000140443	NM_000875.5(IGF1R):c.384T>C (p.Ile128=)	ATT	ATC	Growth delay due to insulin-like growth factor I resistance	1.13	0.17
COL4A5	ENSG00000188153	NM_033380.3(COL4A5):c.3588A>G (p.Gly1196=)	GGA	GGG	Hearing impairment;Bilateral sensorineural hearing impairment;Nephritis;Proteinuria;Global glomerulosclerosis	0.89	-0.17
H6PD	ENSG00000049239	NM_004285.4(H6PD):c.960G>A (p.Val320=)	GTG	GTA	Cortisone reductase deficiency 1 (CORTRD1)	0.3	-1.74
COL2A1	ENSG00000139219	NM_001844.5(COL2A1):c.2862C>T (p.Gly954=)	GGC	GGT		0.55	-0.87
PKD1	ENSG00000008710	NM_001009944.3(PKD1):c.678G>A (p.Glu226=)	GAG	GAA	Polycystic kidney disease, adult type (PKD1)	0.86	-0.22
BAAT	ENSG00000136881	NM_001701.4(BAAT):c.858C>G (p.Ser286=)	TCC	TCG	Atypical hemolytic-uremic syndrome 1 (AHUS1)	0.23	-2.09
SPAST	ENSG00000021574	NM_014946.4(SPAST):c.780T>G (p.Leu260=)	CTT	CTG		2.54	1.35
A4GALT	ENSG00000128274	NM_017436.7(A4GALT):c.42C>T (p.Gly14=)	GGC	GGT	Infantile cortical hyperostosis (CAFYD)	0.55	-0.87
SLC35A1	ENSG00000164414	NM_006416.5(SLC35A1):c.147T>C (p.Cys49=)	TGT	TGC	Congenital disorder of glycosylation type 2F (CDG2F)	1.03	0.05
GALT	ENSG00000213930	NM_000155.4(GALT):c.777G>A (p.Arg259=)	CGG	CGA	Deficiency of UDPglucose-hexose-1-phosphate uridylyltransferase (GALAC1)	0.6	-0.73
DICER1	ENSG00000100697	NM_177438.3(DICER1):c.5439G>A (p.Glu1813=)	GAG	GAA	DICER1-related pleuropulmonary blastoma cancer predisposition syndrome (PPBFTDS)	0.86	-0.22
GATA4	ENSG00000136574	NM_002052.5(GATA4):c.1263C>T (p.Ser421=)	AGC	AGT	Congenital heart disease (CHD)	0.72	-0.48
PLP1	ENSG00000123560	NM_000533.5(PLP1):c.441A>T (p.Gly147=)	GGA	GGT	Hereditary spastic paraplegia 2 (SPG2)	0.63	-0.67
ODAD2	ENSG00000169126	NM_018076.5(ODAD2):c.3030G>A (p.Leu1010=)	CTG	CTA	Primary ciliary dyskinesia 23 (CILD23)	0.21	-2.27
DHX37	ENSG00000150990	NM_032656.4(DHX37):c.1399C>T (p.Leu467=)	CTG	TTG	Neurodevelopmental disorder with brain anomalies and with or without vertebral or cardiac anomalies	0.37	-1.42
PNPT1	ENSG00000138035	NM_033109.5(PNPT1):c.1818T>G (p.Val606=)	GTT	GTG	Combined oxidative phosphorylation deficiency 13 (COXPD13);Deafness, autosomal recessive 70 (DFNB70)	2.18	1.13
COL7A1	ENSG00000114270	NM_000094.4(COL7A1):c.6861A>G (p.Gly2287=)	GGA	GGG	Dystrophic epidermolysis bullosa	0.89	-0.17
COL17A1	ENSG00000065618	NM_000494.4(COL17A1):c.3156C>T (p.Gly1052=)	GGC	GGT	Epithelial recurrent erosion dystrophy (ERED)	0.55	-0.87
ATP6AP2	ENSG00000182220	NM_005765.3(ATP6AP2):c.321C>T (p.Asp107=)	GAC	GAT	Mental retardation, X-linked, syndromic, Hedera type (MRXSH)	0.99	-0.01
F8	ENSG00000185010	NM_000132.3(F8):c.1569G>T (p.Leu523=)	CTG	CTT	Hereditary factor VIII deficiency disease (HEMA)	0.39	-1.35
COL7A1	ENSG00000114270	NM_000094.4(COL7A1):c.2142A>G (p.Gly714=)	GGA	GGG	Dystrophic epidermolysis bullosa	0.89	-0.17
POLK	ENSG00000122008	NM_016218.3(POLK):c.1341G>A (p.Gln447=)	CAG	CAA	Malignant tumor of prostate	0.4	-1.32
NEUROD1	ENSG00000162992	NM_002500.4(NEUROD1):c.309C>G (p.Arg103=)	CGC	CGG	Maturity-onset diabetes of the young type 6 (MODY6)	1.22	0.29

MTHFR	ENSG00000177000	NM_005957.4(MTHFR):c.1320G>A (p.Ser440=)	TCG	TCA	Homocystinuria due to methylene tetrahydrofolate reductase deficiency	3.5	1.81
EPG5	ENSG00000152223	NM_020964.3(EPG5):c.2598A>G (p.Gln866=)	CAA	CAG	Vici syndrome (VICIS)	2.49	1.32
ATP6AP2	ENSG00000182220	NM_005765.3(ATP6AP2):c.345C>T (p.Ser115=)	TCC	TCT	Parkinsonism with spasticity, X-linked (XPDS)	0.98	-0.03
ABCA4	ENSG00000198691	NM_000350.3(ABCA4):c.4269C>T (p.Gly1423=)	GGC	GGT	Cone-rod dystrophy	0.55	-0.87
ATR	ENSG00000175054	NM_001184.4(ATR):c.2022A>G (p.Gly674=)	GGA	GGG	Seckel syndrome 1 (SCKL1)	0.89	-0.17
TECTA	ENSG00000109927	NM_005422.2(TECTA):c.5331G>A (p.Leu1777=)	CTG	CTA	Deafness, autosomal dominant 12 (DFNA12)	0.21	-2.27
RPE65	ENSG00000116745	NM_000329.3(RPE65):c.1101A>G (p.Arg367=)	AGA	AGG	Leber congenital amaurosis (LCA)	0.91	-0.14
POLK	ENSG00000122008	NM_016218.3(POLK):c.1692G>A (p.Lys564=)	AAG	AAA	Malignant tumor of prostate	0.87	-0.2
UBA1	ENSG00000130985	NM_003334.4(UBA1):c.1731C>T (p.Asn577=)	AAC	AAT	Spinal muscular atrophy, X-linked 2 (SMAX2)	1.01	0.02
FANCC	ENSG00000158169	NM_000136.3(FANCC):c.1494T>G (p.Ala498=)	GCT	GCG	Fanconi anemia, complementation group C (FANCC)	0.31	-1.67
HEXA	ENSG00000213614	NM_000520.6(HEXA):c.972T>A (p.Val324=)	GTT	GTA	Gm2-gangliosidosis, subacute	0.65	-0.62
RFX5	ENSG00000143390	NM_001025603.2(RFX5):c.1032C>T (p.Ile344=)	ATC	ATT	Bare lymphocyte syndrome, type II, complementation group c	0.89	-0.17
HGF	ENSG00000019991	NM_000601.6(HGF):c.495G>A (p.Ser165=)	TCG	TCA	Deafness, autosomal recessive 39 (DFNB39)	3.5	1.81
GATA4	ENSG00000136574	NM_002052.5(GATA4):c.27C>A (p.Ala9=)	GCC	GCA	Congenital heart disease (CHD)	0.67	-0.59
CYP21A2	ENSG00000231852	NM_000500.9(CYP21A2):c.1357C>T (p.Leu453=)	CTG	TTG		0.37	-1.42
CYP21A2	ENSG00000231852	NM_000500.9(CYP21A2):c.1066C>T (p.Leu356=)	CTG	TTG		0.37	-1.42
SLC52A2	ENSG00000185803	NM_001363118.2(SLC52A2):c.865C>T (p.Leu289=)	CTG	TTG	Brown-Vialetto-Van Laere syndrome 2 (BVVLS2)	0.37	-1.42
FRMD7	ENSG00000165694	NM_194277.2(FRMD7):c.252G>A (p.Val84=)	GTG	GTA	Infantile nystagmus, X-linked (NYS1)	0.3	-1.74
ADGRV1	ENSG00000164199	NM_032119.4(ADGRV1):c.1626A>T (p.Thr542=)	ACA	ACT	Usher syndrome, type 2A (USH2A)	0.86	-0.21
RNASEH2A	ENSG00000104889	NM_006397.2(RNASEH2A):c.75C>T (p.Arg25=)	CGC	CGT	Aicardi Goutieres syndrome 4 (AGS4)	0.52	-0.93
IL7R	ENSG00000168685	NM_002185.5(IL7R):c.333T>A (p.Val111=)	GTT	GTA	Severe combined immunodeficiency, autosomal recessive, T cell-negative, B cell-positive, NK cell-positive	0.65	-0.62
POLK	ENSG00000122008	NM_016218.3(POLK):c.1284G>A (p.Ala428=)	GCG	GCA	Malignant tumor of prostate	2.88	1.52
POT1	ENSG00000128513	NM_015450.3(POT1):c.1227A>G (p.Pro409=)	CCA	CCG	Melanoma, cutaneous malignant, susceptibility to, 10 (CMM10)	0.33	-1.61
MANBA	ENSG00000109323	NM_005908.4(MANBA):c.375A>G (p.Arg125=)	AGA	AGG	Beta-D-mannosidosis (MANSB)	0.91	-0.14
DLEC1	ENSG00000008226	NM_007335.4(DLEC1):c.5212C>A (p.Arg1738=)	CGG	AGG	Malignant tumor of esophagus	1.15	0.2
MPIG6B	ENSG00000204420	NM_138272.3(MPIG6B):c.558C>T (p.Thr186=)	ACC	ACT	Thrombocytopenia, anemia, and myelofibrosis (THAMY)	0.8	-0.31
CYP21A2	ENSG00000231852	NM_000500.9(CYP21A2):c.952C>T (p.Leu318=)	CTG	TTG		0.37	-1.42
CDC45	ENSG00000093009	NM_001178010.2(CDC45):c.333C>T (p.Asn111=)	AAC	AAT	Meier-gorlin syndrome 7 (MGORS7)	1.01	0.02
CDC45	ENSG00000093009	NM_001178010.2(CDC45):c.318C>T (p.Val106=)	GTC	GTT	Meier-gorlin syndrome 7 (MGORS7)	0.88	-0.19
THPO	ENSG00000090534	NM_000460.4(THPO):c.753C>T (p.His251=)	CAC	CAT	Thrombocythemia 1 (THCYT1)	0.81	-0.3
SLC25A11	ENSG00000108528	NM_003562.5(SLC25A11):c.708C>T (p.Ala236=)	GCC	GCT	Paragangliomas 6	0.74	-0.44
INSL3	ENSG00000248099	NM_005543.4(INSL3):c.304C>T (p.Arg102Cys)	ACC	ACT	Cryptorchidism	0.8	-0.31
INSL3	ENSG00000248099	NM_005543.4(INSL3):c.217C>T (p.Arg73Ter)	GAC	GAT	Cryptorchidism	0.99	-0.01
ODAPH	ENSG00000174792	NM_001206981.2(ODAPH):c.273C>T (p.His91=)	CAC	CAT	Amelogenesis imperfecta, hypomaturation type IIA4 (AI2A4)	0.81	-0.3
TWNK	ENSG00000107815	NM_021830.5(TWNK):c.1287C>T (p.Ala429=)	GCC	GCT	Infantile onset spinocerebellar ataxia (MTDPS7)	0.74	-0.44
GALT	ENSG00000213930	NM_000155.4(GALT):c.336T>C (p.Ser112=)	AGT	AGC	Deficiency of UDPglucose-hexose-1-phosphate uridylyltransferase (GALAC1)	1.4	0.48
RNASEH2A	ENSG00000104889	NM_006397.2(RNASEH2A):c.69G>A (p.Val23=)	GTG	GTA	Aicardi Goutieres syndrome 4 (AGS4)	0.3	-1.74
KRT6A	ENSG00000205420	NM_005554.4(KRT6A):c.1694A>G (p.Ter565=)	TAA	TGA	Pachyonychia congenita 3 (PC3)	1.82	0.86
SEMA3A	ENSG00000075213	NM_006080.3(SEMA3A):c.2315G>A (p.Ter772=)	TGA	TAA	Hypogonadotropic hypogonadism 16 with or without anosmia (HH16)	0.55	-0.86

TMEM38B	ENSG00000095209	NM_018112.3(TMEM38B):c.875A>G (p.Ter292=)	TAA	TGA	Osteogenesis imperfecta, type xiv (OI14)	1.82	0.86
TYMP	ENSG00000025708	NM_001953.5(TYMP):c.1160-2A>G	GCA	GCG	Mitochondrial DNA depletion syndrome 1 (MNGIE type) (MTDPS1)	0.35	-1.52
TYMP	ENSG00000025708	NM_001953.5(TYMP):c.1160-2A>C	GCA	GCC	Mitochondrial DNA depletion syndrome 1 (MNGIE type) (MTDPS1)	1.5	0.59
MASP1	ENSG00000127241	NM_139125.4(MASP1):c.2186G>A (p.Ter729=)	TGA	TAA	3MC syndrome 1	0.55	-0.86
CYP27A1	ENSG00000135929	NM_000784.4(CYP27A1):c.1595G>A (p.Ter532=)	TGA	TAA	Cholestanol storage disease (CTX)	0.55	-0.86
HSD17B10	ENSG00000072506	NM_001037811.2(HSD17B10):c.568+6C>A	CGG	AGG	HSD10 disease (HSD10MD)	1.15	0.2
VHL	ENSG00000134086	NM_000551.4(VHL):c.222C>A (p.Val74=)	GTC	GTA	Erythrocytosis, familial, 2 (ECYT2)	0.57	-0.8
ACAT1	ENSG00000075239	NM_000019.4(ACAT1):c.951C>T (p.Asp317=)	GAC	GAT	Deficiency of acetyl-CoA acetyltransferase	0.99	-0.01
DPY19L2	ENSG00000177990	NM_173812.5(DPY19L2):c.2276G>A (p.Ter759=)	TGA	TAA	Spermatogenic failure 9 (SPGF9)	0.55	-0.86
KRT6C	ENSG00000170465	NM_173086.5(KRT6C):c.1694A>G (p.Ter565=)	TAA	TGA	Palmoplantar keratoderma, nonepidermolytic, focal or diffuse (PPKNEFD)	1.82	0.86
CPT2	ENSG00000157184	NM_000098.3(CPT2):c.1977A>G (p.Ter659=)	TAA	TAG	Carnitine palmitoyltransferase II deficiency, infantile	0.79	-0.33
NLRC4	ENSG00000091106	NM_001199138.2(NLRC4):c.3075A>G (p.Ter1025=)	TAA	TAG	Autoinflammation with infantile enterocolitis (AIFEC)	0.79	-0.33
TECR	ENSG00000099797	NM_138501.6(TECR):c.926G>A (p.Ter309=)	TGA	TAA	Mental retardation, autosomal recessive 14 (MRT14)	0.55	-0.86
LAGE3	ENSG00000196976	NM_006014.4(LAGE3):c.431A>G (p.Ter144=)	TAA	TGA	Galloway-Mowat syndrome 2, X-linked	1.82	0.86
IDH2	ENSG00000182054	NM_002168.4(IDH2):c.1359G>A (p.Ter453=)	TAG	TAA	D-2-hydroxyglutaric aciduria 2 (D2HGA2)	1.26	0.33
TBX6	ENSG00000149922	NM_004608.3(TBX6):c.1227G>A (p.Pro409=)	CCG	CCA	Spondylocostal dysostosis 5 (SCDO5);	3.05	1.61
NR3C1	ENSG00000113580	NM_000176.3(NR3C1):c.66G>A (p.Glu22=)	GAG	GAA	Glucocorticoid resistance, relative;Glucocorticoid resistance, generalized (GCCR)	0.86	-0.22
LRRK2	ENSG00000188906	NM_198578.4(LRRK2):c.3342A>G (p.Leu1114=)	TTA	TTG	Parkinson disease 8, autosomal dominant (PARK8);	1.53	0.61
ALDH3A2	ENSG00000072210	NM_000382.3(ALDH3A2):c.909T>G (p.Gly303=)	GGT	GGG	Sjögren-Larsson syndrome (SLS);	1.41	0.5
L1CAM	ENSG00000198910	NM_001278116.2(L1CAM):c.924C>T (p.Gly308=)	GGC	GGT	X-linked hydrocephalus syndrome (HSAS);	0.55	-0.87
WRN	ENSG00000165392	NM_000553.6(WRN):c.561A>G (p.Lys187=)	AAA	AAG	Werner syndrome (WRN)	1.15	0.2
HBA2	ENSG00000188536	NM_000517.6(HBA2):c.69C>T (p.Gly23=)	GGC	GGT	Alpha plus thalassemia; alpha Thalassemia	0.55	-0.87
ABCA4	ENSG00000198691	NM_000350.3(ABCA4):c.6342G>A (p.Val2114=)	GTG	GTA	Stargardt disease 1 (STGD1);Retinal dystrophy	0.3	-1.74
MAPT	ENSG00000186868	NM_016841.5(MAPT):c.649-3868T>C	AAT	AAC	Frontotemporal dementia (FTD);	0.99	-0.02
LMNA	ENSG00000160789	NM_170707.4(LMNA):c.1821G>A (p.Val607=)	GTG	GTA	Hutchinson-Gilford syndrome (HGPS);	0.3	-1.74
PDHA1	ENSG00000131828	NM_000284.4(PDHA1):c.483C>T (p.Tyr161=)	TAC	TAT	Pyruvate dehydrogenase E1-alpha deficiency (PDHAD)	0.9	-0.15
ALDH7A1	ENSG00000164904	NM_001182.5(ALDH7A1):c.834G>A (p.Val278=)	GTG	GTA	Pyridoxine-dependent epilepsy (EPD);	0.3	-1.74
AR	ENSG00000169083	NM_000044.6(AR):c.2667C>T (p.Ser889=)	AGC	AGT	Androgen resistance syndrome (AIS);Androgen resistance syndrome (AIS);Kennedy disease	0.72	-0.48
NF1	ENSG00000196712	NM_000267.3(NF1):c.2709G>A (p.Val903=)	GTG	GTA	Neurofibromatosis, type 1 (NF1);Hereditary cancer-predisposing syndrome	0.3	-1.74
MECP2	ENSG00000169057	NM_001110792.2(MECP2):c.48C>T (p.Gly16=)	GGC	GGT	Rett syndrome (RTT);	0.55	-0.87
COL7A1	ENSG00000114270	NM_000094.4(COL7A1):c.5499C>T	GGC	GGT	Dystrophic epidermolysis bullosa	0.55	-0.87
TUBGCP4	ENSG00000137822	NM_014444.5(TUBGCP4):c.1746G>T (p.Leu582=)	CTG	CTT	Microcephaly and chorioretinopathy, autosomal recessive, 3 (MCCRP3); Autosomal recessive chorioretinopathy-microcephaly syndrome	0.39	-1.35
FBN1	ENSG00000166147	NM_000138.5(FBN1):c.6354C>T (p.Ile2118=)	ATC	ATT	Marfan syndrome (MFS);Cardiovascular phenotype; Marfan Syndrome/Loeys-Dietz Syndrome/Familial Thoracic Aortic Aneurysms and Dissections;Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.89	-0.17

USH1C	ENSG00000006611	NM_153676.4(USH1C):c.216G>A (p.Val72=)	GTG	GTA	Usher syndrome, type 1C (USH1C);Usher syndrome type 1 (USH1);Usher syndrome; Usher syndrome, type 1C (USH1C);Deafness, autosomal recessive 18 (DFNB18A);Usher syndrome type 1 (USH1);Rare genetic deafness;Deafness, autosomal recessive 18 (DFNB18A)	0.3	-1.74
KAT6B	ENSG00000156650	NM_012330.4(KAT6B):c.3147G>A (p.Pro1049=)	CCG	CCA	Blepharophimosis - intellectual disability syndrome, SBBYS type (SBBYSS);Intellectual disability	3.05	1.61
GBA	ENSG00000177628	NM_000157.4(GBA):c.1497G>C (p.Val499=)	GTG	GTC	s disease, type 1 (GD1)", "Acute neuronopathic Gaucher's disease (GD2)", "Subacute neuronopathic Gaucher's disease (GD3)", 'Gaucher disease, perinatal lethal;	0.52	-0.94
LMNA	ENSG00000160789	NM_170707.4(LMNA):c.1824C>T (p.Gly608=)	GGC	GGT	Hutchinson-Gilford syndrome (HGPS);Lethal tight skin contracture syndrome; Primary dilated cardiomyopathy (DCM);Hutchinson-Gilford syndrome (HGPS);Charcot-Marie-Tooth disease, type 2	0.55	-0.87
USH2A	ENSG00000042781	NM_206933.4(USH2A):c.949C>A (p.Arg317=)	CGG	AGG	Usher syndrome, type 2A (USH2A); Blindness;Rod-cone dystrophy;Pigmentary retinopathy;Abnormal macular morphology;Retinal pigment epithelial atrophy;Usher syndrome, type 2A (USH2A);Retinitis pigmentosa 39 (RP39);Rare genetic deafness;Retinitis pigmentosa 39 (RP39);Retinal dystrophy;Usher syndrome type 2	1.15	0.2
POMGNT1	ENSG00000085998	NM_017739.3(POMGNT1):c.636C>T (p.Phe212=)	TTC	TTT	Limb-girdle muscular dystrophy-dystroglycanopathy, type C3 (MDDGC3);Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B3 (MDDGB3);Muscle eye brain disease (MEB);Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B3 (MDDGB3);Limb-girdle muscular dystrophy-dystroglycanopathy, type C3 (MDDGC3);Retinitis pigmentosa 76 (RP76)	0.98	-0.02
FLNA	ENSG00000196924	NM_001110556.2(FLNA):c.1923C>T (p.Gly641=)	GGC	GGT	Periventricular nodular heterotopia 1 (PVNH1);Cardiac valvular dysplasia, X-linked (CVD1);Periventricular nodular heterotopia 1 (PVNH1);Melnick-Needles syndrome (MNS);Oto-palato-digital syndrome, type II (OPD2);Frontometaphyseal dysplasia (FMD1)	0.55	-0.87
LMNA	ENSG00000160789	NM_170707.4(LMNA):c.768G>A (p.Val256=)	GTG	GTA	Primary dilated cardiomyopathy (DCM);Charcot-Marie-Tooth disease, type 2;Dilated cardiomyopathy 1A (CMD1A)	0.3	-1.74
MITF	ENSG00000187098	NM_001354604.2(MITF):c.1230G>A (p.Thr410=)	ACG	ACA	Waardenburg syndrome type 2A (WS2A)	2.96	1.57
HBB	ENSG00000244734	NM_000518.5(HBB):c.75T>A (p.Gly25=)	GGT	GGA	Beta-plus-thalassemia;beta Thalassemia (BTHAL); Hb SS disease (SCD)	1.59	0.67
MPZ	ENSG00000158887	NM_000530.8(MPZ):c.411C>T (p.Gly137=)	GGC	GGT	Charcot-Marie-Tooth disease, type I (CMT1);Dejerine-Sottas disease	0.55	-0.87
RPGRIP1	ENSG00000092200	NM_020366.3(RPGRIP1):c.564A>G (p.Glu188=)	GAA	GAG	Leber congenital amaurosis (LCA);Cone-rod dystrophy 13 (CORD13);Leber congenital amaurosis 6 (LCA6)	1.16	0.22
CEP290	ENSG00000198707	NM_025114.4(CEP290):c.2343T>C (p.Asn781=)	AAT	AAC	Joubert syndrome 5 (JBTS5);Retinal dystrophy	0.99	-0.02
LDLR	ENSG00000130164	NM_000527.4(LDLR):c.666C>T (p.Cys222=)	TGC	TGT	Familial hypercholesterolemia 1 (FHCL1);Familial hypercholesterolemia (FH)	0.97	-0.05
MPZ	ENSG00000158887	NM_000530.8(MPZ):c.276G>A (p.Val92=)	GTG	GTA	Charcot-Marie-Tooth disease, demyelinating, type 1b (CMT1B);Charcot-Marie-Tooth disease;Charcot-Marie-Tooth disease, type I (CMT1)	0.3	-1.74
HSD17B4	ENSG00000133835	NM_000414.4(HSD17B4):c.101C>T (p.Ala34Val)	AGC	AGT	Perrault syndrome 1 (PRLTS1);Bifunctional peroxisomal enzyme deficiency (DBIF);	0.72	-0.48
LDLR	ENSG00000130164	NM_000527.5(LDLR):c.1813C>T (p.Leu605=)	CTG	TTG	Familial hypercholesterolemia 1 (FHCL1)	0.37	-1.42
LDLR	ENSG00000130164	NM_000527.5(LDLR):c.621C>T (p.Gly207=)	GGC	GGT	Familial hypercholesterolemia 1 (FHCL1)	0.55	-0.87

ZNF142	ENSG00000115568	NM_001105537.4(ZNF142):c.4185G>A (p.Leu1395=)	CTG	CTA	Neurodevelopmental disorder with impaired speech and hyperkinetic movements	0.21	-2.27
FBN1	ENSG00000166147	NM_000138.5(FBN1):c.6453C>T	TGC	TGT	Marfan syndrome (MFS);Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.97	-0.05
PHEX	ENSG00000102174	NM_000444.6(PHEX):c.591A>G (p.Gln197=)	CAA	CAG	Familial X-linked hypophosphatemic vitamin D refractory rickets (XLHR);	2.49	1.32
LDLR	ENSG00000130164	NM_000527.5(LDLR):c.1216C>A (p.Arg406=)	CGG	AGG	Familial hypercholesterolemia 1 (FHCL1);Familial hypercholesterolemia (FH)	1.15	0.2
G6PC1	ENSG00000131482	NM_000151.4(G6PC1):c.648G>T (p.Leu216=)	CTG	CTT	Glycogen storage disease due to glucose-6-phosphatase deficiency type IA (GSD1A);	0.39	-1.35
VHL	ENSG00000134086	NM_000551.4(VHL):c.414A>G (p.Pro138=)	CCA	CCG	Von Hippel-Lindau syndrome (VHLS);Hereditary cancer-predisposing syndrome;Erythrocytosis, familial, 2 (ECYT2);Von Hippel-Lindau syndrome (VHLS)	0.33	-1.61
GABBR2	ENSG00000136928	NM_005458.8(GABBR2):c.360A>G (p.Ala120=)	GCA	GCG	Tobacco addiction, susceptibility to	0.35	-1.52
APOL1	ENSG00000100342	NM_003661.4(APOL1):c.1104T>G (p.Ala368=)	GCT	GCG	Focal segmental glomerulosclerosis 4, susceptibility to (FSGS4)	0.31	-1.67
CFH	ENSG00000000971	NM_000186.3(CFH):c.1419G>C (p.Ala473=)	GCG	GCC	Age-related macular degeneration 4 (ARMD4)	4.32	2.11
IFITM3	ENSG00000142089	NM_021034.3(IFITM3):c.42T>C (p.Ser14=)	AGT	AGC	Influenza	1.4	0.48
SEPTIN12	ENSG00000140623	NM_144605.5(SEPTIN12):c.474G>A (p.Val158=)	GTG	GTA	Spermatogenic failure 10 (SPGF10)	0.3	-1.74
CR2	ENSG00000117322	NM_001006658.3(CR2):c.1776G>A (p.Leu592=)	CTG	CTA	Systemic lupus erythematosus 9 (SLEB9);	0.21	-2.27
ACADM	ENSG00000117054	NM_000016.5(ACADM):c.351A>C (p.Thr117=)	ACA	ACC	MCAD deficiency, modifier of; Medium-chain acyl-coenzyme A dehydrogenase deficiency (ACADMD)	1.07	0.1
RET	ENSG00000165731	NM_020975.6(RET):c.1941C>T (p.Ile647=)	ATC	ATT	Hirschsprung disease 1 (HSCR1);Hereditary cancer-predisposing syndrome; Multiple endocrine neoplasia, type 2a (MEN2A);Multiple endocrine neoplasia, type 2 (MEN2)	0.89	-0.17
CHRNA3	ENSG00000080644	NM_000743.5(CHRNA3):c.645C>T (p.Tyr215=)	TAC	TAT	Lung cancer susceptibility 2 (LNCR2);Smoking as a quantitative trait locus 3 (SQTL3);nicotine response - Toxicity/ADR	0.9	-0.15
PEX7	ENSG00000112357	NM_000288.4(PEX7):c.615C>T (p.Asp205=)	GAC	GAT	Rhizomelic chondrodysplasia punctata type 1 (RCDP1); Peroxisome biogenesis disorder 9B (PBD9B)	0.99	-0.01
VCP	ENSG00000165280	NM_007126.5(VCP):c.1584C>T (p.Ala528=)	GCC	GCT	Amyotrophic lateral sclerosis 14, with or without frontotemporal dementia (FTDALS6);Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia (IBMPFD1);Amyotrophic lateral sclerosis 14, with or without frontotemporal dementia (FTDALS6);Inclusion body myopathy with early-onset Paget disease with or without frontotemporal dementia 1 (IBMPFD1)	0.74	-0.44
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.11430G>A (p.Thr3810=)	ACG	ACA	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	2.96	1.57
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.5259T>C (p.Ile1753=)	ATT	ATC	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	1.13	0.17
PSAP	ENSG00000197746	NM_002778.4(PSAP):c.714C>G (p.Ala238=)	GCC	GCG	Krabbe disease, atypical, due to saposin A deficiency;Gaucher disease, atypical, due to saposin C deficiency;Combined saposin deficiency;Sphingolipid activator protein 1 deficiency	0.23	-2.11
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.4560C>T (p.Phe1520=)	TTC	TTT	Miyoshi myopathy; Limb-Girdle Muscular Dystrophy, Recessive;Qualitative or quantitative defects of dysferlin	0.98	-0.02

PSAP	ENSG00000197746	NM_002778.4(PSAP):c.1278C>T (p.Asn426=)	AAC	AAT	Krabbe disease, atypical, due to saposin A deficiency;Gaucher disease, atypical, due to saposin C deficiency;Combined saposin deficiency;Sphingolipid activator protein 1 deficiency;Metachromatic leukodystrophy (MLD)	1.01	0.02
KCNJ10	ENSG00000177807	NM_002241.5(KCNJ10):c.615A>G (p.Lys205=)	AAA	AAG	Deafness, autosomal recessive 4, with enlarged vestibular aqueduct (DFNB4); EAST syndrome (SESAMES)	1.15	0.2
MMP2	ENSG00000087245	NM_004530.6(MMP2):c.1233G>A (p.Leu411=)	CTG	CTA	Multicentric osteolysis, nodulosis and arthropathy (MONA);	0.21	-2.27
PEX1	ENSG00000127980	NM_000466.3(PEX1):c.939T>C (p.His313=)	CAT	CAC	Peroxisome biogenesis disorder 1A (Zellweger) (PBD1A)	1.23	0.3
LIG4	ENSG00000174405	NM_206937.2(LIG4):c.1983T>C (p.Asp661=)	GAT	GAC	Severe combined immunodeficiency due to DCLRE1C deficiency (RS-SCID);Lig4 syndrome	1.01	0.01
TPO	ENSG00000115705	NM_001206744.2(TPO):c.1857C>G (p.Ala619=)	GCC	GCG	Deficiency of iodide peroxidase (TDH2A);	0.23	-2.11
MCPH1	ENSG00000147316	NM_024596.5(MCPH1):c.1458A>G (p.Lys486=)	AAA	AAG		1.15	0.2
GALC	ENSG00000054983	NM_000153.4(GALC):c.525C>T (p.Val175=)	GTC	GTT	Galactosylceramide beta-galactosidase deficiency	0.88	-0.19
SPATA7	ENSG00000042317	NM_018418.5(SPATA7):c.387G>A (p.Pro129=)	CCG	CCA	Retinitis pigmentosa (RP);Leber congenital amaurosis 3 (LCA3)	3.05	1.61
SPATA7	ENSG00000042317	NM_018418.5(SPATA7):c.57G>T (p.Pro19=)	CCG	CCT	Retinitis pigmentosa (RP);Leber congenital amaurosis 3 (LCA3)	3.11	1.64
DYNC2H1	ENSG00000187240	NM_001377.3(DYNC2H1):c.2550G>A (p.Leu850=)	TTG	TTA	Short-rib thoracic dysplasia 3 with or without polydactyly (SRTD3);Jeune thoracic dystrophy (ATD1)	0.65	-0.61
NEB	ENSG00000183091	NM_001271208.2(NEB):c.18786C>T (p.Tyr6262=)	TAC	TAT	Nemaline myopathy 2 (NEM2)	0.9	-0.15
ABCC9	ENSG00000069431	NM_005691.3(ABCC9):c.1332C>T (p.Gly444=)	GGC	GGT	Hypertrichotic osteochondrodysplasia Cantu type;Dilated cardiomyopathy 1O (CMD1O)	0.55	-0.87
LIG4	ENSG00000174405	NM_206937.2(LIG4):c.1252T>C (p.Leu418=)	TTG	CTG	Severe combined immunodeficiency due to DCLRE1C deficiency (RS-SCID);Lig4 syndrome	2.67	1.42
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.2265G>A (p.Pro755=)	CCG	CCA	Autosomal recessive polycystic kidney disease (ARPKD)	3.05	1.61
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.5478G>A (p.Ala1826=)	GCG	GCA	Autosomal recessive polycystic kidney disease (ARPKD)	2.88	1.52
F2	ENSG00000180210	NM_000506.4(F2):c.1464G>A (p.Thr488=)	ACG	ACA	Thrombophilia due to thrombin defect (THPH1);Prothrombin deficiency, congenital	2.96	1.57
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.5193G>A (p.Val1731=)	GTG	GTA	Autosomal recessive polycystic kidney disease (ARPKD)	0.3	-1.74
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.3048T>C (p.Asn1016=)	AAT	AAC	Autosomal recessive polycystic kidney disease (ARPKD)	0.99	-0.02
TRIP11	ENSG00000100815	NM_004239.4(TRIP11):c.4620T>C (p.Val1540=)	GTT	GTC	Achondrogenesis, type IA (ACG1A)	1.14	0.19
TRIP11	ENSG00000100815	NM_004239.4(TRIP11):c.1774C>T (p.Leu592=)	CTA	TTA	Achondrogenesis, type IA (ACG1A)	1.18	0.24
SERPINA1	ENSG00000197249	NM_000295.5(SERPINA1):c.43C>T (p.Leu15=)	CTG	TTG	Alpha-1-antitrypsin deficiency (A1ATD)	0.37	-1.42
CERKL	ENSG00000188452	NM_201548.5(CERKL):c.900T>C (p.His300=)	CAT	CAC	Retinitis pigmentosa (RP);	1.23	0.3
PLCB1	ENSG00000182621	NM_015192.4(PLCB1):c.714A>C (p.Pro238=)	CCA	CCC	Early infantile epileptic encephalopathy 12 (DEE12)	1	0.01
PMM2	ENSG00000140650	NM_000303.3(PMM2):c.441C>T (p.Leu147=)	CTC	CTT	Congenital disorder of glycosylation, type Ia (CDG1A)	0.8	-0.33
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.633G>A (p.Gly211=)	GGG	GGA	Autosomal recessive polycystic kidney disease (ARPKD)	1.13	0.17
SMARCAL1	ENSG00000138375	NM_014140.3(SMARCAL1):c.927C>T (p.Ser309=)	AGC	AGT	Schimke immuno-osseous dysplasia (SIOD)	0.72	-0.48
PLCB1	ENSG00000182621	NM_015192.4(PLCB1):c.2088C>T (p.Tyr696=)	TAC	TAT	Early infantile epileptic encephalopathy 12 (DEE12)	0.9	-0.15
ABCC2	ENSG00000023839	NM_000392.5(ABCC2):c.3492C>T (p.Ser1164=)	AGC	AGT	Dubin-Johnson syndrome (DJS);	0.72	-0.48
CEP135	ENSG00000174799	NM_025009.5(CEP135):c.1740A>G (p.Arg580=)	AGA	AGG		0.91	-0.14
FAH	ENSG00000103876	NM_000137.3(FAH):c.747A>G (p.Pro249=)	CCA	CCG	Tyrosinemia type I (TYRSN1)	0.33	-1.61
WRN	ENSG00000165392	NM_000553.6(WRN):c.3453G>A (p.Glu1151=)	GAG	GAA	Werner syndrome (WRN)	0.86	-0.22
STRA6	ENSG00000137868	NM_022369.4(STRA6):c.357C>T (p.Pro119=)	CCC	CCT	Matthew-Wood syndrome (MCOPS9)	1.02	0.02
NPC1	ENSG00000141458	NM_000271.5(NPC1):c.3012G>A (p.Ser1004=)	TCG	TCA	Niemann-Pick disease type C1 (NPC1)	3.5	1.81
AGA	ENSG00000038002	NM_000027.4(AGA):c.762C>T (p.Ala254=)	GCC	GCT	Aspartylglucosaminuria (AGU)	0.74	-0.44
ABCG8	ENSG00000143921	NM_022437.3(ABCG8):c.1785C>T (p.Phe595=)	TTC	TTT	Sitosterolemia 1 (STSL1);	0.98	-0.02

TNFRSF11B	ENSG00000164761	NM_002546.4(TNFRSF11B):c.234C>T (p.Asp78=)	GAC	GAT	Hyperphosphatasemia with bone disease (PDB5);	0.99	-0.01
VWF	ENSG00000110799	NM_000552.4(VWF):c.5277C>T (p.Asp1759=)	GAC	GAT	von Willebrand disorder (VWD);	0.99	-0.01
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.9210G>A (p.Pro3070=)	CCG	CCA	Autosomal dominant cerebellar ataxia;Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O)	3.05	1.61
CHRNA1	ENSG00000138435	NM_001039523.3(CHRNA1):c.888G>A (p.Leu296=)	CTG	CTA	Congenital myasthenic syndrome (CMS);Lethal multiple pterygium syndrome (LMPS)	0.21	-2.27
ALDH5A1	ENSG00000112294	NM_001080.3(ALDH5A1):c.1107C>T (p.Arg369=)	CGC	CGT	Succinate-semialdehyde dehydrogenase deficiency (SSADHD)	0.52	-0.93
ALG6	ENSG00000088035	NM_013339.4(ALG6):c.1314T>C (p.Ile438=)	ATT	ATC	Congenital disorder of glycosylation type 1C (CDG1C)	1.13	0.17
PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.1257C>T (p.Val419=)	GTC	GTT	Autosomal recessive polycystic kidney disease (ARPKD)	0.88	-0.19
ATR	ENSG00000175054	NM_001184.4(ATR):c.2226T>C (p.Cys742=)	TGT	TGC	Seckel syndrome 1 (SCKL1);	1.03	0.05
KCNA1	ENSG00000111262	NM_000217.3(KCNA1):c.1464G>A (p.Lys488=)	AAG	AAA	Episodic ataxia (EA);Episodic ataxia type 1 (EA1)	0.87	-0.2
B3GLCT	ENSG00000187676	NM_194318.4(B3GLCT):c.288C>T (p.Leu96=)	CTC	CTT	Peters plus syndrome (PTRPLS)	0.8	-0.33
DMP1	ENSG00000152592	NM_004407.4(DMP1):c.1107C>T (p.Asp369=)	GAC	GAT	Autosomal recessive hypophosphatemic vitamin D refractory rickets (ARHR1);	0.99	-0.01
NPC1	ENSG00000141458	NM_000271.5(NPC1):c.1431G>A (p.Thr477=)	ACG	ACA	Niemann-Pick disease type C1 (NPC1)	2.96	1.57
ABCC2	ENSG00000023839	NM_000392.5(ABCC2):c.3576C>G (p.Thr1192=)	ACC	ACG	Dubin-Johnson syndrome (DJS);	0.31	-1.67
CHRNA1	ENSG00000138435	NM_001039523.3(CHRNA1):c.1323G>A (p.Ala441=)	GCG	GCA	Congenital myasthenic syndrome (CMS);Lethal multiple pterygium syndrome (LMPS)	2.88	1.52
CHRNA1	ENSG00000138435	NM_001039523.3(CHRNA1):c.1368C>T (p.Leu456=)	CTC	CTT	Congenital myasthenic syndrome (CMS);Lethal multiple pterygium syndrome (LMPS)	0.8	-0.33
OBSL1	ENSG00000124006	NM_015311.3(OBSL1):c.4588C>T (p.Leu1530=)	CTG	TTG	Three M syndrome 2 (3M2);	0.37	-1.42
B3GLCT	ENSG00000187676	NM_194318.4(B3GLCT):c.1371A>G (p.Gln457=)	CAA	CAG	Peters plus syndrome (PTRPLS)	2.49	1.32
GH1	ENSG00000259384	NM_000515.5(GH1):c.16C>A (p.Arg6=)	CGG	AGG	Growth hormone deficiency;	1.15	0.2
STXBP2	ENSG00000076944	NM_006949.4(STXBP2):c.1569G>A (p.Lys523=)	AAG	AAA	Hemophagocytic lymphohistiocytosis, familial, 5 (FHL5)	0.87	-0.2
NPC1	ENSG00000141458	NM_000271.5(NPC1):c.1011G>T (p.Arg337=)	CGG	CGT	Niemann-Pick disease type C1 (NPC1)	0.43	-1.22
B3GLCT	ENSG00000187676	NM_194318.4(B3GLCT):c.1104C>T (p.Ser368=)	TCC	TCT	Peters plus syndrome (PTRPLS)	0.98	-0.03
PRICKLE1	ENSG00000139174	NM_153026.3(PRICKLE1):c.435G>A (p.Ala145=)	GCG	GCA	Progressive myoclonus epilepsy with ataxia (EPM1B);	2.88	1.52
CHRND	ENSG00000135902	NM_000751.3(CHRND):c.525G>A (p.Thr175=)	ACG	ACA	Congenital myasthenic syndrome (CMS);Lethal multiple pterygium syndrome (LMPS)	2.96	1.57
NEB	ENSG00000183091	NM_001271208.2(NEB):c.4149C>T (p.Thr1383=)	ACC	ACT	Nemaline myopathy 2 (NEM2)	0.8	-0.31
TCIRG1	ENSG00000110719	NM_006019.4(TCIRG1):c.1278A>G (p.Arg426=)	CGA	CGG	Autosomal recessive osteopetrosis 1;	1.65	0.73
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.3012G>A (p.Lys1004=)	AAG	AAA	Pitt-Hopkins-like syndrome 2 (PTHSL2)	0.87	-0.2
SERPINA1	ENSG00000197249	NM_000295.5(SERPINA1):c.1206T>C (p.Asn402=)	AAT	AAC	Alpha-1-antitrypsin deficiency (A1ATD)	0.99	-0.02
NAGA	ENSG00000198951	NM_000262.3(NAGA):c.993G>T (p.Leu331=)	CTG	CTT	Alpha-N-acetylgalactosaminidase deficiency type 2;Alpha-N-acetylgalactosaminidase deficiency type 1	0.39	-1.35
LDLRAP1	ENSG00000157978	NM_015627.2(LDLRAP1):c.423C>T (p.Leu141=)	CTC	CTT	Familial hypercholesterolemia 4 (FHCL4)	0.8	-0.33
CTSK	ENSG00000143387	NM_000396.4(CTSK):c.684C>T (p.Pro228=)	CCC	CCT	Pyknodysostosis;	1.02	0.02
LIPA	ENSG00000107798	NM_000235.4(LIPA):c.1026G>A (p.Gly342=)	GGG	GGA	Wolman disease;Lysosomal acid lipase deficiency	1.13	0.17
NEB	ENSG00000183091	NM_001271208.2(NEB):c.22215A>G (p.Pro7405=)	CCA	CCG	Nemaline myopathy 2 (NEM2)	0.33	-1.61
CHRND	ENSG00000135902	NM_000751.3(CHRND):c.651G>A (p.Pro217=)	CCG	CCA	Congenital myasthenic syndrome (CMS);Lethal multiple pterygium syndrome (LMPS)	3.05	1.61
IL10RA	ENSG00000110324	NM_001558.4(IL10RA):c.931T>C (p.Leu311=)	TTG	CTG	Inflammatory bowel disease 28, autosomal recessive (IBD28)	2.67	1.42
FAH	ENSG00000103876	NM_000137.3(FAH):c.648C>A (p.Ile216=)	ATC	ATA	Tyrosinemia type I (TYRSN1)	0.44	-1.2
TCIRG1	ENSG00000110719	NM_006019.4(TCIRG1):c.1195C>T (p.Leu399=)	CTG	TTG	Autosomal recessive osteopetrosis 1;	0.37	-1.42

LIPA	ENSG00000107798	NM_000235.4(LIPA):c.846A>G (p.Thr282=)	ACA	ACG	Lysosomal acid lipase deficiency	0.34	-1.57
TPO	ENSG00000115705	NM_001206744.2(TPO):c.9G>A (p.Ala3=)	GCG	GCA	Deficiency of iodide peroxidase (TDH2A);	2.88	1.52
APC	ENSG00000134982	NM_000038.6(APC):c.5931A>G (p.Gln1977=)	CAA	CAG	Familial adenomatous polyposis 1 (FAP1);Hereditary cancer-predisposing syndrome	2.49	1.32
PLCB1	ENSG00000182621	NM_015192.4(PLCB1):c.2127G>A (p.Arg709=)	AGG	AGA	Early infantile epileptic encephalopathy 12 (DEE12)	1.1	0.14
TCIRG1	ENSG00000110719	NM_006019.4(TCIRG1):c.1227C>T (p.His409=)	CAC	CAT	Autosomal recessive osteopetrosis 1;	0.81	-0.3
DHCR7	ENSG00000172893	NM_001360.2(DHCR7):c.1155C>T (p.Ala385=)	GCC	GCT	Smith-Lemli-Opitz syndrome (SLOS)	0.74	-0.44
BCOR	ENSG00000183337	NM_001123385.2(BCOR):c.4320T>C (p.Pro1440=)	CCT	CCC		0.98	-0.02
KCTD7	ENSG00000243335	NM_153033.4(KCTD7):c.621C>A (p.Leu207=)	CTC	CTA	Epilepsy, progressive myoclonic 3 (EPM3)	0.42	-1.25
ST3GAL5	ENSG00000115525	NM_003896.4(ST3GAL5):c.465G>A (p.Glu155=)	GAG	GAA	GM3 synthase deficiency (SPDRS)	0.86	-0.22
ZEB2	ENSG00000169554	NM_014795.4(ZEB2):c.219C>T (p.His73=)	CAC	CAT	Mowat-Wilson syndrome (MOWS)	0.81	-0.3
PMS2	ENSG00000122512	NM_000535.7(PMS2):c.591C>T (p.Gly197=)	GGC	GGT	Hereditary nonpolyposis colorectal neoplasms;Hereditary cancer-predisposing syndrome	0.55	-0.87
ABCA12	ENSG00000144452	NM_173076.3(ABCA12):c.1296A>G (p.Gln432=)	CAA	CAG	Congenital ichthyosis of skin;	2.49	1.32
DHCR7	ENSG00000172893	NM_001360.2(DHCR7):c.840C>T (p.Tyr280=)	TAC	TAT	Smith-Lemli-Opitz syndrome (SLOS)	0.9	-0.15
LEMD3	ENSG00000174106	NM_014319.5(LEMD3):c.282C>G (p.Val94=)	GTC	GTG	Dermatofibrosis lenticularis disseminata (BOS);	1.92	0.94
ASPM	ENSG00000066279	NM_018136.5(ASPM):c.4443A>G (p.Leu1481=)	TTA	TTG	Primary autosomal recessive microcephaly 5 (MCPH5);	1.53	0.61
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.378G>T (p.Pro126=)	CCG	CCT	Qualitative or quantitative defects of dysferlin	3.11	1.64
ARSA	ENSG00000100299	NM_000487.6(ARSA):c.918G>A (p.Thr306=)	ACG	ACA	Metachromatic leukodystrophy (MLD)	2.96	1.57
ASPM	ENSG00000066279	NM_018136.5(ASPM):c.1185A>G (p.Gln395=)	CAA	CAG	Primary autosomal recessive microcephaly 5 (MCPH5);	2.49	1.32
SLC26A4	ENSG00000091137	NM_000441.2(SLC26A4):c.1905G>A (p.Glu635=)	GAG	GAA	Pendred syndrome (PDS);	0.86	-0.22
PCNT	ENSG00000160299	NM_006031.6(PCNT):c.6819G>A (p.Gly2273=)	GGG	GGA	Microcephalic osteodysplastic primordial dwarfism type II (MOPD2)	1.13	0.17
PEX19	ENSG00000162735	NM_002857.3(PEX19):c.402T>C (p.Ser134=)	AGT	AGC	Peroxisome biogenesis disorder 12A (PBD12A)	1.4	0.48
IGF1R	ENSG00000140443	NM_000875.5(IGF1R):c.2745G>A (p.Ser915=)	TCG	TCA	Growth delay due to insulin-like growth factor I resistance;	3.5	1.81
CHRNA1	ENSG00000138435	NM_001039523.3(CHRNA1):c.1407C>T (p.Ala469=)	GCC	GCT	Congenital myasthenic syndrome (CMS);Lethal multiple pterygium syndrome (LMPS)	0.74	-0.44
ERCC8	ENSG00000049167	NM_000082.3(ERCC8):c.66G>A (p.Glu22=)	GAG	GAA	Cockayne syndrome type A (CSA);	0.86	-0.22
IL10RA	ENSG00000110324	NM_001558.4(IL10RA):c.96G>A (p.Val32=)	GTG	GTA	Inflammatory bowel disease 28, autosomal recessive (IBD28)	0.3	-1.74
GAA	ENSG00000171298	NM_000152.5(GAA):c.510C>T (p.Asp170=)	GAC	GAT	Glycogen storage disease, type II (GSD2)	0.99	-0.01
ATM	ENSG00000149311	NM_000051.3(ATM):c.6891A>G (p.Gln2297=)	CAA	CAG	Ataxia-telangiectasia syndrome (AT);Hereditary cancer-predisposing syndrome	2.49	1.32
DNM2	ENSG00000079805	NM_001005360.2(DNM2):c.2418G>A (p.Ala806=)	GCG	GCA	Myopathy, centronuclear, 1 (CNM1);Charcot-Marie-Tooth disease, dominant intermediate B (CMTDIB)	2.88	1.52
PDE6C	ENSG00000095464	NM_006204.4(PDE6C):c.252G>T (p.Leu84=)	CTG	CTT	Achromatopsia;Cone dystrophy 4 (COD4)	0.39	-1.35
IL10RA	ENSG00000110324	NM_001558.4(IL10RA):c.72A>C (p.Thr24=)	ACA	ACC	Inflammatory bowel disease 28, autosomal recessive (IBD28);	1.07	0.1
MAN1B1	ENSG00000177239	NM_016219.5(MAN1B1):c.1312C>T (p.Leu438=)	CTG	TTG	Mental retardation, autosomal recessive 15 (RAFQS)	0.37	-1.42
CHRND	ENSG00000135902	NM_000751.3(CHRND):c.411C>T (p.Gly137=)	GGC	GGT	Congenital myasthenic syndrome (CMS);Lethal multiple pterygium syndrome (LMPS)	0.55	-0.87
DGUOK	ENSG00000114956	NM_080916.3(DGUOK):c.664C>T (p.Leu222=)	CTG	TTG	Mitochondrial DNA-depletion syndrome 3, hepatocerebral (MTDPS3);	0.37	-1.42
STK11	ENSG00000118046	NM_000455.4(STK11):c.1245C>T (p.Arg415=)	CGC	CGT	Peutz-Jeghers syndrome (PJS);Hereditary cancer-predisposing syndrome	0.52	-0.93
CNTNAP2	ENSG00000174469	NM_014141.6(CNTNAP2):c.2340A>G (p.Ser780=)	TCA	TCG	Pitt-Hopkins-like syndrome 1 (PTHSL1)	0.29	-1.81
SGSH	ENSG00000181523	NM_000199.5(SGSH):c.1296C>T (p.Tyr432=)	TAC	TAT	Mucopolysaccharidosis, MPS-III-A (MPS3A)	0.9	-0.15

PEX12	ENSG00000108733	NM_000286.3(PEX12):c.84T>C (p.Ser28=)	AGT	AGC	Peroxisome biogenesis disorder 3A (PBD3A)	1.4	0.48
PEX12	ENSG00000108733	NM_000286.3(PEX12):c.1002G>A (p.Arg334=)	AGG	AGA	Peroxisome biogenesis disorder 3A (PBD3A)	1.1	0.14
IFT140	ENSG00000187535	NM_014714.4(IFT140):c.2787G>A (p.Thr929=)	ACG	ACA	Saldino-Mainzer syndrome (SRTD9)	2.96	1.57
MSH6	ENSG00000116062	NM_000179.2(MSH6):c.1740G>T (p.Ser580=)	TCG	TCT	Hereditary nonpolyposis colorectal neoplasms;Hereditary cancer-predisposing syndrome	4.18	2.06
CAPN3	ENSG00000092529	NM_000070.3(CAPN3):c.1437C>T (p.Ser479=)	AGC	AGT	Limb-girdle muscular dystrophy, type 2A (LGMDR1)	0.72	-0.48
MPI	ENSG00000178802	NM_002435.3(MPI):c.678C>A (p.Ala226=)	GCC	GCA	MPI-CDG	0.67	-0.59
CTSD	ENSG00000117984	NM_001909.5(CTSD):c.111G>A (p.Ser37=)	TCG	TCA	Neuronal ceroid lipofuscinosis;	3.5	1.81
NPC1	ENSG00000141458	NM_000271.5(NPC1):c.3717C>T (p.His1239=)	CAC	CAT	Niemann-Pick disease type C1 (NPC1)	0.81	-0.3
CAPN3	ENSG00000092529	NM_000070.3(CAPN3):c.1947G>A (p.Glu649=)	GAG	GAA	Limb-girdle muscular dystrophy, type 2A (LGMDR1)	0.86	-0.22
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.12099C>T (p.His4033=)	CAC	CAT	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	0.81	-0.3
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.18090C>T (p.Ser6030=)	TCC	TCT	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	0.98	-0.03
DYNC2H1	ENSG00000187240	NM_001377.3(DYNC2H1):c.3012T>C (p.Gly1004=)	GGT	GGC	Short Rib Polydactyly Syndrome;Jeune thoracic dystrophy (ATD1);	1.82	0.87
AICDA	ENSG00000111732	NM_020661.4(AICDA):c.48A>G (p.Lys16=)	AAA	AAG	Hyper-IgM syndrome type 2;	1.15	0.2
VSX2	ENSG00000119614	NM_182894.3(VSX2):c.750G>A (p.Pro250=)	CCG	CCA	Microphthalmia, isolated, with coloboma 3 (MCOPCB3);Microphthalmia, isolated 2 (MCOP2);Microphthalmia	3.05	1.61
C8orf37	ENSG00000156172	NM_177965.4(C8orf37):c.528A>G (p.Thr176=)	ACA	ACG	Retinitis pigmentosa (RP);Cone-rod dystrophy 16 (CORD16);	0.34	-1.57
ARX	ENSG00000004848	NM_139058.3(ARX):c.300G>A (p.Ala100=)	GCG	GCA	Epileptic encephalopathy, early infantile, 1 (DEE1);Mental retardation, with or without seizures, ARX-related, X-linked (MRXARX)	2.88	1.52
CPT2	ENSG00000157184	NM_000098.3(CPT2):c.1806T>C (p.Phe602=)	TTT	TTC	Carnitine palmitoyltransferase II deficiency (CPT2);	1.02	0.02
TWNK	ENSG00000107815	NM_021830.5(TWNK):c.384C>T (p.Ser128=)	AGC	AGT	Infantile onset spinocerebellar ataxia (MTDPS7); Sensory ataxic neuropathy-dysarthria-ophthalmoparesis syndrome (SANDO);Autosomal dominant progressive external ophthalmoplegia with mitochondrial DNA deletions 3 (PEOA3);Autosomal recessive cerebellar ataxia	0.72	-0.48
KIF1A	ENSG00000130294	NM_004321.7(KIF1A):c.3585C>T (p.Arg1195=)	CGC	CGT	Spastic paraplegia 30, autosomal recessive (SPG30); Spastic paraplegia 30, autosomal recessive (SPG30);Hereditary sensory and autonomic neuropathy type IIC (HSN2C);Intellectual disability, autosomal dominant 9 (NESCAVS);History of neurodevelopmental disorder	0.52	-0.93
FH	ENSG00000091483	NM_000143.3(FH):c.33G>C (p.Ser11=)	TCG	TCC	Multiple Cutaneous and Uterine Leiomyomas;Fumarase deficiency (FMRD);Hereditary leiomyomatosis and renal cell cancer (HLRCC);Hereditary cancer-predisposing syndrome;	4.26	2.09
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.5094C>T (p.Ala1698=)	GCC	GCT	Lissencephaly, Recessive;Familial thoracic aortic aneurysm and aortic dissection (TAAD);Aortic aneurysm, familial thoracic 4 (AAT4);	0.74	-0.44
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.5094C>T (p.Ile1698=)	ATC	ATT	Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	0.89	-0.17
PGM1	ENSG00000079739	NM_002633.3(PGM1):c.900T>C (p.His300=)	CAT	CAC	Congenital disorder of glycosylation (CDG);Congenital disorder of glycosylation type 1t (CDG1T);	1.23	0.3
DHCR7	ENSG00000172893	NM_001360.2(DHCR7):c.927C>A (p.Gly309=)	GGC	GGA	Smith-Lemli-Opitz syndrome (SLOS);History of neurodevelopmental disorder	0.87	-0.2
EYS	ENSG00000188107	NM_001142800.2(EYS):c.2613C>T (p.Asp871=)	GAC	GAT	Retinitis pigmentosa (RP); Retinitis pigmentosa 25 (RP25)	0.99	-0.01
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.3075G>A (p.Thr1025=)	ACG	ACA	Cohen syndrome (COH1);History of neurodevelopmental disorder	2.96	1.57

PKHD1	ENSG00000170927	NM_138694.4(PKHD1):c.11007G>A (p.Ser3669=)	TCG	TCA	Autosomal recessive polycystic kidney disease (ARPKD);	3.5	1.81
MFN2	ENSG00000116688	NM_014874.3(MFN2):c.1269G>A (p.Thr423=)	ACG	ACA	Hereditary motor and sensory neuropathy with optic atrophy (HMSN6A);Charcot-Marie-Tooth disease, type 2;Charcot-Marie-Tooth disease	2.96	1.57
POR	ENSG00000127948	NM_000941.3(POR):c.687C>T (p.Ala229=)	GCC	GCT	Disordered steroidogenesis due to cytochrome p450 oxidoreductase deficiency (ABS1);none provided	0.74	-0.44
VSX2	ENSG00000119614	NM_182894.3(VSX2):c.939T>A (p.Ala313=)	GCT	GCA	Microphthalmia, isolated, with coloboma 3 (MCOPCB3);Microphthalmia, isolated 2 (MCOP2);Microphthalmia	0.9	-0.14
LAMA2	ENSG00000196569	NM_000426.3(LAMA2):c.8223G>A (p.Thr2741=)	ACG	ACA	Congenital muscular dystrophy due to partial LAMA2 deficiency; Laminin alpha 2-related dystrophy (LAMA2-RD)	2.96	1.57
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.1041A>G (p.Ser347=)	TCA	TCG	Cohen syndrome (COH1);History of neurodevelopmental disorder	0.29	-1.81
SUCLG1	ENSG00000163541	NM_003849.4(SUCLG1):c.345T>C (p.Ala115=)	GCT	GCC	Mitochondrial DNA depletion syndrome;Mitochondrial DNA depletion syndrome 9 (encephalomyopathic with methylmalonic aciduria) (MTDPS9);	1.36	0.44
CHD7	ENSG00000171316	NM_017780.4(CHD7):c.3222C>T (p.Ser1074=)	TCC	TCT	Hypogonadism with anosmia (KS);CHARGE association (CHARGE);History of neurodevelopmental disorder	0.98	-0.03
CERKL	ENSG00000188452	NM_201548.5(CERKL):c.735G>C (p.Leu245=)	CTG	CTC	Retinitis pigmentosa (RP); Retinitis pigmentosa 26 (RP26)	0.49	-1.02
MBD5	ENSG00000204406	NM_018328.4(MBD5):c.4158C>T (p.Gly1386=)	GGC	GGT	Mental retardation, autosomal dominant 1 (MRD1);	0.55	-0.87
COL3A1	ENSG00000168542	NM_000090.3(COL3A1):c.2490G>A (p.Pro830=)	CCG	CCA	Ehlers-Danlos syndrome, type 4 (EDSVASC);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	3.05	1.61
POLE	ENSG00000177084	NM_006231.3(POLE):c.2964G>A (p.Ser988=)	TCG	TCA	Colorectal cancer, susceptibility to, 12 (CRCS12); Hereditary cancer-predisposing syndrome	3.5	1.81
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.12705G>A (p.Pro4235=)	CCG	CCA	Autosomal dominant cerebellar ataxia;Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O);History of neurodevelopmental disorder	3.05	1.61
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.5421C>T (p.Ala1807=)	GCC	GCT	Lissencephaly, Recessive;Aortic aneurysm, familial thoracic 4 (AAT4);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.74	-0.44
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.5277C>T (p.Val1759=)	GTC	GTT	Lissencephaly, Recessive;Familial thoracic aortic aneurysm and aortic dissection (TAAD); Aortic aneurysm, familial thoracic 4 (AAT4)	0.88	-0.19
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.15175C>T (p.Leu5059=)	CTG	TTG	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4);Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	0.37	-1.42
INSR	ENSG00000171105	NM_000208.4(INSR):c.2736G>A (p.Arg912=)	AGG	AGA	Insulin-resistant diabetes mellitus AND acanthosis nigricans;Leprechaunism syndrome;Pineal hyperplasia AND diabetes mellitus syndrome	1.1	0.14
PEX2	ENSG00000164751	NM_000318.3(PEX2):c.447T>G (p.Gly149=)	GGT	GGG	Peroxisome biogenesis disorder 5a (zellweger) (PBD5A);Zellweger syndrome (ZS)	1.41	0.5
PEX1	ENSG00000127980	NM_000466.3(PEX1):c.1725G>A (p.Leu575=)	CTG	CTA	Peroxisome biogenesis disorder 1A (Zellweger) (PBD1A);Zellweger syndrome (ZS)	0.21	-2.27
PROP1	ENSG00000175325	NM_006261.4(PROP1):c.471C>T (p.Tyr157=)	TAC	TAT	Pituitary hormone deficiency, combined 2 (CPHD2)	0.9	-0.15
LOXHD1	ENSG00000167210	NM_144612.6(LOXHD1):c.5328G>A (p.Glu1776=)	GAG	GAA	Deafness, autosomal recessive 77 (DFNB77)	0.86	-0.22
GALT	ENSG00000213930	NM_000155.4(GALT):c.864C>T (p.Asn288=)	AAC	AAT	Deficiency of UDPglucose-hexose-1-phosphate uridylyltransferase (GALAC1);Galactosemia	1.01	0.02
COL4A3	ENSG00000169031	NM_000091.4(COL4A3):c.4825C>A (p.Arg1609=)	CGA	AGA	Alport syndrome; Alport syndrome 3, autosomal dominant (ATS3)	2.09	1.06

POMGNT1	ENSG00000085998	NM_017739.3(POMGNT1):c.486A>G (p.Leu162=)	CTA	CTG	Congenital Muscular Dystrophy, alpha-dystroglycan related; Limb-girdle muscular dystrophy-dystroglycanopathy, type C3 (MDDGC3);Limb-girdle muscular dystrophy-dystroglycanopathy, type C3 (MDDGC3);Congenital muscular dystrophy-dystroglycanopathy with mental retardation, type B3 (MDDGB3)	4.81	2.27
FH	ENSG00000091483	NM_000143.3(FH):c.1443C>G (p.Thr481=)	ACC	ACG	Multiple Cutaneous and Uterine Leiomyomas;Fumarase deficiency (FMRD);Hereditary leiomyomatosis and renal cell cancer (HLRCC);Hereditary cancer-predisposing syndrome	0.31	-1.67
CDH1	ENSG00000039068	NM_004360.5(CDH1):c.408A>G (p.Gln136=)	CAA	CAG	Hereditary diffuse gastric cancer (HDGC);Hereditary cancer-predisposing syndrome;	2.49	1.32
BARD1	ENSG00000138376	NM_000465.4(BARD1):c.684A>G (p.Glu228=)	GAA	GAG	Hereditary cancer-predisposing syndrome; Familial cancer of breast	1.16	0.22
CHST3	ENSG00000122863	NM_004273.5(CHST3):c.828C>T (p.Arg276=)	CGC	CGT	Larsen syndrome (LRS);Spondyloepiphyseal dysplasia with congenital joint dislocations (SEDCJD);Skeletal dysplasia;Spondyloepiphyseal dysplasia congenita (SEDC)	0.52	-0.93
BRCA1	ENSG00000012048	NM_007294.4(BRCA1):c.1881C>G (p.Val627=)	GTC	GTG	Breast-ovarian cancer, familial 1 (BROVCA1);Hereditary cancer-predisposing syndrome;	1.92	0.94
CHST3	ENSG00000122863	NM_004273.5(CHST3):c.1197C>T (p.Asp399=)	GAC	GAT	Larsen syndrome (LRS);Spondyloepiphyseal dysplasia with congenital joint dislocations (SEDCJD);Spondyloepiphyseal dysplasia congenita (SEDC);Skeletal dysplasia	0.99	-0.01
CHST3	ENSG00000122863	NM_004273.5(CHST3):c.1347C>T (p.Arg449=)	CGC	CGT	Skeletal dysplasia;Spondyloepiphyseal dysplasia with congenital joint dislocations (SEDCJD);Larsen syndrome (LRS);Spondyloepiphyseal dysplasia congenita (SEDC);	0.52	-0.93
NF1	ENSG00000196712	NM_000267.3(NF1):c.3891A>G (p.Leu1297=)	CTA	CTG	Neurofibromatosis, familial spinal (FSNF);Neurofibromatosis, type 1 (NF1);Neurofibromatosis-Noonan syndrome (NFNS);Café-au-lait macules with pulmonary stenosis (WTSN);Hereditary cancer-predisposing syndrome	4.81	2.27
SCN5A	ENSG00000183873	NM_198056.2(SCN5A):c.2988C>T (p.Ala996=)	GCC	GCT	Long QT syndrome (LQTS);Brugada syndrome;Paroxysmal familial ventricular fibrillation;Progressive familial heart block;Sick sinus syndrome;Dilated Cardiomyopathy, Dominant;Romano-Ward syndrome (RWS);Arrhythmia	0.74	-0.44
MYH9	ENSG00000100345	NM_002473.6(MYH9):c.4818G>A (p.Ser1606=)	TCG	TCA	Autosomal dominant nonsyndromic deafness 17 (DFNA17); MYH9-related disorder;	3.5	1.81
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.11127A>G (p.Glu3709=)	GAA	GAG	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	1.16	0.22
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.11355G>A (p.Arg3785=)	AGG	AGA	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	1.1	0.14
SYNE1	ENSG00000131018	NM_182961.4(SYNE1):c.24555C>T (p.Ile8185=)	ATC	ATT	Spinocerebellar ataxia, autosomal recessive 8 (SCAR8); Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4); Spinocerebellar ataxia, autosomal recessive 8 (SCAR8);Emery-Dreifuss muscular dystrophy 4, autosomal dominant (EDMD4)	0.89	-0.17
COL2A1	ENSG00000139219	NM_001844.5(COL2A1):c.3786C>G (p.Leu1262=)	CTC	CTG	Stickler syndrome type 1 (STL1); Type II Collagenopathies;Connective tissue disease;	2.02	1.02
MSH2	ENSG00000095002	NM_000251.3(MSH2):c.1563T>C (p.Tyr521=)	TAT	TAC	Lynch syndrome;Hereditary cancer-predisposing syndrome; Lynch syndrome I (COCA1);Hereditary nonpolyposis colorectal neoplasms;	1.11	0.15

NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.4248G>A (p.Pro1416=)	CCG	CCA	History of neurodevelopmental disorder;Pitt-Hopkins-like syndrome 2 (PTHSL2)	3.05	1.61
MYLK	ENSG00000065534	NM_053025.4(MYLK):c.3915C>T (p.Cys1305=)	TGC	TGT	Aortic aneurysm, familial thoracic 7 (AAT7)	0.97	-0.05
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.1440C>T (p.Phe480=)	TTC	TTT	History of neurodevelopmental disorder;Cohen syndrome (COH1)	0.98	-0.02
PLCB1	ENSG00000182621	NM_015192.4(PLCB1):c.1230G>A (p.Ser410=)	TCG	TCA	Seizures;Early infantile epileptic encephalopathy 12 (DEE12)	3.5	1.81
PLCB1	ENSG00000182621	NM_015192.4(PLCB1):c.1881G>A (p.Gln627=)	CAG	CAA	Seizures;Early infantile epileptic encephalopathy 12 (DEE12)	0.4	-1.32
VPS13B	ENSG00000132549	NM_017890.4(VPS13B):c.5682G>A (p.Thr1894=)	ACG	ACA	History of neurodevelopmental disorder;Cohen syndrome (COH1)	2.96	1.57
PSEN2	ENSG00000143801	NM_000447.3(PSEN2):c.336C>T (p.Tyr112=)	TAC	TAT	Dilated cardiomyopathy 1V (CMD1V); Alzheimer disease, type 4 (AD4)	0.9	-0.15
PLCB1	ENSG00000182621	NM_015192.4(PLCB1):c.2841A>G (p.Glu947=)	GAA	GAG	Seizures;Early infantile epileptic encephalopathy 12 (DEE12)	1.16	0.22
TSEN2	ENSG00000154743	NM_025265.4(TSEN2):c.1332A>G (p.Lys444=)	AAA	AAG	Pontoneocerebellar hypoplasia;	1.15	0.2
FAM161A	ENSG00000170264	NM_001201543.2(FAM161A):c.2064T>C (p.Ile688=)	ATT	ATC	Retinitis pigmentosa (RP);Retinitis pigmentosa 28 (RP28);	1.13	0.17
CDK5RAP2	ENSG00000136861	NM_018249.6(CDK5RAP2):c.1218G>A (p.Gln406=)	CAG	CAA	Primary autosomal recessive microcephaly 3 (MCPH3);	0.4	-1.32
PIGV	ENSG00000060642	NM_017837.3(PIGV):c.348G>A (p.Leu116=)	CTG	CTA	Hyperphosphatasia with mental retardation syndrome 1 (HPMRS1);	0.21	-2.27
STIL	ENSG00000123473	NM_001048166.1(STIL):c.1005A>G (p.Glu335=)	GAA	GAG	Primary autosomal recessive microcephaly 7 (MCPH7);	1.16	0.22
ASPM	ENSG00000066279	NM_018136.5(ASPM):c.7551T>C (p.Tyr2517=)	TAT	TAC	Primary autosomal recessive microcephaly 5 (MCPH5);	1.11	0.15
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.6339G>A (p.Arg2113=)	AGG	AGA	Autosomal dominant cerebellar ataxia; Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O)	1.1	0.14
PRKAR1A	ENSG00000108946	NM_212472.2(PRKAR1A):c.309G>A (p.Glu103=)	GAG	GAA	Acrodysostosis 1 with or without hormone resistance (ACRDYS1);Hereditary cancer-predisposing syndrome;Carney complex, type 1 (CNC1)	0.86	-0.22
POLG	ENSG00000140521	NM_002693.2(POLG):c.1905G>A (p.Pro635=)	CCG	CCA	POLG-Related Spectrum Disorders;	3.05	1.61
DYNC1H1	ENSG00000197102	NM_001376.5(DYNC1H1):c.11913C>G (p.Pro3971=)	CCC	CCG	Autosomal dominant cerebellar ataxia; Charcot-Marie-Tooth disease, axonal, type 2O (CMT2O)	0.33	-1.62
SMPD1	ENSG00000166311	NM_000543.5(SMPD1):c.297C>G (p.Thr99=)	ACC	ACG	Niemann-Pick disease, type A;Niemann-Pick disease, type B;Niemann-Pick disease, type A;Sphingomyelin/cholesterol lipidosis	0.31	-1.67
TRMU	ENSG00000100416	NM_018006.5(TRMU):c.1218C>T (p.Ser406=)	AGC	AGT	Acute infantile liver failure due to synthesis defect of mtDNA-encoded proteins;	0.72	-0.48
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.4998C>T (p.Thr1666=)	ACC	ACT	Cardiovascular phenotype;Familial thoracic aortic aneurysm and aortic dissection (TAAD); Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD);Geleophysic dysplasia;Weill-Marchesani syndrome;Ectopia lentis, isolated, autosomal dominant (ECTOL1);Acromicric dysplasia (ACMICD);Stiff skin syndrome (SSKS);Marfan syndrome (MFS)	0.8	-0.31
RELN	ENSG00000189056	NM_005045.4(RELN):c.5136G>A (p.Thr1712=)	ACG	ACA	Norman-Roberts syndrome (LIS2); Norman-Roberts syndrome (LIS2);Epilepsy, familial temporal lobe, 7 (ETL7)	2.96	1.57
MYH11	ENSG00000133392	NM_002474.3(MYH11):c.4899C>T (p.Ala1633=)	GCC	GCT	Lissencephaly, Recessive; Aortic aneurysm, familial thoracic 4 (AAT4);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	0.74	-0.44
UGT1A6	ENSG00000242366	NM_001072.4(UGT1A6):c.862-6606C>T	ATC	ATT	Hyperbilirubinemia; Lucey-Driscoll syndrome (HBLRTFN);Crigler-Najjar syndrome	0.89	-0.17
COL11A1	ENSG00000060718	NM_001854.4(COL11A1):c.3639G>A (p.Gly1213=)	GGG	GGA	Fibrochondrogenesis 1 (FBCG1);Stickler syndrome type 2 (STL2);	1.13	0.17
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.3219C>T (p.Asn1073=)	AAC	AAT	History of neurodevelopmental disorder;Pitt-Hopkins-like syndrome 2 (PTHSL2)	1.01	0.02

MSH6	ENSG00000116062	NM_000179.3(MSH6):c.3936T>C (p.Val1312=)	GTT	GTC	Lynch syndrome; Hereditary cancer-predisposing syndrome;Hereditary nonpolyposis colorectal neoplasms;Hereditary nonpolyposis colorectal cancer type 5 (HNPCC5)	1.14	0.19
RYR1	ENSG00000196218	NM_000540.2(RYR1):c.3924G>C (p.Pro1308=)	CCG	CCC	Malignant hyperthermia, susceptibility to, 1 (MHS1);Central core myopathy (CCD);Neuromuscular disease, congenital, with uniform type 1 fiber (CNMDU1);Minicore myopathy with external ophthalmoplegia; RYR1-Related Disorders	3.07	1.62
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.7992T>A (p.Ile2664=)	ATT	ATA	Hereditary cancer-predisposing syndrome;Breast-ovarian cancer, familial 2 (BROVCA2); Breast and/or ovarian cancer;Hereditary breast and ovarian cancer syndrome (HBOC);Breast-ovarian cancer, familial 2 (BROVCA2);Hereditary breast and ovarian cancer syndrome (HBOC)	0.49	-1.02
ABCB4	ENSG00000005471	NM_000443.4(ABCB4):c.3037A>C (p.Arg1013=)	AGA	CGA	Progressive familial intrahepatic cholestasis 3 (PFIC3); Cholestasis, intrahepatic, of pregnancy 3 (ICP3);	0.48	-1.06
DNM2	ENSG00000079805	NM_001005360.2(DNM2):c.633C>T (p.Asp211=)	GAC	GAT	Myopathy, centronuclear, 1 (CNM1); Charcot-Marie-Tooth disease, dominant intermediate B (CMTDIB)	0.99	-0.01
TPP1	ENSG00000166340	NM_000391.4(TPP1):c.225A>G (p.Gln75=)	CAA	CAG	Ceroid lipofuscinosis neuronal 2 (CLN2);Neuronal ceroid lipofuscinosis	2.49	1.32
PRRT2	ENSG00000167371	NM_145239.3(PRRT2):c.1011C>T (p.Gly337=)	GGC	GGT	Paroxysmal kinesigenic dyskinesia (EKD1)	0.55	-0.87
PALB2	ENSG00000083093	NM_024675.3(PALB2):c.2559C>T (p.Gly853=)	GGC	GGT	Familial cancer of breast;Hereditary cancer-predisposing syndrome; Familial cancer of breast;Hereditary cancer-predisposing syndrome	0.55	-0.87
BRCA2	ENSG00000139618	NM_000059.3(BRCA2):c.9057A>G (p.Lys3019=)	AAA	AAG	Hereditary breast and ovarian cancer syndrome (HBOC);Hereditary cancer-predisposing syndrome	1.15	0.2
PKP2	ENSG00000057294	NM_001005242.3(PKP2):c.2352C>T (p.Gly784=)	GGC	GGT	Arrhythmogenic right ventricular dysplasia 9 (ARVD9);Cardiomyopathy (CMYO)	0.55	-0.87
NPC1	ENSG00000141458	NM_000271.5(NPC1):c.2292G>A (p.Ala764=)	GCG	GCA	Niemann-Pick disease type C1 (NPC1)	2.88	1.52
AIFM1	ENSG00000156709	NM_004208.4(AIFM1):c.720C>T (p.Asp240=)	GAC	GAT	AIFM1-related hypomyelination with spondylometaphyseal dysplasia;Spondyloepimetaphyseal dysplasia, X-linked, with hypomyelinating leukodystrophy (SEMDHL)	0.99	-0.01
PTCH1	ENSG00000185920	NM_000264.5(PTCH1):c.297C>T (p.Gly99=)	GGC	GGT	Gorlin syndrome (BCNS);Hereditary cancer-predisposing syndrome	0.55	-0.87
RET	ENSG00000165731	NM_020975.6(RET):c.1947G>A (p.Ser649=)	TCG	TCA	Congenital central hypoventilation (CCHS);Hirschsprung disease 1 (HSCR1);Multiple endocrine neoplasia, type 2b (MEN2B);Pheochromocytoma;Familial medullary thyroid carcinoma (MTC);Multiple endocrine neoplasia, type 2a (MEN2A);Multiple endocrine neoplasia, type 2 (MEN2)	3.5	1.81
PRKAG2	ENSG00000106617	NM_016203.4(PRKAG2):c.138G>A (p.Pro46=)	CCG	CCA	Familial hypertrophic cardiomyopathy 6 (CMH6);Wolff-Parkinson-White pattern; Cardiomyopathy (CMYO)	3.05	1.61
PSAP	ENSG00000197746	NM_002778.4(PSAP):c.1476T>C (p.Thr492=)	ACT	ACC	Krabbe disease, atypical, due to saposin A deficiency;Combined saposin deficiency;Gaucher disease, atypical, due to saposin C deficiency;Sphingolipid activator protein 1 deficiency	1.24	0.31
CASR	ENSG00000036828	NM_000388.4(CASR):c.2064C>T (p.Phe688=)	TTC	TTT	Hypocalciuric hypercalcemia, familial, type 1 (HHC1);Hypocalcemia, autosomal dominant 1 (HYPOC1);Familial isolated hypoparathyroidism (FIH);Neonatal severe hyperparathyroidism (NSHPT); Inborn genetic diseases;Familial hypocalciuric hypercalcemia (FHH);Hypocalcemia, autosomal dominant 1 (HYPOC1)	0.98	-0.02

PSEN2	ENSG00000143801	NM_000447.3(PSEN2):c.690C>G (p.Ala230=)	GCC	GCG	Dilated cardiomyopathy 1V (CMD1V); Alzheimer disease, type 4 (AD4)	0.23	-2.11
LIPA	ENSG00000107798	NM_000235.4(LIPA):c.891C>T (p.Ser297=)	AGC	AGT	Wolman disease; Lysosomal acid lipase deficiency	0.72	-0.48
HSPG2	ENSG00000142798	NM_005529.7(HSPG2):c.8961C>T (p.Gly2987=)	GGC	GGT	Lethal Kniest-like syndrome (DDSH);Schwartz-Jampel syndrome;	0.55	-0.87
HSPG2	ENSG00000142798	NM_005529.7(HSPG2):c.6141T>C (p.Asp2047=)	GAT	GAC	Lethal Kniest-like syndrome (DDSH);Schwartz-Jampel syndrome;	1.01	0.01
LIPA	ENSG00000107798	NM_000235.4(LIPA):c.615C>T (p.Ser205=)	TCC	TCT	Wolman disease; Lysosomal acid lipase deficiency	0.98	-0.03
LAMA3	ENSG00000053747	NM_198129.3(LAMA3):c.8829G>A (p.Arg2943=)	AGG	AGA	Junctional epidermolysis bullosa gravis of Herlitz;Laryngo-onycho-cutaneous syndrome;	1.1	0.14
LEP	ENSG00000174697	NM_000230.3(LEP):c.21C>T (p.Cys7=)	TGC	TGT	Leptin deficiency or dysfunction (LEPD);Monogenic Non-Syndromic Obesity;	0.97	-0.05
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.4125C>T (p.Leu1375=)	CTC	CTT	Miyoshi myopathy;Limb-Girdle Muscular Dystrophy, Recessive;Qualitative or quantitative defects of dysferlin	0.8	-0.33
PALB2	ENSG00000083093	NM_024675.3(PALB2):c.2571G>A (p.Leu857=)	TTG	TTA	Familial cancer of breast; Hereditary cancer-predisposing syndrome	0.65	-0.61
NRXN1	ENSG00000179915	NM_001330078.2(NRXN1):c.600C>T (p.Gly200=)	GGC	GGT	Pitt-Hopkins-like syndrome 2 (PTHSL2);Schizophrenia 17 (SCZD17);Pitt-Hopkins-like syndrome 2 (PTHSL2)	0.55	-0.87
ATM	ENSG00000149311	NM_000051.3(ATM):c.8187A>G (p.Gln2729=)	CAA	CAG	Ataxia-telangiectasia syndrome (AT);Hereditary cancer-predisposing syndrome	2.49	1.32
PEX7	ENSG00000112357	NM_000288.4(PEX7):c.94C>T (p.Leu32=)	CTG	TTG	Rhizomelic chondrodysplasia punctata type 1 (RCDP1); Peroxisome biogenesis disorder 9B (PBD9B)	0.37	-1.42
SEMA4A	ENSG00000196189	NM_022367.4(SEMA4A):c.1086A>C (p.Ser362=)	TCA	TCC	Cone-rod dystrophy 10 (CORD10);Retinitis Pigmentosa, Recessive; Retinitis pigmentosa (RP)	1.22	0.29
HSPG2	ENSG00000142798	NM_005529.7(HSPG2):c.10512C>T (p.His3504=)	CAC	CAT	Schwartz-Jampel syndrome;Lethal Kniest-like syndrome (DDSH); none provided	0.81	-0.3
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.1917G>A (p.Gly639=)	GGG	GGA	Miyoshi myopathy;Limb-Girdle Muscular Dystrophy, Recessive;Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	1.13	0.17
ATM	ENSG00000149311	NM_000051.3(ATM):c.1695A>G (p.Glu565=)	GAA	GAG	Ataxia-telangiectasia syndrome (AT); Hereditary cancer-predisposing syndrome;	1.16	0.22
ATM	ENSG00000149311	NM_000051.3(ATM):c.7566A>G (p.Gln2522=)	CAA	CAG	Ataxia-telangiectasia syndrome (AT); Hereditary cancer-predisposing syndrome;	2.49	1.32
CAPN3	ENSG00000092529	NM_000070.3(CAPN3):c.1830C>T (p.Asn610=)	AAC	AAT	Limb-Girdle Muscular Dystrophy, Recessive;Limb-girdle muscular dystrophy, type 2A (LGMDR1);	1.01	0.02
VLDLR	ENSG00000147852	NM_003383.5(VLDLR):c.792C>T (p.Cys264=)	TGC	TGT	Congenital cerebellar hypoplasia (CHEGDD); Cerebellar ataxia, mental retardation, and dysequilibrium syndrome 1 (CAMRQ1)	0.97	-0.05
CHST3	ENSG00000122863	NM_004273.5(CHST3):c.570C>T (p.Asp190=)	GAC	GAT	Spondyloepiphyseal dysplasia congenita (SEDC);Larsen syndrome (LRS);Spondyloepiphyseal dysplasia with congenital joint dislocations (SEDCJD);Skeletal dysplasia	0.99	-0.01
CHST3	ENSG00000122863	NM_004273.5(CHST3):c.1251G>C (p.Thr417=)	ACG	ACC	Spondyloepiphyseal dysplasia congenita (SEDC);Skeletal dysplasia;Spondyloepiphyseal dysplasia with congenital joint dislocations (SEDCJD);Larsen syndrome (LRS)	3.18	1.67
CAPN3	ENSG00000092529	NM_000070.3(CAPN3):c.1557C>T (p.His519=)	CAC	CAT	Limb-Girdle Muscular Dystrophy, Recessive;Limb-girdle muscular dystrophy, type 2A (LGMDR1);	0.81	-0.3
DSC2	ENSG00000134755	NM_024422.6(DSC2):c.408A>G (p.Arg136=)	AGA	AGG	Cardiovascular phenotype;Arrhythmogenic right ventricular cardiomyopathy, type 11 (ARVD11);Cardiomyopathy (CMYO)	0.91	-0.14
TAFAZZIN	ENSG00000102125	NM_000116.5(TAFAZZIN):c.504G>A (p.Lys168=)	AAG	AAA	Cardiomyopathy, left ventricular noncompaction;Primary dilated cardiomyopathy (DCM);3-Methylglutaconic aciduria type 2 (BTHS);Endocardial fibroelastosis (EFE);	0.87	-0.2

FBN1	ENSG00000166147	NM_000138.4(FBN1):c.1602T>C (p.Cys534=)	TGT	TGC	Weill-Marchesani syndrome;Ectopia lentis;Familial thoracic aortic aneurysm and aortic dissection (TAAD);Geleophysic dysplasia;Stiff skin syndrome (SSKS);Marfan syndrome (MFS);MASS syndrome (OCTD);Acromicric dysplasia (ACMICD); Marfan syndrome (MFS);Familial thoracic aortic aneurysm and aortic dissection (TAAD)	1.03	0.05
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.1311C>T (p.Ile437=)	ATC	ATT	Miyoshi myopathy;Limb-Girdle Muscular Dystrophy, Recessive; Qualitative or quantitative defects of dysferlin	0.89	-0.17
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.225G>A (p.Thr75=)	ACG	ACA	Miyoshi myopathy;Limb-Girdle Muscular Dystrophy, Recessive; Qualitative or quantitative defects of dysferlin;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B)	2.96	1.57
ANO5	ENSG00000171714	NM_213599.2(ANO5):c.720G>T (p.Leu240=)	CTG	CTT	Limb-Girdle Muscular Dystrophy, Recessive;Miyoshi myopathy; Gnathodiaphyseal dysplasia (GDD);Limb-girdle muscular dystrophy, type 2L (LGMDR12);ANO5-Related Muscle Diseases	0.39	-1.35
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.4143C>T (p.Gly1381=)	GGC	GGT	Limb-Girdle Muscular Dystrophy, Recessive;Miyoshi myopathy; Qualitative or quantitative defects of dysferlin	0.55	-0.87
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.1008C>T (p.Asp336=)	GAC	GAT	Limb-Girdle Muscular Dystrophy, Recessive; Miyoshi myopathy;Qualitative or quantitative defects of dysferlin	0.99	-0.01
AIPL1	ENSG00000129221	NM_014336.5(AIPL1):c.780C>T (p.His260=)	CAC	CAT	Retinitis Pigmentosa, Recessive;Retinitis Pigmentosa, Dominant; Leber congenital amaurosis 4 (LCA4)	0.81	-0.3
BCS1L	ENSG00000074582	NM_001079866.2(BCS1L):c.201C>T (p.Leu67=)	CTC	CTT	Leigh syndrome (LS);GRACILE syndrome (FLNMS);Mitochondrial complex III deficiency, nuclear type 1 (MC3DN1);	0.8	-0.33
F5	ENSG00000198734	NM_000130.4(F5):c.4035A>G (p.Gln1345=)	CAA	CAG	Thrombophilia due to factor V Leiden (THPH2);Thrombophilia due to thrombin defect (THPH1);Budd-Chiari syndrome (BDCHS);Factor V deficiency	2.49	1.32
FBN1	ENSG00000166147	NM_000138.4(FBN1):c.8011C>T (p.Leu2671=)	CTG	TTG	Marfan syndrome (MFS);Weill-Marchesani syndrome;Ectopia lentis, isolated, autosomal dominant (ECTOL1);Familial thoracic aortic aneurysm and aortic dissection (TAAD);Stiff skin syndrome (SSKS);Geleophysic dysplasia;Acromicric dysplasia (ACMICD)	0.37	-1.42
DYSF	ENSG00000135636	NM_001130987.2(DYSF):c.3114G>A (p.Pro1038=)	CCG	CCA	Miyoshi myopathy;Limb-Girdle Muscular Dystrophy, Recessive;Autosomal recessive limb-girdle muscular dystrophy type 2B (LGMD2B);Qualitative or quantitative defects of dysferlin	3.05	1.61
F5	ENSG00000198734	NM_000130.4(F5):c.2868T>C (p.Tyr956=)	TAT	TAC	Budd-Chiari syndrome (BDCHS);Thrombophilia due to thrombin defect (THPH1);Factor V deficiency;Thrombophilia due to factor V Leiden (THPH2);	1.11	0.15
TTN	ENSG00000155657	NM_001267550.2(TTN):c.76296T>C (p.Asp25432=)	GAT	GAC	Dilated cardiomyopathy 1G (CMD1G);Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Tibial muscular dystrophy (TMD);	1.01	0.01
TTN	ENSG00000155657	NM_001267550.2(TTN):c.21273A>G (p.Gln7091=)	CAA	CAG	Myopathy, early-onset, with fatal cardiomyopathy (SALMY);Limb-girdle muscular dystrophy, type 2J (LGMDR10);Myopathy, myofibrillar, 9, with early respiratory failure (MFM9);Dilated cardiomyopathy 1G (CMD1G);Tibial muscular dystrophy (TMD);	2.49	1.32