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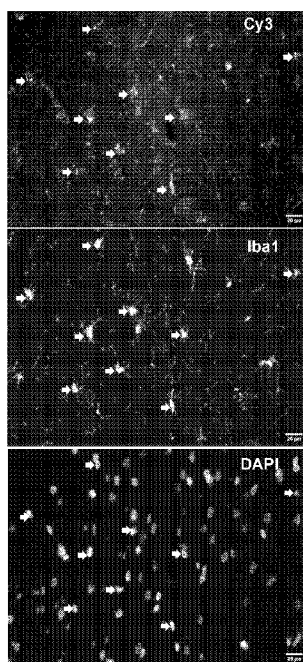
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(54) Title: MICROGLIAL GENE SILENCING USING DOUBLE-STRANDED siRNA

FIG. 1A Cortex



(57) Abstract: Microglia are an essential part of the immune system in the central nervous system, as well as potential sources of disease. Gene silencing employs short interfering RNA (siRNA) to selectively target genes that are the source of such diseases. By employing branched siRNA, distribution of the siRNA throughout the CNS, including to the resident microglial cells, may be enhanced as compared to unbranched siRNA. Methods and compositions for the use of branched siRNA in a therapy are contained herein.

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MICROGLIAL GENE SILENCING USING DOUBLE-STRANDED SIRNA**BACKGROUND OF THE INVENTION**

In many species, introduction of double-stranded RNA (dsRNA) induces potent and specific gene silencing. This phenomenon occurs in both plants and animals and has roles in viral defense and transposon silencing mechanisms. Short interfering RNAs (siRNAs), which are generally much shorter than the target gene, have been shown to be effective at gene silencing.

Microglia are a type of glial cell found in the central nervous system (CNS). Microglia are an essential component of the CNS immune system; however, microglia with dysregulated genes can also be a source of disease. For example, a disease state may precipitate as a result of overactive microglial genes or genes with reduced expression and/or activity in microglia. Therefore, silencing of effector genes or pathway regulatory genes may be needed to restore normal gene network function and ameliorate the disease state. Thus, there remains a need for new and improved therapeutics capable of permeating microglial cells and silencing microglial genes in order to restore genetic and biochemical pathway activity in microglia from a disease state towards a normal healthy state.

SUMMARY OF THE INVENTION

In an aspect, the invention features a method of delivering a branched small interfering RNA (siRNA) molecule to a microglial cell in a subject in need of microglial gene silencing. The method may include administering the branched siRNA molecule to the subject (e.g., to the central nervous system of the subject).

In some embodiments, the subject has been diagnosed as having a disease associated with expression of a dysregulated microglial gene or dysregulated microglial gene pathway. In some embodiments, the subject has been diagnosed as having a disease associated with expression and/or activity of a dysregulated microglial gene (e.g., altered expression and/or activity of a wild-type or mutated microglial gene).

In some embodiments, the dysregulated microglial gene exhibits increased expression and/or activity in microglial cells of the subject as compared to the expression and/or activity of the microglial gene in microglial cells of a reference subject. In some embodiments, the dysregulated microglial gene exhibits reduced expression and/or activity in microglial cells of the subject as compared to the expression and/or activity of the microglial gene in microglial cells of a reference subject.

In some embodiments, the microglial gene is a positive regulator of a gene for which increased expression and/or activity relative to the level of expression and/or activity observed in a reference subject is associated with a disease state.

In some embodiments, the microglial gene is a negative regulator of a gene for which decreased expression and/or activity relative to the level of expression and/or activity observed in a reference subject is associated with a disease state.

In some embodiments, the microglial gene is a splice isoform of a gene for which overexpression of the splice isoform relative to the expression of the splice isoform in a reference subject is associated with a disease state.

In some embodiments, the disease is a neuroinflammatory disease or a neurodegenerative disease. In some embodiments, the disease is Alzheimer's disease. In some embodiments, the disease

is Amyotrophic Lateral Sclerosis. In some embodiments, the disease is Parkinson's disease. In some embodiments, the disease is frontotemporal dementia. In some embodiments, the disease is Huntington's disease. In some embodiments, the disease is multiple sclerosis. In some embodiments, the disease is progressive supranuclear palsy.

In some embodiments, the dysregulated microglial gene is selected from the group consisting of ABCA7, ABI3, ADAM10, APOC1, APOE, AXL, BIN1, C1QA, C3, C9ORF72, CASS4, CCL5, CD2AP, CD33, CD68, CLPTM1, CLU, CR1, CSF1, CST7, CTSB, CTSD, CTSL, CXCL10, CXCL13, DSG2, ECHDC3, EPHA1, FABP5, FERMT2, FTH1, GNAS, GRN, HBEGF, HLA-DRB1, HLA-DRB5, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IGF1, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, ITGAX, LILRB4, LPL, MEF2C, MMP12, MS4A4A, MS4A6A, NLRP3, NME8, NOS2, PICALM, PILRA, PLCG2, PTK2B, SCIMP, SLC24A4, SORL1, SPI1, SPP1, SPPL2A, TBK1, TNF, TREM2, TREML2, TYROBP, and ZCWPW1.

In some embodiments, the subject is a mammal (e.g., a human).

In some embodiments, the branched siRNA is administered to the subject intrathecally, intracerebroventricularly, or intrastriatally.

In some embodiments, the siRNA molecule is di-branched. In some embodiments, the siRNA molecule is tri-branched. In some embodiments, the siRNA molecule is tetra-branched.

In some embodiments, the siRNA comprises (i) an antisense strand having complementarity to a portion of one or more of genes selected from the group consisting of APOE, BIN1, C1QA, C3, C9ORF72, CCL5, CD33, CLU/APOJ, CR1, CXCL10, CXCL13, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, MEF2C, MMP12, NLRP3, NOS2, PILRA, PLCG2, PTK2B, SLC24A4, TBK1, and TNF and (ii) a sense strand having complementarity to the antisense strand.

In some embodiments, the siRNA includes (i) an antisense strand having complementarity to a portion of a gene encoding a positive regulator of a gene for which increased expression and/or activity (relative, e.g., to the level of expression and/or activity observed in a reference subject) is associated with a disease state.

In some embodiments, the siRNA includes (i) an antisense strand having complementarity to a portion of a gene encoding a negative regulator of a gene for which decreased expression and/or activity (relative, e.g., to the level of expression and/or activity observed in a reference subject) is associated with a disease state.

In some embodiments, the siRNA includes (i) an antisense strand having complementarity to a splice isoform of a gene for which overexpression of the splice isoform relative to the expression of the splice isoform in a reference subject is associated with a disease state.

In any of the foregoing embodiments, the siRNA may also include (ii) a sense strand having complementarity to the antisense strand.

In some embodiment, the antisense strand has complementarity (e.g., at least 85% complementarity, such as 85% complementarity, 86% complementarity, 87% complementarity, 88% complementarity, 89% complementarity, 90% complementarity, 91% complementarity, 92% complementarity, 93% complementarity, 94% complementarity, 95% complementarity, 96% complementarity, 97% complementarity, 98% complementarity, 99% complementarity, or 100% complementarity) to a portion of at least 10 contiguous nucleotides of an mRNA molecule encoding one or more of the above genes. For example, the antisense strand may have complementarity to a portion of 10 contiguous nucleotides, 11 contiguous nucleotides, 12 contiguous nucleotides, 13 contiguous

nucleotides, 14 contiguous nucleotides, 15 contiguous nucleotides, 16 contiguous nucleotides, 17 contiguous nucleotides, 18 contiguous nucleotides, 19 contiguous nucleotides, 20 contiguous nucleotides, 21 contiguous nucleotides, 22 contiguous nucleotides, 23 contiguous nucleotides, 24 contiguous nucleotides, 25 contiguous nucleotides, 26 contiguous nucleotides, 27 contiguous nucleotides, 28 contiguous nucleotides, 29 contiguous nucleotides, 30 contiguous nucleotides, 31 contiguous nucleotides, 32 contiguous nucleotides, 33 contiguous nucleotides, 34 contiguous nucleotides, 35 contiguous nucleotides, 36 contiguous nucleotides, 37 contiguous nucleotides, 38 contiguous nucleotides, 39 contiguous nucleotides, 40 contiguous nucleotides, 41 contiguous nucleotides, 42 contiguous nucleotides, 43 contiguous nucleotides, 44 contiguous nucleotides, 45 contiguous nucleotides, 46 contiguous nucleotides, 47 contiguous nucleotides, 48 contiguous nucleotides, 49 contiguous nucleotides, or 50 contiguous nucleotides, or more, of an mRNA molecule encoding one or more of the above genes.

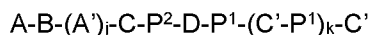
In some embodiments, the antisense strand has complementarity (e.g., at least 85% complementarity, such as 85% complementarity, 86% complementarity, 87% complementarity, 88% complementarity, 89% complementarity, 90% complementarity, 91% complementarity, 92% complementarity, 93% complementarity, 94% complementarity, 95% complementarity, 96% complementarity, 97% complementarity, 98% complementarity, 99% complementarity, or 100% complementarity) to a portion of from 10 to 50 contiguous nucleotides of an mRNA molecule encoding one or more of the above genes. For example, the antisense strand may have complementarity to a portion of from 11 contiguous nucleotides to 45 contiguous nucleotides, from 12 contiguous nucleotides to 40 contiguous nucleotides, from 13 contiguous nucleotides to 35 contiguous nucleotides, from 14 contiguous nucleotides to 30 contiguous nucleotides, from 15 contiguous nucleotides to 29 contiguous nucleotides, from 16 contiguous nucleotides to 28 contiguous nucleotides, from 17 contiguous nucleotides to 27 contiguous nucleotides, from 18 contiguous nucleotides to 26 contiguous nucleotides, or from 19 contiguous nucleotides to 22 contiguous nucleotides of an mRNA molecule encoding one or more of the above genes.

In some embodiments, the antisense strand comprises a region represented by the following chemical formula, in the 5'-to-3' direction:



wherein Z is a 5' phosphorus stabilizing moiety; each A is, independently, a 2'-O-methyl (2'-O-Me) ribonucleoside; each B is, independently, a 2'-fluoro-ribonucleoside; each P is, independently, an internucleoside linkage selected from a phosphodiester linkage and a phosphorothioate linkage; n is an integer from 1 to 5 (e.g., 1, 2, 3, 4, or 5); m is an integer from 1 to 5 (e.g., 1, 2, 3, 4, or 5); and q is an integer between 1 and 15 (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15).

In some embodiments, the antisense strand has a structure represented by Formula A-I, wherein Formula A-I is, in the 5'-to-3' direction:



5 **Formula A-I;**

wherein A is represented by the formula C-P¹-D-P¹;

each A' is represented by the formula C-P²-D-P²;

B is represented by the formula C-P²-D-P²-D-P²-D-P²;

10 each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;

each D is a 2'-F ribonucleoside;

each P¹ is a phosphorothioate internucleoside linkage;

each P² is a phosphodiester internucleoside linkage;

15 j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and

k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7).

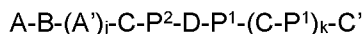
In some embodiments, the antisense strand has a structure represented by Formula A1, wherein Formula A1 is, in the 5'-to-3' direction:

20 A-S-B-S-A-O-B-O-B-O-B-O-A-O-B-O-A-O-B-O-A-O-B-O-A-O-B-S-A-S-A-S-A-S-B-S-A

Formula A1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

25 In some embodiments, the antisense strand has a structure represented by Formula A-II, wherein Formula A-II is, in the 5'-to-3' direction:



Formula A-II;

30 wherein A is represented by the formula C-P¹-D-P¹;

each A' is represented by the formula C-P²-D-P²;

B is represented by the formula C-P²-D-P²-D-P²-D-P²;

each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;

35 each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;

each D is a 2'-F ribonucleoside;

each P¹ is a phosphorothioate internucleoside linkage;

each P² is a phosphodiester internucleoside linkage;

j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and

40 k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7).

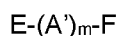
In some embodiments, antisense strand has a structure represented by Formula A2, wherein Formula A2 is, in the 5'-to-3' direction:



5 **Formula A2;**

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

10 In some embodiments, the sense strand has a structure represented by Formula S-III, wherein Formula S-III is, in the 5'-to-3' direction:



Formula S-III;

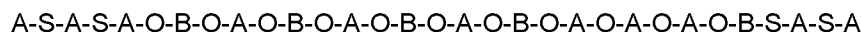
15 wherein E is represented by the formula $(C-P^1)_2$;

F is represented by the formula $(C-P^2)_3-D-P^1-C-P^1-C$, $(C-P^2)_3-D-P^2-C-P^2-C$, $(C-P^2)_3-D-P^1-C-P^1-D$, or $(C-P^2)_3-D-P^2-C-P^2-D$;

A', C, D, P¹, and P² are as defined in Formula II; and

m is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7).

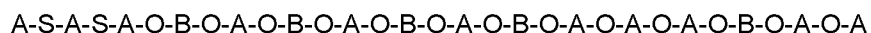
20 In some embodiments, the sense strand has a structure represented by Formula S1, wherein Formula S1 is, in the 5'-to-3' direction:



Formula S1;

25 wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments, the sense strand has a structure represented by Formula S2, wherein Formula S2 is, in the 5'-to-3' direction:



Formula S2;

35 wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

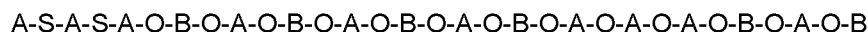
In some embodiments, the sense strand has a structure represented by Formula S3, wherein Formula S3 is, in the 5'-to-3' direction:



5 **Formula S3;**

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

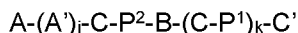
10 In some embodiments, the sense strand has a structure represented by Formula S4, wherein Formula S4 is, in the 5'-to-3' direction:



Formula S4;

15 wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments, the antisense strand has a structure represented by Formula A-IV, wherein Formula A-IV is, in the 5'-to-3' direction:



20 **Formula A-IV;**

wherein A is represented by the formula C-P¹-D-P¹;

each A' is represented by the formula C-P²-D-P²;

B is represented by the formula D-P¹-C-P¹-D-P¹;

25 each C is a 2'-O-Me ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;

each D is a 2'-F ribonucleoside;

each P¹ is a phosphorothioate internucleoside linkage;

each P² is a phosphodiester internucleoside linkage;

30 j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and

k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7).

In some embodiments, the antisense strand has a structure represented by Formula A3, wherein Formula A3 is, in the 5'-to-3' direction:

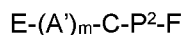


35 **Formula A3;**

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

40

In some embodiments, the sense strand has a structure represented by Formula S-V, wherein Formula S-V is, in the 5'-to-3' direction:



5 **Formula S-V;**

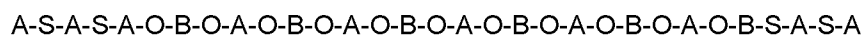
wherein E is represented by the formula $(C-P^1)_2$;

F is represented by the formula $D-P^1-C-P^1-C$, $D-P^2-C-P^2-C$, $D-P^1-C-P^1-D$, or $D-P^2-C-P^2-D$;

A' , C, D, P^1 and P^2 are as defined in Formula IV; and

10 m is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7).

In some embodiments, the sense strand has a structure represented by Formula S5, wherein Formula S5 is, in the 5'-to-3' direction:



15 **Formula S5;**

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments, the sense strand has a structure represented by Formula S6, wherein Formula S6 is, in the 5'-to-3' direction:



Formula S6;

25 wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

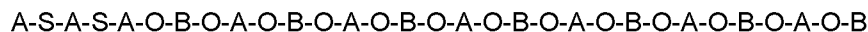
In some embodiments, the sense strand has a structure represented by Formula S7, wherein Formula S7 is, in the 5'-to-3' direction:



Formula S7;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

35 In some embodiments, the sense strand has a structure represented by Formula S8, wherein Formula S8 is, in the 5'-to-3' direction:



Formula S8;

40 wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments, the antisense strand has a structure represented by Formula A-VI, wherein Formula A-VI is, in the 5'-to-3' direction:



5 **Formula A-VI;**

wherein A is represented by the formula C-P¹-D-P¹;

each B is represented by the formula C-P²;

each C is a 2'-O-Me ribonucleoside;

10 each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;

each D is a 2'-F ribonucleoside;

each E is represented by the formula D-P²-C-P²;

F is represented by the formula D-P¹-C-P¹;

each G is represented by the formula C-P¹;

15 each P¹ is a phosphorothioate internucleoside linkage;

each P² is a phosphodiester internucleoside linkage;

j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7);

k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and

l is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7).

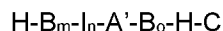
20 In some embodiments, the antisense strand has a structure represented by Formula A4, wherein Formula A4 is, in the 5'-to-3' direction:



Formula A4;

25 wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments, the sense strand has a structure represented by Formula S-VII, wherein Formula S-VII is, in the 5'-to-3' direction:



Formula S-VII;

wherein A' is represented by the formula C-P²-D-P²;

35 each H is represented by the formula (C-P¹)₂;

each I is represented by the formula (D-P²);

B, C, D, P¹ and P² are as defined in Formula VI;

m is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7);

n is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and

40 o is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7).

In some embodiments, the sense strand has a structure represented by Formula S9, wherein Formula S9 is, in the 5'-to-3' direction:



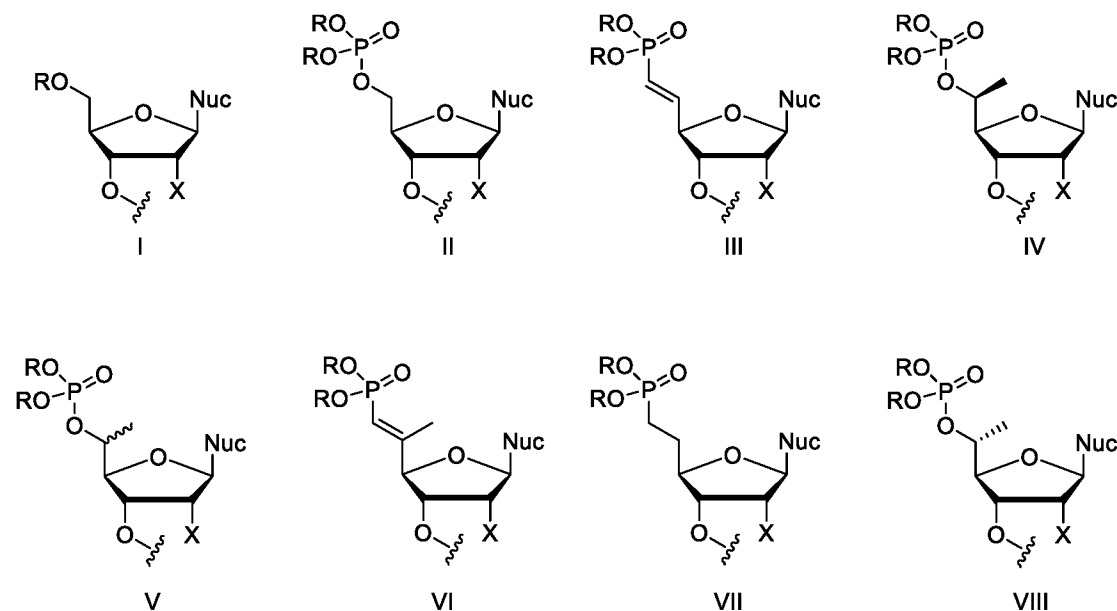
Formula S9;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments, the antisense strand also has a 5' phosphorus stabilizing moiety at the 5' end of the antisense strand.

In some embodiments, the sense strand also has a 5' phosphorus stabilizing moiety at the 5' end of the sense strand.

In some embodiments, each 5'-phosphorus stabilizing moiety is, independently represented by any one of Formula I-VIII:



wherein Nuc represents a nucleobase, such as adenine, uracil, guanine, thymine, or cytosine, and R represents optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl (e.g., optionally substituted C1-C6 alkyl, optionally substituted C2-C6 alkenyl, or optionally substituted C2-C6 alkynyl), phenyl, benzyl, hydroxy, or hydrogen.

In some embodiments, Z is (E)-vinylphosphonate as represented in Formula III.

In some embodiments, n is from 1 to 4. In some embodiments, n is from 1 to 3. In some embodiments, n is from 1 to 2. In some embodiments, n is 1.

In some embodiments, m is from 1 to 4. In some embodiments, m is from 1 to 3. In some embodiments, m is from 1 to 2. In some embodiments, m is 1.

In some embodiments, n and m are each 1.

In some embodiments, 50% or more of the ribonucleotides in the antisense strand are 2'-O-Me ribonucleotides (e.g., 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%,

82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the ribonucleotides in the antisense strand may be 2'-O-Me ribonucleotides).

In some embodiments, 60% or more of the ribonucleotides in the antisense strand are 2'-O-Me ribonucleotides (e.g., 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the ribonucleotides in the antisense strand may be 2'-O-Me ribonucleotides).

In some embodiments, 70% or more of the ribonucleotides in the antisense strand are 2'-O-Me ribonucleotides (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the ribonucleotides in the antisense strand may be 2'-O-Me ribonucleotides).

In some embodiments, 80% or more of the ribonucleotides in the antisense strand are 2'-O-Me ribonucleotides (e.g., 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the ribonucleotides in the antisense strand may be 2'-O-Me ribonucleotides).

In some embodiments, 90% or more of the ribonucleotides in the antisense strand are 2'-O-Me ribonucleotides (e.g., 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the ribonucleotides in the antisense strand may be 2'-O-Me ribonucleotides).

In some embodiments, 10% or less of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages. In some embodiments, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.

In some embodiments, 100% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.

In some embodiments, 9 internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.

In some embodiments, the length of the antisense strand is between 10 and 30 nucleotides (e.g., 10 nucleotides, 11 nucleotides, 12 nucleotides, 13 nucleotides, 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides, 26 nucleotides, 27 nucleotides, 28 nucleotides, 29 nucleotides, or 30 nucleotides), 15 and 25 nucleotides (e.g., 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, or 25 nucleotides), or 18 and 23 nucleotides (e.g., 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, or 23 nucleotides). In some embodiments, the length of the antisense strand is 20 nucleotides. In some embodiments, the length of the antisense strand is 21 nucleotides. In some embodiments, the length of the antisense strand is 22 nucleotides. In some embodiments, the length of the antisense strand is 23 nucleotides. In some embodiments, the length of the antisense strand is 24 nucleotides. In some embodiments, the length of the antisense strand is 25 nucleotides. In some embodiments, the length of the antisense strand is 26 nucleotides. In some embodiments, the length of the antisense strand is 27 nucleotides. In some embodiments, the length of the antisense strand is 28 nucleotides. In some embodiments, the length of the antisense strand is 29 nucleotides. In some embodiments, the length of the antisense strand is 30 nucleotides.

In some embodiments, the siRNA molecules of the branched compound are joined to one another by way of a linker (e.g., an ethylene glycol oligomer, such as tetraethylene glycol). In some embodiments, the siRNA molecules of the branched compound are joined to one another by way of a linker between the sense strand of one siRNA molecule and the sense strand of the other siRNA molecule. In some embodiments, the siRNA molecules are joined by way of linkers between the antisense strand of one siRNA molecule and the antisense strand of the other siRNA molecule. In some embodiments, the siRNA molecules of the branched compound are joined to one another by way of a linker between the sense strand of one siRNA molecule and the antisense strand of the other siRNA molecule.

In some embodiments, the length of the sense strand is between 12 and 30 nucleotides (e.g., 12 nucleotides, 13 nucleotides, 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides, 26 nucleotides, 27 nucleotides, 28 nucleotides, 29 nucleotides, or 30 nucleotides), or 14 and 18 nucleotides (e.g., 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, or 18 nucleotides). In some embodiments, the length of the sense strand is 15 nucleotides. In some embodiments, the length of the sense strand is 16 nucleotides. In some embodiments, the length of the sense strand is 17 nucleotides. In some embodiments, the length of the sense strand is 18 nucleotides. In some embodiments, the length of the sense strand is 19 nucleotides. In some embodiments, the length of the sense strand is 20 nucleotides. In some embodiments, the length of the sense strand is 21 nucleotides. In some embodiments, the length of the sense strand is 22 nucleotides. In some embodiments, the length of the sense strand is 23 nucleotides. In some embodiments, the length of the sense strand is 24 nucleotides. In some embodiments, the length of the sense strand is 25 nucleotides. In some embodiments, the length of the sense strand is 26 nucleotides. In some embodiments, the length of the sense strand is 27 nucleotides. In some embodiments, the length of the sense strand is 28 nucleotides. In some embodiments, the length of the sense strand is 29 nucleotides. In some embodiments, the length of the sense strand is 30 nucleotides.

In some embodiments, 4 internucleoside linkages are phosphorothioate linkages.

In some embodiments, the antisense strand is 18 nucleotides in length and the sense strand is 14 nucleotides in length.

In some embodiments, the antisense strand is 18 nucleotides in length and the sense strand is 15 nucleotides in length.

In some embodiments, the antisense strand is 18 nucleotides in length and the sense strand is 16 nucleotides in length.

In some embodiments, the antisense strand is 18 nucleotides in length and the sense strand is 17 nucleotides in length.

In some embodiments, the antisense strand is 18 nucleotides in length and the sense strand is 18 nucleotides in length.

In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 14 nucleotides in length.

In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 15 nucleotides in length.

In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 16 nucleotides in length.

In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 17 nucleotides in length.

5 In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 18 nucleotides in length.

In some embodiments, the antisense strand is 19 nucleotides in length and the sense strand is 19 nucleotides in length.

10 In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 14 nucleotides in length.

In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 15 nucleotides in length.

In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 16 nucleotides in length.

15 In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 17 nucleotides in length.

In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 18 nucleotides in length.

20 In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 19 nucleotides in length.

In some embodiments, the antisense strand is 20 nucleotides in length and the sense strand is 20 nucleotides in length.

In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 14 nucleotides in length.

25 In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 15 nucleotides in length.

In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 16 nucleotides in length.

30 In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 17 nucleotides in length.

In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 18 nucleotides in length.

In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 19 nucleotides in length.

35 In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 20 nucleotides in length.

In some embodiments, the antisense strand is 21 nucleotides in length and the sense strand is 21 nucleotides in length.

40 In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 14 nucleotides in length.

In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 15 nucleotides in length.

In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 16 nucleotides in length.

In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 17 nucleotides in length.

5 In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 18 nucleotides in length.

In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 19 nucleotides in length.

10 In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 20 nucleotides in length.

In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 21 nucleotides in length.

In some embodiments, the antisense strand is 22 nucleotides in length and the sense strand is 22 nucleotides in length.

15 In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 14 nucleotides in length.

In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 15 nucleotides in length.

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In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 17 nucleotides in length.

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In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 20 nucleotides in length.

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In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 22 nucleotides in length.

In some embodiments, the antisense strand is 23 nucleotides in length and the sense strand is 23 nucleotides in length.

35 In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 14 nucleotides in length.

In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 15 nucleotides in length.

40 In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 16 nucleotides in length.

In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 17 nucleotides in length.

In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 18 nucleotides in length.

In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 19 nucleotides in length.

5 In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 20 nucleotides in length.

In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 21 nucleotides in length.

10 In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 22 nucleotides in length.

In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 23 nucleotides in length.

In some embodiments, the antisense strand is 24 nucleotides in length and the sense strand is 24 nucleotides in length.

15 In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 14 nucleotides in length.

In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 15 nucleotides in length.

20 In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 16 nucleotides in length.

In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 17 nucleotides in length.

In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 18 nucleotides in length.

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In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 20 nucleotides in length.

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In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 22 nucleotides in length.

In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 23 nucleotides in length.

35 In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 24 nucleotides in length.

In some embodiments, the antisense strand is 25 nucleotides in length and the sense strand is 25 nucleotides in length.

40 In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 14 nucleotides in length.

In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 15 nucleotides in length.

In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 16 nucleotides in length.

In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 17 nucleotides in length.

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In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 24 nucleotides in length.

20 In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 25 nucleotides in length.

In some embodiments, the antisense strand is 26 nucleotides in length and the sense strand is 26 nucleotides in length.

In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 14 nucleotides in length.

25 In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 15 nucleotides in length.

In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 16 nucleotides in length.

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In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 25 nucleotides in length.

5 In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 26 nucleotides in length.

In some embodiments, the antisense strand is 27 nucleotides in length and the sense strand is 27 nucleotides in length.

10 In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 14 nucleotides in length.

In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 15 nucleotides in length.

In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 16 nucleotides in length.

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In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 18 nucleotides in length.

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In some embodiments, the antisense strand is 28 nucleotides in length and the sense strand is 28 nucleotides in length.

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In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 15 nucleotides in length.

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In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 24 nucleotides in length.

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In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 26 nucleotides in length.

In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 27 nucleotides in length.

25 In some embodiments, the antisense strand is 29 nucleotides in length and the sense strand is 28 nucleotides in length.

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In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 27 nucleotides in length.

15 In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 28 nucleotides in length.

In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 29 nucleotides in length.

20 In some embodiments, the antisense strand is 30 nucleotides in length and the sense strand is 30 nucleotides in length.

In another aspect, the invention features a branched siRNA molecule including a sense strand and an antisense strand, wherein the antisense strand includes a region having complementarity to a segment of contiguous nucleotides within a gene selected from the group consisting of APOE, BIN1, C1QA, C3, C9ORF72, CCL5, CD33, CLU/APOJ, CR1, CXCL10, CXCL13, IFIT1, IFIT3, IFITM3, IFNAR1, 25 IFNAR2, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, MEF2C, MMP12, NLRP3, NOS2, PILRA, PLCG2, PTK2B, SLC24A4, TBK1, and TNF.

In some embodiments, the antisense strand has complementarity to a portion of a gene encoding a positive regulator of a gene for which increased expression and/or activity relative to the level of expression and/or activity observed in a reference subject is associated with a disease state.

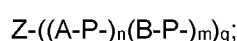
30 In some embodiments, the antisense strand has complementarity to a portion of a gene encoding a negative regulator of a gene for which decreased expression and/or activity relative to the level of expression and/or activity observed in a reference subject is associated with a disease state.

In some embodiments, the antisense strand has complementarity to a splice isoform of a gene for which overexpression of the splice isoform relative to the expression of the splice isoform in a reference 35 subject is associated with a disease state.

In some embodiments, the sense strand has complementarity to the antisense strand.

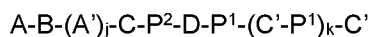
In some embodiments, the siRNA molecule is di-branched. In some embodiments, the siRNA molecule is tri-branched. In some embodiments, the siRNA molecule is tetra-branched.

40 In some embodiments, the antisense strand of the branched siRNA has the following Formula in the 5'-to-3' direction:



wherein Z is a 5' phosphorus stabilizing moiety; each A is, independently, a 2'-O-Me ribonucleoside; each B is, independently, a 2'-fluoro-ribonucleoside; each P is, independently, an internucleoside linkage selected from a phosphodiester linkage and a phosphorothioate linkage; n is an integer from 1 to 5 (e.g., 1, 2, 3, 4, or 5); m is an integer from 1 to 5 (e.g., 1, 2, 3, 4, or 5); and q is an integer between 1 and 15 (e.g., 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15).

In some embodiments, the antisense strand has a structure represented by Formula A-I, wherein Formula A-I is, in the 5'-to-3' direction:



Formula A-I;

wherein A is represented by the formula C-P¹-D-P¹;

each A' is represented by the formula C-P²-D-P²;

B is represented by the formula C-P²-D-P²-D-P²-D-P²;

each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;

each D is a 2'-F ribonucleoside;

each P¹ is a phosphorothioate internucleoside linkage;

each P² is a phosphodiester internucleoside linkage;

j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and

k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7).

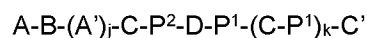
In some embodiments, the antisense strand has a structure represented by Formula A1, wherein Formula A1 is, in the 5'-to-3' direction:



Formula A1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments, the antisense strand has a structure represented by Formula A-II, wherein Formula A-II is, in the 5'-to-3' direction:



Formula A-II;

wherein A is represented by the formula C-P¹-D-P¹;

each A' is represented by the formula C-P²-D-P²;

B is represented by the formula C-P²-D-P²-D-P²-D-P²;

each C is a 2'-O-methyl (2'-O-Me) ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside;

each D is a 2'-F ribonucleoside;

each P¹ is a phosphorothioate internucleoside linkage;
 each P² is a phosphodiester internucleoside linkage;
 j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and
 k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7).

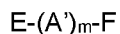
5 In some embodiments, antisense strand has a structure represented by Formula A2, wherein Formula A2 is, in the 5'-to-3' direction:



Formula A2;

10 wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments, the sense strand has a structure represented by Formula S-III, wherein Formula S-III is, in the 5'-to-3' direction:



Formula S-III;

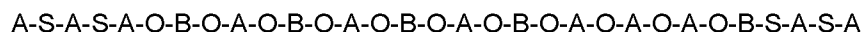
wherein E is represented by the formula (C-P¹)₂;

20 F is represented by the formula (C-P²)₃-D-P¹-C-P¹-C, (C-P²)₃-D-P²-C-P²-C, (C-P²)₃-D-P¹-C-P¹-D, or (C-P²)₃-D-P²-C-P²-D;

A', C, D, P¹, and P² are as defined in Formula II; and

m is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7).

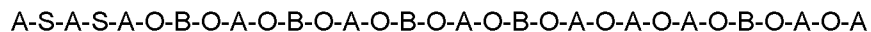
25 In some embodiments, the sense strand has a structure represented by Formula S1, wherein Formula S1 is, in the 5'-to-3' direction:



Formula S1;

30 wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments, the sense strand has a structure represented by Formula S2, wherein Formula S2 is, in the 5'-to-3' direction:



Formula S2;

40 wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

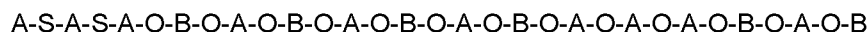
In some embodiments, the sense strand has a structure represented by Formula S3, wherein Formula S3 is, in the 5'-to-3' direction:



5 **Formula S3;**

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

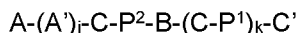
10 In some embodiments, the sense strand has a structure represented by Formula S4, wherein Formula S4 is, in the 5'-to-3' direction:



Formula S4;

15 wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments, the antisense strand has a structure represented by Formula A-IV, wherein Formula A-IV is, in the 5'-to-3' direction:



20 **Formula A-IV;**

wherein A is represented by the formula C-P¹-D-P¹;

each A' is represented by the formula C-P²-D-P²;

B is represented by the formula D-P¹-C-P¹-D-P¹;

25 each C is a 2'-O-Me ribonucleoside;

each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;

each D is a 2'-F ribonucleoside;

each P¹ is a phosphorothioate internucleoside linkage;

each P² is a phosphodiester internucleoside linkage;

30 j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and

k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7).

In some embodiments, the antisense strand has a structure represented by Formula A3, wherein Formula A3 is, in the 5'-to-3' direction:

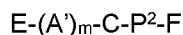


35 **Formula A3;**

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

40

In some embodiments, the sense strand has a structure represented by Formula S-V, wherein Formula S-V is, in the 5'-to-3' direction:



5 **Formula S-V;**

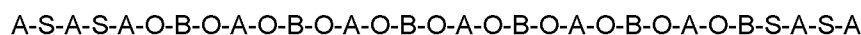
wherein E is represented by the formula $(C-P^1)_2$;

F is represented by the formula $D-P^1-C-P^1-C$, $D-P^2-C-P^2-C$, $D-P^1-C-P^1-D$, or $D-P^2-C-P^2-D$;

A' , C, D, P^1 and P^2 are as defined in Formula IV; and

10 m is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7).

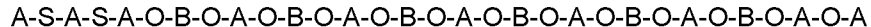
In some embodiments, the sense strand has a structure represented by Formula S5, wherein Formula S5 is, in the 5'-to-3' direction:



15 **Formula S5;**

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments, the sense strand has a structure represented by Formula S6, wherein Formula S6 is, in the 5'-to-3' direction:



Formula S6;

25 wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

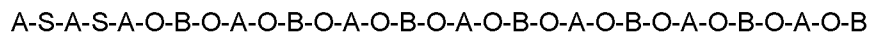
In some embodiments, the sense strand has a structure represented by Formula S7, wherein Formula S7 is, in the 5'-to-3' direction:



Formula S7;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

35 In some embodiments, the sense strand has a structure represented by Formula S8, wherein Formula S8 is, in the 5'-to-3' direction:



Formula S8;

40 wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments, the antisense strand has a structure represented by Formula A-VI, wherein Formula A-VI is, in the 5'-to-3' direction:



5

Formula A-VI;

wherein A is represented by the formula C-P¹-D-P¹;

each B is represented by the formula C-P²;

each C is a 2'-O-Me ribonucleoside;

10 each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside;

each D is a 2'-F ribonucleoside;

each E is represented by the formula D-P²-C-P²;

F is represented by the formula D-P¹-C-P¹;

each G is represented by the formula C-P¹;

15 each P¹ is a phosphorothioate internucleoside linkage;

each P² is a phosphodiester internucleoside linkage;

j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7);

k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and

l is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7).

20 In some embodiments, the antisense strand has a structure represented by Formula A4, wherein Formula A4 is, in the 5'-to-3' direction:



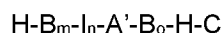
Formula A4;

25

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments, the sense strand has a structure represented by Formula S-VII, wherein Formula S-VII is, in the 5'-to-3' direction:

30



Formula S-VII;

wherein A' is represented by the formula C-P²-D-P²;

35 each H is represented by the formula (C-P¹)₂;

each I is represented by the formula (D-P²);

B, C, D, P¹ and P² are as defined in Formula VI;

m is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7);

n is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and

40 o is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7).

In some embodiments, the sense strand has a structure represented by Formula S9, wherein Formula S9 is, in the 5'-to-3' direction:



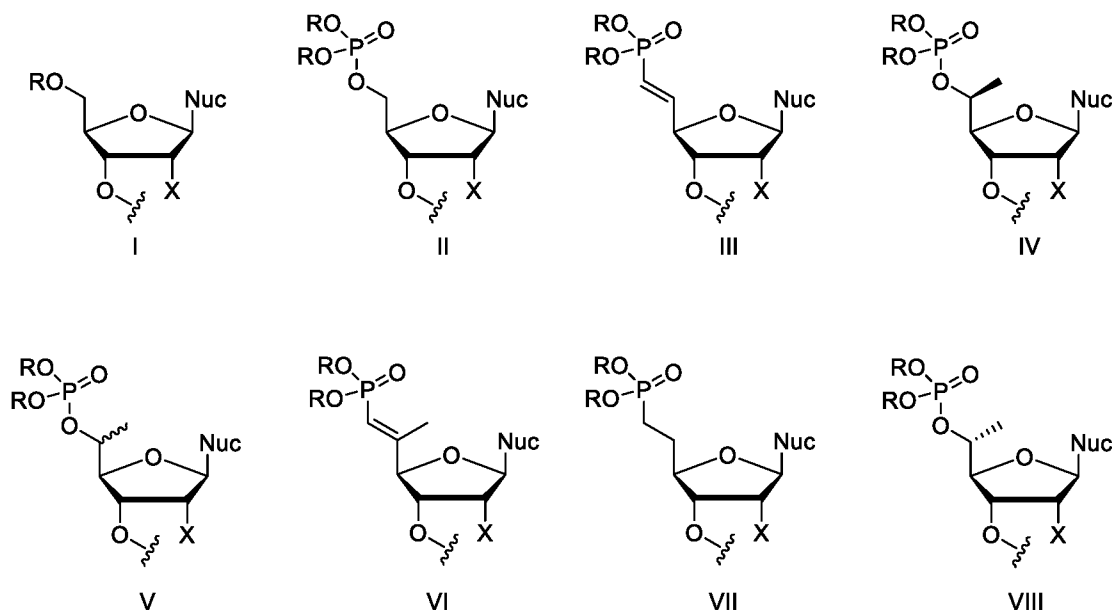
Formula S9;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments, the antisense strand also has a 5' phosphorus stabilizing moiety at the 5' end of the antisense strand.

In some embodiments, the sense strand also has a 5' phosphorus stabilizing moiety at the 5' end of the sense strand.

In some embodiments, each 5'-phosphorus stabilizing moiety is, independently, represented by any one of Formula I-VIII:



wherein Nuc represents a nucleobase, such as adenine, uracil, guanine, thymine, or cytosine, and R represents optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl (e.g., optionally substituted C1-C6 alkyl, optionally substituted C2-C6 alkenyl, or optionally substituted C2-C6 alkynyl), phenyl, benzyl, hydroxy, or hydrogen.

In some embodiments, Z is (E)-vinylphosphonate as represented in Formula III.

In some embodiments, each P is independently selected from phosphodiester and phosphorothioate.

In some embodiments, n is from 1 to 4 (e.g., 1, 2, 3, or 4), 1 to 3 (e.g., 1, 2, or 3), or 1 to 2. In some embodiments, n is 1.

In some embodiments, m is from 1 to 4 (e.g., 1, 2, 3, or 4), 1 to 3 (e.g., 1, 2, or 3), or 1 to 2. In some embodiments, m is 1.

In some embodiments, n and m are each 1.

In some embodiments, 50% or more of the ribonucleotides in the antisense strand are 2'-O-Me ribonucleotides (e.g., 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the ribonucleotides in the antisense strand may be 2'-O-Me ribonucleotides).

In some embodiments, 60% or more of the ribonucleotides in the antisense strand are 2'-O-Me ribonucleotides (e.g., 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the ribonucleotides in the antisense strand may be 2'-O-Me ribonucleotides).

In some embodiments, 70% or more of the ribonucleotides in the antisense strand are 2'-O-Me ribonucleotides (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the ribonucleotides in the antisense strand may be 2'-O-Me ribonucleotides).

In some embodiments, 80% or more of the ribonucleotides in the antisense strand are 2'-O-Me ribonucleotides (e.g., 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the ribonucleotides in the antisense strand may be 2'-O-Me ribonucleotides).

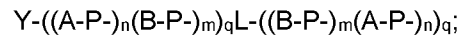
In some embodiments, 90% or more of the ribonucleotides in the antisense strand are 2'-O-Me ribonucleotides (e.g., 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% of the ribonucleotides in the antisense strand may be 2'-O-Me ribonucleotides).

In some embodiments, 10% or less of the internucleoside linkages are phosphodiester linkages or phosphorothioate. In some embodiments, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the internucleoside linkages are phosphodiester linkages or phosphorothioate. In some embodiments, 100% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.

In some embodiments, the length of the antisense strand is between 10 and 30 nucleotides (e.g., 10 nucleotides, 11 nucleotides, 12 nucleotides, 13 nucleotides, 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides, 26 nucleotides, 27 nucleotides, 28 nucleotides, 29 nucleotides, or 30 nucleotides), 15 and 25 nucleotides (e.g., 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, or 25 nucleotides), or 18 and 23 nucleotides (e.g., 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, or 23 nucleotides). In some embodiments, the length of the antisense strand is 21 nucleotides. In some embodiments, the length of the antisense strand is 22 nucleotides. In some embodiments, the length of the antisense strand is 23 nucleotides. In some embodiments, the length of the antisense strand is 24 nucleotides. In some embodiments, the length of the antisense strand is 25 nucleotides. In some embodiments, the length of the antisense strand is 26 nucleotides. In some embodiments, the length of the antisense strand is 27 nucleotides. In some embodiments, the length of the antisense strand is 28 nucleotides. In some embodiments, the length of the antisense strand is 29 nucleotides. In some embodiments, the length of the antisense strand is 30 nucleotides.

In some embodiments, 9 internucleoside linkages are phosphorothioate.

In some embodiments, the sense strand of the branched siRNA has the following formula in the 5'-to-3' direction:



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wherein Y is a hydrophobic moiety (e.g., cholesterol, vitamin D, or tocopherol); L is a linker; each A is, independently, a 2'-O-Me ribonucleoside; each B is, independently, a 2'-fluoro-ribonucleoside; each P is, independently, an internucleoside linkage selected from a phosphodiester linkage and a phosphorothioate linkage; n is an integer from 1 to 5 (1, 2, 3, 4, or 5); m is an integer from 1 to 5 (1, 2, 3, 4, or 5); and q is an integer between 1 and 15 (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15).

10

In some embodiments, Y is cholesterol.

In some embodiments, Y tocopherol.

In some embodiments, L is an ethylene glycol oligomer.

In some embodiments, L is tetraethylene glycol.

15

In some embodiments, each P is independently selected from phosphodiester and phosphorothioate.

In some embodiments, n is from 1 to 4 (e.g., 1, 2, 3, or 4), 1 to 3 (e.g., 1, 2, or 3), or 1 to 2. In some embodiments, n is 1.

In some embodiments, m is from 1 to 4 (e.g., 1, 2, 3, or 4), 1 to 3 (e.g., 1, 2, or 3), or 1 to 2. In some embodiments, m is 1.

20

In some embodiments, n and m are each 1.

In some embodiments, 10% or less of the ribonucleosides are 2'-O-Me ribonucleoside.

In some embodiments, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the ribonucleosides are 2'-O-Me ribonucleoside.

25

In some embodiments, 10% or less of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages. In some embodiments, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages. In some embodiments, 100% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.

30

In some embodiments, the length of the sense strand is between 12 and 30 nucleotides (e.g., 12 nucleotides, 13 nucleotides, 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides, 26 nucleotides, 27 nucleotides, 28 nucleotides, 29 nucleotides, or 30 nucleotides), or 14 and 18 nucleotides (e.g., 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides). In some embodiments, the length of the sense strand is 16 nucleotides. In some embodiments, the length of the sense strand is 17 nucleotides. In some embodiments, the length of the sense strand is 18 nucleotides. In some embodiments, the length of the sense strand is 19 nucleotides. In some embodiments, the length of the sense strand is 20 nucleotides. In some embodiments, the length of the sense strand is 21 nucleotides. In some embodiments, the length of the sense strand is 22 nucleotides. In some embodiments, the length of the sense strand is 23 nucleotides. In some embodiments, the length of the sense strand is 24 nucleotides. In some embodiments, the length of the sense strand is 25 nucleotides. In some embodiments, the length of the sense strand is 26

40

nucleotides. In some embodiments, the length of the sense strand is 27 nucleotides. In some embodiments, the length of the sense strand is 28 nucleotides. In some embodiments, the length of the sense strand is 29 nucleotides. In some embodiments, the length of the sense strand is 30 nucleotides.

In some embodiments, 4 internucleoside linkages are phosphorothioate.

5 In another aspect, the invention features a method of treating a subject diagnosed as having a disease associated with expression of a dysregulated microglial gene (e.g., wild-type or mutated microglial gene), the method includes administering to the subject the branched siRNA molecule of any one of the above aspects or embodiments.

In some embodiments, the dysregulated microglial gene is selected from the group consisting of
 10 ABCA7, ABI3, ADAM10, APOC1, APOE, AXL, BIN1, C1QA, C3, C9ORF72, CASS4, CCL5, CD2AP, CD33, CD68, CLPTM1, CLU, CR1, CSF1, CST7, CTSB, CTSD, CTSL, CXCL10, CXCL13, DSG2, ECHDC3, EPHA1, FABP5, FERMT2, FTH1, GNAS, GRN, HBEGF, HLA-DRB1, HLA-DRB5, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IGF1, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, ITGAX, LILRB4, LPL, MEF2C, MMP12, MS4A4A, MS4A6A, NLRP3, NME8, NOS2, PICALM, PILRA, PLCG2, PTK2B, SCIMP,
 15 SLC24A4, SORL1, SPI1, SPP1, SPPL2A, TBK1, TNF, TREM2, TREML2, TYROBP, and ZCWPW1.

In some embodiments, the dysregulated microglial gene exhibits increased expression and/or activity in microglial cells of the subject as compared to the expression and/or activity of the same gene in microglial cells of a reference subject.

In some embodiments, the dysregulated microglial gene exhibits reduced expression and/or
 20 activity in microglial cells of the subject as compared to the expression and/or activity of the same gene in microglial cells of a reference subject.

In some embodiments, the administering of the branched siRNA molecule to the subject results in silencing of gene in the subject.

In some embodiments, the silencing of a gene comprises silencing any one of the genes selected
 25 from the group consisting of APOE, BIN1, C1QA, C3, C9ORF72, CCL5, CD33, CLU/APOJ, CR1, CXCL10, CXCL13, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, MEF2C, MMP12, NLRP3, NOS2, PILRA, PLCG2, PTK2B, SLC24A4, TBK1, and TNF.

In some embodiments, silencing of a gene comprises silencing of a positive regulator of a gene for which increased expression and/or activity relative to the level of expression and/or activity observed
 30 in a reference subject is associated with a disease state.

In some embodiments, silencing of a gene comprises silencing of a negative regulator of a gene for which decreased expression and/or activity relative to the level of expression and/or activity observed in a reference subject is associated with a disease state.

In some embodiments, silencing of a gene comprises silencing of a splice isoform of a gene for
 35 which overexpression of the splice isoform relative to the expression of the splice isoform in a reference subject is associated with a disease state.

In some embodiments, the subject is a human.

BRIEF DESCRIPTION OF THE DRAWINGS

40 **FIGS. 1A-1D** are a series of fluorescence images of brain and spinal cord tissue of cynomolgus macaques treated with a single intrathecal injection of Cy3-labeled di-siRNA of the disclosure. Fluorescence images were acquired from representative regions of the brain, including cortex (FIG. 1A),

hippocampus (FIG. 1B), caudate nucleus (FIG 1C), and of the spinal cord (FIG. 1D). Microglia cells (Iba1 channel), di-siRNAs (Cy3 channel), and cell nuclei (DAPI) were labeled. White arrows indicate colocalization of Cy3 di-siRNA signal within microglial cells labeled with the Iba1 antibody. Scale bars = 20 μ m.

5

DEFINITIONS

Unless otherwise defined herein, scientific, and technical terms used herein have the meanings that are commonly understood by those of ordinary skill in the art. In the event of any latent ambiguity, definitions provided herein take precedent over any dictionary or extrinsic definition. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. The use of "or" means "and/or" unless stated otherwise. The use of the term "including," as well as other forms, such as "includes" and "included," is not limiting.

10

As used herein, the term "nucleic acids" refers to RNA or DNA molecules consisting of a chain of ribonucleotides or deoxyribonucleotides, respectively. As used herein, the term "therapeutic nucleic acid" refers to a nucleic acid molecule (e.g., ribonucleic acid) that has partial or complete complementarity to, and interacts with, a disease-associated target mRNA and mediates silencing of expression of the mRNA.

15

As used herein, the term "carrier nucleic acid" refers to a nucleic acid molecule (e.g., ribonucleic acid) that has sequence complementarity with, and hybridizes with, a therapeutic nucleic acid. As used herein, the term "3' end" refers to the end of the nucleic acid that contains an unmodified hydroxyl group at the 3' carbon of the ribose ring.

20

As used herein, the term "nucleoside" refers to a molecule made up of a heterocyclic base and its sugar.

As used herein, the term "nucleotide" refers to a nucleoside having a phosphate group on its 3' or 5' sugar hydroxyl group.

25

As used herein, the term "siRNA" refers to small interfering RNA duplexes that induce the RNA interference (RNAi) pathway. siRNA molecules can vary in length (generally, between 18-30 base pairs) and contain varying degrees of complementarity to their target mRNA. The term "siRNA" includes duplexes of two separate strands, as well as single strands that optionally form hairpin structures comprising a duplex region.

30

As used herein, the term "antisense strand" refers to the strand of the siRNA duplex that contains some degree of complementarity to the target gene.

As used herein, the term "sense strand" refers to the strand of the siRNA duplex that contains complementarity to the antisense strand.

35

As used herein, the terms "chemically modified nucleotide" or "nucleotide analog" or "altered nucleotide" or "modified nucleotide" refer to a non-standard nucleotide, including non-naturally occurring ribonucleotides or deoxyribonucleotides. Exemplary nucleotide analogs are modified at any position so as to alter certain chemical properties of the nucleotide yet retain the ability of the nucleotide analog to perform its intended function.

40

As used herein, the term "metabolically stabilized" refers to RNA molecules that contain ribonucleotides that have been chemically modified from 2'-hydroxyl groups to 2'-O-methyl groups.

As used herein, the term "phosphorothioate" refers to the phosphate group of a nucleotide that is modified by substituting one or more of the oxygens of the phosphate group with sulfur.

As used herein, the term "ethylene glycol chain" refers to a carbon chain with the formula $((\text{CH}_2\text{OH})_2)$.

As used herein, "alkyl" refers to a saturated hydrocarbon group. Alkyl groups may be acyclic or cyclic and contain only C and H when unsubstituted. When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed and described; thus, for example, "butyl" is meant to include *n*-butyl, *sec*-butyl, and *iso*-butyl. Examples of alkyl include ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. In some embodiments, alkyl may be substituted. Suitable substituents that may be introduced into an alkyl group include, for example, hydroxy, alkoxy, amino, alkylamino, and halo, among others.

As used herein, "alkenyl" refers to an acyclic or cyclic unsaturated hydrocarbon group having at least one site of olefinic unsaturation (i.e., having at least one moiety of the formula $\text{C}=\text{C}$). Alkenyl groups contain only C and H when unsubstituted. When an alkenyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed and described; thus, for example, "butenyl" is meant to include *n*-butenyl, *sec*-butenyl, and *iso*-butenyl. Examples of alkenyl include $-\text{CH}=\text{CH}_2$, $-\text{CH}_2-\text{CH}=\text{CH}_2$, and $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}=\text{CH}_2$. In some embodiments, alkenyl may be substituted. Suitable substituents that may be introduced into an alkenyl group include, for example, hydroxy, alkoxy, amino, alkylamino, and halo, among others.

As used herein, "alkynyl" refers to an acyclic or cyclic unsaturated hydrocarbon group having at least one site of acetylenic unsaturation (i.e., having at least one moiety of the formula $\text{C}\equiv\text{C}$). Alkynyl groups contain only C and H when unsubstituted. When an alkynyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed and described; thus, for example, "pentynyl" is meant to include *n*-pentynyl, *sec*-pentynyl, *iso*-pentynyl, and *tert*-pentynyl. Examples of alkynyl include $-\text{C}\equiv\text{CH}$ and $-\text{C}\equiv\text{C}-\text{CH}_3$. In some embodiments, alkynyl may be substituted. Suitable substituents that may be introduced into an alkynyl group include, for example, hydroxy, alkoxy, amino, alkylamino, and halo, among others.

As used herein the term "phenyl" denotes a monocyclic arene in which one hydrogen atom from a carbon atom of the ring has been removed. A phenyl group can be unsubstituted or substituted with one or more suitable substituents, wherein the substituent replaces an H of the phenyl group.

As used herein, the term "benzyl" refers to monovalent radical obtained when a hydrogen atom attached to the methyl group of toluene is removed. A benzyl generally has the formula of phenyl- CH_2 -. A benzyl group can be unsubstituted or substituted with one or more suitable substituents. For example, the substituent may replace an H of the phenyl component and/or an H of the methylene ($-\text{CH}_2$ -) component.

As used herein, the term "amide" refers to an alkyl or aromatic group that is attached to an amino-carbonyl functional group.

As used herein, the term "internucleoside" and "internucleotide" refer to the bonds between nucleosides and nucleotides, respectively.

As used herein, the term "triazol" refers to heterocyclic compounds with the formula (C₂H₃N₃), having a five-membered ring of two carbons and three nitrogens, the positions of which can change resulting in multiple isomers.

As used herein, the term "terminal group" refers to the group at which a carbon chain or nucleic acid ends.

As used herein, the term "lipophilic amino acid" refers to an amino acid comprising a hydrophobic moiety (e.g., an alkyl chain or an aromatic ring).

As used herein, the term "antagomiRs" refers to nucleic acids that can function as inhibitors of miRNA activity.

As used herein, the term "gapmers" refers to chimeric antisense nucleic acids that contain a central block of deoxynucleotide monomers sufficiently long to induce RNase H cleavage. The deoxynucleotide block is flanked by ribonucleotide monomers or ribonucleotide monomers containing modifications.

As used herein, the term "mixmers" refers to nucleic acids that are comprised of a mix of locked nucleic acids (LNAs) and DNA.

As used herein, the term "guide RNAs" refers to nucleic acids that have sequence complementarity to a specific sequence in the genome immediately or 1 base pair upstream of the protospacer adjacent motif (PAM) sequence as used in CRISPR/Cas9 gene editing systems. Alternatively, "guide RNAs" may refer to nucleic acids that have sequence complementarity (e.g., are antisense) to a specific messenger RNA (mRNA) sequence. In this context, a guide RNA may also have sequence complementarity to a "passenger RNA" sequence of equal or shorter length, which is identical or substantially identical to the sequence of mRNA to which the guide RNA hybridizes.

As used herein, the term "target of delivery" refers to the organ or part of the body that is desired to deliver the branched oligonucleotide compositions to.

As used herein, the term "branched siRNA" refers to a compound containing two or more double-stranded siRNA molecules covalently bound to one another. Branched siRNA molecules may be "di-branched," also referred to herein as "di-siRNA," wherein the siRNA molecule comprises 2 siRNA molecules covalently bound to one another, e.g., by way of a linker. Branched siRNA molecules may be "tri-branched," also referred to herein as "tri-siRNA," wherein the siRNA molecule comprises 3 siRNA molecules covalently bound to one another, e.g., by way of a linker. Branched siRNA molecules may be "tetra-branched," also referred to herein as "tetra-siRNA," wherein the siRNA molecule comprises 4 siRNA molecules covalently bound to one another, e.g., by way of a linker.

As used herein, the term "5' phosphorus stabilizing moiety" refers to a terminal phosphate group that includes phosphates as well as modified phosphates (e.g., phosphorothioates, phosphodiester, phosphonates). The phosphate moiety can be located at either terminus but is preferred at the 5'-terminal nucleoside. In one aspect, the terminal phosphate is unmodified having the formula —O—P(=O)(OH)OH. In another aspect, the terminal phosphate is modified such that one or more of the O and OH groups are replaced with H, O, S, N(R'), or alkyl where R' is H, an amino protecting group, or unsubstituted or substituted alkyl. In some embodiments, the 5' and or 3' terminal group can comprise from 1 to 3 phosphate moieties that are each, independently, unmodified (di- or tri-phosphates) or modified.

As used herein, the term “between X and Y” is inclusive of the values of X and Y. For example, “between X and Y” refers to the range of values between the value of X and the value of Y, as well as the value of X and the value of Y.

As used herein, an “amino acid” refers to a molecule containing amine and carboxyl functional groups and a side chain specific to the amino acid. :

In some embodiments the amino acid is chosen from the group of proteinogenic amino acids. In other embodiments, the amino acid is an L-amino acid or a D-amino acid. In other embodiments, the amino acid is a synthetic amino acid (e.g., a beta-amino acid).

It is understood that certain internucleotide linkages provided herein, including, e.g., phosphodiester and phosphorothioate, comprise a formal charge of -1 at physiological pH, and that said formal charge will be balanced by a cationic moiety, e.g., an alkali metal such as sodium or potassium, an alkali earth metal such as calcium or magnesium, or an ammonium or guanidinium ion.

The phosphate group of the nucleotide may also be modified, e.g., by substituting one or more of the oxygens of the phosphate group with sulfur (e.g., phosphorothioates), or by making other substitutions which allow the nucleotide to perform its intended function such as described in, for example, Eckstein, *Antisense Nucleic Acid Drug Dev.* 2000 Apr. 10(2):117-21, Rusckowski et al. *Antisense Nucleic Acid Drug Dev.* 2000 Oct. 10(5):333-45, Stein, *Antisense Nucleic Acid Drug Dev.* 2001 Oct. 11(5): 317-25, Vorobjev et al. *Antisense Nucleic Acid Drug Dev.* 2001 Apr. 11(2):77-85, and U.S. Pat. No. 5,684,143. Certain of the above-referenced modifications (e.g., phosphate group modifications) preferably decrease the rate of hydrolysis of, for example, polynucleotides comprising said analogs in vivo or in vitro.

As used herein, the term “complementary” refers to two nucleotides that form canonical Watson-Crick base pairs. For the avoidance of doubt, Watson-Crick base pairs in the context of the present disclosure include adenine-thymine, adenine-uracil, and cytosine-guanine base pairs. A proper Watson-Crick base pair is referred to in this context as a “match,” while each unpaired nucleotide, and each incorrectly paired nucleotide, is referred to as a “mismatch.” Alignment for purposes of determining percent nucleic acid sequence complementarity can be achieved in various ways that are within the capabilities of one of skill in the art, for example, using publicly available computer software such as BLAST, BLAST-2, or Megalign software.

As used herein, the term “percent (%) sequence complementarity” with respect to a reference polynucleotide sequence is defined as the percentage of nucleic acids in a candidate sequence that are complementary to the nucleic acids in the reference polynucleotide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence complementarity. A given nucleotide is considered to be “complementary” to a reference nucleotide as described herein if the two nucleotides form canonical Watson-Crick base pairs. For the avoidance of doubt, Watson-Crick base pairs in the context of the present disclosure include adenine-thymine, adenine-uracil, and cytosine-guanine base pairs. A proper Watson-Crick base pair is referred to in this context as a “match,” while each unpaired nucleotide, and each incorrectly paired nucleotide, is referred to as a “mismatch.” Alignment for purposes of determining percent nucleic acid sequence complementarity can be achieved in various ways that are within the capabilities of one of skill in the art, for example, using publicly available computer software such as BLAST, BLAST-2, or Megalign software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any

algorithms needed to achieve maximal complementarity over the full length of the sequences being compared. As an illustration, the percent sequence complementarity of a given nucleic acid sequence, A, to a given nucleic acid sequence, B, (which can alternatively be phrased as a given nucleic acid sequence, A that has a certain percent complementarity to a given nucleic acid sequence, B) is calculated as follows:

$$100 \text{ multiplied by (the fraction } X/Y)$$

where X is the number of complementary base pairs in an alignment (e.g., as executed by computer software, such as BLAST) in that program's alignment of A and B, and where Y is the total number of nucleic acids in B. It will be appreciated that where the length of nucleic acid sequence A is not equal to the length of nucleic acid sequence B, the percent sequence complementarity of A to B will not equal the percent sequence complementarity of B to A. As used herein, a query nucleic acid sequence is considered to be "completely complementary" to a reference nucleic acid sequence if the query nucleic acid sequence has 100% sequence complementarity to the reference nucleic acid sequence.

The term "gene silencing" refers to the suppression of gene expression, e.g., transgene, heterologous gene and/or endogenous gene expression, which may be mediated through processes that affect transcription and/or through processes that affect post-transcriptional mechanisms. In some embodiments, gene silencing occurs when an RNAi molecule initiates the inhibition or degradation of the mRNA transcribed from a gene of interest in a sequence-specific manner via RNA interference, thereby preventing translation of the gene's product.

The phrase "overactive disease driver gene," as used herein, refers to a microglial gene having increased activity and/or expression that contributes to or causes a disease state in a subject (e.g., a human). The disease state may be caused or exacerbated by the overactive disease driver gene directly or by way of an intermediate gene(s).

The term "negative regulator," as used herein, refers to a microglial gene that negatively regulates (e.g., reduces or inhibits) the expression and/or activity of another microglial gene or set of genes (e.g., dysregulated microglial gene or dysregulated microglial gene pathway).

The term "positive regulator," as used herein, refers to a microglial gene that positively regulates (e.g., increases or saturates) the expression and/or activity of another microglial gene or set of microglial genes (e.g., dysregulated microglial gene or dysregulated microglial gene pathway).

The term "phosphate moiety" as used herein, refers to a terminal phosphate group that includes phosphates as well as modified phosphates. The phosphate moiety can be located at either terminus but is preferred at the 5'-terminal nucleoside. In one aspect, the terminal phosphate is unmodified having the formula —O—P(=O)(OH)OH . In another aspect, the terminal phosphate is modified such that one or more of the O and OH groups are replaced with H, O, S, N(R') or alkyl where R' is H, an amino protecting group or unsubstituted or substituted alkyl. In some embodiments, the 5' and or 3' terminal group can comprise from 1 to 3 phosphate moieties that are each, independently, unmodified (di or tri-phosphates) or modified.

In the context of this invention, the term "oligonucleotide" refers to an oligomer or polymer of ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) or mimetics thereof. This term includes oligonucleotides composed of naturally-occurring nucleobases, sugars and covalent internucleoside

(backbone) linkages as well as oligonucleotides having non-naturally-occurring portions that function similarly. Such modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases.

As used herein, the term "reference subject" refers to a healthy control subject of the same or similar, e.g., age, sex, geographical region, and/or education level as a subject treated with a composition of the disclosure. A healthy reference subject is one that does not suffer from a disease associated with expression of a dysregulated microglial gene or a dysregulated microglial gene pathway. Moreover, a healthy reference subject is one that does not suffer from a disease associated with altered (e.g., increased or decreased) expression and/or activity of a microglial gene.

As used herein, the terms "treat," "treated," or "treating" mean both therapeutic treatment and prophylactic or preventative measures wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder, or disease, or obtain beneficial or desired clinical results. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of a condition, disorder, or disease; stabilized (i.e., not worsening) state of condition, disorder, or disease; delay in onset or slowing of condition, disorder, or disease progression; amelioration of the condition, disorder, or disease state or remission (whether partial or total), whether detectable or undetectable; an amelioration of at least one measurable physical parameter, not necessarily discernible by the patient; or enhancement or improvement of condition, disorder, or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment.

Genes described herein

As used herein, the term "ABCA7" refers to the gene encoding Phospholipid-transporting ATPase ABCA7. The terms "ABCA7" and "Phospholipid-transporting ATPase ABCA7" include wild-type forms of the ABCA7 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type ABCA7. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type ABCA7 nucleic acid sequence (e.g., SEQ ID NO: 1, European Nucleotide Archive (ENA) accession number AF250238). SEQ ID NO: 1 is a wild-type gene sequence encoding ABCA7 protein, and is shown below:

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ATGGCCTTCTGGACACAGCTGATGCTGCTGCTCTGGAAGAATTCATGTATCGCCGGAGA
CAGCCGGTCCAGCTCCTGGTCTGAATTGCTGTGGCCTCTCTTCTCTTCTTCATCCTGGTG
GCTGTTCCGCACTCCCACCCGCCCTGGAGCACCATGAATGCCACTTCCCAAACAAGCCA
CTGCCATCGGCGGGCACCCTGCCCTGGCTCCAGGGTCTCATCTGTAATGTGAACAACACC
TGCTTTCCGCAGCTGACACCGGGCGAGGAGCCCGGGCGCCTGAGCAACTTCAACGACTCC
CTGGTCTCCCGGCTGCTAGCCGATGCCCGCACTGTGCTGGGAGGGGCCAGTGCCACAGG
ACGCTGGCTGGCCTAGGGAAGCTGATCGCCACGCTGAGGGCTGCACGCAGCACGGCCCAG
CCTCAACCAACCAAGCAGTCTCCACTGGAACCAACCATGCTGGATGTGCGGGAGCTGCTG
ACGTCACTGCTGCGCACGGAATCCCTGGGGTTGGCACTGGGCCAAGCCCAGGAGCCCTTG
CACAGCTTGTTGGAGGCCGCTGAGGACCTGGCCCAGGAGCTCCTGGCGCTGCGCAGCCTG

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GTGGAGCTTCGGGCACTGCTGCAGAGACCCCGAGGGACCAGCGGCCCCCTGGAGTTGCTG
TCAGAGGCCCTCTGCAGTGTGAGGGGACCTAGCAGCACAGTGGGCCCCCTCCCTCAACTGG
TACGAGGCTAGTGACCTGATGGAGCTGGTGGGGCAGGAGCCAGAATCCGCCCTGCCAGAC
AGCAGCCTGAGCCCCGCCTGCTCGGAGCTGATTGGAGCCCTGGACAGCCACCCGCTGTCC
5 CGCCTGCTCTGGAGACGCCTGAAGCCTCTGATCCTCGGGAAGCTACTCTTTGCACCAGAT
ACACCTTTTACCCGGAAGCTCATGGCCCAGGTCAACCGGACCTTCGAGGAGCTCACCCCTG
CTGAGGGATGTCCGGGAGGTGTGGGAGATGCTGGGACCCCGGATCTTCACCTTCATGAAC
GACAGTTCCAATGTGGCCATGCTGCAGCGGCTCCTGCAGATGCAGGATGAAGGAAGAAGG
CAGCCCAGACCTGGAGGCCGGGACCACATGGAGGCCCTGCGATCCTTTCTGGACCCTGGG
10 AGCGGTGGCTACAGCTGGCAGGACGCACACGCTGATGTGGGGCACCTGGTGGGCACGCTG
GGCCGAGTGACGGAGTGCCTGTCCTTGGACAAGCTGGAGGCGGCACCCTCAGAGGCAGCC
CTGGTGTGCGGGGCCCTGCAACTGCTCGCGGAACATCGATTCTGGGCGGCGTCTCTTC
TTGGGACCTGAGGACTCTTCAGACCCACAGAGCACCCAACCCAGACCTGGGCCCCGGC
CACGTGCGCATCAAAATCCGCATGGACATTGACGTGGTCACGAGGACCAATAAGATCAGG
15 GACAGTTTTTGGGACCCTGGCCCAGCCGCGGACCCCTGACCGACCTGCGCTACGTGTGG
GGCGGCTTCGTGTACCTGCAAGACCTGGTGGAGCGTGCAGCCGTCCGCGTGTCTCAGCGGC
GCCAACCCCCGGGCGGCCTCTACCTGCAGCAGATGCCCTATCCGTGCTATGTGGACGAC
GTGTTCTGCGTGTGCTGAGCCGGTCGCTGCCGCTCTTCTGACGCTGGCCTGGATCTAC
TCCGTGACACTGACAGTGAAGGCCGTGGTGCGGGAGAAGGAGACGCGGCTGCGGGACACC
20 ATGCGCGCCATGGGGCTCAGCCGCGCGGTGCTCTGGCTAGGCTGGTTCCTCAGCTGCCTC
GGGCCCTTCCTGCTCAGCGCCGCACTGCTGGTTCTGGTGTCTAAGCTGGGAGACATCCTC
CCCTACAGCCACCCGGGCGTGGTCTTCTGTTCTTGGCAGCCTTCGCGGTGGCCACGGTG
ACCCAGAGCTTCCTGCTCAGCGCCTTCTTCTCCCGCGCCAACCTGGCTGCGGCCTGCGGC
GGCCTGGCCTACTTCTCCCTCTACCTGCCCTACGTGCTGTGTGTGGCTTGGCGGGACCGG
25 CTGCCCCGCGGGTGGCCGCGTGGCCGCGAGCCTGCTGTGCCCCGTGGCCTTCGGCTTCGGC
TGCGAGAGCCTGGCTCTGCTGGAGGAGCAGGGCGAGGGCGCGCAGTGGCACAACGTGGGC
ACCCGGCCTACGGCAGACGTCTTCAGCCTGGCCCAGGTCTCTGGCCTTCTGCTGCTGGAC
GCGGCGCTCTACGGCCTCGCCACCTGGTACCTGGAAGCTGTGTGCCAGGCCAGTACGGG
ATCCCTGAACCATGGAATTTTCTTTTCGGAGGAGCTACTGGTGCAGGACCTCGGCCCCC
30 AAGAGTCCAGCCCCTTGCCCCACCCCGCTGGACCCAAAGGTGCTGGTAGAAGAGGCACCG
CCCGGCCCTGAGTCCTGGCGTCTCCGTTGCGAGCCTGGAGAAGCGCTTTCTGGAAGCCCG
CAGCCAGCCCTGCGGGGGCTCAGCCTGGACTTCTACCAGGGCCACATCACCGCCTTCCTG
GGCCACAACGGGGCCGCAAGACCACACCTGTCCATCTTGAGTGGCCTCTTCCCACCC
AGTGGTGGCTCTGCCTTCATCCTGGGCCACGACGTCCGCTCCAGCATGGCCGCCATCCGG
35 CCCCACCTGGGCGTCTGTCCTCAGTACAACGTGCTGTTTGACATGCTGACCGTGGACGAG
CACGTCTGGTTCTATGGGCGGCTGAAGGGTCTGAGTGCCGCTGTAGTGGGCCCCGAGCAG
GACCGTCTGCTGCAGGATGTGGGGCTGGTCTCCAAGCAGAGTGTGCAGACTCGCCACCTC
TCTGGTGGGATGCAACGGAAGCTGTCCGTGGCCATTGCCTTTGTGGGCGGCTCCCAAGTT
GTTATCCTGGACGAGCCTACGGCTGGCGTGGATCCTGCTTCCCGCCGCGGTATTTGGGAG
40 CTGCTGCTCAAATACCGAGAAGGTGCGACGCTGATCCTCTCCACCCACCACCTGGATGAG
GCAGAGCTGCTGGGAGACCGTGTGGCTGTGGTGGCAGGTGGCCGCTTGTGCTGCTGTGGC
TCCCCACTCTTCTGCGCCGTACCTGGGCTCCGGCTACTACCTGACGCTGGTGAAGGCC

CGCCTGCCCCTGACCACCAATGAGAAGGCTGACACTGACATGGAGGGCAGTGTGGACACC
AGGCAGGAAAAGAAGAATGGCAGCCAGGGCAGCAGAGTCGGCACTCCTCAGCTGCTGGCC
CTGGTACAGCACTGGGTGCCCCGGGCACGGCTGGTGGAGGAGCTGCCACACGAGCTGGTG
CTGGTGCTGCCCTACACGGGTGCCCATGACGGCAGCTTCGCCACACTCTTCCGAGAGCTA
5 GACACGCGGCTGGCGGAGCTGAGGCTCACTGGCTACGGGATCTCCGACACCAGCCTCGAG
GAGATCTTCCTGAAGGTGGTGGAGGAGTGTGCTGCGGACACAGATATGGAGGATGGCAGC
TGCGGGCAGCACCTATGCACAGGCATTGCTGGCCTAGACGTAACCCTGCGGCTCAAGATG
CCGCCACAGGAGACAGCGCTGGAGAACGGGGAACCAGCTGGGTGAGCCCCAGAGACTGAC
CAGGGCTCTGGGCCAGACGCCGTGGGCCGGGTACAGGGCTGGGCACTGACCCGCCAGCAG
10 CTCCAGGCCCTGCTTCTCAAGCGCTTTCTGCTTGCCCGCCGACGCCGCCGCGGCTGTTC
GCCCAGATCGTGCTGCCCTGCCCTCTTTGTGGGCTGGCCCTCGTGTTTCAAGCTCATCGTG
CCTCCTTTCCGGCACTACCCGGCTCTGCGGCTCAGTCCCACCATGTACGGTGCTCAGGTG
TCCTTCTTCACTGAGGACGCCCCAGGGGACCCTGGACGTGCCCGGCTGCTCGAGGCGCTG
CTGCAGGAGGCAGGACTGGAGGAGCCCCAGTGCAGCATAGCTCCCACAGGTTCTCGGCA
15 CCAGAAGTTCCTGCTGAAGTGGCCAAGGTCTTGGCCAGTGGCAACTGGACCCCAGAGTCT
CCATCCCCAGCCTGCCAGTGTAGCCAGCCCGGTGCCCGGCGCCTGCTGCCCGACTGCCCG
GCTGCAGCTGGTGGTCCCCCTCCGCCCCAGGCAGTGACCGGCTCTGGGGAAGTGGTTCAG
AACCTGACAGGCCGGAACCTGTCTGACTTCTGGTCAAGACCTACCCGCGCCTGGTGCGC
CAGGGCCTGAAGACTAAGAAGTGGGTGAATGAGGTACGGAGGCTTCTCGCTGGGG
20 GGCCGAGACCCAGGCCTGCCCTCGGGCCAAGAGTTGGGCCGCTCAGTGGAGGAGTTGTGG
GCGCTGCTGAGTCCCCTGCCTGGCGGGGCCCTCGACCGTGTCTGAAAAACCTCACAGCC
TGGGCTCACAGCCTGGACGCTCAGGACAGTCTCAAGATCTGGTTCAACAACAAAGGCTGG
CACTCCATGGTGGCCTTTGTCAACCGAGCCAGCAACGCAATCCTCCGTGCTCACCTGCCC
CCAGGCCCGGGCCCGCCACGCCACAGCATCACCACTCAACCACCCCTTGAACCTCACC
25 AAGGAGCAGCTGTTTGAGGCTGCATTGATGGCCTCCTCGGTGGACGTCCTCGTCTCCATC
TGTGTGGTCTTTGCCATGTCTTTGTCCCGGCCAGCTTCACTCTTGTCTCATTGAGGAG
CGAGTCACCCGAGCCAAGCACCTGCAGCTCATGGGGGGCCTGTCCCCACCCCTCTACTGG
CTTGGCAACTTTCTCTGGGACATGTGTAATACTTGGTGCCAGCATGCATCGTGGTGCTC
ATCTTTCTGGCCTTCCAGCAGAGGGCATATGTGGCCCTGCCAACCTGCCTGCTCTCCTG
30 CTGTTGCTACTACTGTATGGCTGGTGCATCACACCGCTCATGTACCCAGCCTCCTTCTTC
TTCTCCGTGCCAGCACAGCCTATGTGGTGTCTACCTGCATAAACCTCTTTATTGGCATC
AATGGAAGCATGGCCACCTTTGTGCTTGAGCTCTTCTCTGATCAGAAGCTGCAGGAGGTG
AGCCGGATCTTGAACAGGTCTTCTTATCTTCCCCCACTTCTGCTTGGGCCGGGGGCTT
ATTGACATGGTGCAGAACAGGCCATGGCTGATGCCTTTGAGCGCTTGGGAGACAGGCAG
35 TTCCAGTCACCCCTGCGCTGGGAGGTGGTGGCAAGAACCTCTTGGCCATGGTGATACAG
GGGCCCTCTTCTTCTCTTACACTACTGCTGCAGCACCGAAGCCAACCTCCTGCCACAG
CCCAGGGTGAGGTCTCTGCCACTCCTGGGAGAGGAGGACGAGGATGTAGCCCGTGAACGG
GAGCGGGTGGTCCAAGGAGCCACCCAGGGGGATGTGTTGGTGCTGAGGAACTTGACCAAG
GTATACCGTGGGCAGAGGATGCCAGCTGTTGACCGCTTGTGCCTGGGGATTCCCCCTGGT
40 GAGTGTGTTTGGGCTGCTGGGTGTGAATGGAGCAGGGAAGACGTCCACGTTTTGCATGGTG
ACGGGGGACACATTGGCCAGCAGGGGCGAGGCTGTGCTGGCAGGCCACAGCGTGGCCCGG
GAACCCAGTGCTGCGCACCTCAGCATGGGATACTGCCCTCAATCCGATGCCATCTTTGAG

CTGCTGACGGGCGCGAGCACCTGGAGCTGCTTGCGCGCCTGCGCGGTGTCCCGGAGGCC
 CAGGTTGCCAGACCGCTGGCTCGGGCCTGGCGCGTCTGGGACTCTCATGGTACGCAGAC
 CGGCCTGCAGGCACCTACAGCGGAGGGAACAAACGCAAGCTGGCGACGGCCCTGGCGCTG
 GTTGGGGACCCAGCCGTGGTGTCTTCTGGACGAGCCGACCACAGGCATGGACCCAGCGCG
 5 CGGCGCTTCCTTTGGAACAGCCTTTTGCCGTGGTGCGGGAGGGCCGTTCAGTGATGCTC
 ACCTCCCATAGCATGGAGGAGTGTGAAGCGCTCTGCTCGCGCCTAGCCATCATGGTGAAT
 GGGCGGTTCCGCTGCCTGGGCAGCCCGCAACATCTCAAGGGCAGATTCGCGGCGGGTCAC
 AACTGACCCTGCGGGTGGCCGCCGCAAGGTCCCAGCCGGCAGCGGCCCTTCGTGGCGGCC
 GAGTTCCCTGGGTGCGAGCTGCGCGAGGCACATGGAGGCCGCTGCGCTTCCAGCTGCCG
 10 CCGGGAGGGCGCTGCGCCCTGGCGCGCGTCTTTGGAGAGCTGGCGGTGCACGGCGCAGAG
 CACGGCGTGGAGGACTTTTCCGTGAGCCAGACGATGCTGGAGGAGGTATTCTTGTACTTC
 TCCAAGGACCAGGGGAAGGACGAGGACACCGAAGAGCAGAAGGAGGCAGGAGTGGGAGTG
 GACCCCGCGCCAGGCCTGCAGCACCCCAAACGCGTCAGCCAGTTCCTCGATGACCCTAGC
 ACTGCCGAGACTGTGCTCTGAGCCTCCCTCCCTGCGGGGCCGCGGGGAGGCCCTGGGAA
 15 TGGCAAGGGCAAGGTAGAGTGCCTAGGAGCCCTGGACTCAGGCTGGCAGAGGGGCTGGTG
 CCCTGGAGAAAATAAAGAGAAGGCTGGAGAGAAGCCGTGCTTGGTGAA
 (SEQ ID NO: 1)

As used herein, the term "ABI3" refers to the gene encoding ABI gene family member 3. The
 20 terms "ABI3" and "ABI gene family member 3" include wild-type forms of the ABI3 gene, as well as
 variants (e.g., splice variants and polymorphisms) of wild-type ABI3. Examples of such variants are
 nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%,
 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type ABI3 nucleic acid sequence (e.g., SEQ
 25 ID NO: 2, ENA accession number AF037886). SEQ ID NO: 2 is a wild-type gene sequence encoding
 ABI3 protein, and is shown below:

TCCTATCCACCCTCCACTCCCCTGTCCCTTGGTGACTCATCCCTGAGCTTCCCAAGGAAG
 CCCCCACCCTCTGCCCTTTCTCCCGCCTTCCATGAGTGGAATCCACCTCCGCCCCCT
 30 ATAGCAGGCCAGCCCCCTTCTCCCAAGTCTCCGACCCCATCCCCAGCCGACCAGTTTC
 CTCTCCAGGACCAGGGAGCAATCACAGCTGCCCCGACCTTGGCTTCTCTGCTGGGTGGG
 ATTGGGGGCTGGGCCCCCAAATGGGCCCTGGCTTCCCCCTTCTCTGGGCAGGGGACAG
 AGAGACACAGGCTCGGGGAGCAGGACTGACTTCTCTTGTCCCGGAATGAGCATGCCTGC
 CCTTTGCAAGCAGGTTTGGGTCTCACGCAGAGGAAACCAAAGCAATAAGAGGGAGGGAA
 35 GGCAGAGCAACCAATCAAGGGCAGGGTGAGACTCAAACGAGCGGGCTCCCTGGGGAGCC
 AGACAGAGGCTGGGGGTGATGGCGGAGCTACAGCAGCTGCAGGAGTTTGAGATCCCCACT
 GGCCGGGAGGCTCTGAGGGGCAACCACAGTGCCCTGCTGCGGGTCGCTGACTACTGCGAG
 GACAATATGTGCAGGCCACAGACAAGCGGAAGGCGCTGGAGGAGACCATGGCCTTCACT
 ACCCAGGCACTGGCCAGCGTGGCCTACCAGGTGGGCAACCTGGCCGGGCACACTCTGCGC
 40 ATGTTGGACCTGCAGGGGGCCGCCCTGCGGCAGGTGGAAGCCCGTGTAAAGCACGCTGGGC
 CAGATGGTGAACATGCATATGGAGAAGGTGGCCCGAAGGGAGATCGGCACCTTAGCCACT
 GTCCAGCGGCTGCCCCCGGCCAGAAAGGTCATCGCCCCAGAGAACCTACCCCTCTCACG

CCCTACTGCAGGAGACCCCTCAACTTTGGCTGCCTGGACGACATTGGCCATGGGATCAAG
 GACCTCAGCACGCAGCTGTCAAGAACAGGCACCCTGTCTCGAAAGAGCATCAAGGCCCT
 GCCACACCCGCTCCGCCACCTTGGGGAGACCACCCCGATTCCCGAGCCAGTGCACCTG
 CCGGTGGTGCCCGACGGCAGACTCTCCGCCGCCTCCTCTGCGTCTTCCCTGGCCTCGGCC
 5 GGCAGCGCCGAAGGTGTCCGTGGGGCCCCCACGCCAAGGGGCAGGCAGCACCTCCAGCC
 CCACCTCTCCCCAGCTCCTTGGACCCACCTCCTCCACCAGCAGCCGTCGAGGTGTTCCAG
 CGGCCTCCCACGCTGGAGGAGTTGTCCCCACCCCCACCGGACGAAGAGCTGCCCCTGCCA
 CTGGACCTGCCTCCTCCTCCACCCCTGGATGGAGATGAATTGGGGCTGCCTCCACCCCCA
 CCAGGATTTGGGCCTGATGAGCCCAGCTGGGTGCCTGCCTCATACTTGGAGAAAGTGGTG
 10 AACTGTACCCATACACCAGCCAGAAGGACAATGAGCTCTCCTTCTCTGAGGGCACTGTC
 ATCTGTGTCACTCGCCGCTACTCCGATGGCTGGTGCGAGGGCGTCAGCTCAGAGGGGACT
 GGATTCTTCCCTGGGAATATGTGGAGCCCAGCTGCTGACAGCCCAGGGCTCTCTGGGCA
 GCTGATGTCTGCACTGAGTGGGTTTCATGAGCCCCAAGCCAAAACCAGCTCCAGTCACAG
 CTGGACTGGGTCTGCCACCTCTTGGGCTGTGAGCTGTGTTCTGTCCTTCCCTCCCATCGG
 15 AGGGAGAAGGGGTCTTGGGGAGAGAGAATTTATCCAGAGGCCTGCTGCAGATGGGGAAGA
 GCTGGAACCAAGAAGTTTGTCAACAGAGGACCCCTACTCCATGCAGGACAGGGTCTCCT
 GCTGCAAGTCCCAACTTTGAATAAAACAGATGATGTCCTGTGACTGCCCCACAGAGATAA
 GGGGCCAGGAGGGATTGAAAGGCATCCCAGTTCTAAGGCTGCTGCTAATTACAGCCCCCA
 ACCTCCAACCCACCAGCTGACCTAGAAGCAGCATCTTCCCATTTCCTCAGTACCCACAAA
 20 GTGCAGCCCACATTGGACCCAGACACCCTCTGCAGCCATTGACTGCAACTTGTTCTTT
 TGCCCATTAATAAAAAAAAAAAAAAAAAAAAAA
 (SEQ ID NO: 2)

As used herein, the term "ADAM10" refers to the gene encoding ADAM Metallopeptidase Domain
 25 10. The terms "ADAM10" and "ADAM Metallopeptidase Domain 10" include wild-type forms of the
 ADAM10 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type ADAM10.
 Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%,
 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%,
 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type ADAM10
 30 nucleic acid sequence (e.g., SEQ ID NO: 3, NCBI Reference Sequence: NM_001110.3). SEQ ID NO: 3
 is a wild-type gene sequence encoding ADAM10 protein, and is shown below:

GCGGCGGCAGGCCTAGCAGCACGGGAACCGTCCCCCGCGCGCATGCGCGCGCCCCTGAAGCGCC
 TGGGGGACGGGTAGGGGCGGGAGGTAGGGGCGCGGCTCCGCGTGCCAGTTGGGTGCCCGCGCG
 35 TCACGTGGTGAGGAAGGAGGCGGAGGTCTGAGTTTCGAAGGAGGGGGGAGAGAAGAGGGAACG
 AGCAAGGGAAGGAAAGCGGGGAAAGGAGGAAGGAAACGAACGAGGGGGGAGGGAGGTCCCTGTTTT
 GGAGGAGCTAGGAGCGTTGCCGGCCCCCTGAAGTGGAGCGAGAGGGAGGTGCTTCGCCGTTTCTCC
 TGCCAGGGGAGGTCCCGGCTTCCCGTGGAGGCTCCGGACCAAGCCCCTTCAGCTTCTCCCTCCGG
 ATCGATGTGCTGCTGTTAACCCGTGAGGAGGCGGCGGCGGCGGCAGCGGCAGCGGAAGATGGTGT
 40 TGCTGAGAGTGTTAATTCTGCTCCTCTCCTGGGCGGCGGGGATGGGAGGTGAGTATGGGAATCCTT
 TAAATAAATATATCAGACATTATGAAGGATTATCTTACAATGTGGATTCATTACACCAAAAACACCAGC
 GTGCCAAAAGAGCAGTCTCACATGAAGACCAATTTTACGTCTAGATTTCCATGCCCATGGAAGACAT

TTCAACCTACGAATGAAGAGGGACACTTCCCTTTTCAGTGATGAATTTAAAGTAGAAACATCAAATAA
AGTACTTGATTATGATACCTCTCATATTTACACTGGACATATTTATGGTGAAGAAGGAAGTTTTAGCCA
TGGGTCTGTTATTGATGGAAGATTTGAAGGATTCATCCAGACTCGTGGTGGCACATTTTATGTTGAGC
CAGCAGAGAGATATATTAAAGACCGAACTCTGCCATTTCACTCTGTCATTTATCATGAAGATGATATTA
5 ACTATCCCCATAAATACGGTCCTCAGGGGGGCTGTGCAGATCATTAGTATTTGAAAGAATGAGGAA
ATACCAGATGACTGGTGTAGAGGAAGTAACACAGATACCTCAAGAAGAACATGCTGCTAATGGTCCA
GAACTTCTGAGGAAAAAACGTACAACCTTCAGCTGAAAAAATACTTGTGAGCTTTATATTCAGACTGA
TCATTTGTTCTTTAAATATTACGGAACACGAGAAGCTGTGATTGCCAGATATCCAGTCATGTTAAAG
CGATTGATACAATTTACCAGACCACAGACTTCTCCGGAATCCGTAACATCAGTTTCATGGTGAAACGC
10 ATAAGAATCAATACAACCTGCTGATGAGAAGGACCCTACAAATCCTTTCCGTTTCCCAAATATTGGTGT
GGAGAAGTTTCTGGAATTGAATTCTGAGCAGAATCATGATGACTACTGTTTGGCCTATGTCTTCACAG
ACCGAGATTTTGTGATGGCGTACTTGGTCTGGCTTGGGTTGGAGCACCTTCAGGAAGCTCTGGAG
GAATATGTGAAAAAAGTAACTCTATTGAGATGGTAAGAAGAAGTCCTTAACACTGGAATTATTACT
GTTTCAGAACTATGGGTCTCATGTACCTCCCAAAGTCTCTCACATTACTTTTGCTCACGAAGTTGGACA
15 TAACTTTGGATCCCCACATGATTCTGGAACAGAGTGCACACCAGGAGAATCTAAGAATTTGGGTCAA
AAAGAAAATGGCAATTACATCATGTATGCAAGAGCAACATCTGGGGACAACTTAACAACAATAAATT
CTCACTCTGTAGTATTAGAAATATAAGCCAAGTTCTTGAGAAGAAGAGAAACAACCTGTTTTGTTGAAT
CTGGCCAACCTATTTGTGGAATGGAATGGTAGAACAAGGTGAAGAATGTGATTGTGGCTATAGTGA
CCAGTGTAAGATGAATGCTGCTTCGATGCAAATCAACCAGAGGGAAGAAAATGCAAACTGAAACCT
20 GGGAAACAGTGCAGTCCAAGTCAAGTCTTGTGTACAGCACAGTGTGCATTCAAGTCAAAGTCTG
AGAAGTGTCGGGATGATTCAGACTGTGCAAGGGAAGGAATATGTAATGGCTTCACAGCTCTCTGCCC
AGCATCTGACCCTAAACCAAACCTTCACAGACTGTAATAGGCATACACAAGTGTGCATTAATGGGCAAT
GTGCAGGTTCTATCTGTGAGAAATATGGCTTAGAGGAGTGTACGTGTGCCAGTTCTGATGGCAAAGA
TGATAAAGAATTATGCCATGTATGCTGTATGAAGAAAATGGACCCATCAACTTGTGCCAGTACAGGGT
25 CTGTGCAGTGGAGTAGGCACTTCAGTGGTGAACCATCACCTGCAACCTGGATCCCCTTGCAACG
ATTTTAGAGTTACTGTGATGTTTTCATGCGGTGCAGATTAGTAGATGCTGATGGTCCCTAGCTAGG
CTTAAAAAAGCAATTTTTAGTCCAGAGCTCTATGAAAACATTGCTGAATGGATTGTGGCTCATTGGTG
GGCAGTATTACTTATGGGAATTGCTCTGATCATGCTAATGGCTGGATTATTAAGATATGCAGTGTTT
ATACTCCAAGTAGTAATCCAAAGTTGCCTCCTCCTAAACCACTTCCAGGCACTTTAAAGAGGAGGAG
30 ACCTCCACAGCCCATTGAGCAACCCCAGCGTCAGCGGCCCCGAGAGAGTTATCAAATGGGACACAT
GAGACGCTAACTGCAGCTTTTGCCTTGGTTCTTCTAGTGCTTACAATGGGAAAACCTTCACTCCAAA
GAGAAACCTATTAAGTCATCATCTCCAACTAAACCCTCACAAGTAACAGTTGAAGAAAAAATGGCAA
GAGATCATATCCTCAGACCAGGTGGAATTACTTAAATTTTAAAGCCTGAAAATTCGAATTTGGGGGTG
GGAGGTGGAAAAGGAACCCAATTTTCTTATGAACAGATATTTTAACTTAATGGCACAAAGTCTTAGA
35 ATATTATTATGTGCCCCGTGTTCCCTGTTCTTCGTTGCTGCATTTTCTTCACTTGCAGGCAAACTTGG
CTCTCAATAAACTTTTACCACAAATTGAAATAAATATATTTTTTTCAACTGCCAATCAAGGCTAGGAGG
CTCGACCACCTCAACATTGGAGACATCACTTGCCAATGTACATACCTTGTTATATGCAGACATGTATT
TCTTACGTACACTGTACTTCTGTGTGCAATTGTAAACAGAAATTGCAATATGGATGTTTCTTTGTATTA
TAAAATTTTCCGCTCTTAATTAATAAATTACTGTTTAATTGACATACTCAGGATAACAGAGAATGGTGG
40 TATTCAGTGGTCCAGGATTCTGTAATGCTTTACACAGGCAGTTTTGAAATGAAAATCAATTTACCTTTC
TGTTACGATGGAGTTGGTTTTGATACTCATTTTTTCTTTATCACATGGCTGCTACGGGCACAAGTGAC
TATACTGAAGAACACAGTTAAGTGTTGTGCAAACTGGACATAGCAGCACATACTACTTCAGAGTTCAT

GATGTAGATGTCTGGTTTCTGCTTACGTCTTTTAACTTTCTAATTCAATTCCATTTTTCAATTAATAGG
 TGAAATTTTATTCATGCTTTGATAGAAATTATGTCAATGAAATGATTCTTTTTATTTGTAGCCTACTTAT
 TTGTGTTTTTTCATATATCTGAAATATGCTAATTATGTTTTCTGTCTGATATGGAAAAGAAAAGCTGTGT
 CTTTATCAAAATATTTAAACGGTTTTTTTCAGCATATCATCACTGATCATTGGTAACCACTAAAGATGAG
 5 TAATTTGCTTAAGTAGTAGTTAAAATTGTAGATAGGCCTTCTGACATTTTTTTTCTAAAATTTTAAACA
 GCATTGAAGGTGAAACAGCACAATGTCCCATTCCAAATTTATTTTTGAAACAGATGTAAATAATTGGC
 ATTTTAAAGAGAAAAGCAAAAACATTTAATGTATTAACAGGCTTATTGCTATGCAGGAAATAGAAGGGG
 CATTACAAAATTGAAGCTTGTGACATATTTATTGCTTCTGTTTTCCAACACTACATCACTTCAACTAGAA
 GTAAAGCTATGATTTTCTGACTTCACATAGGAGGCAAATTTAGAGAAAGTTGTAAAGATTCTATGTT
 10 TTGGGTTTTTTTTTTTTTCTTTTTTTTTTAAAGAGTATAAGGTTTACACAATCATTCTCATAATGTGACGC
 AAGCCAGCAAGGCCAAAATGCTAGAGAAAATAACGGGATCTCTTCCTTGTAACCTTGACAGTATGT
 GGTGACTTTTTCAAATACAGCTTTTTGTACATGATTTAGAGACAAATTTGTACATGAAACCCAGAT
 AGACTATAAATAATTCTAAACAAACAAGTAGGTAGATATGTATGTAATTGCTTTTAAATCATTTAAATGC
 CTTTGTTTTTGGACTGTGCAAAGGTTGGAAGTGGGTTTGCATTTCTAAAATGGTGACTTTTATTCTGC
 15 AAGAGTTCCTTAGTAACCTTCTTGAGTGTGGTAGACTTTGGAACATGTAAATTTTTTGCTTGTAATGTTAT
 CCTGTGGTAGGATTTTGGCAGGTACACACACTGCCCTATTTTATTTGAGTCTAAGTTAAATGTTTTCT
 GAAAAGAGATACATGCACTGAACTCTTCCACTGCGAATCAAGATGTGGTAATATAAAAGGATCAAGA
 CAAATGAGATCTAATACTACTGTCAGTTTAAATGTCCACTGTGTTTTATACAGTATCTTTTTTTGTTTAC
 TTTGGAAATTTTACTAAAAATTGCAAAAATAAAGTATTGTGCAAAGATGTAAGGTTTTTTGAACTTG
 20 AAATGCATTAATAAATAGACGATTAAATCAACTTGAAGGTTCTATACTCTTGAACCTCTGAGAACTATC
 ACAAGAAGCTTCCCACAAGGCAGTGTTTTCTTACAGTTGTCTCTTCCTACAAAAGTATAGATTATCTTT
 ATTCTTAATACTTTGGAATCCATGTAGAAAATTTCCAGTTAGATACTCTGCGTACACACAATAAACCTT
 TTTAAACACCCAAAAAAAAAAAAAAAAAAAAA
 (SEQ ID NO: 3)

25

The terms "APOC1" and "Apolipoprotein C1" include wild-type forms of the APOC1 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type APOC1. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type APOC1 nucleic acid sequence (e.g., SEQ ID NO: 4, NCBI Reference Sequence: NM_001645). SEQ ID NO: 4 is a wild-type gene sequence encoding APOC1 protein, and is shown below:

AACGCTCACGGGACAGGGGCAGAGGAGAAAAACGTGGGTGGACAGAGGGAGGCAGGCGGTCAGG
 35 GGAAGGCTCAGGAGGAGGGAGATCAACATCAACCTGCCCCGCCCCCTCCCCAGCCTGATAAAGGT
 CCTGCGGGCAGGACAGGACCTCCCAACCAAGCCCTCCAGCAAGGATTCAGAGTGCCCTCCGGCC
 TCGCCATGAGGCTCTTCCTGTGCTCGCTCCCGGTCCTGGTGGTGGTTCTGTGATCGTCTTGGAAGGCC
 CAGCCCCAGCCCAGGGGACCCCAGACGTCTCCAGTGCCTTGGATAAGCTGAAGGAGTTTGGAAACA
 CACTGGAGGACAAGGCTCGGGAACATCAGCCGCATCAAACAGAGTGAACTTTCTGCCAAGATGC
 40 GGGAGTGGTTTTTCAGAGACATTTAGAAAAGTGAAGGAGAACTCAAGATTGACTCATGAGGACCTGA
 AGGGTGACATCCCAGGAGGGGCCTCTGAAATTTCCACACCCCAGCGCCTGTGCTGAGGACTCCCT
 CCATGTGGCCCCAGGTGCCACCAATAAAATCCTACAGAAAATTCAAAAAAAAAAAAAAAAAAAAAA

(SEQ ID NO: 4)

As used herein, the term "APOE" refers to the gene encoding Apolipoprotein E. The terms "APOE" and "Apolipoprotein E" include wild-type forms of the APOE gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type APOE. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type APOE nucleic acid sequence (e.g., SEQ ID NO: 5, ENA accession number M12529). SEQ ID NO: 5 is a wild-type gene sequence encoding APOE protein, and is shown below:

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CCCCAGCGGAGGTGAAGGACGTCCTTCCCCAGGAGCCGACTGGCCAATCACAGGCAGGAA
GATGAAGGTTCTGTGGGCTGCGTTGCTGGTCACATTCTGGCAGGATGCCAGGCCAAGGT
GGAGCAAGCGGTGGAGACAGAGCCGGAGCCCGAGCTGCGCCAGCAGACCGAGTGGCAGAG
CGGCCAGCGCTGGGAAGTGGCACTGGGTGCGCTTTTGGGATTACCTGCGCTGGGTGCAGAC
ACTGTCTGAGCAGGTGCAGGAGGAGCTGCTCAGCTCCCAAGTCACCCAAGAACTGAGGGC
GCTGATGGACGAGACCATGAAGGAGTTGAAGGCCTACAAATCGGAAGTGGAGGAACAAGT
GACCCCGGTAGCGGAGGAGACGCGGGCACGGCTGTCCAAGGAGCTGCAGACGGCGCAGGC
CCGGCTGGGCGCGGACATGGAGGACGTGTGCGGCCGCTGGTGCAGTACCGCGGCGAGGT
GCAGGCCATGCTCGGCCAGAGCACCGAGGAGCTGCGGGTGCGCCTCGCCTCCACCTGCG
CAAGCTGCGTAAGCGGCTCCTCCGCGATCCCGATGACCTGCAGAAGCGCCTGGCAGTGTA
CCAGGCCCGGGGCCCGCGAGGGCGCCGAGCGCGGCCTCAGCGCCATCCGCGAGCGCCTGGG
GCCCCTGGTGGAAACAGGGCCGCGTGCGGGCCGCCACTGTGGGCTCCCTGGCCGGCCAGCC
GCTACAGGAGCGGGCCCAGGCCTGGGGCGAGCGGCTGCGCGCGCGGATGGAGGAGATGGG
CAGTCGGACCCGCGACCGCCTGGACGAGGTGAAGGAGCAGGTGGCGGAGGTGCGCGCCAA
GCTGGAGGAGCAGGCCAGCAGATACGCCTGCAGGCCGAGGCCTTCCAGGCCCGCCTCAA
GAGCTGGTTCGAGCCCCCTGGTGGAAAGACATGCAGCGCCAGTGGGCCGGGCTGGTGGAGAA
GGTGCAGGCTGCCGTGGGCACCAGCGCCGCCCTGTGCCAGCGACAATCACTGAACGCC
GAAGCCTGCAGCCATGCGACCCACGCCACCCCGTGCTCCTGCCTCCGCGCAGCCTGCA
GCGGGAGACCCTGTCCCCGCCCCAGCCGTCTCCTGGGGTGGACCCTAGTTTAATAAAGA
TTCACCAAGTTTCACGC

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(SEQ ID NO: 5)

As used herein, the term "AXL" refers to the gene encoding Tyrosine-protein kinase receptor UFO. The terms "AXL" and "Tyrosine-protein kinase receptor UFO" include wild-type forms of the AXL gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type AXL. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type AXL nucleic acid sequence (e.g., SEQ ID NO: 6, ENA accession number M76125). SEQ ID NO: 6 is a wild-type gene sequence encoding AXL protein, and is shown below:

GCTGGGCAAAGCCGGTGGCAAGGGCCTCCCCTGCCGCTGTGCCAGGCAGGCAGTGCCAAA
TCCGGGGAGCCTGGAGCTGGGGGGAGGGCCGGGGACAGCCCCGGCCCTGCCCCCTCCCCCG
CTGGGAGCCCAGCAACTTCTGAGGAAAGTTTGGCACCCATGGCGTGGCGGTGCCCCAGGA
TGGGCAGGGTCCCCTGGCCTGGTGTCTTGGCGCTGTGCGGCTGGGCGTGCATGGCCCCCA
5 GGGGCACGCAGGCTGAAGAAAGTCCCTTCGTGGGCAACCCAGGGAATATCACAGGTGCCC
GGGGA CTACGGGCACCCTTCGGTGTGAGCTCCAGGTTTCAGGGAGAGCCCCCGAGGTAC
ATTGGCTTCGGGATGGACAGATCCTGGAGCTCGCGGACAGCACCCAGACCCAGGTGCCCC
TGGGTGAGGATGAACAGGATGACTGGATAGTGGTCAGCCAGCTCAGAATCACCTCCCTGC
AGCTTTCCGACACGGGACAGTACCAGTGTTTGGTGTCTTGGGACATCAGACCTTCGTGT
10 CCCAGCCTGGCTATGTTGGGCTGGAGGGCTTGCCCTACTTCCTGGAGGAGCCCCGAAGACA
GGACTGTGGCCGCCAACACCCCTTCAACCTGAGCTGCCAAGCTCAGGGACCCCCAGAGC
CCGTGGACCTACTCTGGCTCCAGGATGCTGTCCCCCTGGCCACGGCTCCAGGTCACGGCC
CCCAGCGCAGCCTGCATGTTCCAGGGCTGAACAAGACATCCTCTTTCTCCTGCGAAGCCC
ATAACGCCAAGGGGGTCAACACATCCCGCACAGCCACCATCACAGTGCTCCCCCAGCAGC
15 CCGTAACCTCCACCTGGTCTCCCGCCAACCCACGGAGCTGGAGGTGGCTTGGACTCCAG
GCCTGAGCGGCATCTACCCCTGACCCACTGCACCCTGCAGGCTGTGCTGTCAGACGATG
GGATGGGCATCCAGGCGGGAGAACCAGACCCCCCAGAGGAGCCCTCACCTCGCAAGCAT
CCGTGCCCCCCCATCAGCTTCGGCTAGGCAGCCTCCATCCTCACACCCCTTATCACATCC
GCGTGGCATGCACCAGCAGCCAGGGCCCCCTCATCCTGGACCCACTGGCTTCCTGTGGAGA
20 CGCCGGAGGGAGTGCCCTGGGCCCCCTAAGAACATTAGTGCTACGCGGAATGGGAGCC
AGGCCTTCGTGCATTGGCAAGAGCCCCGGGCGCCCCTGCAGGGTACCCTGTTAGGGTACC
GGCTGGCGTATCAAGGCCAGGACACCCAGAGGTGCTAATGGACATAGGGCTAAGGCAAG
AGGTGACCCTGGAGCTGCAGGGGGACGGGTCTGTGTCCAATCTGACAGTGTGTGTGGCAG
CCTACACTGCTGCTGGGGATGGACCCTGGAGCCTCCAGTACCCCTGGAGGCCTGGCGCC
25 CAGTGAAGGAACCTTCAACTCCTGCCTTCTCGTGGCCCTGGTGGTATGTA CTGCTAGGAG
CAGTCGTGGCCGCTGCCTGTGTCTCATCTTGGCTCTCTTCCTTGCCACCGGCGAAAGA
AGGAGACCCGTTATGGAGAAGTGTTTGAACCAACAGTGGAAGAGGTGAACTGGTAGTCA
GGTACCGCGTGC GCAAGTCCTACAGTCGTCGGACCACTGAAGCTACCTTGAACAGCCTGG
GCATCAGTGAAGAGCTGAAGGAGAAGCTGCGGGATGTGATGGTGGACCGGCACAAGGTGG
30 CCCTGGGGAAGACTCTGGGAGAGGGAGAGTTTGGAGCTGTGATGGAAGGCCAGCTCAACC
AGGACGACTCCATCCTCAAGGTGGCTGTGAAGACGATGAAGATTGCCATCTGCACGAGGT
CAGAGCTGGAGGATTTCTGAGTGAAGCGGTCTGCATGAAGGAATTTGACCATCCCAACG
TCATGAGGCTCATCGGTGTCTGTTTCCAGGGTTCTGAACGAGAGAGCTTCCCAGCACCTG
TGGTCATCTTACCTTTTCATGAAACATGGAGACCTACACAGCTTCCTCCTCTATTCCCGGC
35 TCGGGGACCAGCCAGTGACCTGCCCCTCAGATGCTAGTGAAGTTCATGGCAGACATCG
CCAGTGGCATGGAGTATCTGAGTACCAAGAGATTCTACACCGGGACCTGGCGGCCAGGA
ACTGCATGCTGAATGAGAACATGTCCGTGTGTGTGGCGGACTTCGGGCTCTCCAAGAAGA
TCTACAATGGGGACTACTACCGCCAGGGACGTATCGCCAAGATGCCAGTCAAGTGGATTG
CCATTGAGAGTCTAGCTGACCGTGTCTACACCAGCAAGAGCGATGTGTGGTCCCTTCGGGG
40 TGACAATGTGGGAGATTGCCACAAGAGGCCAAACCCCATATCCGGGCGTGGAGAACAGCG
AGATTTATGACTATCTGCGCCAGGGAAATCGCCTGAAGCAGCCTGCGGACTGTCTGGATG
GACTGTATGCCTTGATGTGCGGTGCTGGGAGCTAAATCCCCAGGACCGGCCAAGTTTTA

CAGAGCTGCGGGAAGATTTGGAGAACACACTGAAGGCCTTGCCTCCTGCCCAGGAGCCTG
 ACGAAATCCTCTATGTCAACATGGATGAGGGTGGAGGTTATCCTGAACCCCCTGGAGCTG
 CAGGAGGAGCTGACCCCCCAACCCAGCCAGACCCTAAGGATTCCTGTAGCTGCCTCACTG
 CGGCTGAGGTCCATCCTGCTGGACGCTATGTCCTCTGCCCTTCCACAACCCCTAGCCCCG
 5 CTCAGCCTGCTGATAGGGGCTCCCCAGCAGCCCCAGGGCAGGAGGATGGTGCCTGAGACA
 ACCCTCCACCTGGTACTCCCTCTCAGGATCCAAGCTAAGCACTGCCACTGGGGAAAACCTC
 CACCTTCCCACCTTTTCCACCCCACGCCTTATCCCCACTTGCAGCCCTGTCTTCCTACCTA
 TCCCACCTCCATCCCAGACAGGTCCCTCCCCTTCTCTGTGCAGTAGCATCACCTTGAAAG
 CAGTAGCATCACCATCTGTAAAAGGAAGGGGTTGGATTGCAATATCTGAAGCCCTCCCAG
 10 GTGTTAACATTCCAAGACTCTAGAGTCCAAGGTTTAAAGAGTCTAGATTCAAAGGTTCTA
 GGTTTCAAAGATGCTGTGAGTCTTTGGTTCTAAGGACCTGAAATTCCAAAGTCTCTAATT
 CTATTAAAGTGCTAAGGTTCTAAGGCCAAAAAAAAAAAAAAAAAAAAA
 (SEQ ID NO: 6)

15 As used herein, the term "BIN1" refers to the gene encoding Myc box-dependent-interacting
 protein 1. The terms "BIN1" and "Myc box-dependent-interacting protein 1" include wild-type forms of the
 BIN1 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type BIN1. Examples of
 such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%,
 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%,
 20 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type BIN1 nucleic acid
 sequence (e.g., SEQ ID NO: 7, ENA accession number AF004015). SEQ ID NO: 7 is a wild-type gene
 sequence encoding BIN1 protein, and is shown below:

ATGGCAGAGATGGGCAGTAAAGGGGTGACGGCGGGAAAGATCGCCAGCAACGTGCAGAAG
 25 AAGCTCACCCGCGCGCAGGAGAAGGTTCTCCAGAAGCTGGGGAAGGCAGATGAGACCAAG
 GATGAGCAGTTTGAGCAGTGCGTCCAGAATTTCAACAAGCAGCTGACGGAGGGCACCCGG
 CTGCAGAAGGATCTCCGGACCTACCTGGCCTCCGTCAAAGCCATGCACGAGGCTTCCAAG
 AAGCTGAATGAGTGTCTGCAGGAGGTGTATGAGCCCGATTGGCCCGGCAGGGATGAGGCA
 AACAAGATCGCAGAGAACAACGACCTGCTGTGGATGGATTACCACCAGAAGCTGGTGGAC
 30 CAGGCGCTGCTGACCATGGACACGTACCTGGGCCAGTTCCCCGACATCAAGTCACGCATT
 GCCAAGCGGGGGCGCAAGCTGGTGGACTACGACAGTGCCCGGCACCACTACGAGTCCCTT
 CAAACCGCCAAAAAGAAGGATGAAGCCAAAATTGCCAAGCCTGTCTCGCTGCTTGAGAAA
 GCCGCCCCCAGTGGTGCCAAGGCCAACTGCAGGCTCATCTCGTAGCTCAAACCTAACCTG
 CTCCGAAATCAGGCCGAGGAGGAGCTCATCAAAGCCCAGAAGGTGTTTGAGGAGATGAAT
 35 GTGGATCTGCAGGAGGAGCTGCCGTCCCTGTGGAACAGCCGCGTAGGTTTCTACGTCAAC
 ACGTTCCAGAGCATCGCGGGCCTGGAGGAAAACCTTCCACAAGGAGATGAGCAAGCTCAAC
 CAGAACCTCAATGATGTGCTGGTTCGGCCTGGAGAAGCAACACGGGAGCAACACCTTCACG
 GTCAAGGCCAGCCAGTGACAACGCGCCTGCAAAAGGGAACAAGAGCCCTTCGCCTCCA
 GATGGCTCCCCTGCCGCCACCCCCGAGATCAGAGTCAACCACGAGCCAGAGCCGGCCGGC
 40 GGGGCCACGCCCCGGGGCCACCCTCCCCAAGTCCCCATCTCAGCTCCGGAAAGGCCACCA
 GTCCCTCCGCCTCCCAAACACACCCCGTCCAAGGAAGTCAAGCAGGAGCAGATCCTCAGC
 CTGTTTGAGGACACGTTTGTCCCTGAGATCAGCGTGACCACCCCTCCAGTTTGAGGCC

CCGGGGCCTTTCTCGGAGCAGGCCAGTCTGCTGGACCTGGACTTTGACCCCCTCCCGCCC
 GTGACGAGCCCTGTGAAGGCACCCACGCCCTCTGGTCAGTCAATTCCATGGGACCTCTGG
 GAGCCACAGAGAGTCCAGCCGGCAGCCTGCCTTCCGGGGAGCCCAGCGCTGCCGAGGGC
 ACCTTTGCTGTGTCCTGGCCCAGCCAGACGGCCGAGCCGGGGCCTGCCCAACCAGCAGAG
 5 GCCTCGGAGGTGGCGGGTGGGACCCAACCTGCGGCTGGAGCCCAGGAGCCAGGGGAGACG
 GCGGCAAGTGAAGCAGCCTCCAGCTCTCTTCTGCTGTCTGCTGGTGGAGACCTTCCCAGCA
 ACTGTGAATGGCACCGTGGAGGGCGGCAGTGGGGCCGGGCGCTTGGACCTGCCCCCAGGT
 TTCATGTTCAAGGTACAGGCCCAGCAGACTACACGGCCACTGACACAGACGAGCTGCAG
 CTCAAGGCTGGTGTATGTGGTGTGCTGGTGTATCCCCTTCCAGAACCCTGAAGAGCAGGATGAA
 10 GGCTGGCTCATGGGCGTGAAGGAGAGCGACTGGAACCAGCACAAGGAGCTGGAGAAGTGC
 CGTGGCGTCTTCCCCGAGAACTTCACTGAGAGGGTCCCATGA
 (SEQ ID NO: 7)

As used herein, the term "C1QA" refers to the gene encoding Complement C1q A Chain. The
 15 terms "C1QA" and " Complement C1q A Chain " include wild-type forms of the C1QA gene, as well as
 variants (e.g., splice variants and polymorphisms) of wild-type C1QA. Examples of such variants are
 nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%,
 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type C1QA nucleic acid sequence (e.g., SEQ
 20 ID NO: 8, NCBI Reference Sequence: NM_015991.3). SEQ ID NO: 8 is a wild-type gene sequence
 encoding C1QA protein, and is shown below:

AGTCTTGCTGAAGTCTGCTTGAATGTCCCTGGTGAGCTTCTGGCCACTGGGGAAGTTCAGGGGGC
 AGGTCTGAAGAAGGGGAAGTAGGAAGGGATGTGAACTTGGCCACAGCCTGGAGCCACTCCTGCTG
 25 GGCAGCCCACAGGGTCCCTGGGCGGAGGGCAGGAGCATCCAGTTGGAGTTGACAACAGGAGGCA
 GAGGCATCATGGAGGGTCCCCGGGGATGGCTGGTGTCTGTGTGCTGGCCATATCGCTGGCCTCT
 ATGGTGACCGAGGACTTGTGCCGAGCACCAGACGGGAAGAAAGGGGAGGCAGGAAGACCTGGCAG
 ACGGGGGCGGCCAGGCCTCAAGGGGGAGCAAGGGGAGCCGGGGGGCCCCTGGCATCCGGACAGG
 CATCCAAGGCCTTAAAGGAGACCAGGGGGAACCTGGGCCCTCTGGAACCCCGGCAAGGTGGGCT
 30 ACCCAGGGCCCAGCGGCCCCCTCGGAGCCCGTGGCATCCCGGGAATTAAAGGCACCAAGGGCAGC
 CCAGGAAACATCAAGGACCAGCCGAGGCCAGCCTTCTCCGCCATTGCGCGGAACCCCCCAATGGG
 GGGCAACGTGGTCATCTTCGACACGGTCATCACCAACCAGGAAGAACCGTACCAGAACCACTCCGG
 CCGATTCTGCTGCACTGTACCCGGCTACTACTTACCTTCCAGGTGCTGTCCCAGTGGGAAATC
 TGCCTGTCCATCGTCTCCTCCTCAAGGGGCCAGGTCCGACGCTCCCTGGGCTTCTGTGACACCACC
 35 AACAAGGGGCTCTTCCAGGTGGTGTGAGGGGGCATGGTGCTTCAGCTGCAGCAGGGTGACCAGGT
 CTGGGTTGAAAAGACCCCAAAAAGGGTCACATTTACCAGGGCTCTGAGGCCGACAGCGTCTTCAG
 CGGCTTCCTCATCTTCCCATCTGCCTGAGCCAGGGAAGGACCCCTCCCCACCCACCTCTCTGGC
 TTCCATGCTCCGCCTGTAAATGGGGGCGCTATTGCTTCAGCTGCTGAAGGGAGGGGGCTGGCTCT
 GAGAGCCCCAGGACTGGCTGCCCCGTGACACATGCTCTAAGAAGCTCGTTTCTTAGACCTCTTCTG
 40 GAATAAACATCTGTGTCTGTGTCTGCTGAACATGAGCTTCAGTTGCTACTCGGAGCATTGAGAGGGA
 GGCCTAAGAATAATAACAATCCAGTGCTTAAGAGTCAAAAAAAAAAAAA
 (SEQ ID NO: 8)

As used herein, the term "C3" refers to the gene encoding Complement C3. The terms "C3" and " Complement C3 " include wild-type forms of the C3 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type C3. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type C3 nucleic acid sequence (e.g., SEQ ID NO: 9, NCBI Reference Sequence: NM_000064.3). SEQ ID NO: 9 is a wild-type gene sequence encoding C3 protein, and is shown below:

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10 AGATAAAAAGCCAGCTCCAGCAGGCGCTGCTCACTCCTCCCCATCCTCTCCCTCTGTCCCTCTGTCC
CTCTGACCCTGCACTGTCCCAGCACCATGGGACCCACCTCAGGTCCCAGCCTGCTGCTCCTGTCTAC
TAACCCACCTCCCCCTGGCTCTGGGGAGTCCCATGTACTCTATCATCACCCCCAACATCTTGCGGCT
15 GGAGAGCGAGGAGACCATGGTGCTGGAGGCCCCACGACGCGCAAGGGGATGTTCCAGTCACTGTTA
CTGTCCACGACTTCCCAGGCAAAAACTAGTGCTGTCCAGTGAGAAGACTGTGCTGACCCCTGCCA
CCAACCACATGGGCAACGTACCTTCACGATCCCAGCCAACAGGGAGTTCAAGTCAGAAAAGGGGC
GCAACAAGTTTCGTGACCGTGACGGCCACCTTCGGGACCCAAGTGGTGGAGAAGGTGGTGCTGGTC
AGCCTGCAGAGCGGGTACCTCTTCATCCAGACAGACAAGACCATCTACACCCCTGGCTCCACAGTT
CTCTATCGGATCTTCAACGTCAACCACAAGCTGCTACCCGTGGGCCGGACGGTCATGGTCAACATT
20 GAGAACCCGGAAGGCATCCCGGTCAAGCAGGACTCCTTGCTTCTCAGAACCAGCTTGGCGTCTTG
CCCTTGCTTGGGACATTCCGGAACCTCGTCAACATGGGCCAGTGGAAGATCCGAGCCTACTATGAAA
ACTCACACAGCAGGTCTTCTCCACTGAGTTTGAGGTGAAGGAGTACGTGCTGCCAGTTTCGAGGT
CATAGTGGAGCCTACAGAGAAATTCTACTACATCTATAACGAGAAGGGCCTGGAGGTCACCATCACC
GCCAGGTTCTCTACGGGAAGAAAGTGGAGGGAACTGCCTTTGTCTATCTTCGGGATCCAGGATGGC
25 GAACAGAGGATTTCCCTGCCTGAATCCCTCAAGCGCATTCCGATTGAGGATGGCTCGGGGGAGGTT
GTGCTGAGCCGGAAGGTACTGCTGGACGGGGTGCAGAACCCCCGAGCAGAAGACCTGGTGGGGAA
GTCTTTGTACGTGTCTGCCACCGTCATCTTGCACTCAGGCAGTGACATGGTGCAGGCAGAGCGCAG
CGGGATCCCCATCGTGACCTCTCCCTACCAGATCCACTTCACCAAGACACCCAAGTACTTCAAACCA
GGAATGCCCTTTGACCTCATGGTGTTCGTGACGAACCTGATGGCTCTCCAGCCTACCGAGTCCCC
30 GTGGCAGTCCAGGGCGAGGACACTGTGCAGTCTCTAACCCAGGGAGATGGCGTGGCCAAACTCAG
CATCAACACACACCCCAGCCAGAAGCCCTTGAGCATCACGGTGCGCACGAAGAAGCAGGAGCTCTC
GGAGGCAGAGCAGGCTACCAGGACCATGCAGGCTCTGCCCTACAGCACCGTGGGCAACTCCAACA
ATTACCTGCATCTCTCAGTGCTACGTACAGAGCTCAGACCCGGGAGACCCTCAACGTCAACTTCCT
CCTGCGAATGGACCGCGCCACGAGGCCAAGATCCGCTACTACACCTACCTGATCATGAACAAGGG
35 CAGGCTGTTGAAGGCGGGACGCCAGGTGCGAGAGCCCGGCCAGGACCTGGTGGTGCTGCCCTG
TCCATCACCACCGACTTCATCCCTTCCTTCGCTGGTGGCGTACTACACGCTGATCGGTGCCAGC
GGCCAGAGGGAGGTGGTGGCCGACTCCGTGTGGGTGGACGTCAAGGACTCCTGCGTGGGCTCGCT
GGTGGTAAAAAGCGGCCAGTCAGAAGACCGGCAGCCTGTACCTGGGCAGCAGATGACCCTGAAGA
TAGAGGGTGACCACGGGGCCCGGGTGGTACTGGTGGCCGTGGACAAGGGCGTGTTCTGTGCTGAAT
40 AAGAAGAACAACTGACGCAGAGTAAGATCTGGGACGTGGTGGAGAAGGCAGACATCGGCTGCACC
CCGGGCAGTGGGAAGGATTACGCCGGTGTCTTCTCCGACGCAGGGCTGACCTTCACGAGCAGCAG
TGGCCAGCAGACCGCCAGAGGGCAGAACTTCAGTGCCCGCAGCCAGCCGCCCGCCGACGCCGTT
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CCGTGCAGCTCACGGAGAAGCGAATGGACAAAGTCGGCAAGTACCCCAAGGAGCTGCGCAAAGTGC
TGCGAGGACGGCATGCGGGAGAACCCCATGAGGTTCTCGTGCCAGCGCCGGACCCGTTTCATCTC
CCTGGGCGAGGCGTGCAAGAAGGTCTTCCTGGACTGCTGCAACTACATCACAGAGCTGCGGCGGC
AGCACGCGCGGGCCAGCCACCTGGGCCTGGCCAGGAGTAACCTGGATGAGGACATCATTGCAGAA
5 GAGAACATCGTTTCCCGAAGTGAGTTCCAGAGAGCTGGCTGTGGAACGTTGAGGACTTGAAAGAG
CCACCGAAAAATGGAATCTCTACGAAGCTCATGAATATATTTTTGAAAGACTCCATCACCACGTGGGA
GATTCTGGCTGTGAGCATGTGCGACAAGAAAGGGATCTGTGTGGCAGACCCCTTCGAGGTCACAGT
AATGCAGGACTTCTTCATCGACCTGCGGCTACCCTACTCTGTTGTTTCGAAACGAGCAGGTGGAAATC
CGAGCCGTTCTCTACAATTACCGGCAGAACCAAGAGCTCAAGGTGAGGGTGGAATACTCCACAAT
10 CCAGCCTTCTGCAGCCTGGCCACCACCAAGAGGCGTCACCAGCAGACCGTAACCATCCCCCCCCAAG
TCCTCGTTGTCCGTTCCATATGTCATCGTGCCGCTAAAGACCGGCCTGCAGGAAGTGGAAGTCAAG
GCTGCTGTCTACCATCATTTTCATCAGTGACGGTGTGAGGAAGTCCCTGAAGGTCGTGCCGGAAGGA
ATCAGAATGAACAAAACCTGTGGCTGTTTCGCACCCTGGATCCAGAACGCCTGGGCCGTGAAGGAGTG
CAGAAAGAGGACATCCACCTGCAGACCTCAGTGACCAAGTCCCGGACACCGAGTCTGAGACCAGA
15 ATTCTCCTGCAAGGGACCCAGTGGCCAGATGACAGAGGATGCCGTGACGCGGAACGGCTGAA
GCACCTCATTGTGACCCCTCGGGCTGCGGGGAACAGAACATGATCGGCATGACGCCACGGTCAT
CGCTGTGCATTACCTGGATGAAACGGAGCAGTGGGAGAAGTTCGGCCTAGAGAAGCGGCAGGGGG
CCTTGAGGCTCATCAAGAAGGGGTACACCCAGCAGCTGGCCTTCAGACAACCCAGCTCTGCCTTTG
CGGCCTTCGTGAAACGGGCACCCAGCACCTGGCTGACCGCCTACGTGGTCAAGGTCTTCTCTCTGG
20 CTGTCAACCTCATCGCCATCGACTCCCAAGTCTCTGCGGGGCTGTTAAATGGCTGATCCTGGAGAA
GCAGAAGCCCGACGGGGTCTTCCAGGAGGATGCGCCCGTGATACACCAAGAAATGATTGGTGGATT
ACGGAACAACAACGAGAAAGACATGGCCCTCACGGCCTTTGTTCTCATCTCGCTGCAGGAGGCTAA
AGATATTTGCGAGGAGCAGGTCAACAGCCTGCCAGGCAGCATCACTAAAGCAGGAGACTTCCTTGA
AGCCAACTACATGAACCTACAGAGATCCTACACTGTGGCCATTGCTGGCTATGCTCTGGCCCAGATG
25 GGCAGGCTGAAGGGGCCTCTTCTTAACAAATTTCTGACCACAGCCAAAGATAAGAACCGCTGGGAG
GACCCTGGTAAGCAGCTCTACAACGTGGAGGCCACATCCTATGCCCTCTTGGCCCTACTGCAGCTA
AAAGACTTTGACTTTGTGCCTCCCGTCGTGCGTTGGCTCAATGAACAGAGATACTACGGTGGTGGCT
ATGGCTCTACCCAGGCCACCTTCATGGTGTTCAGCCTTGGCTCAATACCAAAAGGACGCCCCTGA
CCACCAGGAACCTGAACCTTGATGTGTCCCTCCAAGTCCCAGCCGCAGCTCCAAGATCACCCACCG
30 TATCCACTGGGAATCTGCCAGCCTCCTGCGATCAGAAGAGACCAAGGAAAATGAGGGTTTCACAGTC
ACAGCTGAAGGAAAAGGCCAAGGCACCTTGTGCGTGGTGACAATGTACCATGCTAAGGCCAAAGAT
CAACTCACCTGTAATAAATTCGACCTCAAGGTCACCATAAAACCAGCACCGGAAACAGAAAAGAGGC
CTCAGGATGCCAAGAACAATATGATCCTTGAGATCTGTACCAGGTACCGGGGAGACCAGGATGCCA
CTATGTCTATATTGGACATATCCATGATGACTGGCTTTGCTCCAGACACAGATGACCTGAAGCAGCT
35 GGCCAATGGTGTGACAGATACATCTCCAAGTATGAGCTGGACAAAGCCTTCTCCGATAGGAACACC
CTCATCATCTACCTGGACAAGGTCTCACACTCTGAGGATGACTGTCTAGCTTTCAAAGTTACCAATA
CTTTAATGTAGAGCTTATCCAGCCTGGAGCAGTCAAGGTCTACGCCTATTACAACCTGGAGGAAAGC
TGTACCCGGTTCTACCATCCGAAAAGGAGGATGGAAAGCTGAACAAGCTCTGCCGTGATGAACTG
TGCCGCTGTGCTGAGGAGAATTGCTTCATACAAAAGTCGGATGACAAGGTCACCCTGGAAGAACGG
40 CTGGACAAGGCCTGTGAGCCAGGAGTGGACTATGTGTACAAGACCCGACTGGTCAAGGTTTCAAGCTG
TCCAATGACTTTGACGAGTACATCATGGCCATTGAGCAGACCATCAAGTCAGGCTCGGATGAGGTGC
AGGTTGGACAGCAGCGCACGTTTCATCAGCCCCATCAAGTGCAGAGAAGCCCTGAAGCTGGAGGAGA

AGAAACACTACCTCATGTGGGGTCTCTCCTCCGATTTCTGGGGAGAGAAGCCCCAACCTCAGCTACAT
 CATCGGGAAGGACACTTGGGTGGAGCACTGGCCCCGAGGAGGACGAATGCCAAGACGAAGAGAACC
 AGAAACAATGCCAGGACCTCGGCGCCTTCACCGAGAGCATGGTTGTCTTTGGGTGCCCCAACTGAC
 CACACCCCCATTCCCCCACTCCAGATAAAGCTTCAGTTATATCTCAAAAAAAAAAAAAAAAAAAAA

5 (SEQ ID NO: 9)

As used herein, the term "C9orf72" refers to the gene encoding Guanine nucleotide exchange C9orf72. The terms "C9orf72" and "Guanine nucleotide exchange C9orf72" include wild-type forms of the C9orf72 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type C9orf72.

10 Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type C9orf72 nucleic acid sequence (e.g., SEQ ID NO: 10, ENA accession number JN681271). SEQ ID NO: 10 is a wild-type gene sequence encoding C9orf72 protein, and is shown below:

15

AGGAAAGAGAGGTGCGTCAAACAGCGACAAGTTCCGCCCACGTAAAAGATGACGCTTGGT
 GTGTCAGCCGTCCCTGCTGCCCCGTTGCTTCTCTTTGGGGCGGGGTCTAGCAAGAGCA
 GGTGTGGGTTTAGGAGATATCTCCGGAGCATTGGATAATGTGACAGTTGGAATGCAGTG
 ATGTCGACTCTTTGCCACCGCCATCTCCAGCTGTTGCCAAGACAGAGATTGCTTTAAGT
 20 GGCAAATCACCTTTATTAGCAGCTACTTTTGCTTACTGGGACAATATTCTTGGTCCTAGA
 GTAAGGCACATTTGGGCTCCAAAGACAGAACAGGTAATTCTCAGTGATGGAGAAATAACT
 TTTCTTGCCAACCACACTCTAAATGGAGAAATCCTTCGAAATGCAGAGAGTGGTGCTATA
 GATGTAAAGTTTTTTGTCTTGTCTGAAAAGGGAGTGATTATTGTTTCATTAATCTTTGAT
 GGAACTGGAATGGGGATCGCAGCACATATGGACTATCAATTATACTTCCACAGACAGAA
 25 CTTAGTTTCTACCTCCCACTTCATAGAGTGTGTGTTGATAGATTAACACATATAATCCGG
 AAAGGAAGAATATGGATGCATAAGGAAAGACAAGAAAATGTCCAGAAGATTATCTTAGAA
 GGCACAGAGAGAATGGAAGATCAGGGTCAGAGTATTATTCCAATGCTTACTGGAGAAGTG
 ATTCCTGTAATGGAAGTCTTTTCATCTATGAAATCACACAGTGTTCTGAAGAAATAGAT
 ATAGCTGATACAGTACTCAATGATGATGATATTGGTGACAGCTGTCATGAAGGCTTTCTT
 30 CTCAATGCCATCAGCTCACACTTGCAAACCTGTGGCTGTTCCGTTGTAGTAGGTAGCAGT
 GCAGAGAAAGTAAATAAGATAGTCAGAACATTATGCCTTTTTCTGACTCCAGCAGAGAGA
 AAATGCTCCAGGTTATGTGAAGCAGAATCATCATTTAAATATGAGTCAGGGCTCTTTGTA
 CAAGGCCTGCTAAAGGATTCAACTGGAAGCTTTGTGCTGCCTTTCCGGCAAGTCATGTAT
 GCTCCATATCCCACCACACACATAGATGTGGATGTCAATACTGTGAAGCAGATGCCACCC
 35 TGTCATGAACATATTTATAATCAGCGTAGATACATGAGATCCGAGCTGACAGCCTTCTGG
 AGAGCCACTTCAGAAGAAGACATGGCTCAGGATACGATCATCTACACTGACGAAAGCTTT
 ACTCCTGATTTGAATATTTTTCAAGATGTCTTACACAGAGACACTCTAGTGAAAGCCTTC
 CTGGATCAGGTCTTTCAGCTGAAACCTGGCTTATCTCTCAGAAGTACTTTCTTGACAG
 TTTCTACTTGTCTTACAGAAAAGCCTTGACACTAATAAAATATATAGAAGACGATACG
 40 CAGAAGGGGAAAAAGCCCTTTAAATCTCTTCGGAACCTGAAGATAGACCTTGATTTAACA
 GCAGAGGGCGATCTTAACATAATAATGGCTCTGGCTGAGAAAATTAACCAGGCCTACAC
 TCTTTTATCTTTGGAAGACCTTTCTACACTAGTGTGCAAGAACGAGATGTTCTAATGACT

TTTTAAATGTGTAACCTTAATAAGCCTATTCCATCACAATCATGATCGCTGGTAAAGTAGC
 TCAGTGGTGTGGGGAAACGTTCCCCTGGATCATACTCCAGAATTCTGCTCTCAGCAATTG
 CAGTTAAGTAAGTTACACTACAGTTCTCACAAGAGCCTGTGAGGGGATGTCAGGTGCATC
 ATTACATTGGGTGTCTCTTTTCCTAGATTTATGCTTTTGGGATACAGACCTATGTTTACA
 5 ATATAATAAATATTATTGCTATCTTTTAAAGATATAATAATAGGATGTAACTTGACCAC
 AACTACTGTTTTTTTTGAAATACATGATTCATGGTTTACATGTGTCAAGGTGAAATCTGAG
 TTGGCTTTTACAGATAGTTGACTTTCTATCTTTTGGCATTCTTTGGTGTGTAGAATTACT
 GTAATACTTCTGCAATCAACTGAAAAGTAGAGCCTTTAAATGATTTCAATTCCACAGAAA
 GAAAGTGAGCTTGAACATAGGATGAGCTTTAGAAAGAAAATTGATCAAGCAGATGTTTAA
 10 TTGGAATTGATTATTAGATCCTACTTTGTGGATTTAGTCCCTGGGATTCAGTCTGTAGAA
 ATGTCTAATAGTTCTCTATAGTCCTTGTTCTGGTGAACCACAGTTAGGGTGTGTTTGTGTT
 ATTTTATTGTTCTTGCTATTGTTGATATTCTATGTAGTTGAGCTCTGTAAAAGGAAATTG
 TATTTTATGTTTTAGTAATTGTTGCCAACTTTTTAAATTAATTTTCATTATTTTTGAGCC
 AAATTGAAATGTGCACCTCCTGTGCCTTTTTTCTCCTTAGAAAATCTAATTACTTGGAAC
 15 AAGTTCAGATTTCACTGGTCAGTCATTTTCATCTTGTTTTCTTCTTGCTAAGTCTTACCA
 TGTACCTGCTTTGGCAATCATTGCAACTCTGAGATTATAAAATGCCTTAGAGAATATACT
 AACTAATAAGATCTTTTTTTCAGAAACAGAAAATAGTTCCTTGAGTACTTCCTTCTTGCA
 TTTCTGCCTATGTTTTTGAAGTTGTTGCTGTTTGCCTGCAATAGGCTATAAGGAATAGCA
 GGAGAAATTTTACTGAAGTGCTGTTTTCTAGGTGCTACTTTGGCAGAGCTAAGTTATCT
 20 TTTGTTTTCTTAATGCGTTTGGACCATTTTGCTGGCTATAAAATAACTGATTAATATAAT
 TCTAACACAATGTTGACATTGTAGTTACACAAACACAAATAAATATTTTATTTAAAATTC
 TGGAAGTAATATAAAAGGGGAAAATATATTTATAAGAAAGGGATAAAGGTAATAGAGCCCT
 TCTGCCCCCACCACCAAATTTACACAACAAAATGACATGTTTGAATGTGAAAGGTCAT
 AATAGCTTTCCCATCATGAATCAGAAAGATGTGGACAGCTTGATGTTTTAGACAACCACT
 25 GAACTAGATGACTGTTGTACTGTAGCTCAGTCATTTAAAAAATATATAAATACTACCTTG
 TAGTGTCCCATACTGTGTTTTTTACATGGTAGATTCTTATTTAAGTGCTAACTGGTTATT
 TTCTTTGGCTGGTTTATTGTACTGTTATACAGAATGTAAAGTTGTACAGTGAAATAAGTTA
 TTAAAGCATGTGTAAACATTGTTATATATCTTTTCTCCTAAATGGAGAATTTTGAATAAA
 ATATATTTGAAATTTT
 30 (SEQ ID NO: 10)

As used herein, the term "CASS4" refers to the gene encoding Cas scaffolding protein family member 4. The terms "CASS4" and "Cas scaffolding protein family member 4" include wild-type forms of the CASS4 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type CASS4.

35 Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type CASS4 nucleic acid sequence (e.g., SEQ ID NO: 11, ENA accession number AJ276678). SEQ ID NO: 11 is a wild-type gene sequence encoding CASS4 protein, and is shown below:

40 GAAGAGTGGTGTGTTTTTTCTTCTTCTTCTTTTGTGGTTTCACATAGCAAATGAGTGA
 CAGTCTCTACTTACAGACAAAGTGAGACGTCAGGCATTGAGACATAGCTCCATAGAATTC

AGTTTCTGAGAACCAGCCAGAAGCATGCAGTGACATTGCACAATCTGCCTCTGAAGCTGG
AGATACTAGCTGCAGAGCTCAGGGGAGCTGCTCCACATCACCGACATGAAGGGAACAGGC
ATCATGGACTGTGCGCCCAAGGCACTCCTGGCCAGGGCACTTTATGACAACTGCCCTGAC
TGCTCTGACGAGCTGGCTTTCAGCAGAGGGGACATCCTGACCATTCTGGAGCAACACGTG
5 CCAGAAAGCGAGGGTTGGTGGAAAGTGTGCTCCATGGGAGGCAAGGCCTGGCCCCCTGCC
AACCGCCTCCAAATCCTCACGGAGGTCGCTGCAGACAGGCCGTGCCCCCATTCTGAGA
GGCCTGGAAGAAGCTCCTGCCAGCTCAGAGGAGACCTATCAGGTGCCCACTCTACCCCGC
CCTCCCACTCCAGGCCCCGTTTATGAGCAGATGAGGAGTTGGGCGGAGGGGGCCCCAGCCC
CCTACTGCCCAAGTCTATGAATTCCCCGACCCTCCCACCAGTGCCAGAATCATCTGTGAA
10 AAGACTCTCAGCTTTCAAAACAGGCCATCCTCACGCTTCCCAGACCTGTCCGGGCCTCA
CTGCCGACTCTGCCTTCCCAGGTGTATGACGTGCCTACCCAGCACCCGGGGCCCCGTGGTC
CTGAAGGAGCCAGAGAAGCAGCAGTTATATGACATACCAGCCAGCCCCAAGAAGGCAGGA
CTCCATCCCCCAGACAGCCAAGCAAGTGGGCAGGGTGTTCCTTGATATCAGTGACTACC
TTAAGAAGAGGCGGTTACAGCACATTACCAAATCCTCAGAAATCGGAATGGATTTATGAC
15 ACTCCAGTGTCTCCAGGAAAGGCCAGCGTCAGAAACACGCCTCTCACCAGCTTTGCGGAA
GAATCAAGGCCCCACGCTCTCCCCAGTTCCAGCTCCACTTTCTACAATCCTCCAAGTGGC
AGATCCAGGTCCCTCACTCCACAACCTGAATAACAATGTGCCCATGCAGAAAAAACTCAGC
CTTCCAGAAATTCCTTCTTATGGCTTTCTTGTAACCCAGAGGCACATTTCTTTGGATGAA
GATGTCAGCAACAAGGTTCTTCAAGCTTCTCTGATTCCCCGAGTGGACAGCAGAACACC
20 AAGCCCAATATAGACATCCCTAAAGCAACGTGAGTGTTTCTCAGGCTGGGAAGGAGCTG
GAGAAAGCCAAGGAGGTGTCAGAGAATTCCGCGGGCCATAATTCCTCATGGTTCTCCAGA
CGGACAACCTCCCCATCTCCTGAACCGGACAGATTATCAGGTTCCAGTTCTGACAGCAGA
GCTAGCATCGTTTCCTCGTGCTCCACCACATCCACCGACGACTCCTCCAGCTCTTCCTCG
GAGGAGTCAGCAAAGGAGCTCTCCTTGACCTGGATGTGGCCAAGGAGACAGTGATGGCT
25 CTGCAGCACAAGGTGGTCAGCTCTGTGCTGGCCTGATGCTCTTTGTCAGCAGGAAGTGG
AGATTCCGAGACTATCTGGAGGCCAACATTGATGCAATCCACAGGTCCACTGATCACATA
GAAGCCTCTGTAAGAGAATTTCTGGATTTTGCCCGAGGAGTCCATGGGACTGCCTGTAAC
CTCACTGACAGTAACCTTCAGAACAGAATTCGGGACCAGATGCAGACCATCTCCAACCTCC
TACCGCATCCTGCTTGAAACAAAGGAAAGCTTGATAATCGCAATTGGCCTCTGGAAGTT
30 CTTGTGACTGACAGTGTCCAGAACAGCCCAGATGACCTTGAGAGGTTTGTGATGGTGGCA
CGGATGCTTCCAGAAGACATCAAGAGGTTTGCTCCATTGTGATTGCCAATGGAAGGCTC
CTTTTTAAGCGGAACCTGTGAAAAGGAAGAGACTGTGCAGTTGACCCCAAATGCAGAATTT
AAGTGTGAAAAATACATCCAGCCTCCCCAAAGAGAACTGAATCACACCAAAGAGTACC
CCTTCCACTAAGCAAAGGGAAGATGAACACTCTTCTGAACTATTAAAGAAAAATAGAGCA
35 AATATCTGTGGACAGAATCCTGGCCCTCTTATACCTCAGCCTTCGAGTCAACAGACTCCT
GAGAGGAAACCCCGCTTATCTGAACACTGCCGGCTGTACTTTGGGGCGCTCTTCAAAGCC
ATCAGCGCATTTACGGCAGCCTCAGCAGCAGCCAGCCCGCGGAGATCATCACTCAGAGC
AAGCTGGTCATCATGGTGGGACAGAAGCTGGTGGACACGCTGTGCATGGAGACCCAGGAG
AGGGACGTGCGCAATGAGATCCTCCGCGGCAGCAGTCACCTCTGCAGCCTGCTCAAGGAC
40 GTAGCGCTGGCCACTAAGAATGCCGTGCTCACATACCCAGCCCTGCCGCGCTGGGGCAC
CTCCAGGCGGAGGCTGAGAAGCTGGAGCAACACACGCGGCAGTTCAGAGGGACACTGGGA
TGAGGACTGTCTACCTCCCTTCTCCTCTGCTCACC

(SEQ ID NO: 11)

As used herein, the term "CCL5" refers to the gene encoding C-C motif chemokine 5. The terms "CCL5" and "C-C motif chemokine 5" include wild-type forms of the CCL5 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type CCL5. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type CCL5 nucleic acid sequence (e.g., SEQ ID NO: 12, ENA accession number M21121). SEQ ID NO: 12 is a wild-type gene sequence encoding CCL5 protein, and is shown below:

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CCTCCGACAGCCTCTCCACAGGTACCATGAAGGTCTCCGCGGCACGCCTCGCTGTCATCC
TCATTGCTACTGCCCTCTGCGCTCCTGCATCTGCCTCCCCATATTCCTCGGACACCACAC
CCTGCTGCTTTGCCTACATTGCCCGCCCACTGCCCCGTGCCACATCAAGGAGTATTTCT
ACACCAGTGGCAAGTGTCCAACCCAGCAGTCGTCTTTGTACCCGAAAGAACCGCCAAG
TGTGTGCCAACCCAGAGAAGAAATGGGTTCGGGAGTACATCAACTCTTTGGAGATGAGCT
AGGATGGAGAGTCCTTGAACCTGAACCTACACAAATTTGCCTGTTTCTGCTTGCTCTTGT
CCTAGCTTGGGAGGCTTCCCCTCACTATCCTACCCACCCGCTCCTTGAAGGGCCCAGAT
TCTGACCACGACGAGCAGCAGTTACAAAAACCTTCCCAGGCTGGACGTGGTGGCTCAGC
CTTGTAATCCCAGCACTTTGGGAGGCCAAGGTGGGTGGATCACTTGAGGTCAGGAGTTTCG
AGACAGCCTGGCCAACATGATGAAACCCCATGTGTACTAAAAATACAAAAAATTAGCCGG
GCGTGGTAGCGGGCGCCTGTAGTCCCAGCTACTCGGGAGGCTGAGGCAGGAGAATGGCGT
GAACCCGGGAGCGGAGCTTGCAGTGAGCCGAGATCGCGCCACTGCACTCCAGCCTGGGCG
ACAGAGCGAGACTCCGTCTCAAAAAAAAAAAAAAAAAAAAAAAAAAATACAAAAATTAGCC
GCGTGGTGGCCCACGCCTGTAATCCCAGCTACTCGGGAGGCTAAGGCAGGAAAATTGTTT
GAACCCAGGAGGTGGAGGCTGCAGTGAGCTGAGATTGTGCCACTTCACTCCAGCCTGGGT
GACAAAGTGAGACTCCGTACACAACAACAACAAAAGCTTCCCCAACTAAAGCCTAGA
AGAGCTTCTGAGGCGCTGCTTTGTCAAAGGAAGTCTCTAGGTTCTGAGCTCTGGCTTTG
CCTTGGCTTTGCAAGGGCTCTGTGACAAGGAAGGAAGTCAGCATGCCTCTAGAGGCAAGG
AAGGGAGGAACACTGCACTCTTAAGCTTCCGCCGTCTCAACCCCTCACAGGAGCTTACTG
GCAAACATGAAAAATCGGGG

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(SEQ ID NO: 12)

As used herein, the term "CD2AP" refers to the gene encoding CD2-associated protein. The terms "CD2AP" and "CD2-associated protein" include wild-type forms of the CD2AP gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type CD2AP. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type CD2AP nucleic acid sequence (e.g., SEQ ID NO: 13, ENA accession number AF146277). SEQ ID NO: 13 is a wild-type gene sequence encoding CD2AP protein, and is shown below:

GGAATTCCGGGAGGAGCGGACGTCGGCTTCTCCCCGCGGGAGCCCCAGCATGGTTGACT
ATATTGTGGAGTATGACTATGATGCTGTACATGATGATGAATTAAGTATTCGAGTTGGAG
AAATCATCAGGAATGTGAAAAAGCTACAGGAGGAAGGGTGGCTGGAAGGAGAACTAAATG
GGAGAAGAGGAATGTTCCCTGACAATTTCTGTTAAGGAAATTAAGAGAGACGGAATTCA
5 AGGATGACAGTTTGCCCATCAAACGGGAAAGGCATGGGAATGTAGCAAGTCTTGACAAAC
GAATAAGCACCTATGGACTTCCAGCTGGAGGAATTCAGCCACATCCACAAACCAAAAACA
TTAAGAAGAAGACCAAGAAGCGTCAGTGTAAGTTCTTTTTGAGTACATTCCACAAAATG
AGGATGAACTGGAGCTGAAAGTGGGAGATATTATTGATATTAATGAAGAGGTAGAAGAAG
GCTGGTGGAGTGGAACCCTGAATAACAAGTTGGGACTGTTTCCCTCAAATTTTGTGAAAG
10 AATTAGAGGTAACAGATGATGGTGAACTCATGAAGCCAGGACGATTTCAGAACTGTTT
TGGCTGGGCCTACTTCACCTATACCTTCTCTGGGAAATGTGAGTGAACTGCATCTGGAT
CAGTTACACAGCCAAAGAAAATTCGAGGAATTGGATTTGGAGACATTTTTAAAGAAGGTT
CTGTGAACTTCGGACAAGAACATCCAGTAGTGAAACAGAAGAGAAAAAACAGAAAAGC
CCTTAATCCTACAGTCACTGGGACCCAAAACCTCAGAGTGTGGAGATAACAAAAACAGATA
15 CCGAAGGTAAAATTAAGCTAAAGAATATTGTAGAACATTATTTGCCTATGAAGGTACTA
ATGAAGATGAACTTACTTTTTAAAGAGGGGGAGATAATCCATTTGATAAGTAAGGAGACTG
GAGAAGCTGGCTGGTGGAGGGGCGAACTTAATGTTAAAGAAGGAGTATTTCCAGACAATT
TTGCTGTCCAGATAAATGAACTTGATAAAGACTTTCCAAAACCAAGAAACCACCACCTC
CTGCTAAGGCTCCAGCTCCAAAGCCTGAACTGATAGCTGCAGAGAAGAAATATTTTTCTT
20 TAAAGCCTGAAGAAAAGGATGAAAAATCAACACTGGAACAGAAACCTTCTAAACCAGCAG
CTCCACAAGTCCCACCCAAGAAACCTACTCCACCTACCAAAGCCAGTAATTTATTGAGAT
CTTCTGGAACAGTGACCCAAAGCGACCTGAAAAACCAGTTCCTCCACCACCTCCTATAG
CCAAGATTAATGGGGAAGTTTCTAGCATTTTCATCAAATTTGAACTGAGCCAGTATCAA
AACTAAAGCTAGATTCTGAACAGCTGCCCTTAGACCAAATCAGTAGACTTTGATTAC
25 TTACAGTAAGGACCTCCAAAGAAACAGATGTTGTAAATTTTGATGACATAGCTTCCTCAG
AAAACCTTGCTTCATCTCACTGCAATAGACCAAAGATGCCTGGAAGAAGGTTGCCGGGGCC
GTTTCAATGGTGGACATTCTCCAACCTCACAGCCCCGAAAAATCTTGAAGTTACCAAAAG
AAGAAGACAGTGCCAACCTGAAGCCATCTGAATTAAGAAAAAGATACATGCTACTCTCCAA
AGCCATCTGTGTACCTTTCAACACCTTCCAGTGCTTCTAAAGCAAATACAACCTGCTTTCC
30 TGAATCCATTAGAAATCAAAGCTAAAGTGGAAACAGATGATGTGAAAAAAATTCCCTGG
ATGAACTTAGAGCCAGATTATTGAATTGTTGTGCATTGTAGAAGCACTGAAAAAGGATC
ACGGGAAAGAACTGGAAAACTGCGAAAAGATTTGGAAGAAGAGAAGACAATGAGAAGTA
ATCTAGAGATGGAAATAGAGAAGCTGAAAAAAGCTGTCCTGTCTTCTTGAGTGGTGTGGA
CCTGGTGTTCATAATGTTCCAGGGATTGAGAAGCAACGCTATGAACTTCAGCTGACTTGT
35 TACTTAAAAATTGTGAATTCTGTTGTTGTGATAAATATGAGCAAATGAAGTGTAATATCT
ATAGAAAAGTAGAGTGAGGGTGAATTTATATATATATTTTGTGTTTGCCAATATGAAGAAA
AAGAGGCCTTATTTCTTAACTGTGCTGGGATTGCAAACACTTTTTAAAAAATTGTTTGCT
TGAAAATACTACTGAATATAAATAAGAATGTGCTCAGTAGTTTTTTTATTGAACTTGTA
TTATTTTTTAAAGAGATCTATACTATAAATATGGTGATATATTTACAAGTAATCTGTAAGA
40 TATACTATTTGAGAGGGACAGATTAGCCTTTTAGTAAGTATAGTCACTACTTTTTCCATA
ATGCATAAGGGATATAAACTCTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGT
ATATATATATATATATTTTTACTTTTATCCTCTTACCGAAGGTTACACTGTTGTGCCTGT

TTGTCTGCAATGCTGTTTATATTTTGGGTGATGAAATAGGAGTTTCCTAGCTATATAAAC
 CAGATTACTCACCCATGCATATAGTAAGAATAATGAATAATCAAATAATTTTCATCAAC
 TTTTAGAATATTTTATGTTGCTTGCCTATAGGAGTCATAAAAGGAAGTTAGTTAAAATA
 TGTTGGATTGTTAAACATTTGGGGAAATATGAACTGTATTTTAAATTTGTTAGGTCTGAA
 5 AAATCTAAACTGTTAATTTAACCTTAAGTTGTGCCTAGAACTACAGCACATATAAAA
 TATGTAAACACCAGCCTGTTGCTGTACTTTTCTGCTTATTTTACAGCCTCAAATATTTCT
 CATTATCTTGTCACTTAGTTCTTCATGTTTCTCCTTCTGACTTTTAATAATGGTAATAGG
 AAAACAAAACCCAAAGCTTTTCAAAGTTTCAAGTGTGAGGTTTCCTATTTTGACAAGTTAAC
 TTGTAAATACTCAGGTTTTACGATGTATAATTTACCTAATAGACCAAATACTCATGGA
 10 GATATTTTGAAGTATTATTTAGGTACAACTTTATAAAGAATGTTAGTATGTCATAAAAT
 ATAACATTACAGCTTATTTAAAACCAAATATATTGAACATATTTTAAAATACATTTTACA
 GAATGGATGAATTAGTTGTTTCTTCAAAAGTTACTTATGAACAGTTGAATGCCTTTAAAA
 TGTTCTGTCTGTAGGTACATCTAAAAACACAAGTGGGTTTATTTAAATTTTAAAATTTG
 AAATTTTTTATTTGCCAAAAATTGTTTTATGCTTTATTATATCGCAAATGAGTGTGAGAT
 15 TTTTGAGTACCAATGATCATGCTTCCATTTTTTTTTAGTTTTAAACCACCAAACCAATATT
 TTTCTTTAAATTTTAACTTATAATATAGAAATCTTATGTTAATGAAATTTTGTGATGT
 TTCAAATAAAGAAAAGTGAAGTAGAAAATAGAAATGCCAGTAAACAACATAATGTTTAAT
 TTACAAGTTACATTAGGGGTTTGGGGGAATGCTAATTATATATTGAGAATATACATTAGA
 ACTCTTCAAATGGGCTCTTCTAATGAGGTCACTACTGAACAAAATTGTTCCCTCTTCTG
 20 TTAAATAGAATAGGTTTAAATGACTAGTCAAATGAATTATTTTCTCCTTGTTAAATAAAT
 TAAATCTTACTTTCTTTTAAATGACCAACCTTAGGTAAAACAAAATATTGTAATCCTAGA
 AATTATCCTCCAGCTTTCTCACCTGAAAATCTATTGAAGTGATCCCTGGTCATCCTAATA
 ATGGGATGAGGGAAGTTTCCAGCAGATTTTCAAGGCTGTTCTTAAAGTTTTTGTGGTCATT
 TTCTCAATAGTACATGAAATCAAGATGCTTATGAGCATGGAATGTATTTAAAGTTTTTG
 25 CTTGTGTCCTCCTCAGTCAGAATAGAAAAGTAACTGAAATACTCTTACCTTTCTGTCCTT
 GATAAAATAGTAAAGAAAACCAAACAAACCCAGGCCTGATGGGAAAAATGATTCCTTTAT
 TCTAGCAATTACTTTCTGTTGGTATGGGAAATGTTATTAATTTCTATTACTAAAGTTCAT
 ATCACAAAATGATATTTAATAATAACCTTGGGGTAAATCATGAATTTTTTTTTCTACGTG
 TGAGTATAAAAGACAAAAGTTGAACAGCATGGAATCTTCATTGCCAAATTATTAGTGAAT
 30 GTATAGTTCAGGTATTCTTTGAGACACACAGTATCATTAAATTTCCGAATTGTATTTAGT
 GTTATTTTTTTGTTTGTGACCACTAAGCTTCTGTCTTAATACAAAGCTGTTACCTTCTACA
 GAATTTAAGTCTGAAGATGTAAAGAGAGAACAGGCCTTGTGTAAACAGAAAGATACTCTTTT
 TTATGCTCCTTACTGTGATCACAGAAAAATTAAAAATCCAAGTGCTCTCTAGATTTGTTG
 ATAAACATTTTATGCTTGCATTTAACTTGAATGTATGAGCAGAATGAGACAATCAGTT
 35 AAATCAGAAATGAGAAGTATTATAATGTAAAGGCCTTGTGTTTGCTGTAGCAATAAAATGA
 CCAAGTGCAATGACTTGATTTAATAAAATCCGGAATTC
 (SEQ ID NO: 13)

As used herein, the term "CD33" refers to the gene encoding Myeloid cell surface antigen CD33.
 40 The terms "CD33" and "Myeloid cell surface antigen CD33" include wild-type forms of the CD33 gene, as
 well as variants (e.g., splice variants and polymorphisms) of wild-type CD33. Examples of such variants
 are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%,

77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type CD33 nucleic acid sequence (e.g., SEQ ID NO: 14, ENA accession number M23197). SEQ ID NO: 14 is a wild-type gene sequence encoding CD33 protein, and is shown below:

5

GCTTCCTCAGACATGCCGCTGCTGCTACTGCTGCCCCTGCTGTGGGCAGGGGCCCTGGCT
 ATGGATCCAAATTTCTGGCTGCAAGTGCAGGAGTCAGTGACGGTACAGGAGGGTTTGTGC
 GTCCTCGTGCCCTGCACTTTCTTCCATCCCATAACCCTACTACGACAAGAACTCCCCAGTT
 CATGGTTACTGGTTCCGGGAAGGAGCCATTATATCCGGGGACTCTCCAGTGGCCACAAAC
 10 AAGCTAGATCAAGAAGTACAGGAGGAGACTCAGGGCAGATTCCGCCTCCTTGGGGATCCC
 AGTAGGAACAACCTGCTCCCTGAGCATCGTAGACGCCAGGAGGAGGATAATGGTTCATAC
 TTCTTTCCGATGGAGAGAGGAAGTACCAAATACAGTTACAAATCTCCCCAGCTCTCTGTG
 CATGTGACAGACTTGACCCACAGGCCCAAATCCTCATCCCTGGCACTCTAGAACCCGGC
 CACTCCAAAAACCTTACCTGCTCTGTGTCTCTGGGCCTGTGAGCAGGGAACACCCCCGATC
 15 TTCTCCTGGTTGTCAGCTGCCCCACCTCCCTGGGCCCCAGGACTACTCACTCCTCGGTG
 CTCATAATCACCCACGGCCCCAGGACCACGGCACCAACCTGACCTGTCAGGTGAAGTTC
 GCTGGAGCTGGTGTGACTACGGAGAGAACCATCCAGCTCAACGTACCTATGTTCCACAG
 AACCCAACAACCTGGTATCTTTCCAGGAGATGGCTCAGGGAAACAAGAGACCAGAGCAGGA
 CTGGTTCATGGGGCCATTGGAGGAGCTGGTGTTACAGCCCTGCTCGCTCTTTGTCTCTGC
 20 CTCATCTTCTTCATAGTGAAGACCCACAGGAGGAAAGCAGCCAGGACAGCAGTGGGCAGC
 AATGACACCCACCCTACCACAGGGTCAGCCTCCCCGAAACACCAGAAGAACTCCAAGTTA
 CATGGCCCCACTGAAACCTCAAGCTGTTCAAGGTGCCGCCCTACTGTGGAGATGGATGAG
 GAGCTGCATTATGCTTCCCTCAACTTTCATGGGATGAATCCTTCCAAGGACACCTCCACC
 GAATACTCAGAGGTCAGGACCCAGTGAGGAACCCTCAAGAGCATCAGGCTCAGCTAGAAG
 25 ATCCACATCCTCTACAGGTCGGGGACCAAAGGCTGATTCTTGGAGATTTAACTCCCCACA
 GGCAATGGGTTTATAGACATTATGTGAGTTTCTGCTATATTAACATCATCTTGAGACTT
 TGCAAGCAGAGAGTCGTGGAATCAAATCTGTGCTCTTTCATTTGCTAAGTGTATGATGTC
 ACACAAGCTCCTTAACCTTCCATGTCTCCATTTTCTTCTCTGTGAAGTAGGTATAAGAAG
 TCCTATCTCATAGGGATGCTGTGAGCATTAAATAAAGGTACACATGGAAAACACCAG
 30 (SEQ ID NO: 14)

As used herein, the term "CD68" refers to the gene encoding CD68 Molecule. The terms "CD68" and "CD68 molecule" include wild-type forms of the CD68 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type CD68. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type CD68 nucleic acid sequence (e.g., SEQ ID NO: 15, NCBI Reference Sequence: NM_001251.2). SEQ ID NO: 15 is a wild-type gene sequence encoding CD68 protein, and is shown below:

40

TTAATTACAAAACTAATGACTAAGAGAGAGGTGGCTAGAGCTGAGGCCCTGAGTCAGGCTGTGG
 GTGGGATCATCTCCAGTACAGGAAGTGAGACTTTCATTTCTCCTTTCCAAGAGAGGGCTGAGGGAG

CAGGGTTGAGCAACTGGTGCAGACAGCCTAGCTGGACTTTGGGTGAGGCGGTTTCAGCCATGAGGCT
 GGCTGTGCTTTTCTCGGGGGCCCTGCTGGGGCTACTGGCAGCCCAGGGGACAGGGAATGACTGTC
 CTCACAAAAAATCAGCTACTTTGCTGCCATCCTTCACGGTGACACCCACGGTTACAGAGAGCACTGG
 AACAAACCAGCCACAGGACTACCAAGAGCCACAAAACCACCACTCACAGGACAACCACCACAGGCAC
 5 CACCAGCCACGGACCCACGACTGCCACTCACAACCCACCACCAGCCATGGAAACGTCACAGT
 TCATCCAACAAGCAATAGCACTGCCACCAGCCAGGGACCCCTCAACTGCCACTCACAGTCCTGCCAC
 CACTAGTCATGGAAATGCCACGGTTCATCCAACAAGCAACAGCACTGCCACCAGCCCAGGATTCACC
 AGTTCTGCCCACCCAGAACCACCTCCACCCTCTCCGAGTCCTAGCCCAACCTCCAAGGAGACCATT
 GGAGACTACACGTGGACCAATGGTTCCCAGCCCTGTGTCCACCTCCAAGCCCAGATTTCAGATTCTGA
 10 GTCATGTACACAACCCAGGGTGGAGGAGAGGCCTGGGGCATCTCTGTACTGAACCCCAACAAAACC
 AAGGTCCAGGGAAGCTGTGAGGGTGCCCATCCCCACCTGCTTCTCTCATTCCCCTATGGACACCTC
 AGCTTTGGATTCATGCAGGACCTCCAGCAGAAGGTTGTCTACCTGAGCTACATGGCGGTGGAGTAC
 AATGTGTCCTTCCCCCACGCAGCACAGTGGACATTCTCGGCTCAGAATGCATCCCTTCGAGATCTCC
 AAGCACCCCTGGGGCAGAGCTTCAGTTGCAGCAACTCGAGCATCATTCTTTCACCAGCTGTCCACCT
 15 CGACCTGCTCTCCCTGAGGCTCCAGGCTGCTCAGCTGCCCCACACAGGGGTCTTTGGGCAAAGTTT
 CTCCTGCCCCAGTGACCGGTCCATCTTGCTGCCTCTCATCATCGGCCTGATCCTTCTTGGCCTCCTC
 GCCCTGGTGCTTATTGCTTTCTGCATCATCCGGAGACGCCCATCCGCCTACCAGGCCCTCTGAGCAT
 TTGCTTCAAACCCAGGGCACTGAGGGGGTTGGGGTGTGGTGGGGGGGTACCCTTATTTCTCTCGAC
 ACGCAACTGGCTCAAAGACAATGTTATTTTCTTCCCTTTCTTGAAGAACAAAAAGAAAGCCGGGCAT
 20 GACGGCTCATGCCTGTAATCCCAGCACTTTGGGAGGCTGAGGCAGGTGGATCACTGGAGGTCAGGA
 GTTTGAGACCAGCCTGGCCAACATGGTGAAACCCTGTCTCTACTAAAAATACAATTAGCCAGGTGTG
 GCGGCGTAATCCCAGCTGGCCTGTAATCCCAGCTACTTGGGAGGCTGAGGCAGAACTGCTTGAACC
 CAGGAGGTGGAGGTTGCAGTGAGCCGTCATCGCGCCACTAAGCCAAGATCGCGCCACTGCACTCC
 AGCCTGGGCGACAGAGCCAGACTGTCTCAAATAAATAAATATGAGATAATGCAGTCGGGAGAAGGG
 25 AGGGAGAGAATTTTATTAAATGTGACGAACTGCCCCCCCCCCCCCCCCCAGCAGGAGAGCAGCAAAA
 TTTATGCAAATCTTTGACGGGGTTTTCTTGTCTGCCAGGATTAAGCCATGAGTTTCTTGTCAAA
 AAAAAAAAAAAAAA
 (SEQ ID NO: 15)

30 As used herein, the term "CLPTM1" refers to the gene encoding CLPTM1 Regulator of GABA
 Type A Receptor Forward Trafficking. The terms "CLPTM1" and "CLPTM1 Regulator of GABA Type A
 Receptor Forward Trafficking" include wild-type forms of the CLPTM1 gene, as well as variants (e.g.,
 splice variants and polymorphisms) of wild-type CLPTM1. Examples of such variants are nucleic acids
 having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%,
 35 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,
 98%, 99%, or 99.9% identity, or more) to a wild-type CLPTM1 nucleic acid sequence (e.g., SEQ ID NO:
 16, NCBI Reference Sequence: NM_001294.3). SEQ ID NO: 16 is a wild-type gene sequence encoding
 CLPTM1 protein, and is shown below:

40 AGGTTGGTCCTTCCATAGCCGGAAGTGGCCTTCCTGAGAGGCGTGGCTGCGGCACTCTTGCCGGAT
 AGGGTGGCCCGCGGGGCTAGGAAAGCGTGAAATCTCGCGCGATTGCGCTGCGAAGTCGGGGAC
 GGGGCGGGGCTGGCGGCGGGGGCGGGGACCCGGAGCGGGAAGATGGCGGCGGCGCAGGAGGC

GGACGGGGCCCCGCAGCGCCGTGGTGGCGGCCGGGGGAGGCAGCTCCGGTCAGGTGACCAGCAAT
GGCAGCATCGGGAGGGACCCGCCAGCGGAGACCCAGCCTCAGAACCCACCGGCCAGCCGGCAC
CCAATGCCTGGCAGGTCATCAAAGGTGTGCTGTTTAGGATCTTCATCATCTGGGCCATCAGCAGTTG
GTTCCGCCGAGGGCCGGCCCCCTCAGGACCAGGCGGGGCCCGGAGGAGCTCCACGCGTCGCCAGC
5 CGCAACCTGTTCCCCAAAGACACTTTAATGAACCTGCATGTGTACATCTCAGAGCACGAGCACTTTA
CAGACTTCAACGCCACGTGCGCACTCTTCTGGGAACAGCACGATCTTGTGTATGGCGACTGGACTA
GCGGCGAGAACTCAGACGGCTGCTACGAGCACTTTGCTGAGCTCGATATCCCACAGAGCGTCCAGC
AGAACGGCTCCATCTACATCCACGTTTACTTCACCAAGAGTGGCTTCCACCCAGACCCCCGGCAGAA
GGCCCTGTACCGCCGGCTTGCCACAGTCCACATGTCCCGGATGATCAACAAATACAAGCGCAGACG
10 ATTTGAGAAAACCAAGAACCTGCTGACAGGAGAGACAGAAAGCGGACCCAGAAATGATCAAGAGGGC
TGAGGACTATGGGCCTGTGGAGGTGATCTCCATTGGCACCCCAACATCACCATCAACATCGTGGA
CGACCACACGCCGTGGGTGAAGGGCAGTGTGCCCCCTCCCCTGGATCAATATGTGAAGTTTCGACGC
CGTGAGCGGTGACTACTATCCCATCATCTACTTCAATGACTACTGGAACCTGCAGAAGGACTACTAC
CCCATCAACGAGAGCCTGGCCAGCCTGCCGCTCCGCGTCTCCTTCTGCCCCACTCTCGCTTTGGCGC
15 TGGCAGCTCTATGCTGCCCAGAGCACCAAGTCGCCCTGGAACCTCCTGGGTGATGAGTTGTACGAG
CAGTCAGATGAGGAGCAGGACTCGGTGAAGGTGGCCCTGCTGGAGACCAACCCCTACCTGCTGGC
GCTCACCATCATCGTGTCTATCGTTCACAGTGTCTTCGAGTTCCTGGCCTTCAAGAATGATATCCAGT
TCTGGAACAGCCGGCAGTCCCTGGAGGGCCTGTCCGTGCGCTCCGTCTTCTTCGGCGTTTTCCAGT
CATTCGTGGTCCTCCTCTACATCCTGGACAACGAGACCAACTTCGTGGTCCAGGTCAGCGTCTTCAT
20 TGGGGTCCTCATCGACCTCTGGAAGATCACCAAGGTCATGGACGTCCGGCTGGACCGAGAGCACAG
GGTGGCAGGAATCTTCCCCCGCCTATCCTTCAAGGACAAGTCCACGTATATCGAGTCCTCGACCAA
GTGTATGATGATATGGCATTCCGGTACCTGTCCTGGATCCTCTTCCCGCTCCTGGGCTGCTATGCCG
TCTACAGTCTTCTGTACCTGGAGCACAAGGGCTGGTACTCCTGGGTGCTCAGCATGCTCTACGGCTT
CCTGCTGACCTTCGGCTTCATCACCATGACGCCCCAGCTCTTCATCAACTACAAGCTCAAGTCTGTG
25 GCCCACCTTCCCTGGCGCATGCTCACCTACAAGGCCCTCAACACATTCATCGACGACCTGTTGCCT
TTGTCATCAAGATGCCCGTTATGTACCGGATCGGCTGCCTGCGGGACGATGTGGTTTTCTTCATCTA
CCTCTACCAACGGTGGATCTACCGCGTCGACCCACCCGAGTCAACGAGTTTGGCATGAGTGGAGA
AGACCCACAGCTGCCGCCCCCGTGGCCGAGGTTCCACAGCAGCAGGGGCCCTCACGCCCACAC
CTGCACCCACACGACCACCGCCACCAGGGAGGAGGCCTCCACGTCCCTGCCACCAAGCCCACC
30 CAGGGGGCCAGCTCTGCCAGCGAGCCCCAGGAAGCCCCTCAAAGCCAGCAGAGGACAAGAAAAA
GGATTAGTCGAGACTGGTCCTCACCTGCTCCGGCTCCTGGCGACCACTACCCCTGCGTCCCGGCC
CCTCGCCTCCCCTCCCTGTGCCCCCTTCCCTGGACAGATCAGGCCGGGGCGGTGGGAGGCCCGCC
TCAGGTCAGGGCCCAGCGTGTGATGTAGGGGGCCGGGGCAGGCCAGGGTTTGTGTTGTGGAGGCGCT
GTCTGTCCCTCTGTCCCTCTGTGTTTCCAGCCATCTCGCCCTGCCAGCCCAGCACCCTGGGAATCA
35 TGGTGAAGCTGATGCAGCGTTGCCGAGGGGGTGGGTGGGGCGGGGGTGGGGCCGGGGCCCCCTA
CGGGATGCCACGGCCGTTTCATCATCTTGTCCCTCGTCCCCCTACCACACTCCCCCTCCTAGACCG
CCGCCCTTTAACACAGTCTGGATTTAATAAATTCATATGGGTGTTTAACTTAACTCAGCACTAAAAA
AAAAAAAAAAAAA
(SEQ ID NO: 16)

40

As used herein, the term "CLU" refers to the gene encoding Clusterin. The terms "CLU" and "Clusterin" include wild-type forms of the CLU gene, as well as variants (e.g., splice variants and

polymorphisms) of wild-type CLU. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type CLU nucleic acid sequence (e.g., SEQ ID NO: 17, ENA accession number M25915). SEQ ID NO: 17 is a wild-type gene sequence encoding CLU protein, and is shown below:

CTGCGAACCTCTCTACTCTCCGAAGGGAATTGTCCTTCCTGGCTTCCACTACTTCCACC
 CCTGAATGCACAGGCAGCCCGGCCCAAGTCTCCCACTAGGGATGCAGATGGATTCCGGTGT
 GAAGGGCTGGCTGCTGTTGCCTCCGGCTCTTGAAAGTCAAGTTCAGAGGCGTGCAAAGAC
 10 TCCAGAATTGGAGGCATGATGAAGACTCTGCTGCTGTTTGTGGGGCTGCTGCTGACCTGG
 GAGAGTGGGCAGGTCCTGGGGGACCAGACGGTCTCAGACAATGAGCTCCAGGAAATGTCC
 AATCAGGGAAGTAAGTACGTCAATAAGGAAATTCAAAATGCTGTCAACGGGGTGAAACAG
 ATAAAGACTCTCATAGAAAAACAAACGAAGAGCGCAAGACACTGCTCAGCAACCTAGAA
 GAAGCCAAGAAGAAGAAAGAGGATGCCCTAAATGAGACCAGGGAATCAGAGACAAAGCTG
 15 AAGGAGCTCCCAGGAGTGTGCAATGAGACCATGATGGCCCTCTGGGAAGAGTGTAAGCCC
 TGCCTGAAACAGACCTGCATGAAGTTCTACGCACGCGTCTGCAGAAAGTGGCTCAGGCCTG
 GTTGGCCGCCAGCTTGAGGAGTTCTGAACCAGAGCTCGCCCTTCTACTTCTGGATGAAT
 GGTGACCGCATCGACTCCCTGCTGGAGAACGACCGGCAGCAGACGCACATGCTGGATGTC
 ATGCAGGACCACTTCAGCCGCGGTCCAGCATCATAGACGAGCTCTTCCAGGACAGGTTCT
 20 TTCACCCGGGAGCCCCAGGATACCTACCACTACCTGCCCTTCAGCCTGCCCCACCGGAGG
 CCTCACTTCTTCTTTCCCAAGTCCCGCATCGTCCGCAGCTTGATGCCCTTCTCTCCGTAC
 GAGCCCCCTGAACCTCCACGCCATGTTCCAGCCCTTCCTTGAGATGATACACGAGGCTCAG
 CAGGCCATGGACATCCACTTCCACAGCCCGGCCTTCAGCACCCGCCAACAGAATTCATA
 CGAGAAGGCGACGATGACCGGACTGTGTGCCGGGAGATCCGCCACAACCTCCACGGGCTGCG
 25 CTGCGGATGAAGGACCAGTGTGACAAGTGCCGGGAGATCTTGTCTGTGGACTGTTCCACC
 AACAACCCCTCCCAGGCTAAGCTGCGGCGGGAGCTCGACGAATCCCTCCAGGTGCTGAG
 AGGTTGACCAGGAAATATAACGAGCTGCTAAAGTCCTACCAAGTGAAGATGCTCAACACC
 TCCTCCTTGCTGGAGCAGCTGAACGAGCAGTTTAACTGGGTGTCCCGGCTGGCAAACCTC
 ACGCAAGGCGAAGACCAGTACTATCTGCGGGTCACCACGGTGGCTTCCCACACTTCTGAC
 30 TCGGACGTTCTTCCGGTGTCACTGAGGTGGTCGTGAAGCTCTTTGACTCTGATCCCATC
 ACTGTGACGGTCCCTGTAGAAGTCTCCAGGAAGAACCCTAAATTTATGGAGACCGTGGCG
 GAGAAAGCGCTGCAGGAATACCGCAAAAAGCACCGGGAGGAGTGAGATGTGGATGTTGCT
 TTTGCACCTACGGGGGCATCTGAGTCCAGCTCCCCCAAGATGAGCTGCAGCCCCCCAGA
 GAGAGCTCTGCACGTCAACCAAGTAACCAGGC
 35 (SEQ ID NO: 17)

As used herein, the term "CR1" refers to the gene encoding Complement receptor type 1. The terms "CR1" and "Complement receptor type 1" include wild-type forms of the CR1 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type CR1. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type CR1 nucleic acid sequence (e.g., SEQ

ID NO: 18, ENA accession number Y00816). SEQ ID NO: 18 is a wild-type gene sequence encoding CR1 protein, and is shown below:

```
CGTGGTTTGTAGATGTGCTTGGGGAGAATGGGGGCCTCTTCTCCAAGAAGCCCGGAGCCT
5  GTCGGGCGCGCGCGCGCGGTCTCCCCTTCTGCTGCGGAGGATCCCTGCTGGCGGTTGTG
  GTGCTGCTTGCCTGCGGTGGCCTGGGGTCAATGCAATGCCCCAGAATGGCTTCCATTT
  GCCAGGCCTACCAACCTAACTGATGAGTTTGAGTTTCCCATTGGGACATATCTGAACTAT
  GAATGCCGCGCCTGTTATTCCGGAAGACCGTTTTCTATCATCTGCCTAAAAAACTCAGTC
  TGGACTGGTGCTAAGGACAGGTGCAGACGTAAATCATGTGTAATCCTCCAGATCCTGTG
10  AATGGCATGGTGCATGTGATCAAAGGCATCCAGTTCGGATCCCAAATTAATATTCTTGT
  ACTAAAGGATACCGACTCATTGGTTCCTCGTCTGCCACATGCATCATCTCAGGTGATACT
  GTCATTTGGGATAATGAAACACCTATTTGTGACAGAATTCTTGTGGGCTACCCCCACC
  ATCACCAATGGAGATTTTCATTAGCACCAACAGAGAGAATTTTCACTATGGATCAGTGGTG
  ACCTACCGCTGCAATCCTGGAAGCGGAGGGAGAAAGGTGTTTGAGCTTGTGGGTGAGCCC
15  TCCATATACTGCACCAGCAATGACGATCAAGTGGGCATCTGGAGCGGCCCCGCCCCCTCAG
  TGCATTATACCTAACAATGCACGCCTCCAAATGTGGAAAATGGAATATTGGTATCTGAC
  AACAGAAGCTTATTTTCTTAAATGAAGTTGTGGAGTTTAGGTGTCAGCCTGGCTTTGTC
  ATGAAAGGACCCCGCCGTGTGAAGTGCCAGGCCCTGAACAAATGGGAGCCGGAGCTACCA
  AGCTGCTCCAGGGTATGTCAGCCACCTCCAGATGTCCTGCATGCTGAGCGTACCCAAAGG
20  GACAAGGACAACCTTTTACCTGGGCAGGAAGTGTCTACAGCTGTGAGCCCGGCTACGAC
  CTCAGAGGGGCTGCGTCTATGCGCTGCACACCCCAGGGAGACTGGAGCCCTGCAGCCCCC
  ACATGTGAAGTGAAATCCTGTGATGACTTCATGGGCCAACTTCTTAATGGCCGTGTGCTA
  TTTCCAGTAAATCTCCAGCTTGGAGCAAAAGTGGATTTTGTGTTGTGATGAAGGATTTCAA
  TTAAGGAGCAGCTCTGCTAGTTACTGTGTCTTGGCTGGAATGGAAAGCCTTTGGAATAGC
25  AGTGTTCCAGTGTGTGAACAAATCTTTTGTCCAAGTCTCCAGTTATTCCTAATGGGAGA
  CACACAGGAAAACCTCTGGAAGTCTTTCCCTTTGGAAAAGCAGTAAATTACACATGCGAC
  CCCCACCCAGACAGAGGGACGAGCTTCGACCTCATTGGAGAGAGCACCATCCGCTGCACA
  AGTGACCCTCAAGGGAATGGGGTTTGGAGCAGCCCTGCCCCCTCGCTGTGGAATTCTGGGT
  CACTGTCAAGCCCCAGATCATTTTCTGTTTGCCAAGTTGAAAACCCAAACCAATGCATCT
30  GACTTTCCCATTGGGACATCTTTAAAGTACGAATGCCGTCCTGAGTACTACGGGAGGCCA
  TTCTCTATCACATGTCTAGATAACCTGGTCTGGTCAAGTCCCAAAGATGTCTGTAAACGT
  AAATCATGTAAACTCCTCCAGATCCAGTGAATGGCATGGTGCATGTGATCACAGACATC
  CAGGTTGGATCCAGAATCAACTATTCTTGTACTACAGGGCACCGACTCATTGGTCACTCA
  TCTGCTGAATGTATCCTCTCGGGCAATGCTGCCCATTTGGAGCACGAAGCCGCCAATTTGT
35  CAACGAATTCCTTGTGGGCTACCCCCACCATCGCCAATGGAGATTTTATTAGCACCAAC
  AGAGAGAATTTTCACTATGGATCAGTGGTGACCTACCGCTGCAATCCTGGAAGCGGAGGG
  AGAAAGGTGTTTGAGCTTGTGGGTGAGCCCTCCATATACTGCACCAGCAATGACGATCAA
  GTGGGCATCTGGAGCGGCCCCGCCCCCTCAGTGCATTATACCTAACAATGCACGCCTCCA
  AATGTGGAATAATGGAATATTGGTATCTGACAACAGAAGCTTATTTTCTTAAATGAAGTT
40  GTGGAGTTTAGGTGTCAGCCTGGCTTTGTCTATGAAAGGACCCCGCCGTGTGAAGTGCCAG
  GCCCTGAACAAATGGGAGCCGGAGCTACCAAGCTGCTCCAGGGTATGTCAGCCACCTCCA
  GATGTCCTGCATGCTGAGCGTACCCAAAGGGACAAGGACAACCTTTTACCCGGGCAGGAA
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GTGTTCTACAGCTGTGAGCCCGGCTATGACCTCAGAGGGGCTGCGTCTATGCGCTGCACA
CCCCAGGGAGACTGGAGCCCTGCAGCCCCCACATGTGAAAGTGAAATCCTGTGATGACTTC
ATGGGCCAACTTCTTAATGGCCGTGTGCTATTTCCAGTAAATCTCCAGCTTGGAGCAAAA
GTGGATTTTGTGTTGTGATGAAGGATTTCAATTA AAAAGGCAGCTCTGCTAGTTATTGTGTC
5 TTGGCTGGAATGGAAAGCCTTTGGAATAGCAGTGTTCCAGTGTTGAACAAATCTTTTGT
CCAAGTCCTCCAGTTATTCCTAATGGGAGACACACAGGAAAACCTCTGGAAGTCTTTCCC
TTTGAAAAGCAGTAAATTACACATGCGACCCCCACCCAGACAGAGGGACGAGCTTCGAC
CTCATTGGAGAGAGCACCATCCGCTGCACAAGTGACCCTCAAGGGAATGGGGTTTGGAGC
AGCCCTGCCCCTCGCTGTGGAATTCTGGGTCACTGTCAAGCCCCAGATCATTCTGTGTT
10 GCCAAGTTGAAAACCCAAACCAATGCATCTGACTTTCCATTGGGACATCTTTAAAGTAC
GAATGCCGTCCTGAGTACTACGGGAGGCCATTCTCTATCACATGTCTAGATAACCTGGTC
TGGTCAAGTCCCAAAGATGTCTGTAAACGTAAATCATGTAAACTCCTCCAGATCCAGTG
AATGGCATGGTGCATGTGATCACAGACATCCAGGTTGGATCCAGAATCAACTATTCTTGT
ACTACAGGGCACCGACTCATTGGTCACTCATCTGCTGAATGTATCCTCTCAGGCAATACT
15 GCCATTGGAGCACGAAGCCGCCAATTTGTCAACGAATTCCTTGTGGGCTACCCCCAACCC
ATCGCCAATGGAGATTTTCATTAGCACCAACAGAGAGAATTTTCACTATGGATCAGTGGTG
ACCTACCGCTGCAATCTTGAAGCAGAGGGGAGAAAGGTGTTTGAGCTTGTGGGTGAGCCC
TCCATATACTGCACCAGCAATGACGATCAAGTGGGCATCTGGAGCGGCCCCGCCCTCAG
TGCATTATACCTAACAAATGCACGCCTCCAAATGTGGAAAATGGAATATTGGTATCTGAC
20 AACAGAAGCTTATTTTCCTTAAATGAAGTTGTGGAGTTTAGGTGTCAGCCTGGCTTTGTC
ATGAAAGGACCCCGCCGTGTGAAGTGCCAGGCCCTGAACAAATGGGAGCCAGAGTTACCA
AGCTGCTCCAGGGTGTGTCAGCCGCCTCCAGAAATCCTGCATGGTGAGCATACCCCAAGC
CATCAGGACAACCTTTTACCTGGGCAGGAAGTGTCTACAGCTGTGAGCCTGGCTATGAC
CTCAGAGGGGCTGCGTCTCTGCACTGCACACCCCAGGGAGACTGGAGCCCTGAAGCCCCG
25 AGATGTGCAGTGAAATCCTGTGATGACTTCTTGGGTCAACTCCCTCATGGCCGTGTGCTA
TTTCCACTTAATCTCCAGCTTGGGGCAAAGGTGTCCTTTGTCTGTGATGAAGGGTTTCGC
TTAAAGGGCAGTTCCGTTAGTCATTGTGTCTTGGTTGGAATGAGAAGCCTTTGGAATAAC
AGTGTTCCCTGTGTGTGAACATATCTTTGTCCAAATCCTCCAGCTATCCTTAATGGGAGA
CACACAGGAACTCCCTCTGGAGATATTCCTATGGAAAAGAAATATCTTACACATGTGAC
30 CCCCACCCAGACAGAGGGATGACCTTCAACCTCATTGGGGAGAGCACCATCCGCTGCACA
AGTGACCCTCATGGGAATGGGGTTTGGAGCAGCCCTGCCCCTCGCTGTGAACTTTCTGTT
CGTGCTGGTCACTGTAAAACCCCAGAGCAGTTTCCATTTGCCAGTCCTACGATCCCAATT
AATGACTTTGAGTTTCCAGTCGGGACATCTTTGAATTATGAATGCCGTCCTGGGTATTTT
GGGAAAATGTTCTCTATCTCCTGCCTAGAAAACCTTGGTCTGGTCAAGTGTGGAAGACAAC
35 TGTAGACGAAAATCATGTGGACCTCCACCAGAACCCTTCAATGGAATGGTGCATATAAAC
ACAGATACACAGTTTGGATCAACAGTTAATTATTCTTGTAAATGAAGGGTTTCGACTCATT
GGTTCCCCATCTACTACTTGTCTCGTCTCAGGCAATAATGTCACATGGGATAAGAAGGCA
CCTATTTGTGAGATCATATCTTGTGAGCCACCTCCAACCATATCCAATGGAGACTTCTAC
AGCAACAATAGAACATCTTTTACAATGGAACGGTGGTAACTTACCAGTGCCACACTGGA
40 CCAGATGGAGAACAGCTGTTTGGAGCTTGTGGGAGAACGGTCAATATATTGCACCAGCAAA
GATGATCAAGTTGGTGTGTTGGAGCAGCCCTCCCCCTCGGTGTATTTCTACTAATAAATGC
ACAGCTCCAGAAGTTGAAAATGCAATTAGAGTACCAGGAAACAGGAGTTTCTTTTCCCTC

ACTGAGATCATCAGATTTAGATGTCAGCCCCGGGTTTGTTCATGGTAGGGTCCCACACTGTG
CAGTGCCAGACCAATGGCAGATGGGGGCCCAAGCTGCCACACTGCTCCAGGGTGTGTCAG
CCGCCTCCAGAAATCCTGCATGGTGAGCATACCCTAAGCCATCAGGACAACCTTTTCACCT
GGGCAGGAAGTGTTCTACAGCTGTGAGCCCAGCTATGACCTCAGAGGGGCTGCGTCTCTG
5 CACTGCACGCCCCAGGGAGACTGGAGCCCTGAAGCCCCTAGATGTACAGTGAAATCCTGT
GATGACTTCCTGGGCCAACTCCCTCATGGCCGTGTGCTACTTCCACTTAATCTCCAGCTT
GGGGCAAAGGTGTCCTTTGTTTGCATGAAGGGTTCCGATTAAAAGGCAGGTCTGCTAGT
CATTGTGTCTTGCTGGAATGAAAGCCCTTTGGAATAGCAGTGTTCCAGTGTGTGAACAA
ATCTTTTGTCCAAATCCTCCAGCTATCCTTAATGGGAGACACACAGGAACTCCCTTTGGA
10 GATATTCCCTATGGAAGAAATATCTTACGCATGCGACACCCACCCAGACAGAGGGATG
ACCTTCAACCTCATTGGGGAGAGCTCCATCCGCTGCACAAGTGACCCTCAAGGGAATGGG
GTTTGGAGCAGCCCTGCCCTCGCTGTGAACTTTCTGTTCCCTGCTGCCTGCCACATCCA
CCCAAGATCCAAACGGGCATTACATTGGAGGACACGTATCTCTATATCTTCCTGGGATG
ACAATCAGCTACACTTGTGACCCCGGCTACCTGTTAGTGGGAAAGGGCTTCATTTTCTGT
15 ACAGACCAGGGAATCTGGAGCCAATTGGATCATTATTGCAAAGAAGTAAATTGTAGCTTC
CCACTGTTTATGAATGGAATCTCGAAGGAGTTAGAAATGAAAAAGTATATCACTATGGA
GATTATGTGACTTTGAAGTGTGAAGATGGGTATACTCTGGAAGGCAGTCCCTGGAGCCAG
TGCCAGGCGGATGACAGATGGGACCCTCCTCTGGCCAAATGTACCTCTCGTGCACATGAT
GCTCTCATAGTTGGCACTTTATCTGGTACGATCTTCTTTATTTTACTCATATTTTCCTC
20 TCTTGGATAATTCTAAAGCACAGAAAAGGCAATAATGCACATGAAAACCCTAAAGAAGTG
GCTATCCATTTACATTCTCAAGGAGGCAGCAGCGTTCATCCCCGAACCTCTGCAAACAAAT
GAAGAAAATAGCAGGGTCCTTCCTTGACAAAGTACTATACAGCTGAAGAACATCTCGAAT
ACAATTTTGGTGGGAAAGGAGCCAATTGATTTCAACAGAATCAGATCTGAGCTTCATAAA
GTCTTTGAAGTGACTTCACAGAGACGCAGACATGTGCACTTGAAGATGCTGCCCCCTTCCC
25 TGGTACCTAGCAAAGCTCCTGCCTCTTTGTGTGCGTCACTGTGAAACCCCCACCCTTCTG
CCTCGTGCTAAACGCACACAGTATCTAGTCAGGGGAAAAGACTGCATTTAGGAGATAGAA
AATAGTTTGGATTACTTAAAGGAATAAGGTGTTGCCTGGAATTTCTGGTTTGTAAAGGTGG
TCACTGTTCTTTTTTAAATATTTGTAATATGGAATGGGCTCAGTAAGAAGAGCTTGGAA
AATGCAGAAAGTTATGAAAAATAAGTCACTTATAATTATGCTACCTACTGATAACCACTC
30 CTAATATTTTGATTCATTTTCTGCCTATCTTCTTTCACATATGTGTTTTTTTACATACGT
ACTTTTCCCCCCTTAGTTTGTTTCCTTTTATTTTATAGAGCAGAACCCTAGTCTTTTAA
CAGTTTAGAGTGAAATATATGCTATATCAGTTTTTACTTTCTCTAGGGAGAAAAATTAAT
TACTAGAAAGGCATGAAATGATCATGGGAAGAGTGGTTAAGACTACTGAAGAGAAATAT
TTGGAAAATAAGATTTGATATCTTCTTTTTTTTTGAGATGGAGTCTGGCTCTGTCTCCC
35 AGGCTGGAGTGCAGTGGCGTAATCTCGGCTCACTGCAACGTCCGCCTCCCG
(SEQ ID NO: 18)

As used herein, the term "CSF1" refers to the gene encoding Macrophage colony-stimulating factor 1. The terms "CSF1" and "Macrophage colony-stimulating factor 1" include wild-type forms of the
40 CSF1 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type CSF1. Examples of
such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%,
75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%,

93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type CSF1 nucleic acid sequence (e.g., SEQ ID NO: 19, ENA accession number M37435). SEQ ID NO: 19 is a wild-type gene sequence encoding CSF1 protein, and is shown below:

```
5  CCTGGGTCCTCTCGGCGCCAGAGCCGCTCTCCGCATCCCAGGACAGCGGTGCGGCCCTCG
   GCCGGGGCGCCCACTCCGCAGCAGCCAGCGAGCCAGCTGCCCCGTATGACCGCGCCGGGC
   GCCGCCGGGCGCTGCCCTCCCACGACATGGCTGGGCTCCCTGCTGTTGTTGGTCTGTCTC
   CTGGCGAGCAGGAGTATCACCGAGGAGGTGTGCGAGTACTGTAGCCACATGATTGGGAGT
   GGACACCTGCAGTCTCTGCAGCGGCTGATTGACAGTCAGATGGAGACCTCGTGCCAAATT
10  ACATTTGAGTTTGTAGACCAGGAACAGTTGAAAGATCCAGTGTGCTACCTTAAGAAGGCA
   TTTCTCCTGGTACAAGACATAATGGAGGACACCATGCGCTTCAGAGATAACACCGCCAAT
   CCCATCGCCATTGTGCAGCTGCAGGAACTCTCTTTGAGGCTGAAGAGCTGCTTCACCAAG
   GATTATGAAGAGCATGACAAGGCCTGCGTCCGAACCTTTCTATGAGACACCTCTCCAGTTG
   CTGGAGAAGGTCAAGAATGTCTTTAATGAAACAAAGAATCTCCTTGACAAGGACTGGAAT
15  ATTTTCAGCAAGAACTGCAACAACAGCTTTGCTGAATGCTCCAGCCAAGATGTGGTGACC
   AAGCCTGATTGCAACTGCCTGTACCCCAAAGCCATCCCTAGCAGTGACCCGGCCTCTGTC
   TCCCCTCATCAGCCCTCGCCCCCTCCATGGCCCCCTGTGGCTGGCTTGACCTGGGAGGAC
   TCTGAGGGAACTGAGGGCAGCTCCCTCTTGCTGGTGAGCAGCCCCTGCACACAGTGGAT
   CCAGGCAGTGCCAAGCAGCGGCCACCCAGGAGCACCTGCCAGAGCTTTGAGCCGCCAGAG
20  ACCCCAGTTGTCAAGGACAGCACCATCGGTGGCTCACCAAGCCTCGCCCCCTCTGTGGG
   GCCTTCAACCCCGGGATGGAGGATATTCTTGACTCTGCAATGGGCACTAATTGGGTCCCA
   GAAGAAGCCTCTGGAGAGGCCAGTGAGATTCCCGTACCCCAAGGGACAGAGCTTTCCCCC
   TCCAGGCCAGGAGGGGGCAGCATGCAGACAGAGCCCGCCAGACCCAGCAACTTCTCTCA
   GCATCTTCTCCACTCCCTGCATCAGCAAAGGGCCAACAGCCGGCAGATGTAAGTGTACA
25  GCCTTGCCCAGGGTGGGCCCCGTGATGCCCACTGGCCAGGACTGGAATCACACCCCCCAG
   AAGACAGACCATCCATCTGCCCTGCTCAGAGACCCCCCGGAGCCAGGCTCTCCCAGGATC
   TCATCACTGCGCCCCCAGGCCCTCAGCAACCCCTCCACCCTCTCTGCTCAGCCACAGCTT
   TCCAGAAGCCACTCCTCGGGCAGCGTGCTGCCCCCTTGGGGAGCTGGAGGGCAGGAGGAGC
   ACCAGGGATCGGACGAGCCCCGCAGAGCCAGAAGCAGCACCAGCAAGTGAAGGGGCAGCC
30  AGGCCCCCTGCCCCGTTTTAACTCCGTTCTTTGACTGACACAGGCCATGAGAGGCAGTCC
   GAGGGATCCTCCAGCCCGCAGCTCCAGGAGTCTGTCTTCCACCTGCTGGTGCCAGTGTCT
   ATCCTGGTCTTGCTGGCTGTGCGAGGCCTCTTGTCTACAGGTGGAGGCGGCGGAGCCAT
   CAAGAGCCTCAGAGAGCGGATTCTCCCTTGAGCAACCAGAGGGCAGCCCCCTGACTCAG
   GATGACAGACAGGTGGAAGTCCAGTGTAGAGGGAATTCTAAGCTGGACGCACAGAACAG
35  TCTCTTCGTGGGAGGAGACATTATGGGGCGTCCACCACCACCCCTCCCTGGCCATCCTCC
   TGGAATGTGGTCTGCCCTCCACCAGAGCTCCTGCCTGCCAGGACTGGACCAGAGCAGCCA
   GGCTGGGGCCCCCTCTGTCTCAACCCGCAGACCCTTGACTGAATGAGAGAGGCCAGAGGAT
   GCTCCCCATGCTGCCACTATTTATTGTGAGCCCTGGAGGCTCCCATGTGCTTGAGGAAGG
   CTGGTGAGCCCGGCTCAGGACCCTCTTCCCTCAGGGGCTGCAGCCTCCTCTCACTCCCTT
40  CCATGCCGGAACCCAGGCCAGGGACCCACCGGCCTGTGGTTTTGTGGGAAAGCAGGGTGCA
   CGCTGAGGAGTGAAACAACCCTGCACCCAGAGGGCCTGCCTGGTGCCAAGGTATCCCAGC
   CTGGACAGGCATGGACCTGTCTCCAGACAGAGGAGCCTGAAGTTCGTGGGGCGGGACAGC
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CTCGGCCTGATTTCCCGTAAAGGTGTGCAGCCTGAGAGACGGGAAGAGGAGGCCTCTGCA
 CCTGCTGGTCTGCACTGACAGCCTGAAGGGTCTACACCCTCGGCTCACCTAAGTCCCTGT
 GCTGGTTGCCAGGCCAGAGGGGAGGCCAGCCCTGCCCTCAGGACCTGCCTGACCTGCCA
 GTGATGCCAAGAGGGGGATCAAGCACTGGCCTCTGCCCTCCTCCTTCCAGCACCTGCCA
 5 GAGCTTCTCCAGCAGGCCAAGCAGAGGCTCCCCTCATGAAGGAAGCCATTGCACTGTGAA
 CACTGTACCTGCCTGCTGAACAGCCTCCCCCGTCCATCCATGAGCCAGCATCCGTCCGT
 CCTCCACTCTCCAGCCTCTCCCCAGCCTCCTGCACTGAGCTGGCCTCACCAGTCGACTGA
 GGGAGCCCCTCAGCCCTGACCTTCTCCTGACCTGGCCTTTGACTCCCCGGAGTGAGTGG
 GGTGGGAGAACCTCCTGGGCCGCCAGCCAGAGCCGCTCTTTAGGCTGTGTTCTTCGCCCA
 10 GGTTTCTGCATCTTCCACTTTGACATTCCCAAGAGGGAAGGGACTAGTGGGAGAGAGCAA
 GGGAGGGGAGGGCACAGACAGAGAGCCTACAGGGCGAGCTCTGACTGAAGATGGGCCTTT
 GAAATATAGGTATGCACCTGAGGTTGGGGGAGGGTCTGCACTCCCAAACCCAGCGCAGT
 GTCCTTTCCCTGCTGCCGACAGGAACCTGGGGCTGAGCAGGTTATCCCTGTCAGGAGCCC
 TGGACTGGGCTGCATCTCAGCCCCACCTGCATGGTATCCAGCTCCCATCCACTTCTCACC
 15 CTTCTTTCCTCCTGACCTTGGTCAGCAGTGATGACCTCCAACCTCTACCCACCCCTCTA
 CCATCACCTCTAACCAGGCAAGCCAGGGTGGGAGAGCAATCAGGAGAGCCAGGCCTCAGC
 TTCCAATGCCTGGAGGGCCTCCACTTTGTGGCCAGCCTGTGGTGTGCTGAGGCCTA
 GGCAACGAGCGACAGGGCTGCCAGTTGCCCTGGGTTCTTTGTGCTGCTGTGTGCCTCC
 TCTCCTGCCGCCCTTTGTCTCCGCTAAGAGACCCTGCCCTACCTGGCCGCTGGGCCCCG
 20 TGACTTTCCTTCCCTGCCCAGGAAAGTGAGGGTCGGCTGGCCCCACCTTCCCTGTCCTGA
 TGCCGACAGCTTAGGGAAGGGCACTGAACTTGCATATGGGGCTTAGCCTTCTAGTCACAG
 CCTCTATATTTGATGCTAGAAAACACATATTTTTAAATGGAAGAAAAATAAAAAGGCATT
 CCCCCTTCATCCCCCTACCTTAAACATATAATTTTTAAAGGTCAAAAAGCAATCCAAC
 CCACTGCAGAAGCTCTTTTTGAGCACTTGGTGGCATCAGAGCAGGAGGAGCCCCAGAGCC
 25 ACCTCTGGTGTCCCCCAGGCTACCTGCTCAGGAACCCCTTCTGTTCTCTGAGAACTCAAC
 AGAGGACATTGGCTCACGCACTGTGAGATTTGTTTTATACTTGCAACTGGTGAATTAT
 TTTTTATAAAGTCATTTAAATATCTATTTAAAAGATAGGAAGCTGCTTATATATTTAATA
 ATAAAAGAAGTGACAAGCTGCCGTTGACGTAGCTCGAG
 (SEQ ID NO: 19)

30 As used herein, the term "CST7" refers to the gene encoding Cystatin-F. The terms "CST7" and
 "Cystatin-F" include wild-type forms of the CST7 gene, as well as variants (e.g., splice variants and
 polymorphisms) of wild-type CST7. Examples of such variants are nucleic acids having at least 70%
 sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%,
 35 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9%
 identity, or more) to a wild-type CST7 nucleic acid sequence (e.g., SEQ ID NO: 20, ENA accession
 number AF031824). SEQ ID NO: 20 is a wild-type gene sequence encoding CST7 protein, and is shown
 below:

40 GGCTCAGCACAGGCACAAACCATTGCCCGGCACTGGCCCGTGCTGCCTGAGAAGGATTGG
 CACGGGCACAGACCACTGCCCCACCTGCCCTGCGCCATCTACCCAAGAAGGCTCGGCAC
 GGGCACCAACCACTGCCTCCAACCTGCCCCATGCTGCCTGAGAAGGCACTGCACGGCCACC

C C C C A A C T G C C C C G C A C T G T C C C T A C C C G G G C A G C C A T G C G A G C G G C T G G A A C T C T G C T G G
 C C T T C T G C T G C C T G G T C T T G A G C A C C A C T G G G G G C C C T T C C C C A G A T A C T T G T T C C C A G G
 A C C T T A A C T C A C G T G T G A A G C C A G G A T T T C C T A A A C A A T A A A G A C C A A T G A C C C A G G A G
 T C C T C C A A G C A G C C A G A T A C A G T G T T G A A A G T T C A A C A A C T G C A C G A A C G A C A T G T T C T
 5 T G T T C A A G G A G T C C C G C A T C A C A A G G G C C C T A G T T C A G A T A G T G A A A G G C C T G A A A T A T A
 T G C T G G A G G T G G A A A T T G G C A G A A C T A C C T G C A A G A A A A C C A G C A C C T G C G T C T G G A T G
 A C T G T G A C T T C C A A C C A A C C A C A C C T T G A A G C A G A C T C T G A G C T G C T A C T C T G A A G T C T
 G G G T C G T G C C C T G G C T C C A G C A C T T C G A G G T G C C T G T T C T C C G T T G T C A C T G A C C C C C G C
 C T C T T C A G C A A G A C C A C A G C C A T G A C A A A C A C C A G G A T G C A T G C T C C T T G T C C C C T C C C A
 10 C C C G C C T C A T G A C C C A G C C T C A C A G A C C C T C T C A G G C C T C T G A C G A G T G A G C G G G T G A A G
 T G C C A C T G G G T C A C C G C A G G G C A G C T G G A A T G G C A G C A T G G T A G C A C C T C C T A A C A G A T T
 A A A T A G A T C A C A T T T G C T T C T A A A A T T
 (SEQ ID NO: 20)

15 As used herein, the term "CTSB" refers to the gene encoding Cathepsin B. The terms "CTSB"
 and "Cathepsin B" include wild-type forms of the CTSB gene, as well as variants (e.g., splice variants and
 polymorphisms) of wild-type CTSB. Examples of such variants are nucleic acids having at least 70%
 sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%,
 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9%
 20 identity, or more) to a wild-type CTSB nucleic acid sequence (e.g., SEQ ID NO: 21, ENA accession
 number M14221). SEQ ID NO: 21 is a wild-type gene sequence encoding CTSB protein, and is shown
 below:

A A T T C C G C G G C A A C C G C T C C G G C A A C G C C A A C C G C T C C G C T G C G C G C A G G C T G G G C T G C A
 25 G G C T C T C G G C T G C A G C G C T G G G C T G G T G T G C A G T G G T G C G A C C A C G G C T C A C G G C A G C C T
 C A G C C A C C C A G A T G T A A G C G A T C T G G T T C C C A C C T C A G C C T T C C G A G T A G T G G A T C T A G G
 A T C T G G C T T C C A A C A T G T G G C A G C T C T G G G C C T C C C T C T G C T G C C T G C T G G T G T T G G C C A
 A T G C C C G G A G C A G G C C C T C T T T C C A T C C C G T G T C G G A T G A G C T G G T C A A C T A T G T C A A C A
 A A C G G A A T A C C A C G T G G C A G G C C G G G C A C A A C T T C T A C A A C G T G G A C A T G A G C T A C T T G A
 30 A G A G G C T A T G T G G T A C C T T C C T G G G T G G G C C C A A G C C A C C C C A G A G A G T T A T G T T T A C C G
 A G G A C C T G A A G C T G C C T G C A A G C T T C G A T G C A C G G G A A C A A T G G C C A C A G T G T C C C A C C A
 T C A A A G A G A T C A G A G A C C A G G G C T C C T G T G G C T C C T G C T G G G C C T T C G G G G C T G T G G A A G
 C C A T C T C T G A C C G C A T C T G C A T C C A C A C C A A T G C G C A C G T C A G C G T G G A G G T G T C G G C G G
 A G G A C C T G C T C A C C T G C T G T G G C A G C A T G T G T G G G G A C G G C T G T A A T G G T G G C T A T C C T G
 35 C T G A A G C T T G G A A C T T C T G G A C A A G A A A A G G C C T G G T T T C T G G T G G C C T C T A T G A A T C C C
 A T G T A G G G T G C A G A C C G T A C C A T C C C T C C C T G T G A G C A C C A C G T C A A C G G C T C C C G G C
 C C C C A T G C A C G G G G G A G G G A G A T A C C C C C A A G T G T A G C A A G A T C T G T G A G C C T G G C T A C A
 G C C C G A C C T A C A A C A G G A C A A G C A C T A C G G A T A C A A T T C C T A C A G C G T C T C C A A T A G C G
 A G A A G G A C A T C A T G G C C G A G A T C T A C A A A A C G G C C C C G T G G A G G G A G C T T T C T C T G T G T
 40 A T T C G G A C T T C C T G C T C T A C A A G T C A G G A G T G T A C C A A C A C G T C A C C G G A G A G A T G A T G G
 G T G G C C A T G C C A T C C G C A T C C T G G G C T G G G G A G T G G A G A A T G G C A C A C C C T A C T G G C T G G
 T T G C C A A C T C C T G G A A C A C T G A C T G G G G T G A C A A T G G C T T C T T T A A A A T A C T C A G A G G A C

AGGATCACTGCGGAATCGAATCAGAAAGTGGTGGCTGGAATTCCACGCACCGATCAGTACT
 GGGAAAAGATCTAATCTGCCGTGGGCCTGTCGTGCCAGTCCTGGGGGCGAGATCGGGGTA
 GAAAGTCATTTTATTCTTTAAGTTCACGTAAGATAACAAGTTTCAGGCAGGGTCTGAAGGA
 CTGGATTGGCCAAAGTCCTCCAAGGAGACCAAGTCCTGGCTACATCCCAGCCTGTGGTTA
 5 CAGTGCAGACAGGCCATGTGAGCCACCGCTGCCAGCACAGAGCGTCCTTCCCCCTGTAGA
 CTAGTGCCGTGGGAGTACCTGCTGCCAGCTGCTGTGGCCCCCTCCGTGATCCATCCATC
 TCCAGGGAGCAAGACAGAGACGCAGGATGGAAAGCGGAGTTCCTAACAGGATGAAAGTTC
 CCCCATCAGTTCCCCCAGTACCTCCAAGCAAGTAGCTTTCCACATTTGTCACAGAAATCA
 GAGGAGAGATGGTGTGGGAGCCCTTTGGAGAACGCCAGTCTCCAGGTCCCCCTGCATCT
 10 ATCGAGTTTGCAATGTCACAACCTCTCTGATCTTGTGCTCAGCATGATTCTTTAATAGAA
 GTTTTATTTTTCGTGCACTCTGCTAATCATGTGGGTGAGCCAGTGGAACAGCGGGAGCCT
 GTGCTGGTTTGAGATTGCCTCCTAATGACGCGGCTCAAAAGGAAACCAAGTGGTCAGGA
 GTTGTCTGACCCACTGATCTCTACTACCACAAGGAAAATAGTTTAGGAGAAACCAGCT
 TTTACTGTTTTTGAAAAATTACAGCTTCACCCTGTCAAGTTAACAAGGAATGCCTGTGCC
 15 AATAAAAGGTTTCTCCAACCTG
 (SEQ ID NO: 21)

As used herein, the term "CTSD" refers to the gene encoding Cathepsin D. The terms "CTSD"
 and "Cathepsin D" include wild-type forms of the CTSD gene, as well as variants (e.g., splice variants and
 20 polymorphisms) of wild-type CTSD. Examples of such variants are nucleic acids having at least 70%
 sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%,
 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9%
 identity, or more) to a wild-type CTSD nucleic acid sequence (e.g., SEQ ID NO: 22, ENA accession
 number M11233). SEQ ID NO: 22 is a wild-type gene sequence encoding CTSD protein, and is shown
 25 below:

GGCTATAAGCGCACGGCCTCGGCGACCCTCTCCGACCCGGCCGCCGCCATGCAGCCC
 TCCAGCCTTCTGCCGCTCGCCCTCTGCCTGCTGGCTGCACCCGCCTCCGCGCTCGTCAGG
 ATCCCGCTGCACAAGTTCACGTCCATCCGCCGGACCATGTCCGAGGTTGGGGGCTCTGTG
 30 GAGGACCTGATTGCCAAAGGCCCCGTCTCAAAGTACTCCCAGGCGGTGCCAGCCGTGACC
 GAGGGGCCCCATTCCCAGAGGTGCTCAAGAACTACATGGACGCCAGTACTACGGGGAGATT
 GGCATCGGGACGCCCCCCCCAGTGCTTCACAGTCGTCTTCGACACGGGCTCCTCCAACCTG
 TGGGTCCCCTCCATCCACTGCAAAGTCTGGACATCGCTTGCTGGATCCACCACAAGTAC
 AACAGCGACAAGTCCAGCACCTACGTGAAGAATGGTACCTCGTTTGACATCCACTATGGC
 35 TCGGGCAGCCTCTCCGGGTACCTGAGCCAGGACACTGTGTCCGGTGCCCTGCCAGTCAGCG
 TCGTCAGCCTCTGCCCTGGGCGGTGTCAAAGTGGAGAGGCAGGTCTTTGGGGAGGCCACC
 AAGCAGCCAGGCATCACCTTCATCGCAGCCAAGTTCGATGGCATCCTGGGCATGGCCTAC
 CCCCAGCATCTCCGTCAACAACGTGCTGCCCGTCTTCGACAACCTGATGCAGCAGAAGCTG
 GTGGACCAGAACATCTTCTCCTTCTACCTGAGCAGGGACCCAGATGCGCAGCCTGGGGGT
 40 GAGCTGATGCTGGGTGGCACAGACTCCAAGTATTACAAGGGTTCTCTGTCTACCTGAAT
 GTCACCCGCAAGGCCTACTGGCAGGTCCACCTGGACCAGGTGGAGGTGGCCAGCGGGCTG
 ACCCTGTGCAAGGAGGGCTGTGAGGCCATTGTGGACACAGGCACTTCCCTCATGGTGGGC

CCGGTGGATGAGGTGCGCGAGCTGCAGAAGGCCATCGGGGCCGTGCCGCTGATTACAGGGC
 GAGTACATGATCCCCTGTGAGAAGGTGTCCACCCTGCCCGCGATCACACTGAAGCTGGGA
 GGCAAAGGCTACAAGCTGTCCCCAGAGGACTACACGCTCAAGGTGTGCGAGGCCGGGAAG
 ACCCTCTGCCTGAGCGGCTTCATGGGCATGGACATCCCGCCACCCAGCGGGCCACTCTGG
 5 ATCCTGGGCGACGTCTTCATCGGCCGCTACTACACTGTGTTTGACCGTGACAACAACAGG
 GTGGGCTTCGCCGAGGCTGCCCGCCTCTAGTTCCCAAGGCGTCCGCGCGCCAGCACAGAA
 ACAGAGGAGAGTCCCAGAGCAGGAGGCCCCCTGGCCCAGCGGCCCTCCACACACACCCA
 CACACTCGCCCGCCCACTGTCCTGGGCGCCCTGGAAGCCGCGGCCCAAGCCCGACTTGC
 TGTTCCTGTTCTGTGGTTTTCCCTCCCTGGGTTTCAGAAATGCTGCCTGCCTGTCTGTCTC
 10 TCCATCTGTTTGGTGGGGGTAGAGCTGATCCAGAGCACAGATCTGTTTCGTGCATTGGAA
 GACCCACCCAAGCTTGGCAGCCGAGCTCGTGTATCCTGGGGCTCCCTTCATCTCCAGGG
 AGTCCCCTCCCCGGCCCTACCAGCGCCCGCTGGGCTGAGCCCCTACCCACACCAGGCCG
 TCCTCCCGGGCCCTCCCTTGGAACCTGCCCTGCCTGAGGGCCCCCTCTGCCAGCTTGGG
 CCCAGCTGGGCTCTGCCACCCTACCTGTTCACTGTCCCGGGCCCGTTGAGGATGAGGCCG
 15 CTAGAGGCCTGAGGATGAGCTGGAAGGAGTGAGAGGGGACAAAACCCACCTTGTTGGAGC
 CTGCAGGGTGGTGCTGGGACTGAGCCAGTCCCAGGGGCATGTATTGGCCTGGAGGTGGGG
 TTGGGATTGGGGGCTGGTGCCAGCCTTCCTCTGCAGCTGACCTCTGTTGTCTCCCTTG
 GGCGGCTGAGAGCCCCAGCTGACATGGAATACAGTTGTTGGCCTCCGGCCTCCCTC
 (SEQ ID NO: 22)

20

As used herein, the term "CTSL" refers to the gene encoding Cathepsin L1. The terms "CTSL" and "Cathepsin L1" include wild-type forms of the CTSL gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type CTSL. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%,
 25 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type CTSL nucleic acid sequence (e.g., SEQ ID NO: 23, ENA accession number X12451). SEQ ID NO: 23 is a wild-type gene sequence encoding CTSL protein, and is shown below:

30 AGAACCGCGACCTCCGCAACCTTGAGCGGCATCCGTGGAGTGCGCCTGCAGCTACGACCG
 CAGCAGGAAAGCGCCGCCGAGGCCAGCTGTGGCCGACAGGGACTGGAAGAGAGGA
 CGCGGTGAGTAGGTGTGCACCAGCCCTGGCAACGAGAGCGTCTACCCCGAACTCTGCTG
 GCCTTGAGGTGGGGAAGCCGGGAGGGCAGTTGAGGACCCCGCGGAGGCGCGTGAAGTGGT
 TGAGCGGGCAGGCCAGCCTCCGAGCCGGGTGGACACAGGTTTTAAACATGAATCCTACA
 35 CTCATCCTTGCTGCCTTTGCCTGGGAATTGCCTCAGCTACTCTAACATTTGATCACAGT
 TTAGAGGCACAGTGGACCAAGTGAAGGCGATGCACAACAGATTATACGGCATGAATGAA
 GAAGGATGGAGGAGAGCAGTGTGGGAGAAGAACATGAAGATGATTGAACTGCACAATCAG
 GAATACAGGGAAGGGAACACAGCTTCACAATGGCCATGAACGCCTTTGGAGACATGACC
 AGTGAAGAATTCAGGCAGGTGATGAATGGCTTTCAAACCGTAAGCCCAGGAAGGGGAAA
 40 GTGTTCCAGGAACCTCTGTTTTATGAGGCCCCAGATCTGTGGATTGGAGAGAGAAAGGC
 TACGTGACTCCTGTGAAGAATCAGGGTCAGTGTGGTTCTTGTGGGCTTTTAGTGCTACT
 GGTGCTCTTGAAGGACAGATGTTCCGGAAAACCTGGGAGGCTTATCTCACTGAGTGAGCAG

AATCTGGTAGACTGCTCTGGGCCTCAAGGCAATGAAGGCTGCAATGGTGGCCTAATGGAT
 TATGCTTTCCAGTATGTTTCAGGATAATGGAGGCCTGGACTCTGAGGAATCCTATCCATAT
 GAGGCAACAGAAGAATCCTGTAAGTACAATCCCAAGTATTCTGTTGCTAATGACACCGGC
 TTTGTGGACATCCCTAAGCAGGAGAAGGCCCTGATGAAGGCAGTTGCAACTGTGGGGCCC
 5 ATTTCTGTTGCTATTGATGCAGGTCATGAGTCCTTCCTGTTCTATAAAGAAGGCATTTAT
 TTTGAGCCAGACTGTAGCAGTGAAGACATGGATCATGGTGTGCTGGTGGTTGGCTACGGA
 TTTGAAAGCACAGAATCAGATAACAATAAATATTGGCTGGTGAAGAACAGCTGGGGTGAA
 GAATGGGGCATGGGTGGCTACGTAAAGATGGCCAAAGACCGGAGAAACCATTGTGGAATT
 GCCTCAGCAGCCAGCTACCCCACTGTGTGAGCTGGTGGACGGTGATGAGGAAGGACTTGA
 10 CTGGGGATGGCGCATGCATGGGAGGAATTCATCTTCAGTCTACCAGCCCCCGCTGTGTCTG
 GATACACACTCGAATCATTGAAGATCCGAGTGTGATTGAATTCTGTGATATTTTCACAC
 TGGTAAATGTTACCTCTATTTTAATTACTGCTATAAATAGGTTTATATTATTGATTCACT
 TACTGACTTTGCATTTTCGTTTTTAAAAGGATGTATAAATTTTACCTGTTTAAATAAAA
 TTTAATTTCAAATGT
 15 (SEQ ID NO: 23)

As used herein, the term "CXCL10" refers to the gene encoding C-X-C motif chemokine 10. The
 terms "CXCL10" and "C-X-C motif chemokine 10" include wild-type forms of the CXCL10 gene, as well as
 variants (e.g., splice variants and polymorphisms) of wild-type CXCL10. Examples of such variants are
 20 nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%,
 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type CXCL10 nucleic acid sequence (e.g.,
 SEQ ID NO: 24, ENA accession number X02530). SEQ ID NO: 24 is a wild-type gene sequence
 encoding CXCL10 protein, and is shown below:

25 GAGACATTCCTCAATTGCTTAGACATATTCTGAGCCTACAGCAGAGGAACCTCCAGTCTC
 AGCACCATGAATCAAACCTGCGATTCTGATTTGCTGCCTTATCTTTCTGACTCTAAGTGGC
 ATTCAAGGAGTACCTCTCTCTAGAACCGTACGCTGTACCTGCATCAGCATTAGTAATCAA
 CCTGTTAATCCAAGGTCTTTAGAAAACTTGAAATTATTCCTGCAAGCCAATTTTGTCCA
 30 CGTGTTGAGATCATTGCTACAATGAAAAAGAAGGGTGAGAAGAGATGTCTGAATCCAGAA
 TCGAAGGCCATCAAGAATTTACTGAAAGCAGTTAGCAAGGAAATGTCTAAAAGATCTCCT
 TAAAACCAGAGGGGAGCAAAATCGATGCAGTGCTTCCAAGGATGGACCACACAGAGGCTG
 CCTCTCCCATCACTTCCCTACATGGAGTATATGTCAAGCCATAATTGTTCTTAGTTTGCA
 GTTACACTAAAAGGTGACCAATGATGGTCACCAAATCAGCTGCTACTACTCCTGTAGGAA
 35 GGTTAATGTTTCATCATCCTAAGCTATTCAGTAATAACTCTACCCTGGCACTATAATGTAA
 GCTCTACTGAGGTGCTATGTTCTTAGTGGATGTTCTGACCCTGCTTCAAATATTTCCCTC
 ACCTTTCCCATCTTCCAAGGGTACTAAGGAATCTTTCTGCTTTGGGGTTTATCAGAATTC
 TCAGAATCTCAAATAACTAAAAGGTATGCAATCAAATCTGCTTTTTAAAGAATGCTCTTT
 ACTTCATGGACTTCCACTGCCATCCTCCCAAGGGGCCCAAATCTTTTCAGTGGCTACCTA
 40 CATACAATTCCAAACACATACAGGAAGGTAGAAATATCTGAAAATGTATGTGTAAGTATT
 CTTATTTAATGAAAGACTGTACAAAGTATAAGTCTTAGATGTATATATTTCCCTATATTGT
 TTTCAAGTGTACATGGAATAACATGTAATTAAGTACTATGTATCAATGAGTAACAGGAAAA

TTTTAAAAATACAGATAGATATATGCTCTGCATGTTACATAAGATAAATGTGCTGAATGG
 TTTTCAAATAAAAATGAGGTACTCTCCTGGAAATATTAAGAAAGACTATCTAAATGTTGA
 AAGATCAAAGGTTAATAAAGTAATTATAACT
 (SEQ ID NO: 24)

5

As used herein, the term "CXCL13" refers to the gene encoding C-X-C motif chemokine 13. The terms "CXCL13" and "C-X-C motif chemokine 13" include wild-type forms of the CXCL13 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type CXCL13. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type CXCL13 nucleic acid sequence (e.g., SEQ ID NO: 25, ENA accession number AF044197). SEQ ID NO: 25 is a wild-type gene sequence encoding CXCL13 protein, and is shown below:

15 TTCGGCACTTGGGAGAAGATGTTTGAAAAAACTGACTCTGCTAATGAGCCTGGACTCAGA
 GCTCAAGTCTGAACTCTACCTCCAGACAGAATGAAGTTCATCTCGACATCTCTGCTTCTC
 ATGCTGCTGGTCAGCAGCCTCTCTCCAGTCCAAGGTGTTCTGGAGGTCTATTACACAAGC
 TTGAGGTGTAGATGTGTCCAAGAGAGCTCAGTCTTTATCCCTAGACGCTTCATTGATCGA
 ATTCAAATCTTGCCCCGTGGGAATGGTTGTCCAAGAAAAGAAATCATAGTCTGGAAGAAG
 20 AACAAGTCAATTGTGTGTGTGGACCCTCAAGCTGAATGGATACAAAGAAATGATGGAAGTA
 TTGAGAAAAAGAAGTTCTTCAACTCTACCAGTTCAGTGTTTAAGAGAAAGATTCCCTGA
 TGCTGATATTTCCACTAAGAACACCTGCATTCTTCCCTTATCCCTGCTCTGGATTTTAGT
 TTTGTGCTTAGTTAAATCTTTTCCAGGGAGAAAGAACTTCCCCATACAAATAAGGCATGA
 GGACTATGTGAAAAATAACCTTGCAGGAGCTGATGGGGCAAACCTCAAGCTTCTTCACTCA
 25 CAGCACCCCTATATACACTTGGAGTTTGCATTCTTATTCATCAGGGAGGAAAGTTTCTTTG
 AAAATAGTTATTCAAGTTATAAGTAATACAGGATTATTTTGATTATATACTTGTGTTTAA
 TGTTTAAAATTTCTTAGAAAACAATGGAATGAGAATTTAAGCCTCAAATTTGAACATGTG
 GCTTGAATTAAGAAGAAAATTATGGCATATATTAAGCAGGCTTCTATGAAAGACTCAA
 AAAGCTGCCTGGGAGGCAGATGGAACCTTGAGCCTGTCAAGAGGCAAAGGAATCCATGTAG
 30 TAGATATCCTCTGCTTAAAACTCACTACGGAGGAGAAATTAAGTCCTACTTTTAAAGAAT
 TTCTTTATAAAATTTACTGTCTAAGATTAATAGCATTCTGAAGATCCCCAGACTTCATAGA
 ATACTCAGGGAAAGCATTAAAGGGTGATGTACACATGTATCCTTTCACACATTTGCCTT
 GACAACTTCTTTCACTCACATCTTTTTCACTGACTTTTTTTGTGGGGGCGGGGCCGGGG
 GGACTCTGGTATCTAATTCTTTAATGATTCTATAAATCTAATGACATTCAATAAAGTTG
 35 AGCAAACATTTTACTT
 (SEQ ID NO: 25)

As used herein, the term "DSG2" refers to the gene encoding Desmoglein 2. The terms "DSG2" and "Desmoglein 2" include wild-type forms of the DSG2 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type DSG2. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9%

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identity, or more) to a wild-type DSG2 nucleic acid sequence (e.g., SEQ ID NO: 26, NCBI Reference Sequence: NM_001943.4). SEQ ID NO: 26 is a wild-type gene sequence encoding DSG2 protein, and is shown below:

```
5  CCACCTCTGTAAAAGCGGCCCGGGCCGGCCCCCGGCTCCATTTTCTCGCGGCGGCCACACCTGGA
   GCCGCGCCTTTGGGTTGGGCTGGGCTGGGCGCGCAACCGCCACGGGAAGACAGCCCTCGGGGC
   GGGGAGGGAGAGGGTGGCCGGGCCGGGGGGAGGCCGGGGCCAGGGAGGAGCCGAGTGCGCGC
   TCGGGGCAGGCGGCGGCGGAGCGGTGCGGCGGCGGGAGGCGGAGGCGAGGGTGCATGGC
   GCGGAGCCCCGGGACGCGCGTACGCCCTGCTGCTTCTCCTGATCTGCTTTAACGTTGGAAGTGGACT
10  TCACTTACAGGTCTTAAGCACAAGAAATGAAAATAAGCTGCTTCCTAAACATCCTCATTTAGTGCGGC
   AAAAGCGCGCCTGGATCACCGCCCCCGTGGCTCTTCGGGAGGGAGAGGATCTGTCCAAGAAGAAT
   CCAATTGCCAAGATACATTCTGATCTTGCAAGAAGAGGACTCAAATTACTTACAAATACACTGG
   AAAAGGGATTACAGAGCCACCTTTTGGTATATTTGTCTTTAACAAAGATACTGGAGAAGTGAATGTTA
   CCAGCATTCTTGATCGAGAAGAAACACCATTTTTCTGCTAACAGGTTACGCTTTGGATGCAAGAGGA
15  AACAATGTAGAGAAACCCTTAGAGCTACGCATTAAGGTTCTTGATATCAATGACAACGAACCAAGTGTT
   CACACAGGATGTCTTTGTTGGGTCTGTTGAAGAGTTGAGTGCAGCACATACTCTTGTGATGAAAATCA
   ATGCAACAGATGCAGATGAGCCCAATACCCTGAATTCGAAAATTTCTATAGAATCGTATCTCTGGAG
   CCTGCTTATCCTCCAGTGTTCTACCTAAATAAAGATACAGGAGAGATTTATACAACCAAGTGTTACCTT
   GGACAGAGAGGAACACAGCAGCTACACTTTGACAGTAGAAGCAAGAGATGGCAATGGAGAAGTTAC
20  AGACAAACCTGTAAAACAAGCTCAAGTTCAGATTTCGTATTTTGGATGTCAATGACAATATACCTGTAG
   TAGAAAATAAAGTGCTTGAAGGGATGGTTGAAGAAAATCAAGTCAACGTAGAAGTTACGCGCATAAA
   AGTGTTTCGATGCAGATGAAATAGGTTCTGATAATTGGCTGGCAAATTTTACATTTGCATCAGGAAATG
   AAGGAGGTTATTTCCACATAGAAACAGATGCTCAAACCTAACGAAGGAATTGTGACCCTTATTAAGGAA
   GTAGATTATGAAGAAATGAAGAATCTTGACTTCAGTGTTATTGTGCTAATAAAGCAGCTTTTCACAA
25  GTCGATTAGGAGTAAATACAAGCCTACACCCATTCCCATCAAGGTCAAAGTGAAAAATGTGAAAGAA
   GGCATTCATTTTAAAAGCAGCGTCATCTCAATTTATGTTAGCGAGAGCATGGATAGATCAAGCAAAGG
   CCAAATAATTGGAAATTTTCAAGCTTTTGATGAGGACACTGGACTACCAGCCCATGCAAGATATGTAA
   AATTAGAAGATAGAGATAATTGGATCTCTGTGGATTCTGTGCATCTGAAATTAACCTTGCAAACTTC
   CTGATTTTGAATCTAGATATGTTCAAATGGCACATACACTGTAAAGATTGTGGCCATATCAGAAGATT
30  ATCCTAGAAAAACCATCACTGGCACAGTCCTTATCAATGTTGAAGACATCAACGACAACCTGTCCCACA
   CTGATAGAGCCTGTGCAGACAATCTGTCACGATGCAGAGTATGTGAATGTTACTGCAGAGGACCTGG
   ATGGACACCCAAACAGTGGCCCTTTCAGTTTCTCCGTCAATTGACAAACCACCTGGCATGGCAGAAAA
   ATGGAAAATAGCACGCCAAGAAAGTACCAGTGTGCTGCTGCAACAAAGTGAGAAAAAGCTTGGGAG
   AAGTGAAATTCAGTTCCTGATTTTCAAGACAATCAGGGTTTTAGTTGTCCTGAAAAGCAGGTCCTTACAC
35  TCACAGTTTGTGAGTGTCTGCATGGCAGCGGCTGCAGGGAAGCACAGCATGACTCCTATGTGGGCC
   TGGGACCCGCGAGCAATTGCGCTCATGATTTTGGCCTTTCTGCTCCTGCTATTGGTACCACTTTTACTG
   CTGATGTGCCATTGCGGAAAGGGCGCCAAAGGCTTTACCCCCATACCTGGCACCATAGAGATGCTG
   CATCCTTGAATAATGAAGGAGCACCACTGAAGACAAGGTGGTGCCATCATTTCTGCCAGTGGATC
   AAGGGGGCAGTCTAGTAGGAAGAAATGGAGTAGGAGGTATGGCCAAGGAAGCCACGATGAAAGGA
40  AGTAGCTCTGCTTCCATTGTCAAAGGGCAACATGAGATGTCCGAGATGGATGGAAGGTGGGAAGAA
   CACAGAAGCCTGCTTTCTGGTAGAGCTACCCAGTTTACAGGGGCCACAGGCGCTATCATGACCACT
   GAAACCACGAAGACCGCAAGGGCCACAGGGGCTTCCAGAGACATGGCCGGAGCTCAGGCAGCTGC
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TGTTGCACTGAACGAAGAATTCTTAAGAAATTATTTCACTGATAAAGCGGCCTCTTACACTGAGGAAG
ATGAAAATCACACAGCCAAAGATTGCCTTCTGGTTTATTCTCAGGAAGAACTGAATCGCTGAATGCT
TCTATTGGTTGTTGCAGTTTTATTGAAGGAGAGCTAGATGACCGCTTCTTAGATGATTTGGGACTTAA
ATTCAAGACACTAGCTGAAGTTTGCCTGGGTCAAAAAATAGATATAAATAAGGAAATTGAGCAGAGAC
5 AAAAACTGCCACAGAAACAAGTATGAACACAGCTTCACATTCACCTCTGTGAGCAAACTATGGTTAAT
TCAGAGAATACCTACTCCTCTGGCAGTAGCTTCCCAGTTCCAAAATCTTTGCAAGAAGCCAATGCAG
AGAAAGTAACTCAGGAAATAGTCACTGAAAGATCTGTGTCTTCTAGGCAGGCGCAAAAGGTAGCTAC
ACCTCTTCCTGACCCAATGGCTTCTAGAAATGTGATAGCAACAGAACTTCCTATGTCACAGGGTCCA
CTATGCCACCAACCACTGTGATCCTGGGTCTAGCCAGCCACAGAGCCTTATTGTGACAGAGAGGG
10 TGTATGCTCCAGCTTCTACCTTGGTAGATCAGCCTTATGCTAATGAAGGTACAGTTGTGGTCACTGAA
AGAGTAATACAGCCTCATGGGGGTGGATCGAATCCTCTGGAAGGCACTCAGCATCTTCAAGATGTAC
CTTACGTCATGGTGAGGGAAAGAGAGAGCTTCCTTGCCCCAGCTCAGGTGTGCAGCCTACTCTGG
CCATGCCTAATATAGCAGTAGGACAGAATGTGACAGTGACAGAAAGAGTTCTAGCACCTGCTTCAC
TCTGCAATCCAGTTACCAGATTCCCCTGAAAATTCTATGACGGCTAGGAACACCACGGTGTCTGGA
15 GCTGGAGTCCCTGGCCCTCTGCCAGATTTTGGTTTAGAGGAATCTGGTCATTCTAATTCTACCATAAC
CACATCTTCCACCAGAGTTACCAAGCATAGCACTGTACAGCATTCTTACTCCTAAACAGCAGTCAGCC
ACAACTGACCCAGAGTTTAATTAGCAGTGACTAATTTTCATGTTTCCAATGTACCTGATTTTTTCATGAG
CCTTACAGACACACAGAGACACATACACATTGATCTTAAAATTTTTCTCAGTCACTGATATGCAAAGG
ACCACACTGTCTCTGCTTCCAGGAGTATTTTAGAAATGTTCCACAATTTACTGAAGACATAGAGATGA
20 TGCTGCTGCTTAGGTGCCTTTTAGCAAGCTATGCAACAATCCTGATAAAACAAGATACATAGAGAGT
CAATCTGGCTTCTGAGAATTTACCAAGTGAACAGAGTACCTAGTTCATCAGCCGTCCAGTAAAGCAA
CCCAGGAACTGACTGGGTCTCTTTGCCTACCGTATTAACATTAAACATTGATGTTCTGTATTCTGTA
CTTTACTGCACCCAGCAGACTTTCAACAACCTATTGATCCAAAGATACATGCACAGTCTGAGCACCAG
CTATGGTGCTCATAACTTCTTTAAGACTTGAACCCTTTCAATCTGTGTGATTCAATTAATTGGACCATT
25 GATGATAAGAATACACATTGTATGTTTCTGTGCACATGACAGTGTGTGTGTGTGCACGTACATACTGT
ATAGTCTTAAAAATAGCATTATACTGGCCAGGGGTGGTGGCTAACGCCTGTAATCCCAGCACTTTGG
GAGGCCGAGGCGGGTGGATCAACTGTGGTCAGGAGTTTGAGATCAGCCAGGCCAACCTGGTGAAA
CCCCGTCTCTACTAAAAATACAAAATTAGCTGGGCGTGATGGTGGGCGCCTGTAATCCCAGCTACT
TGGGAGGCTGAGGCAGGAGAATCACTTGAACCCGGGAGGCGGAGGTTGCAGTGAGCCGAGATCGC
30 ACCATTGCACTCCAGTCTGGGCAACAGAGTGAGATTCCGTCTCAAAAAAAAAAAGAAAAGGAAAAAA
AAATAGCATTATACCTCTTCTTGTCTCAACCGCCATGAAAATTCTGAACACTCCAAATTCAGTTGAAT
AATCCAAAACAAAATTTATAAGTATAAAATAATTTTACTTCTTATAGTAATAGTATACTTTAAAAAGCCT
CAGGGTATATTATCTTCTAACAGCTACAATTCAGTGACGTACATTAACCAACTATGTTCTCTAGTTG
AGAACAACCTAGGCCTATTTCACTGCTGTGTAGCCTCAGTGCCTAACATGGGTGCCAAATAAATATTCG
35 TAGAATTACACTGAATTGTAAAAACCATTGTTTTTGTGTTACAATTGCCAAAAATCTCAAAGGCCCTG
TATTTATGTAATCTTTGAAATTATTATTTTATTTGATTTCTCAGTTATTGACTGGCTGGGTGTGACTT
AGTACATAAGTACTCAATATTATAAAAACCTCAAATAATTGACTTGATTTTACACAACATCCTTCCCTTT
TCTACAAGTTAATTTTTTTTACAAATCATTTGGGTATCTCCTAAATAGGTTATATTTTATTGCTTCTAGA
AACAATGTTTCAAATATATGTGCATTATCAGTAATAATTTGTATAAATATTTCCCACAACAATTTTCAT
40 AATTTTCAAAGACTAATTTCTTGACTGAAGATATTTTGCTAGGGGAAGTGAACTTTAAAATTTTGTAGA
TTTTAAAAATATTGTTGAATGGTGTGATGCAAAGGATTTATATAGTGTGCTCCCACTAACTGTACAGA
TCAGGACACATATTTTATAGACATCTAAGTCTGTAGCTTAAATGGAGGTTACTCTTCCATCATCTAGAAT

TGTTTACTTAGTAATTGTTGTTTCTTTTATTATTATAGACTTACTATCAGTTTTATTTTGCCAAGTATGCA
 ACAGGTATATCACTAGTATATGAAAATGTAAATATCACTTGTGTACTCAAACAAAAGTTGGTCTTAAGC
 TTCCACCTTGAGCAGCCTTGGAAACCTAACCTGCCTCTTTTAGCATAATCACATTTTCTAAATGATTTT
 CTTTGTTCCTGAAAAAGTGATTTGTATTAGTTTTACATTTGTTTTTTGGAAGATTATATTTGTATATGTA
 5 TCATCATAAAATATTTAAATAAAAAGTATCTTTAGAGTGACCCTTTCCCATAGATTTTTATTTCTCTAT
 TATATTTTACAAGGAATATAACTCAGTTTGTAGGGAGAGTGCCTTAAAGGCAGGTGTTTCTTGGACT
 TTGTTATTTAATTAGATCTGCTTGCAATAAAAAAAGTTGTCGGTTATCTAAAATTCAAAAAAAAAAAAAA
 AAAA

(SEQ ID NO: 26)

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As used herein, the term "ECHDC3" refers to the gene encoding Enoyl-CoA Hydratase Domain
 Containing 3. The terms "ECHDC" and "Enoyl-CoA Hydratase Domain Containing 3" include wild-type
 forms of the ECHDC gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type
 ECHDC. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%,
 15 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%,
 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type
 ECHDC nucleic acid sequence (e.g., SEQ ID NO: 27, NCBI Reference Sequence: NM_024693.4). SEQ
 ID NO: 27 is a wild-type gene sequence encoding ECHDC protein, and is shown below:

20 GGGGCGGGCGTGCCGGGGCGGGGCGTAGTACGGACTGGGCCTGGCCTGGGGCGTCCCCGCGA
 AGCCTGGGCCTGTCAGGCGGTTCCGTCCGGGTCTCGGCCACCGTCGAGTTCCGTGAGTTCCGTC
 CCGGCCCTGCTCACAGCAGCGCCCTCGGAGCGCCCAGCACCTGCGGCCGCGCCAGGCAGCGCGAT
 CCTGCGGCGTCTGGCCATCCCGAATGCTATGGCCGCCGTCGCCGTCTTGCGGGCCTTCGGGGCAA
 GTGGGGCCCATGTGTCTCCGGCGCGGGCCCTGGGGCCAGCTCCCCGCCCGCTTCTGCAGCCGGGA
 25 CCGGGCCGGGGCGGGGCGGCGGGAGTCGGAGCCGCGGCCACCAGCGCGCGGCAGCTGGACGG
 CATAAGGAACATCGTCTTGAGCAATCCCAAGAAGAGGAACACGTTGTCACTTGCAATGCTGAAATCT
 CTCCAAAGTGACATTCTTCATGACGCTGACAGCAACGATCTGAAAGTCATTATCATCTCGGCTGAGG
 GGCCTGTGTTTTCTTCTGGGCATGACTTAAAGGAGCTGACAGAGGAGCAAGGCCGTGATTACCATG
 CCGAAGTATTTTACAGACCTGTTCCAAGGTCATGATGCACATCCGGAACCACCCCGTCCCCGTCATTGC
 30 CATGGTCAATGGCCTGGCCACGGCTGCCGGCTGTCAACTGGTTGCCAGCTGCGACATTGCCGTGG
 CGAGCGACAAGTCCTCTTTTGCCACTCCTGGGGTGAACGTCGGGCTCTTCTGTTCTACCCCTGGGG
 TTGCCTTGGCAAGAGCAGTGCCTAGAAAGGTGGCCTTGGAGATGCTCTTTACTGGTGAGCCCATTTC
 TGCCCAGGAGGCCCTGCTCCACGGGCTGCTTAGCAAGGTGGTGCCAGAGGCGGAGCTGCAGGAG
 GAGACCATGCGGATCGCTAGGAAGATCGCATCGCTGAGCCGTCCGGTGGTGTCCCTGGGCAAAGC
 35 CACCTTCTACAAGCAGCTGCCCCAGGACCTGGGGACGGCTTACTACCTCACCTCCCAGGCCATGGT
 GGACAACCTGGCCCTGCGGGACGGGCAGGAGGGCATCACGGCCTTCCTCCAGAAGAGAAAACCTG
 TCTGGTCACACGAGCCAGTGTGAGTGGAGGCAGAGGAGTGAGGCCACGGGCAGCGCCCAGGAG
 CCCACCTTCCCCTCTGGCCCAGCCACCACTGCCTCTCAGCTTCAACAGGTGACAGGCTGCTTTTCGT
 GACTTGATATTGGTGTATAGCATTTGGCCTACATTAAGCCACAATTTTCATGGGGAAAGGACAAAA
 40 TGGAGAGTGACTGAGGTGCTGACCTCAGTGCAAGGCTGGTGAACCTGCAGCGGGGCCAGCTATGG
 TGGGAAGCCTGGCATTGTTGGGGTGCTCCTTGCAACGTCTTAAGCAAGCGACCCCCCTGACATAGCAA
 AAGGTGGCAACCCATGGAGGCAGAAAGAAGGACGCCAGCCTGACCCTTATCTGAAACGTCCTAAGC

AGAGTTAATCCTGGCTGCTCAGGAGAGGCGACACATTTCAAATCTCCACGAGATATTCTCCACACAG
 AAAATCTTCTTGATTCTATAGAGACTTAATCATGCCTATGGCTTTGAATAATCTTATGTGATTAAATAA
 ATTAAATCTTTATAAAAAAAAAAAAAAAAAAAAAA
 (SEQ ID NO: 27)

5

As used herein, the term "EPHA1" refers to the gene encoding Ephrin type-A receptor 1. The terms "EPHA1" and "Ephrin type-A receptor 1" include wild-type forms of the EPHA1 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type EPHA1. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type EPHA1 nucleic acid sequence (e.g., SEQ ID NO: 28, ENA accession number M18391). SEQ ID NO: 28 is a wild-type gene sequence encoding EPHA1 protein, and is shown below:

15 GCGCGCTGCTCCTAGTCCCTTGCAACCTGGCGCTGCATCCGGGCC
 ACTGTCCCAGGTCCCAGGTCCCGGCCCGGAGCTATGGAGCGGCGCTGGCCCCTGGGGCTA
 GGGCTGGTGTGCTGCTCTGCGCCCCGCTGCCCCCGGGGCGCGCGCCAAGGAAGTTACT
 CTGATGGACACAAGCAAGGCACAGGGAGAGCTGGGCTGGCTGCTGGATCCCCCAAAGAT
 GGGTGGAGTGAACAGCAACAGATACTGAATGGGACACCCCTCTACATGTACCAGGACTGC
 20 CCAATGCAAGGACGCGAGAGACACTGACCACTGGCTTCGCTCCAATTGGATCTACCGCGGG
 GAGGAGGCTTCCCGCGTCCACGTGGAGCTGCAGTTCACCGTGCGGGACTGCAAGAGTTTC
 CCTGGGGGAGCCGGGCCTCTGGGCTGCAAGGAGACCTTCAACCTTCTGTACATGGAGAGT
 GACCAGGATGTGGGCATTGAGCTCCGACGGCCCTGTTCCAGAAGGTAACCACGGTGGCT
 GCAGACCAGAGCTTCACCATTCGAGACCTTGCGTCTGGCTCCGTGAAGCTGAATGTGGAG
 25 CGCTGCTCTCTGGGCCGCTGACCCGCCGTGGCCTCTACCTCGCTTCCACAACCCGGGT
 GCCTGTGTGGCCCTGGTGTCTGTCCGGGTCTTCTACCAGCGCTGTCTGAGACCCTGAAT
 GGCTTGGCCCAATTCCCAGACACTCTGCCTGGCCCCGCTGGGTTGGTGAAGTGGCGGGC
 ACCTGCTTGCCCCACGCGCGGGCCAGCCCCAGGCCCTCAGGTGCACCCCGCATGCACTGC
 AGCCCTGATGGCGAGTGGCTGGTGCCTGTAGGACGGTGCCACTGTGAGCCTGGCTATGAG
 30 GAAGGTGGCAGTGGCGAAGCATGTGTTGCCTGCCCTAGCGGCTCCTACCGGATGGACATG
 GACACACCCCATTTGCTCACGTGCCCCCAGCAGAGCACTGCTGAGTCTGAGGGGGCCACC
 ATCTGTACCTGTGAGAGCGGCCATTACAGAGCTCCCGGGGAGGGCCCCCAGGTGGCATGC
 ACAGGTCCCCCTCGGCCCCCCGAAACCTGAGCTTCTCTGCCTCAGGGACTCAGCTCTCC
 CTGCGTTGGGAACCCCCAGCAGATACGGGGGGACGCCAGGATGTCAGATACAGTGTGAGG
 35 TGTTCACAGTGTGAGGGCACAGCACAGGACGGGGGGCCCTGCCAGCCCTGTGGGGTGGGC
 GTGCACTTCTCGCCGGGGGGCCCGGGCGCTCACACACCTGCAGTGCATGTCAATGGCCTT
 GAACCTTATGCCAACTACACCTTTAATGTGGAAGCCCCAAAATGGAGTGTGAGGGCTGGGC
 AGCTCTGGCCATGCCAGCACCTCAGTCAGCATCAGCATGGGGCATGCAGAGTCACTGTCA
 GGCCTGTCTCTGAGACTGGTGAAGAAAGAACCGAGGCAACTAGAGCTGACCTGGGCGGGG
 40 TCCCGGCCCGAAGCCCTGGGGCGAACCTGACCTATGAGCTGCACGTGCTGAACCAGGAT
 GAAGAACGGTACCAGATGGTTCTAGAACCCAGGGTCTTGCTGACAGAGCTGCAGCCTGAC
 ACCACATACATCGTCAGAGTCCGAATGCTGACCCCACTGGGTCTGGCCCTTCTCCCT

GATCATGAGTTTCGGACCAGCCCACCAGTGTCCAGGGGCCTGACTGGAGGAGAGATTGTA
 GCCGTCACTTTGGGCTGCTGCTTGGTGCAGCCTTGCTGCTTGGGATTCTCGTTTTCCGG
 TCCAGGAGAGCCCAGCGGCAGAGGCAGCAGAGGCACGTGACCGCGCCACCGATGTGGATC
 GAGAGGACAAGCTGTGCTGAAGCCTTATGTGGTACCTCCAGGCATACGAGGACCCTGCAC
 5 AGGGAGCCTTGGACTTTACCCGGAGGCTGGTCTAATTTTCCTTCCCGGGAGCTTGATCCA
 GCGTGGCTGATGGTGGACACTGTCATAGGAGAAGGAGAGTTTGGGGAAGTGTATCGAGGG
 ACCCTCAGGCTCCCCAGCCAGGACTGCAAGACTGTGGCCATTAAGACCTTAAAAGACACA
 TCCCCAGGTGGCCAGTGGTGGAACTTCCTTCGAGAGGCAACTATCATGGGCCAGTTTAGC
 CACCCGCATATTCTGCATCTGGAAGGCGTCGTCACAAAGCGAAAGCCGATCATGATCATC
 10 ACAGAAATTTATGGAGAATGCAGCCCTGGATGCCTTCCTGAGGGAGCGGGAGGACCAGCTG
 GTCCCTGGGCAGCTAGTGGCCATGCTGCAGGGCATAGCATCTGGCATGAACTACCTCAGT
 AATCACAATTATGTCCACCGGGACCTGGCTGCCAGAAACATCTTGGTGAATCAAAACCTG
 TGCTGCAAGGTGTCTGACTTTGGCCTGACTCGCCTCCTGGATGACTTTGATGGCACATAC
 GAAACCCAGGGAGGAAAGATCCCTATCCGTTGGACAGCCCCTGAAGCCATTGCCCATCGG
 15 ATCTTCACCACAGCCAGCGATGTGTGGAGCTTTGGGATTGTGATGTGGGAGGTGCTGAGC
 TTTGGGGACAAGCCTTATGGGGAGATGAGCAATCAGGAGGTTATGAAGAGCATTGAGGAT
 GGGTACCGGTTGCCCCCTCCTGTGGACTGCCCTGCCCTCTGTATGAGCTCATGAAGAAC
 TGCTGGGCATATGACCGTGCCCGCCGGCCACACTTCCAGAAGCTTCAGGCACATCTGGAG
 CAACTGCTTGCCAACCCCCACTCCCTGCGGACCATTGCCAACTTTGACCCAGGGTGACT
 20 CTTCGCCTGCCCAGCCTGAGTGGCTCAGATGGGATCCCGTATCGAACCGTCTCTGAGTGG
 CTCGAGTCCATACGCATGAAACGCTACATCCTGCACTTCCACTCGGCTGGGCTGGACACC
 ATGGAGTGTGTGCTGGAGCTGACCGCTGAGGACCTGACGCAGATGGGAATCACACTGCCC
 GGGCACCAGAAGCGCATTCTTTGCAGTATTCAGGGATTCAAGGACTGATCCCTCCTCTCA
 CCCCATGCCCAATCAGGGTGCAAGGAGCAAGGACGGGGCCAAGGTCGCTCATGGTCACTC
 25 CCTGCGCCCCCTTCCCACAACCTGCCAGACTAGGCTATCGGTGCTGCTTCTGCCCGCTTTA
 AGGAGAACCCTGCTCTGCACCCCAGAAAACCTCTTTGTTTTAAAAGGGAGGTGGGGGTAG
 AAGTAAAAGGATGATCATGGGAGGGAGCTCAGGGGTTAATATATATACATACATACAT
 ATATATATTGTTGTAAATAAACAGGAAATGATTTTCTGCCTCCATCCCACCCATCAGGGC
 TGCAGGCACT
 30 (SEQ ID NO: 28)

As used herein, the term "FABP5" refers to the gene encoding Fatty acid-binding protein 5. The
 terms "FABP5" and "Fatty acid-binding protein 5" include wild-type forms of the FABP5 gene, as well as
 variants (e.g., splice variants and polymorphisms) of wild-type FABP5. Examples of such variants are
 35 nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%,
 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type FABP5 nucleic acid sequence (e.g., SEQ
 ID NO: 29, ENA accession number M94856). SEQ ID NO: 29 is a wild-type gene sequence encoding
 FABP5 protein, and is shown below:

40 ACCGCCGACGCAGACCCCTCTCTGCACGCCAGCCCGCCCGCACCCACCATGGCCACAGTT
 CAGCAGCTGGAAGGAAGATGGCGCCTGGTGGACAGCAAAGGCTTTGATGAATACATGAAG

GAGCTAGGAGTGGGAATAGCTTTGCGAAAAATGGGCGCAATGGCCAAGCCAGATTGTATC
 ATCACTTGTGATGGTAAAAACCTCACCATAAAAACTGAGAGCACTTTGAAAACAACACAG
 TTTTCTTGTACCCTGGGAGAGAAGTTTGAAGAAACCACAGCTGATGGCAGAAAAACTCAG
 ACTGTCTGCAACTTTACAGATGGTGCATTGGTTCAGCATCAGGAGTGGGATGGGAAGGAA
 5 AGCACAATAACAAGAAAATTGAAAGATGGGAAATTAGTGGTGGAGTGTGTCATGAACAAT
 GTCACCTGTACTCGGATCTATGAAAAAGTAGAATAAAAAATTCCATCATCACTTTGGACAG
 GAGTTAATTAAGAGAATGACCAAGCTCAGTTCAATGAGCAAATCTCCATACTGTTTCTTT
 CTTTTTTTTTTCATTACTGTGTTCAATTATCTTTATCATAAACATTTTACATGCAGCTAT
 TTCAAAGTGTGTTGGATTAATTAGGATCATCCCTTTGGTTAATAAATAAATGTGTTTGTGCT
 10 (SEQ ID NO: 29)

As used herein, the term "FERMT2" refers to the gene encoding Fermitin family homolog 2. The terms "FERMT2" and "Fermitin family homolog 2" include wild-type forms of the FERMT2 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type FERMT2. Examples of such variants are
 15 nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type FERMT2 nucleic acid sequence (e.g., SEQ ID NO: 30, ENA accession number Z24725). SEQ ID NO: 30 is a wild-type gene sequence encoding FERMT2 protein, and is shown below:

20 CAAAAAGTGTGTGGAAAGGTGGATTGAGGGAGCGGGACCCCCGCGGGACCCGAGGGGGCG
 GCAGGCGGGGAACGGGGAGTCAGCCCGCGCTGTGTCTCGGGGCCGGCCGGCAGGAAGGAG
 CCATGGCTCTGGACGGGATAAGGATGCCAGATGGCTGCTACGCGGACGGGACGTGGGAAC
 TGAGTGTCCATGTGACGGACCTGAACCGCGATATCACCCCTGAGAGTGACCGGCGAGGTGC
 25 ACATTGGAGGCGTGATGCTTAAGCTGGTGGAGAACTCGATGTAAAAAAGATTGGTCTG
 ACCATGCTCTCTGGTGGGAAAAGAAGAGAACTTGGCTTCTGAAGACACATTGGACCTTAG
 ATAAGTATGGTATTTCAGGCAGATGCTAAGCTTCAGTTCACCCCTCAGCACAACTGCTCC
 GCCTGCAGCTTCCCAACATGAAGTATGTGAAGGTGAAAGTGAATTTCTCTGATAGAGTCT
 TCAAAGCTGTTTCTGACATCTGTAAGACTTTTAATATCAGACACCCCGAAGAACTTTCTC
 30 TCTTAAAGAAACCCAGAGATCCAACAAAGAAAAAAGAAGAAGCTAGATGACCAGTCTG
 AAGATGAGGCACTTGAATTAGAGGGGCCTCTTATCACTCCTGGATCAGGAAGTATATATT
 CAAGCCCAGGACTGTATAGTAAAACAATGACCCCCACTTATGATGCTCATGATGGAAGCC
 CCTTGTACCAACTTCTGCTTGGTTTGGTGACAGTGCTTTGTCAGAAGGCAATCCTGGTA
 TACTTGCTGTCAGTCAACCAATCACGTACACAGAAATCTTGGCAAAAATGTTCAAGCCTC
 35 AAGCTCTTCTTGATAAAGCAAAAATCAACCAAGGATGGCTTGATTCTCAAGATCTCTCA
 TGAACAAGATGTGAAGGAAAATGAGGCCTTGCTGCTCCGATTCAAGTATTACAGCTTTT
 TTGATTTGAATCCAAAGTATGATGCAATCAGAATCAATCAGCTTTATGAGCAGGCCAAAT
 GGGCCATTCTCCTGGAAGAGATTGAATGCACAGAAGAAGAAATGATGATGTTTGCAGCCC
 TGCAGTATCATATCAATAAGCTGTCAATCATGACATCAGAGAATCATTTGAACAACAGTG
 40 ACAAAGAAGTTGATGAAGTTGATGCTGCCCTTTCAGACCTGGAGATTACTCTGGAAGGGG
 GTAAACGTCAACAATTTTGGGTGACATTACTTCCATTCTGAACTTGCTGACTACATTA
 AAGTTTTCAAGCCAAAAAAGCTGACTCTGAAAGGTTACAAACAATATTGGTGCACCTTCA

AAGACACATCCATTTCTTGTTATAAGAGCAAAGAAGAATCCAGTGGCACACCAGCTCATC
 AGATGAACCTCAGGGGATGTGAAGTTACCCCAGATGTAAACATTTCAAGGCCAAAAATTTA
 ACATTAAACTCCTGATTCCAGTTGCAGAAGGCATGAATGAAATCTGGCTTCGTTGTGACA
 ATGAAAAACAGTATGCACACTGGATGGCAGCCTGCAGATTAGCCTCCAAAGGCAAGACCA
 5 TGGCGGACAGTTCTTACAACCTAGAAGTTCAGAATATTCTTTCCTTTCTGAAGATGCAGC
 ATTTAAACCCAGATCCTCAGTTAATACCAGAGCAGATCACGACTGATATAACTCCTGAAT
 GTTTGGTGTCTCCCCGCTATCTAAAAAAGTATAAGAACAAGCAGATAACAGCGAGAATCT
 TGGAGGCCCATCAGAATGTAGCTCAGATGAGTCTAATTGAAGCCAAGATGAGATTTATTC
 AAGCTTGGCAGTCACTACCTGAATTTGGCATCACTCACTTCATTGCAAGGTTCCAAGGGG
 10 GCAAAAAAGAAGAAGTATTGGAATTGCATACAACAGACTGATTCGGATGGATGCCAGCA
 CTGGAGATGCAATTAACATGGCGTTTCAGCAACATGAAACAGTGAATGTCAACTGGG
 AATCAAAATGGTCACCGTAGAGTTTGCAGATGAAGTACGATTGTCCTTCATTTGTACTG
 AAGTAGATTGCAAAGTGTTTCATGAATTCATTGGTGGCTACATATTTCTCTCAACACGTG
 CAAAAGACCAAAACGAGAGTTTAGATGAAGAGATGTTCTACAACTTACCAGTGGTTGGG
 15 TGTGAATAGAAATACTGTTTAATGAACTCCACGGCCATAACAATTTAACTTTAAAG
 CTGTTTGTATATGCTGCTTAATAAAGTAAGCTTGAAATTTATCATTTTATCATGAAAAC
 TTCTTTGCCTTACCAGACCAGTTAATATGTGCACTAAACAAGCACGACTATTAATCTATC
 ATGTTATGATATAATAAACTTGAATTTGGCACACATTCCTTAGGGCCATGAATTGAAAAC
 TGAAATAGTGGGCAAAACAGGAACAAACCATCACTGATTTACTGATTTAAGCTAGCCAAA
 20 CTGTAAGAAACAAGCCATCTATTTTAAAGCTATCCAGGGCTTAACCTATATGAACTCTAT
 TTATCATGTCTAATGCATGTGATTTAATGTATGTTTAATTTGATATCATGTTTTAAATA
 TCCTACTTCTGGTAGCCATTTAATTCCTCCCCCTACCCCCAAATAAATCAGGCATGCAGG
 AGGCCTGATATTTAGTAATGTCATTGTGTTTGACCTTGAAGGAAAATGCTATTAGTCCGT
 CGTGCTTNATTTGTTTTTGTCTTGAATAAGCATGTTATGTATATNGTCTCGTGTTTTTA
 25 TTTTACACCATATTGTATTACACTTTTAGTATTCACCAGCATAANCACTGTCTGCCTAA
 AATATGCAACTCTTGCATTACAATATGAAGTAAAGTTCTATGAAGTATGCATTTTGTGT
 AACTAATGTAAAAACACAAATTTTATAAAATTGTACAGTTTTTTAAAACTACTCACAAC
 TAGCAGATGGCTTAAATGTAGCAATCTCTGCGTTAATTAATGCCTTTAAGAGATATAAT
 TAACGTGCAGTTTTAATATCTACTAAATTAAGAATGACTTCATTATGATCATGATTGCC
 30 ACAATGTCCTTAACTCTAATGCCTGGACTGGCCATGTTCTAGTCTGTTGCGCTGTTACAA
 TCTGTATTGGTGCTAGTCAGAAAATTCCTAGCTCACATAGCCCAAAGGGTGCAGGGGAG
 AGGTGGATTACCAGTATTGTTCAATAATCCATGGTTCAAAGACTGTATAAATGCATTTTA
 TTTTAAATAAAAGCAAACTTTTATTTAAA
 (SEQ ID NO: 30)

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As used herein, the term "FTH1" refers to the gene encoding Ferritin heavy chain. The terms
 "FTH1" and "Ferritin heavy chain" include wild-type forms of the FTH1 gene, as well as variants (e.g.,
 splice variants and polymorphisms) of wild-type FTH1. Examples of such variants are nucleic acids
 having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%,
 40 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,
 98%, 99%, or 99.9% identity, or more) to a wild-type FTH1 nucleic acid sequence (e.g., SEQ ID NO: 31,

ENA accession number X00318). SEQ ID NO: 31 is a wild-type gene sequence encoding FTH1 protein, and is shown below:

5 CACCGCACCTCGGACTGCCCCAAGGCCCCCGCCGCTCCAGCGCCGCGCAGCCACCGCCGC
CGCCGCGCCTCTCCTTAGTCGCCGCCATGACGACCGCGTCCACCTCGCAGGTGCGCCAGAATA
CCACCAGGACTCAGAGGCCGCCATCAACCGCCAGATCAACCTGGAGCTCTACGCCTCCTACGTTTA
CCTGTCCATGTCTTACTACTTTGACCGCGATGATGTGGCTTTGAAGAACTTTGCCAAATACTTTCTTC
ACCAATCTCATGAGGAGAGGGAACATGCTGAGAACTGATGAAGCTGCAGAACCAACGAGGTGGCC
GAATCTTCCTTCAGGATATCAAGAAACCAGACTGTGATGACTGGGAGAGCGGGCTGAATGCAATGGA
10 GTGTGCATTACATTTGGAAAAAATGTGAATCAGTCACTACTGGAAGTGCACAACTGGCCACTGACA
AAAATGACCCCCATTTGTGTGACTTCATTGAGACACATTACCTGAATGAGCAGGTGAAAGCCATCAAA
GAATTGGGTGACCACGTGACCAACTTGCGCAAGATGGGAGCGCCGAATCTGGCTTGCGGAATAT
CTCTTTGACAAGCACACCTGGGAGACAGTGATAATGAAAGCTAAGCCTCGGGCTAATTTCCCATAGC
CGTGGGGTGACTTCCTGGTCACCAAGGCAGTGCATGCATGTTGGGGTTTCCTTTACCTTTTCTATAA
15 GTTGTACCAAAACATCCACTTAAGTTCTTTGATTTGTACCATTCTTCAAATAAAGAAATTTGGTACCC
(SEQ ID NO: 31)

As used herein, the term "GNAS" refers to the gene encoding Guanine nucleotide-binding protein G(s) subunit alpha isoforms XLas. The terms "GNAS" and "Guanine nucleotide-binding protein G(s)
20 subunit alpha isoforms XLas" include wild-type forms of the GNAS gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type GNAS. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type GNAS nucleic acid sequence (e.g., SEQ ID NO: 32, ENA
25 accession number X04408). SEQ ID NO: 32 is a wild-type gene sequence encoding GNAS protein, and is shown below:

GCGGGCGTGCTGCCGCCGCTGCCGCCGCCGCCGCGAGCCCGGCCGCGCCCCGCCGCCGCCG
CCGCCGCCATGGGCTGCCTCGGGAACAGTAAGACCGAGGACCAGCGCAACGAGGAGAAGG
30 CGCAGCGTGAGGCCAACAAAAAGATCGAGAAGCAGCTGCAGAAGGACAAGCAGGTCTACC
GGGCCACGCACCGCCTGCTGCTGCTGGGTGCTGGAGAATCTGGTAAAAGCACCATTGTGA
AGCAGATGAGGATCCTGCATGTTAATGGGTTTAAATGGAGAGGGCGGCGAAGAGGACCCGC
AGGCTGCAAGGAGCAACAGCGATGGTGAGAAGGCAACCAAGTGCAGGACATCAAAAACA
ACCTGAAAGAGGCGATTGAAACCATTGTGGCCGCCATGAGCAACCTGGTGCCCCCGTGG
35 AGCTGGCCAACCCCGAGAACCAGTTCAGAGTGGACTACATCCTGAGTGTGATGAACGTGC
CTGACTTTGACTTCCCTCCCGAATTCTATGAGCATGCCAAGGCTCTGTGGGAGGATGAAG
GAGTGCGTGCCTGCTACGAACGCTCCAACGAGTACCAGCTGATTGACTGTGCCAGTACT
TCCTGGACAAGATCGACGTGATCAAGCAGGCTGACTATGTGCCGAGCGATCAGGACCTGC
TTCGCTGCCGTGTCCTGACTTCTGGAATCTTTGAGACCAAGTTCCAGGTGGACAAAGTCA
40 ACTTCCACATGTTTGACGTGGGTGGCCAGCGCGATGAACGCCGCAAGTGGATCCAGTGCT
TCAACGATGTGACTGCCATCATCTTCGTGGTGGCCAGCAGCAGCTACAACATGGTCATCC
GGGAGGACAACCAGACCAACCGCCTGCAGGAGGCTCTGAACCTCTTCAAGAGCATCTGGA

ACAACAGATGGCTGCGCACCATCTCTGTGATCCTGTTCTCAACAAGCAAGATCTGCTCG
 CTGAGAAAGTCCTTGCTGGGAAATCGAAGATTGAGGACTACTTTCCAGAATTTGCTCGCT
 AACTACTCCTGAGGATGCTACTCCCCGAGCCCGGAGAGGACCCACGCGTGACCCGGGCCA
 AGTACTTCATTGAGATGAGTTTCTGAGGATCAGCACTGCCAGTGAGATGGGCGTCACT
 5 ACTGCTACCCTCATTTCACCTGCGCTGTGGACACTGAGAACATCCGCCGTGTGTTCAACG
 ACTGCCGTGACATCATTGAGCGCATGCACCTTCGTCAGTACGAGCTGCTCTAAGAAGGGA
 ACCCCCAAATTTAATTAAAGCCTTAAGCACAATTAATTAAGTGAACGTAATTGTACA
 AGCAGTTAATCACCCACCATAGGGCATGATTAACAAAGCAACCTTTCCCTTCCCCCGAGT
 GATTTTGCAGAACCCCTTTTCCCTTCAGCTTGCTTAGATGTTCCAAATTTAGAAAGCTT
 10 AAGGCGGCCTACAGAAAAAGGAAAAAGGCCACAAAAGTTCCCTCTCACTTTAGTAAAA
 ATAAATAAACAGCAGCAGCAAAATAAAATGAAATAAAAGAAACAAATGAAATAAAT
 ATTGTGTTGTGCAGCATTAATAAAAAATCAAAATAAAATTAATGTGAGCAAAG
 (SEQ ID NO: 32)

15 As used herein, the term "GRN" refers to the gene encoding Progranulin. The terms "GRN" and
 "Progranulin" include wild-type forms of the GRN gene, as well as variants (e.g., splice variants and
 polymorphisms) of wild-type GRN. Examples of such variants are nucleic acids having at least 70%
 sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%,
 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9%
 20 identity, or more) to a wild-type GRN nucleic acid sequence (e.g., SEQ ID NO: 33, ENA accession
 number X62320). SEQ ID NO: 33 is a wild-type gene sequence encoding GRN protein, and is shown
 below:

GCTGCTGCCCAAGGACCGCGGAGTCGGACGCAGGCAGACCATGTGGACCCTGGTGAGCTG
 25 GGTGGCCTTAACAGCAGGGCTGGTGGCTGGAACGCGGTGCCAGATGGTCAGTTCTGCCC
 TGTGGCCTGCTGCCTGGACCCCGGAGGAGCCAGCTACAGCTGCTGCCGTCCCCTTCTGGA
 CAAATGGCCCACAACACTGAGCAGGCATCTGGGTGGCCCCTGCCAGGTTGATGCCCACTG
 CTCTGCCGGCCACTCCTGCATCTTTACCGTCTCAGGGACTTCCAGTTGCTGCCCCCTTCCC
 AGAGGCCGTGGCATGCGGGGATGGCCATCACTGCTGCCACGCGGGCTTCCACTGCAGTGC
 30 AGACGGGCGATCCTGCTTCAAAGATCAGGTAACAACCTCCGTGGGTGCCATCCAGTGCCC
 TGATAGTCAGTTCGAATGCCCGGACTTCTCCACGTGCTGTGTTATGGTCGATGGCTCCTG
 GGGGTGCTGCCCCATGCCCCAGGCTTCTGCTGTGAAGACAGGGTGCACTGCTGTCCGCA
 CGGTGCCTTCTGCGACCTGGTTCACACCCGCTGCATCACACCCACGGGCACCCACCCCT
 GGCAAAGAAGCTCCCTGCCAGAGGACTAACAGGGCAGTGGCCTTGTCCAGCTCGGTCAT
 35 GTGTCCGGACGCACGGTCCCGGTGCCCTGATGGTTCTACCTGCTGTGAGCTGCCCAGTGG
 GAAGTATGGCTGCTGCCCAATGCCCAACGCCACCTGCTGCTCCGATCACCTGCACTGCTG
 CCCCCAAGACACTGTGTGTGACCTGATCCAGAGTAAGTGCCTCTCCAAGGAGAACGCTAC
 CACGGACCTCCTACTAAGCTGCCTGCGCACACAGTGGGGGATGTGAAATGTGACATGGA
 GGTGAGCTGCCAGATGGCTATACCTGCTGCCGTCTACAGTCGGGGGCCTGGGGCTGCTG
 40 CCCTTTTACCCAGGCTGTGTGCTGTGAGGACCACATACACTGCTGTCCCGCGGGGTTTAC
 GTGTGACACGCAGAAGGGTACCTGTGAACAGGGGCCCCACCAGGTGCCCTGGATGGAGAA
 GGCCCCAGCTCACCTCAGCCTGCCAGACCCACAAGCCTTGAAGAGAGATGTCCCCTGTGA

TAATGTCAGCAGCTGTCCCTCCTCCGATACCTGCTGCCAACTCACGTCTGGGGAGTGGGG
 CTGCTGTCCAATCCCAGAGGCTGTCTGCTGCTCGGACCACCAGCACTGCTGCCCCCAGGG
 CTACACGTGTGTAGCTGAGGGGCAGTGTGAGCGAGGAAGCGAGATCGTGGCTGGACTGGA
 GAAGATGCCTGCCCCGCCGGGCTTCCTTATCCCACCCCAGAGACATCGGCTGTGACCAGCA
 5 CACCAGCTGCCCCGGTGGGGCAGACCTGCTGCCCCGAGCCTGGGTGGGAGCTGGGCCTGCTG
 CCAGTTGCCCCATGCTGTGTGCTGCGAGGATCGCCAGCACTGCTGCCCCGGCTGGCTACAC
 CTGCAACGTGAAGGCTCGATCCTGCGAGAAGGAAGTGGTCTCTGCCAGCCTGCCACCTT
 CCTGGCCCGTAGCCCTCACGTGGGTGTGAAGGACGTGGAGTGTGGGGAAGGACACTTCTG
 CCATGATAACCAGACCTGCTGCCGAGACAACCGACAGGGCTGGGCCTGCTGTCCCTACCG
 10 CCAGGGCGTCTGTTGTGCTGATCGGCGCCACTGCTGTCTGCTGGCTTCCGCTGCGCAGC
 CAGGGGTACCAAGTGTTCGCGCAGGGAGGCCCGCGCTGGGACGCCCCCTTTGAGGGACCC
 AGCCTTGAGACAGCTGCTGTGAGGGACAGTACTGAAGACTCTGCAGCCCTCGGGACCCCA
 CTCGGAGGGTGCCCTCTGCTCAGGCCTCCCTAGCACCTCCCCCTAACCAATTCTCCCTG
 GACCCCATCTGAGCTCCCCATCACCATGGGAGGTGGGGCCTCAATCTAAGGCCTTCCCT
 15 GTCAGAAGGGGGTTGTGGCAAAGCCACATTACAAGCTGCCATCCCCTCCCCGTTTCAGT
 GGACCCTGTGGCCAGGTGCTTTTCCCTATCCACAGGGGTGTTTGTGTGTGTGCGCGTGTG
 CGTTTCAATAAAGTTTGTACACTTTCAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
 (SEQ ID NO: 33)

20 As used herein, the term "HBEGF" refers to the gene encoding Heparin Binding EGF Like Growth
 Factor. The terms "HBEGF" and "Heparin Binding EGF Like Growth Factor" include wild-type forms of
 the HBEGF gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type HBEGF.
 Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%,
 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%,
 25 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type HBEGF
 nucleic acid sequence (e.g., SEQ ID NO: 34, NCBI Reference Sequence: NM_001945.2). SEQ ID NO:
 34 is a wild-type gene sequence encoding HBEGF protein, and is shown below:

ATTCGGCCGAAGGAGCTACGCGGGCCACGCTGCTGGCTGGCCTGACCTAGGCGCGCGGGGTCTGG
 30 GCGGCCGCGCGGGCGGGCTGAGTGAGCAAGACAAGACACTCAAGAAGAGCGAGCTGCGCCTGGG
 TCCCGGCCAGGCTTGACGCGAGAGGCGGGCGGCAGACGGTGCCCGGCGGAATCTCCTGAGCTCC
 GCCGCCAGCTCTGGTGCCAGCGCCAGTGGCCGCCGCTTCGAAAGTGAAGTGGTGCCTCGCCGCC
 TCCTCTCGGTGCGGGACCATGAAGCTGCTGCCGTCGGTGGTGTGCTGAAGCTCTTTCTGGCTGCAGTT
 CTCTCGGCACTGGTGAAGTGGCGAGAGCCTGGAGCGGCTTCGGAGAGGGCTAGCTGCTGGAACCAG
 35 CAACCCGGACCCTCCCACTGTATCCACGGACCAGCTGCTACCCCTAGGAGGCGGCCGGGACCGGA
 AAGTCCGTGACTTGCAAGAGGCAGATCTGGACCTTTTGAAGTCACTTTATCCTCCAAGCCACAAGC
 ACTGGCCACACCAAACAAGGAGGAGCACGGGAAAAGAAAGAAAGGCAAGGGGCTAGGGAAGA
 AGAGGGACCCATGTCTTCGGAATACAAGGACTTCTGCATCCATGGAGAATGCAAATATGTGAAGGA
 GCTCCGGGCTCCCTCCTGCATCTGCCACCCGGGTACCATGGAGAGAGGTGTCATGGGCTGAGCCT
 40 CCCAGTGGAATCGCTTATATACCTATGACCACACAACCATCCTGGCCGTGGTGGCTGTGGTGTG
 TCATCTGTCTGTCTGCTGGTTCATCGTGGGGCTTCTCATGTTTAGGTACCATAGGAGAGGAGGTTATG
 ATGTGGAAATGAAGAGAAAGTGAAGTTGGGCATGACTAATCCCACTGAGAGAGACTTGTGCTCAA

GGAATCGGCTGGGGACTGCTACCTCTGAGAAGACACAAGGTGATTTGAGACTGCAGAGGGGAAAGA
 CTTCCATCTAGTCACAAAGACTCCTTCGTCCCCAGTTGCCGTCTAGGATTGGGCCTCCCATAATTGC
 TTTGCCAAAATACCAGAGCCTTCAAGTGCCAAACAGAGTATGTCCGATGGTATCTGGGTAAGAAGAA
 AGCAAAAGCAAGGGACCTTCATGCCCTTCTGATTCCCCTCCACCAAACCCCACTTCCCCTCATAAGT
 5 TTGTTTAAACACTTATCTTCTGGATTAGAATGCCGGTTAAATTCCATATGCTCCAGGATCTTTGACTGA
 AAAAAAAAAAGAAGAAGAAGAAGGAGAGCAAGAAGGAAAGATTTGTGAAGTGAAGAAAGCAACAAA
 GATTGAGAAGCCATGTACTCAAGTACCACCAAGGGATCTGCCATTGGGACCCTCCAGTGCTGGATTT
 GATGAGTTAACTGTGAAATACCACAAGCCTGAGAACTGAATTTTGGGACTTCTACCCAGATGGAAAAA
 TAACAACATTTTTTGTGTTGTTGTTGTTGTAAATGCCTCTTAAATTATATATTTATTTATTCTATGTATGT
 10 TAATTTATTTAGTTTTTAACAATCTAACAATAATATTTCAAGTGCCCTAGACTGTTACTTTGGCAATTTCC
 TGGCCCTCCACTCCTCATCCCCACAATCTGGCTTAGTGCCACCCACCTTTGCCACAAAGCTAGGATG
 GTTCTGTGACCCATCTGTAGTAATTTATTGTCTGTCTACATTTCTGCAGATCTCCGTGGTCAGAGTG
 CCACTGCGGGAGCTCTGTATGGTCAGGATGTAGGGGTTAACTTGGTCAGAGCCACTCTATGAGTTG
 GACTTCAGTCTTGCCTAGGCGATTTTGTCTACCATTTGTGTTTTGAAAGCCCAAGGTGCTGATGTCAA
 15 AGTGTAACAGATATCAGTGTCTCCCCGTGTCTCTCCCTGCCAAGTCTCAGAAGAGGTTGGGCTTCC
 ATGCCTGTAGCTTTCTGTGTCCTCACCCCCATGGCCCCAGGCCACAGCGTGGGAACTCACTTTC
 CCTTGTGTCAAGACATTTCTCTAACTCCTGCCATTCTTCTGGTGCTACTCCATGCAGGGGTGAGTGCA
 GCAGAGGACAGTCTGGAGAAGGTATTAGCAAAGCAAAAGGCTGAGAAGGAACAGGGAACATTGGAG
 CTGACTGTTCTTGGTAACTGATTACCTGCCAATTGCTACCGAGAAGGTTGGAGGTGGGGAAGGCTTT
 20 GTATAATCCCACCCACCTACCAAAACGATGAAGTTATGCTGTCATGGTCCTTTCTGGAAGTTTCTGG
 TGCCATTTCTGAACTGTTACAACTTGTATTTCCAAACCTGGTTCATATTTATACTTTGCAATCCAAATAA
 AGATAACCCTTATTCCATAAAAAAAAAAAAAAAAAAAAAAAAAA
 (SEQ ID NO: 34)

As used herein, the term "HLA-DRB1" refers to the gene encoding HLA class II histocompatibility
 25 antigen, DRB1 beta chain. The terms "HLA-DRB1" and "HLA class II histocompatibility antigen, DRB1
 beta chain" include wild-type forms of the HLA-DRB1 gene, as well as variants (e.g., splice variants and
 polymorphisms) of wild-type HLA-DRB1. Examples of such variants are nucleic acids having at least
 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%,
 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or
 30 99.9% identity, or more) to a wild-type HLA-DRB1 nucleic acid sequence (e.g., SEQ ID NO: 35, ENA
 accession number X00699). SEQ ID NO: 35 is a wild-type gene sequence encoding HLA-DRB1 protein,
 and is shown below:

CTGCTCTGGCCCCTGGTCCTGTCTGTTCTCCAGCATGGTGTGTCTGAGGCTCCCTGGAG
 35 GCTCCTGCATGGCAGTTCTGACAGTGACACTGATGGTGCTGAGCTCCCCACTGGCTTTGG
 CTGGGGACACCAGACCAGTTTCTTGGAGTACTCTACGTCTGAGTGTCAATTTCTTCAATG
 GGACGGAGCGGGTGCGGTACCTGGACAGATACTTCCATAACCAGGAGGAGAACGTGCGCT
 TCGACAGCGACGTGGGGGAGTTCCGGGCGGTGACGGAGCTGGGGCGGCCTGATGCCGAGT
 ACTGGAACAGCCAGAAGGACCTCCTGGAGCAGAAGCGGGGCCGGGTGGACAACACTACTGCA
 40 GACACAACACTACGGGGTTGTGGAGAGCTTACAGTGCAGCGGCGAGTCCATCCTAAGGTGA
 CTGTGTATCCTTCAAAGACCCAGCCCCTGCAGCACCATAACCTCCTGGTCTGTTCTGTGA
 GTGGTTTCTATCCAGGCAGCATTGAAGTCAGGTGGTTCCGGAATGGCCAGGAAGAGAAGA

CTGGGGTGGTGTCCACAGGCCTGATCCACAATGGAGACTGGACCTTCCAGACCCTGGTGA
 TGCTGGAAACAGTTCCCTCGGAGTGGAGAGGTTTACACCTGCCAAGTGGAGCACCCAAGCG
 TGACAAGCCCTCTCACAGTGAATGGAGAGCACGGTCTGAATCTGCACAGAGCAAGATGC
 TGAGTGGAGTCGGGGGCTTTGTGCTGGGCCTGCTCTTCTTGGGGCCGGGCTGTTTCATCT
 5 ACTTCAGGAATCAGAAAGGACACTCTGGACTTCAGCCAAGAGGATTCTGAGCTGAAGTG
 CAGATGACACATTCAAAGAAGAACTTTCTGCCCCAGCTTTGCAGGATGAAAAGCTTTCCC
 TCCTGGCTGTTATTCTTCCACAAGAGAGGGCTTTCTCAGGACCTGGTTGCTACTGGTTCA
 GCAACTGCAGAAAATGTCCTCCCTTGTGGCTTCTCAGCTCCTGTTCTTGGCCTGAAGCC
 CCACAGCTTTGATGGCAGTGCCTCATCTTCAACTTTTGTGCTCCCCTTTGCCTAAACCCT
 10 ATGGCCTCCTGTGCATCTGTACTCACCTGTACCA
 (SEQ ID NO: 35)

As used herein, the term "HLA-DRB5" refers to the gene encoding HLA class II histocompatibility antigen, DR beta 5 chain. The terms "HLA-DRB5" and "HLA class II histocompatibility antigen, DR beta 5
 15 chain" include wild-type forms of the HLA-DRB5 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type HLA-DRB5. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type HLA-DRB5 nucleic acid sequence (e.g., SEQ ID NO: 36, ENA
 20 accession number M20429). SEQ ID NO: 36 is a wild-type gene sequence encoding HLA-DRB5 protein, and is shown below:

CCAGCATGGTGTGTCTGAAGCTCCCTGGAGGTTCTACATGGCAAAGCTGACAGTGACAC
 TGATGGTGTCTGAGCTCCCCACTGGCTTTGGCTGGGGACACCCGACCACGTTTCTTGCAGC
 25 AGGATAAGTATGAGTGTCAATTTCTTCAACGGGACGGAGCGGGTGCGGTTCTTGCACAGAG
 ACATCTATAACCAAGAGGAGGACTTGCGCTTCGACAGCGACGTGGGGGAGTACCGGGCGG
 TGACGGAGCTGGGGCGGCCTGACGCTGAGTACTGGAACAGCCAGAAGGACTTCCTGGAAG
 ACAGGCGCGCCGCGGTGGACACCTACTGCAGACACAACCTACGGGGTTGGTGAGAGCTTCA
 CAGTGCAGCGGCGAGTTGAGCCTAAGGTGACTGTGTATCCTGCAAGGACCCAGACCCTGC
 30 AGCACCACAACCTCCTGGTCTGCTCTGTGAATGGTTTCTATCCAGGCAGCATTGAAGTCA
 GGTGGTTCCGGAACAGCCAGGAAGAGAAGGCTGGGGTGGTGTCCACAGGCCTGATTGAGA
 ATGGAGACTGGACCTTCCAGACCCTGGTGATGCTGGAAACAGTTCCTCGAAGTGGAGAGG
 TTTACACCTGCCAAGTGGAGCACCCAAGCGTGACGAGCCCTCTCACAGTGAATGGAGAG
 CACAGTCTGAATCTGCACAGAGCAAGATGCTGAGTGGAGTCGGGGGCTTTGTGCTGGGCC
 35 TGCTCTTCTTGGGGCCGGGCTATTCATCTACTTCAAGAATCAGAAAGGGCACTCTGGAC
 TTCACCAACAGGACTCGTGAGCTGAAGTGCAGATGACCACATTCAAGGGGGAACCTTCT
 GCCCCAGCTTTGCATGATGAAAAGCTTTCTGCTTGGCTCTTATTCTTCCACAAGAGAGG
 ACTTTCTCAGGCCCTGGTTGCTACCGGTTAGCAACTCTGCAGAAAATGTCCATCCTTGT
 GGCTTCCTCAGCTCCTGCCCCCTTGGCCTGAAGTCCCAGCATTGATGGCAGTGCCTCATCT
 40 TCAACTTTAGTGCTCCCCCTTACCTAACCTACGGCCTCCCATGCATCTGTACTCCCCCT
 GTGTGCCACAAATGCACTACGTTATTAAATTTTTCTGAAGCCCAGAGTTAAAAATCATCT
 GTCCACCTGGCTCCAAAGACAAAAAATAAAAA

(SEQ ID NO: 36)

As used herein, the term "IFIT1" refers to the gene encoding Interferon-induced protein with tetratricopeptide repeats 1. The terms "IFIT1" and "Interferon-induced protein with tetratricopeptide repeats 1" include wild-type forms of the IFIT1 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type IFIT1. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type IFIT1 nucleic acid sequence (e.g., SEQ ID NO: 37, ENA accession number X03557). SEQ ID NO: 37 is a wild-type gene sequence encoding IFIT1 protein, and is shown below:

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CCAGATCTCAGAGGAGCCTGGCTAAGCAAAACCCTGCAGAACGGCTGCCTAATTTACAGC
AACCATGAGTACAAATGGTGATGATCATCAGGTCAAGGATAGTCTGGAGCAATTGAGATG
15 TCACTTTACATGGGAGTTATCCATTGATGACGATGAAATGCCTGATTTAGAAAACAGAGT
CTTGATCAGATTGAATTCCTAGACACCAAATACAGTGTGGGAATACACAACCTACTAGC
CTATGTGAAACACCTGAAAGGCCAGAATGAGGAAGCCCTGAAGAGCTTAAAAGAAGCTGA
AAACTTAATGCAGGAAGAACATGACAACCAAGCAAATGTGAGGAGTCTGGTGACCTGGGG
CAACTTTGCCTGGATGTATTACCACATGGGCAGACTGGCAGAAGCCCAGACTTACCTGGA
20 CAAGGTGGAGAACATTTGCAAGAAGCTTTCAAATCCCTTCCGCTATAGAATGGAGTGTCC
AGAAATAGACTGTGAGGAAGGATGGGCCTTGCTGAAGTGTGGAGGAAAGAATTATGAACG
GGCCAAGGCCTGCTTTGAAAAGGTGCTTGAAGTGGACCCTGAAAACCCTGAATCCAGCGC
TGGGTATGCGATCTCTGCCTATCGCCTGGATGGCTTTAAATTAGCCACAAAAAATCACAA
GCCATTTTCTTTGCTTCCCCTAAGGCAGGCTGTCCGCTTAAATCCAGACAATGGATATAT
25 TAAGGTTCTCCTTGCCCTGAAGCTTCAGGATGAAGGACAGGAAGCTGAAGGAGAAAAGTA
CATTGAAGAAGCTCTAGCCAACATGTCTCACAGACCTATGTCTTTTCGATATGCAGCCAA
GTTTTACCGAAGAAAAGGCTCTGTGGATAAAGCTCTTGAGTTATTA AAAAGGCCTTGCA
GGAAACACCCACTTCTGTCTTACTGCATCACCAGATAGGGCTTTGCTACAAGGCACAAAT
GATCCAAATCAAGGAGGCTACAAAAGGGCAGCCTAGAGGGCAGAACAGAGAAAAGCTAGA
30 CAAAATGATAAGATCAGCCATATTTCAATTTGAATCTGCAGTGGAAAAAAGCCACATT
TGAGGTGGCTCATCTAGACCTGGCAAGAATGTATATAGAAGCAGGCAATCACAGAAAAGC
TGAAGAGAATTTTCAAAAATTGTTATGCATGAAACCAGTGGTAGAAGAAACAATGCAAGA
CATACATTTCTACTATGGTCGTTTTAGGAATTTCAAAGAAATCTGACGTCAATGCAAT
TATCCATTATTTAAAAGCTATAAAAATAGAACAGGCATCATTAACAAGGGATAAAAGTAT
35 CAATTCTTTGAAGAAATTGGTTTTAAGGAACTTCGGAGAAAGGCATTAGATCTGGAAAG
CTTGAGCCTCCTTGGGTTTCGTCTACAAATTGGAAGGAAATATGAATGAAGCCCTGGAGTA
CTATGAGCGGGCCCTGAGACTGGCTGCTGACTTTGAGAACTCTGTGAGACAAGGTCCTTA
GGCACCCAGATATCAGCCACTTTCACATTTCAATTTATGCTAACATTTACTAATC
ATCTTTTCTGCTTACTGTTTTTCAGAAACATTATAATTCACTGTAATGATGTAATTCTTGA
40 ATAATAAATCTGACAAAATATT

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(SEQ ID NO: 37)

As used herein, the term "IFIT3" refers to the gene encoding Interferon-induced protein with tetratricopeptide repeats 3. The terms "IFIT3" and "Interferon-induced protein with tetratricopeptide repeats 3" include wild-type forms of the IFIT3 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type IFIT3. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type IFIT3 nucleic acid sequence (e.g., SEQ ID NO: 38, ENA accession number AF026939). SEQ ID NO: 38 is a wild-type gene sequence encoding IFIT3 protein, and is shown below:

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GTGGAAACCTCTTCAGCATTTGCTTGGAATCAGTAAGCTAAAAACAAAATCAACCGGGAC
CCCAGCTTTTCAGAACTGCAGGGAAACAGCCATCATGAGTGAGGTCACCAAGAATTCCCT
GGAGAAAATCCTCCACAGCTGAAATGCCATTTACCTGGAACCTATTCAAGGAAGACAG
TGTCTCAAGGGATCTAGAAGATAGAGTGTGTAACCAGATTGAATTTTTAAACACTGAGTT
CAAAGCTACAATGTACAACCTTGTTGGCCTACATAAAACACCTAGATGGTAACAACGAGGC
AGCCCTGGAATGCTTACGGCAAGCTGAAGAGTTAATCCAGCAAGAACATGCTGACCAAGC
AGAAATCAGAAGTCTAGTCACTTGGGGAAACTACGCCTGGGTCTACTATCACTTGGGCAG
ACTCTCAGATGCTCAGATTTATGTAGATAAGGTGAAACAAACCTGCAAGAAATTTTCAA
TCCATACAGTATTGAGTATTCTGAACTTGACTGTGAGGAAGGGTGGACACAACCTGAAGTG
TGGAAGAAATGAAAGGGCGAAGGTGTGTTTTGAGAAGGCTCTGGAAGAAAAGCCCAACAA
CCCAGAATTCTCCTCTGGACTGGCAATTGCGATGTACCATCTGGATAATCACCAGAGAA
ACAGTTCTCTACTGATGTTTTGAAGCAGGCCATTGAGCTGAGTCCTGATAACCAATACGT
CAAGGTTCTCTTGGGCCTGAACTGCAGAAGATGAATAAAGAAGCTGAAGGAGAGCAGTT
TGTTGAAGAAGCCTTGAAAAGTCTCCTTGCCAAACAGATGTCCTCCGCAGTGCAGCCAA
ATTTTACAGAAGAAAAGGTGACCTAGACAAAGCTATTGAACTGTTTCAACGGGTGTTGGA
ATCCACACCAAACAATGGCTACCTCTATCACCAGATTGGGTGCTGCTACAAGGCAAAAGT
AAGACAAATGCAGAATACAGGAGAATCTGAAGCTAGTGGAATAAAGAGATGATTGAAGC
ACTAAAGCAATATGCTATGGACTATTGGAATAAAGCTCTTGAGAAGGGACTGAATCCTCT
GAATGCATACTCCGATCTCGCTGAGTTCCTGGAGACGGAATGTTATCAGACACCATTCAA
TAAGGAAGTCCCTGATGCTGAAAAGCAACAATCCCATCAGCGCTACTGCAACCTTCAGAA
ATATAATGGGAAGTCTGAAGACACTGCTGTGCAACATGGTTTAGAGGGTTTGTCCATAAG
CAAAAAATCAACTGACAAGGAAGAGATCAAAGACCAACCACAGAATGTATCCGAAAATCT
GCTTCCACAAAATGCACCAAATTATTGGTATCTTCAAGGATTAATTCATAAGCAGAATGG
AGATCTGCTGCAAGCAGCCAAATGTTATGAGAAGGAACTGGGCCGCCTGCTAAGGGATGC
CCCTTCAGGCATAGGCAGTATTTTCTGTGAGCATCTGAGCTTGAGGATGGTAGTGAGGA
AATGGGGCCAGGGCGCAGTCAGCTCCAGTCCCAGAGAGCTCCTCTCTAACTCAGAGCAACT
GAACTGAGACAGAGGAGGAAAACAGAGCATCAGAAGCCTGCAGTGGTGGTTGTGACGGGT
AGGAGGATAGGAAGACAGGGGGGCCCAACCTGGGATTGCTGAGCAGGGAAGCTTTGCATG
TTGCTCTAAGGTACATTTTTAAAGAGTTGTTTTTGGCCGGGCGCAGTGGCTCATGCCTG
TAATCCCAGCACTTTGGGAGGCCGAGGTGGGCGGATCACGAGGTCTGGAGTTTGAGACCA
TCCTGGCTAACACAGTGAAATCCCGTCTCTACTAAAAATACAAAAAATTAGCCAGGCGTG
GTGGCTGGCACCTGTAGTCCCAGCTACTTGGGAGGCTGAGGCAGGAGAATGGCGTGAACC
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TGGAAGGAAGAGGTTGCAGTGAGCCAAGATTGCGCCCCTGCACTCCAGCCTGGGCAACAG
 AGCAAGACTC
 (SEQ ID NO: 38)

5 As used herein, the term "IFITM3" refers to the gene encoding Interferon Induced Transmembrane Protein. The terms "IFITM3" and "Interferon Induced Transmembrane Protein" include wild-type forms of the IFITM3 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type IFITM3. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 10 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type IFITM3 nucleic acid sequence (e.g., SEQ ID NO: 39, NCBI Reference Sequence: NM_021034.2). SEQ ID NO: 39 is a wild-type gene sequence encoding IFITM3 protein, and is shown below:

AGGAAAAGGAACTGTTGAGAAACCGAACTACTGGGGAAAGGGAGGGCTCACTGAGAACCATCCC
 15 AGTAACCCGACCGCCGCTGGTCTTCGCTGGACACCATGAATCACACTGTCCAAACCTTCTTCTCTCC
 TGTCAACAGTGGCCAGCCCCCAACTATGAGATGCTCAAGGAGGAGCACGAGGTGGCTGTGCTGG
 GGGCGCCCCACAACCCTGCTCCCCCGACGTCCACCGTGATCCACATCCGCAGCGAGACCTCCGTG
 CCCGACCATGTCTGCTGGTCCCTGTTCAACACCCTCTTCATGAACCCCTGCTGCCTGGGCTTCATAG
 CATTCGCCTACTCCGTGAAGTCTAGGGACAGGAAGATGGTTGGCGACGTGACCGGGGCCAGGCC
 20 TATGCCTCCACCGCCAAGTGCCTGAACATCTGGGCCCTGATTCTGGGCATCCTCATGACCATTCTGC
 TCATCGTCATCCCAGTGCTGATCTTCCAGGCCTATGGATAGATCAGGAGGCATCACTGAGGCCAGG
 AGCTCTGCCCATGACCTGTATCCACGTACTCCAACTTCCATTCTCGCCCTGCCCCCGGAGCCGA
 GTCCTGTATCAGCCCTTATCCTCACACGCTTTTCTACAATGGCATTCAATAAAGTGACAGTGTCTTCT
 GGTGCTAAAAAAAAAA
 25 (SEQ ID NO: 39)

As used herein, the term "IFNAR1" refers to the gene encoding Interferon alpha/beta receptor 1. The terms "IFNAR1" and "Interferon alpha/beta receptor 1" include wild-type forms of the IFNAR1 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type IFNAR1. Examples of such
 30 variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type IFNAR1 nucleic acid sequence (e.g., SEQ ID NO: 40, ENA accession number J03171). SEQ ID NO: 40 is a wild-type gene sequence encoding IFNAR1 protein, and is shown below:

35 TTAGGACGGGGCGATGGCGGCTGAGAGGAGCTGCGCGTGCGGAACATGTAACCTGGTGGG
 ATCTGCGGCGGCTCCCAGATGATGGTCGTCTCCTGGGCGCGACGACCCTAGTGCTCGTC
 GCCGTGGGCCCATGGGTGTTGTCCGCAGCCGCAGGTGGAAAAAATCTAAATCTCTCAA
 AAAGTAGAGGTGACATCATAGATGACAACTTTATCCTGAGGTGGAACAGGAGCGATGAG
 40 TCTGTCTGGGAATGTGACTTTTTTCATTTCGATTATCAAAAAACTGGGATGGATAATTGGATA
 AAATTGTCTGGGTGTCAGAATATTACTAGTACCAAATGCAACTTTTCTTCACTCAAGCTG
 AATGTTTATGAAGAAATTAAATTGCGTATAAGAGCAGAAAAAGAAAACACTTCTTCATGG

TATGAGGTTGACTCATTTACACCATTTTCGCAAAGCTCAGATTGGTCCTCCAGAAGTACAT
TTAGAAGCTGAAGATAAGGCAATAGTGATACACATCTCTCCTGGAACAAAAGATAGTGTT
ATGTGGGCTTTGGATGGTTTAAGCTTTACATATAGCTTACTTATCTGGAAAACTCTTCA
GGTGTAGAAGAAAGGATTGAAAATATTTATTCCAGACATAAAATTTATAAACTCTCACCA
5 GAGACTACTTATTGTCTAAAAGTTAAAGCAGCACTACTTACGTCATGGAAAATTGGTGTC
TATAGTCCAGTACATTGTATAAAGACCACAGTTGAAAATGAACTACCTCCACCAGAAAAT
ATAGAAGTCAGTGTCCAAAATCAGAACTATGTTCTTAAATGGGATTATACATATGCAAAC
ATGACCTTTCAAGTTCAGTGGCTCCACGCCTTTTTAAAAAGGAATCCTGGAAACCATTTG
TATAAATGGAAACAAATACCTGACTGTGAAAATGTCAAACTACCCAGTGTGTCTTTCT
10 CAAAACGTTTTCCAAAAGGAATTTACCTTCTCCGCGTACAAGCATCTGATGGAAATAAC
ACATCTTTTTGGTCTGAAGAGATAAAGTTTGATACTGAAATACAAGCTTTCTACTTCCT
CCAGTCTTTAACATTAGATCCCTTAGTGATTCCATATCTATATCGGTGCTCCAAAA
CAGTCTGGAAACACGCCTGTGATCCAGGATTATCCACTGATTTATGAAATTATTTTTTGG
GAAAACACTTCAAATGCTGAGAGAAAAATTATCGAGAAAAAACTGATGTTACAGTTCCT
15 AATTTGAAACCACTGACTGTATATTGTGTGAAAGCCAGAGCACACACCATGGATGAAAAG
CTGAATAAAAGCAGTGTTTTTAGTGACGCTGTATGTGAGAAAACAAAACCAGGAAATACC
TCTAAAATTTGGCTTATAGTTGGAATTTGATTGCATTATTTGCTCTCCCGTTTTGTCATT
TATGCTGCGAAAGTCTTCTTGAGATGCATCAATTATGTCTTCTTTCCATCACTTAAACCT
TCTTCCAGTATAGATGAGTATTTCTCTGAACAGCCATTGAAGAATCTTCTGCTTTCAACT
20 TCTGAGGAACAAATCGAAAAATGTTTCATAATTGAAAATATAAGCACAATTGCTACAGTA
GAAGAACTAATCAAACCTGATGAAGATCATAAAAAATACAGTTCCCAACTAGCCAAGAT
TCAGGAAATTATTCTAATGAAGATGAAAGCGAAAGTAAAACAAGTGAAGAACTACAGCAG
GACTTTGTATGACCAGAAATGAACTGTGTCAAGTATAAGGTTTTTCAGCAGGAGTTACAC
TGGGAGCCTGAGGTCCTCACCTTCTCAGTAACTACAGAGAGGACGTTTCTGTTTAG
25 GGAAAGAAAAACATCTTCAGATCATAGGTCCTAAAAATACGGGCAAGCTCTTAACTATT
TAAAAATGAAATTACAGGCCCGGGCACGGTGGCTCACACCTGTAATCCAGCACTTTGGG
AGGCTGAGGCAGGCAGATCATGAGGTCAAGAGATCGAGACCAGCCTGGCCAACGTGGTGA
AACCCCATCTCTACTAAAAATACAAAATTAGCCGGGTAGTAGGTAGGCGCGCCTGTT
GTCTTAGCTACTCAGGAGGCTGAGGCAGGAGAATCGCTTGAAAACAGGAGGTGGAGGTTG
30 CAGTGAGCCGAGATCACGCCACTGCACTCCAGCCTGGTGACAGCGTGAGACTCTTTAAAA
AAAGAAATTAAGAGAGTTGAGACAAACGTTTCTACATTCTTTCCATGTGTAAATCAT
GAAAAAGCCTGTCACCGGACTTGCAATTGGATGAGATGAGTCAGACCAAAACAGTGGCCAC
CCGTCTTCTCCTGTGAGCCTAAGTGCAGCCGTGCTAGCTGCGCACCGTGGCTAAGGATG
ACGTCTGTGTTCTGTCCATCACTGATGCTGCTGGCTACTGCATGTGCCACACCTGTCTG
35 TTCGCCATTCTAACATTCTGTTTCATTCTTCTCGGGAGATATTTCAAACATTTGGTCT
TTTCTTTTAACACTGAGGGTAGGCCCTTAGGAAATTTATTTAGGAAAGTCTGAACACGTT
ATCACTTGGTTTTCTGGAAAGTAGCTTACCCTAGAAAACAGCTGCAAATGCCAGAAAGAT
GATCCCTAAAAATGTTGAGGGACTTCTGTTTATTTCATCCCGAGAACATTGGCTTCCACAT
CACAGTATCTACCCTTACATGGTTTAGGATTAAAGCCAGGCAATCTTTTACTATG
40 (SEQ ID NO: 40)

As used herein, the term "IFNAR2" refers to the gene encoding Interferon alpha/beta receptor 2. The terms "IFNAR2" and "Interferon alpha/beta receptor 2" include wild-type forms of the IFNAR2 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type IFNAR2. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type IFNAR2 nucleic acid sequence (e.g., SEQ ID NO: 41, ENA accession number X77722). SEQ ID NO: 41 is a wild-type gene sequence encoding IFNAR2 protein, and is shown below:

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10  GCTTTTGTCCCCGCCCCGCCGCTTCTGTCCGAGAGGCCGCCCGCGAGGCGCATCCTGACC
    GCGAGCGTCGGGTCCCAGAGCCGGGCGCGGCTGGGGCCCCGAGGCTAGCATCTCTCGGGAG
    CCGCAAGGCGAGAGCTGCAAAGTTTAATTAGACACTTCAGAAATTTGATCACCTAATGTT
    GATTTTCAGATGTAAAAGTCAAGAGAAGACTCTAAAAATAGCAAAGATGCTTTTGAGCCAG
    AATGCCTTCATCGTCAGATCACTTAATTTGGTTCTCATGGTGTATATCAGCCTCGTGTTT
15  GGTATTTTCATATGATTTCGCCTGATTACACAGATGAATCTTGCACTTTCAAGATATCATTG
    CGAAATTTCCGGTCCATCTTATCATGGGAATTAACCACTCCATTGTACCAACTCAC
    TATACATTGCTGTATACAATCATGAGTAAACCAGAAGATTTGAAGGTGGTTAAGAAGTGT
    GCAAATACCACAAGATCATTTTGTGACCTCACAGATGAGTGGAGAAGCACACACGAGGCC
    TATGTCACCGTCCTAGAAGGATTCAGCGGGAACACAACGTTGTTTCAGTTGCTCACACAAT
20  TTCTGGCTGGCCATAGACATGTCTTTTGAACCACCAGAGTTTGAGATTGTTGGTTTTACC
    AACCACATTAATGTGATGGTGAAATTTCCATCTATTGTTGAGGAAGAATTACAGTTTGAT
    TTATCTCTCGTCATTGAAGAACAGTCAGAGGGAATTGTTAAGAAGCATAAACCCGAAATA
    AAAGGAAACATGAGTGGAATTTACCTATATCATTGACAAGTTAATTCCAAACACGAAC
    TACTGTGTATCTGTTTATTTAGAGCACAGTGATGAGCAAGCAGTAATAAAGTCTCCCTTA
25  AAATGCACCCTCCTTCCACCTGGCCAGGAATCAGAATCAGCAGAATCTGCCAAAATAGGA
    GGAATAATTACTGTGTTTTTGTATAGCATTGGTCTTGACAAGCACCATAGTGACACTGAAA
    TGGATTGGTTATATATGCTTAAGAAATAGCCTCCCCAAAGTCTTGAGGCAAGGTCTCACT
    AAGGGCTGGAATGCAGTGGCTATTCACAGGTGCAGTCATAATGCACTACAGTCTGAAACT
    CCTGAGCTCAAACAGTCGTCCTGCCTAAGCTTCCCCAGTAGCTGGGATTACAAGCGTGCA
30  TCCCTGTGCCCCAGTGATTAAGTTTTATTATGTAGAAAATAAAGAGCAAACAGTTACAAA
    AGAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
    (SEQ ID NO: 41)

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As used herein, the term "IGF1" refers to the gene encoding Insulin-like growth factor I. The terms "IGF1" and "Insulin-like growth factor I" include wild-type forms of the IGF1 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type IGF1. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type IGF1 nucleic acid sequence (e.g., SEQ ID NO: 42, ENA accession number X00173). SEQ ID NO: 42 is a wild-type gene sequence encoding IGF1 protein, and is shown below:

CTTCAGAAGCAATGGGAAAAATCAGCAGTCTTCCAACCCAATTATTTAAGTGCTGCTTTT
 GTGATTTCTTGAAGGTGAAGATGCACACCATGTCTCCTCGCATCTCTTCTACCTGGCGC
 TGTGCCTGCTCACCTTCACCAGCTCTGCCACGGCTGGACCGGAGACGCTCTGCGGGGCTG
 AGCTGGTGGATGCTCTTCAGTTCGTGTGTGGAGACAGGGGCTTTTATTTCAACAAGCCCA
 5 CAGGGTATGGCTCCAGCAGTCGGAGGGCGCCTCAGACAGGTATCGTGGATGAGTGCTGCT
 TCCGGAGCTGTGATCTAAGGAGGCTGGAGATGTATTGCGCACCCCTCAAGCCTGCCAAGT
 CAGCTCGCTCTGTCCGTGCCCAGCGCCACACCGACATGCCCAAGACCCAGAAGGAAGTAC
 ATTTGAAGAACGCAAGTAGAGGGAGTGCAGGAAACAAGAACTACAGGATGTAGGAAGACC
 CTCCTGAGGAGTGAAGAGTGACATGCCACCGCAGGATCCTTTGCTCTGCACGAGTTACCT
 10 GTTAAACTTTGGAACACCTACCAAAAAATAAGTTTGATAACATTTAAAGATGGGCGTTT
 CCCCCAATGAAATACACAAGTAAACATTCCAACATTGTCTTTAGGAGTGATTTGCACCTT
 GCAAAAATGGTCCTGGAGTTGGTAGATTGCTGTTGATCTTTTATCAATAATGTTCTATAG
 AAAAG
 (SEQ ID NO: 42)

15

As used herein, the term "IL10RA" refers to the gene encoding Interleukin-10 receptor subunit alpha. The terms "IL10RA" and "Interleukin-10 receptor subunit alpha" include wild-type forms of the IL10RA gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type IL10RA. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type IL10RA nucleic acid sequence (e.g., SEQ ID NO: 43, ENA accession number U00672). SEQ ID NO: 43 is a wild-type gene sequence encoding IL10RA protein, and is shown below:

25 AAAGAGCTGGAGGCGCGCAGGCCGGCTCCGCTCCGGCCCCGGACGATGCGGCGCGCCCAG
 GATGCTGCCGTGCCTCGTAGTGCTGCTGGCGGCGCTCCTCAGCCTCCGTCTTGGCTCAGA
 CGCTCATGGGACAGAGCTGCCAGCCCTCCGTCTGTGTGGTTTGAAGCAGAATTTTTCCA
 CCACATCCTCCACTGGACACCCATCCCAAATCAGTCTGAAAGTACCTGCTATGAAGTGGC
 GCTCCTGAGGTATGGAATAGAGTCCTGGAAGTCCATCTCCAAGTGTAGCCAGACCCTGTC
 30 CTATGACCTTACCGCAGTGACCTTGGACCTGTACCACAGCAATGGCTACCGGGCCAGAGT
 GCGGGCTGTGGACGGCAGCCGGCACTCCAAGTGGACCGTCACCAACACCCGCTTCTCTGT
 GGATGAAGTGAAGTCTGACAGTTGGCAGTGTGAACCTAGAGATCCACAATGGCTTCATCCT
 CGGGAAGATTGAGTACCCAGGCCCAAGATGGCCCCCGCGAATGACACATATGAAAGCAT
 CTTGAGTCACTTCCGAGAGTATGAGATTGCCATTGCAAGGTGCCGGGAACTTCACGTT
 35 CACACACAAGAAAGTAAAACATGAAAACCTTCAGCCTCCTAACCTCTGGAGAAGTGGGAGA
 GTTCTGTGTCCAGGTGAAACCATCTGTGCTTCCCGAAGTAACAAGGGGATGTGGTCTAA
 AGAGGAGTGCATCTCCCTCACCAGGCAGTATTTACCGTGACCAACGTCATCATCTTCTT
 TGCTTTTGTCTGCTGCTCTCCGGAGCCCTCGCCTACTGCCTGGCCCTCCAGCTGTATGT
 GCGGCGCCGAAAGAAGCTACCCAGTGTCTGCTCTTCAAGAAGCCCAGCCCCTTCATCTT
 40 CATCAGCCAGCGTCCCTCCCCAGAGACCCAAAGACACCATCCACCCGCTTGATGAGGAGGC
 CTTTTTGAAGGTGTCCCCAGAGCTGAAGAACTTGGACCTGCACGGCAGCACAGACAGTGG
 CTTTGGCAGCACCAAGCCATCCCTGCAGACTGAAGAGCCCCAGTTCTCTCCTCCCTGACCC

TCACCCCCAGGCTGACAGAACGCTGGGAAACGGGGAGCCCCCTGTGCTGGGGGACAGCTG
CAGTAGTGGCAGCAGCAATAGCACAGACAGCGGGATCTGCCTGCAGGAGCCCAGCCTGAG
CCCCAGCACAGGGCCCCACCTGGGAGCAACAGGTGGGGAGCAACAGCAGGGGGCCAGGATGA
CAGTGGCATTGACTTAGTTCAAACTCTGAGGGCCGGGCTGGGGACACACAGGGGTGGCTC
5 GGCCTTGGGCCACCACAGTCCCCCGGAGCCTGAGGTGCCTGGGGAAGAAGACCCAGCTGC
TGTGGCATTCCAGGGTTACCTGAGGCAGACCAGATGTGCTGAAGAGAAGGCAACCAAGAC
AGGCTGCCTGGAGGAAGAATCGCCCTTGACAGATGGCCTTGGCCCCAAATTCGGGAGATG
CCTGGTTGATGAGGCAGGCTTGCATCCACCAGCCCTGGCCAAGGGCTATTTGAAACAGGA
TCCTCTAGAAATGACTCTGGCTTCCTCAGGGGGCCCCAACGGGACAGTGGAACCAGCCCAC
10 TGAGGAATGGTCACTCCTGGCCTTGAGCAGCTGCAGTGACCTGGGAATATCTGACTGGAG
CTTTGCCCATGACCTTGGCCCTCTAGGCTGTGTGGCAGCCCCAGGTGGTCTCCTGGGCAG
CTTTAACTCAGACCTGGTCACCCTGCCCCCTCATCTCTAGCCTGCAGTCAAGTGAGTGA
CGGGCTGAGAGGCTGCTTTTGATTTTAGCCATGCCTGCTCCTCTGCCTGGACCAGGAGGA
GGGCCCTGGGGCAGAAGTTAGGCACGAGGCAGTCTGGGCACTTTTCTGCAAGTCCACTGG
15 GGCTGGCCCAGCCAGGCTGCAGGGCTGGTCAGGGTGTCTGGGGCAGGAGGAGGCCAACTC
ACTGAACTAGTGCAGGGTATGTGGGTGGCACTGACCTGTTCTGTTGACTGGGGCCCTGCA
GACTCTGGCAGAGCTGAGAAGGGCAGGGACCTTCTCCCTCCTAGGAACTCTTTCCTGTAT
CATAAAGGATTATTTGCTCAGGGGAACCATGGGGCTTTCTGGAGTTGTGGTGAGGCCACC
AGGCTGAAGTCAGCTCAGACCCAGACCTCCCTGCTTAGGCCACTCGAGCATCAGAGCTTC
20 CAGCAGGAGGAAGGGCTGTAGGAATGGAAGCTTCAGGGCCTTGCTGCTGGGGTCATTTTT
AGGGGAAAAAGGAGGATATGATGGTCACATGGGGAACCTCCCCTCATCGGGCCTCTGGGG
CAGGAAGCTTGTCACTGGAAGATCTTAAGGTATATATTTTCTGGACACTCAAACACATCA
TAATGGATTCACTGAGGGGAGACAAAGGGAGCCGAGACCCTGGATGGGGCTTCCAGCTCA
GAACCCATCCCTCTGGTGGGTACCTCTGGCACCCATCTGCAAATATCTCCCTCTCTCAA
25 CAAATGGAGTAGCATCCCCCTGGGGCACTTGCTGAGGCCAAGCCACTCACATCCTCACTT
TGCTGCCCCACCATCTTGCTGACAACTTCCAGAGAAGCCATGGTTTTTTGTATTGGTCAT
AACTCAGCCCTTTGGGCGGCCTCTGGGCTTGGGCACCAGCTCATGCCAGCCCCAGAGGGT
CAGGGTTGGAGGCCTGTGCTTGTGTTTGCTGCTAATGTCCAGCTACAGACCCAGAGGATA
AGCCACTGGGCACTGGGCTGGGGTCCCTGCCTTGTTGGTGTTGAGCTGTGTGATTTTGA
30 CTAGCCACTTGTGAGAGGGCCTCAATCTCCCATCTGTGAAATAAGGACTCCACCTTTAGG
GGACCCTCCATGTTTGCTGGGTATTAGCCAAGCTGGTCCTGGGAGAATGCAGATACTGTC
CGTGGACTACCAAGCTGGCTTGTTCCTTATGCCAGAGGCTAACAGATCCAATGGGAGTCC
ATGGTGTGATGCCAAGACAGTATCAGACACAGCCCCAGAAGGGGGCATTATGGGCCCTGC
CTCCCCATAGGCCATTTGGA CTCTGCCTTCAAACAAAGGCAGTTCAGTCCACAGGCATGG
35 AAGCTGTGAGGGGACAGGCCTGTGCGTGCCATCCAGAGTCATCTCAGCCCTGCCTTTCTC
TGGAGCATTCTGAAACAGATATTCTGGCCCAGGGAATCCAGCCATGACCCCCACCCCTC
TGCCAAAGTACTCTTAGGTGCCAGTCTGGTAACTGAACTCCCTCTGGAGGCAGGCTTGAG
GGAGGATTCTCAGGGTTCCCTTGAAAGCTTTATTTATTTATTTTGTTCATTTATTTATT
GGAGAGGCAGCATTGCACAGTGAAAGAATTCTGGATATCTCAGGAGCCCCGAAATTCTAG
40 CTCTGACTTTGCTGTTTCCAGTGGTATGACCTTGGAGAAGTCACTTATCCTCTTGGAGCC
TCAGTTTCCTCATCTGCAGAATAATGACTGACTTGTCTAATTCATAGGGATGTGAGGTTT
TGCTGAGGAAATGGGTATGAATGTGCCTTGAACACAAAGCTCTGTCAATAAGTGATACAT

GTTTTTTATTCCAATAAATTGTCAAGACCACA
(SEQ ID NO: 43)

As used herein, the term "IL1A" refers to the gene encoding Interleukin-1 alpha. The terms
5 "IL1A" and "Interleukin-1 alpha" include wild-type forms of the IL1A gene, as well as variants (e.g., splice
variants and polymorphisms) of wild-type IL1A. Examples of such variants are nucleic acids having at
least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%,
82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%,
or 99.9% identity, or more) to a wild-type IL1A nucleic acid sequence (e.g., SEQ ID NO: 44, ENA
10 accession number X02531). SEQ ID NO: 44 is a wild-type gene sequence encoding IL1A protein, and is
shown below:

ATGGCCAAAGTTCCAGACATGTTTGAAGACCTGAAGAACTGTTACAGTGAAAATGAAGAA
GACAGTTCCTCCATTGATCATCTGTCTCTGAATCAGAAATCCTTCTATCATGTAAGCTAT
15 GGCCCACTCCATGAAGGCTGCATGGATCAATCTGTGTCTCTGAGTATCTCTGAAACCTCT
AAAACATCCAAGCTTACCTTCAAGGAGAGCATGGTGGTAGTAGCAACCAACGGGAAGGTT
CTGAAGAAGAGACGGTTGAGTTTAAGCCAATCCATCACTGATGATGACCTGGAGGCCATC
GCCAATGACTCAGAGGAAGAAATCATCAAGCCTAGGTCAGCACCTTTTAGCTTCCTGAGC
AATGTGAAATACAACCTTTATGAGGATCATCAAATACGAATTCATCCTGAATGACGCCCTC
20 AATCAAAGTATAATTCGAGCCAATGATCAGTACCTCACGGCTGCTGCATTACATAATCTG
GATGAAGCAGTGAAATTTGACATGGGTGCTTATAAGTCATCAAAGGATGATGCTAAAATT
ACCGTGATTCTAAGAATCTCAAAAACCTCAATTGTATGTGACTGCCCAAGATGAAGACCAA
CCAGTGCTGCTGAAGGAGATGCCTGAGATACCCAAAACCATCACAGGTAGTGAGACCAAC
CTCCTCTTCTTCTGGGAACTCACGGCACTAAGAACTATTTACATCAGTTGCCCATCCA
25 AACTTGTTTATTGCCACAAAGCAAGACTACTGGGTGTGCTTGGCAGGGGGGCCACCCTCT
ATCACTGACTTTTCACTGATACTGGAAAACAGGCGTAGGTCTGGAGTCTCACTTGTCTCACT
TGTGCAGTGTTGACAGTTCATATGTACCATGTACATGAAGAAGCTAAATCCTTTACTGTT
AGTCATTTGCTGAGCATGTACTGAGCCTTGTAATTCTAAATGAATGTTTACACTCTTTGT
AAGAGTGGAACCAACACTAACATATAATGTTGTTATTTAAAGAACACCCTATATTTTGCA
30 TAGTACCAATCATTTTAATTATTATTCTTCATAACAATTTTAGGAGGACCAGAGCTACTG
ACTATGGCTACCAAAAAGACTCTACCCATATTACAGATGGGCAAATTAAGGCATAAGAAA
ACTAAGAAATATGCACAATAGCAGTTGAAACAAGAAGCCACAGACCTAGGATTTTCATGAT
TTCATTTCAACTGTTTGCCTTCTGCTTTTAAGTTGCTGATGAACTCTTAATCAAATAGCA
TAAGTTTCTGGGACCTCAGTTTTATCATTTTCAAATGGAGGGAATAATACCTAAGCCTT
35 CCTGCCGCAACAGTTTTTTATGCTAATCAGGGAGGTCATTTTGGTAAATACTTCTCGAA
GCCGAGCCTCAAGATGAAGGCAAAGCACGAAATGTTATTTTTTAATTATTATTTATATAT
GTATTTATAAATATATTTAAGATAATTATAATATACTATATTTATGGGAACCCCTTCATC
CTCTGAGTGTGACCAGGCATCCTCCACAATAGCAGACAGTGTCTTCTGGGATAAGTAAGT
TTGATTTCATTAATACAGGGCATTCTTGGTCCAAGTTGTGCTTATCCCATAGCCAGGAAAC
40 TCTGCATTCTAGTACTTGGGAGACCTGTAATCATATAATAAATGTACATTAATTACCTTG
AGCCAGTAATTGGTCCGATCTTTGACTCTTTTGCCATTAACTTACCTGGGCATTCTTGT
TTCATTCAATTCCACCTGCAATCAAGTCCTACAAGCTAAAATTAGATGAACTCAACTTG

ACAACCATAGACCACTGTTATCAAACTTTCTTTTCTGGAATGTAATCAATGTTTCTTCT
 AGGTTCTAAAAATTGTGATCAGACCATAATGTTACATTATTATCAACAATAGTGATTGAT
 AGAGTGTTATCAGTCATACTAAATAAAGCTTGCAAGTGAGGGAGTCATTTTCATTGGCGT
 TTGAGTCAGCAAAGAAGTCAAG

5 (SEQ ID NO: 44)

As used herein, the term "IL1B" refers to the gene encoding Interleukin-1 beta. The terms "IL1B" and "Interleukin-1 beta" include wild-type forms of the IL1B gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type IL1B. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type IL1B nucleic acid sequence (e.g., SEQ ID NO: 45, ENA accession number X02770). SEQ ID NO: 45 is a wild-type gene sequence encoding IL1B protein, and is shown below:

15

ACAAACCTTTTCGAGGCAAAAGGCAAAAAGGCTGCTCTGGGATTCTCTTCAGCCAATCT
 TCAATGCTCAAGTGTCTGAAGCAGCCATGGCAGAAGTACCTAAGCTCGCCAGTGAAATGA
 TGGCTTATTACAGTGGCAATGAGGATGACTTGTTCTTTGAAGCTGATGGCCCTAAACAGA
 TGAAGTGCTCCTTCAGGACCTGGACCTCTGCCCTCTGGATGGCGGCATCCAGCTACGAA
 20 TCTCCGACCACCACTACAGCAAGGGCTTCAGGCAGGCCGCGTCAGTTGTTGTGGCCATGG
 ACAAGCTGAGGAAGATGCTGGTTCCCTGCCACAGACCTTCAGGAGAATGACCTGAGCA
 CCTTCTTTCCCTTCATCTTTGAAGAAGAACCTATCTTCTTCGACACATGGGATAACGAGG
 CTTATGTGCACGATGCACCTGTACGATCACTGAACTGCACGCTCCGGGACTCACAGCAAA
 AAAGCTTGGTGATGTCTGGTCCATATGAACTGAAAGCTCTCCACCTCCAGGGACAGGATA
 25 TGGAGCAACAAGTGGTGTCTCCATGTCCTTTGTACAAGGAGAAGAAAGTAATGACAAAA
 TACCTGTGGCCTTGGGCCTCAAGGAAAAGAATCTGTACCTGTCTGCGTGTTGAAAGATG
 ATAAGCCCACTCTACAGCTGGAGAGTGTAGATCCCAAAAATTACCCAAAGAAGAAGATGG
 AAAAGCGATTTGTCTTCAACAAGATAGAAATCAATAACAAGCTGGAATTTGAGTCTGCCC
 AGTTCCCCAACTGGTACATCAGCACCTCTCAAGCAGAAAACATGCCCGTCTTCCTGGGAG
 30 GGACCAAAGGCGGCCAGGATATAACTGACTTCACCATGCAATTTGTGTCTTCCTAAAGAG
 AGCTGTACCCAGAGAGTCCTGTGCTGAATGTGGACTCAATCCCTAGGGCTGGCAGAAAGG
 GAACAGAAAGGTTTTTGTAGTACGGCTATAGCCTGGACTTTCTCTGTTGTCTACACCAATGC
 CCAACTGCCTGCCTTAGGGTAGTGCTAAGAGGATCTCCTGTCCATCAGCCAGGACAGTCA
 GCTCTCTCCTTTTCAGGGCCAATCCCAGCCCTTTTGTGAGCCAGGCCTCTCTCACCTCTC
 35 CTACTCACTTAAAGCCCGCCTGACAGAAACCAGGCCACATTTTGGTTCTAAGAAACCCTC
 CTCTGTCAATTCGCTCCACATTCTGATGAGCAACCGCTTCCCTATTTATTTATTTATTTG
 TTTGTTTGTGTTTGAATCATTGGTCTAATTTATTCAAAGGGGGCAAGAAGTAGCAGTGTCT
 GTAAAAGAGCCTAGTTTTTAATAGCTATGGAATCAATTCAATTTGGACTGGTGTGCTCTC
 TTTAAATCAAGTCCTTTAATTAAGACTGAAAATATATAAGCTCAGATTATTTAAATGGGA
 40 ATATTTATAAATGAGCAAATATCATACTGTTCAATGGTTCTCAAATAAACTTCACT

(SEQ ID NO: 45)

As used herein, the term "IL1RAP" refers to the gene encoding Interleukin-1 receptor accessory protein. The terms "IL1RAP" and "Interleukin-1 receptor accessory protein" include wild-type forms of the IL1RAP gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type IL1RAP.

Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type IL1RAP nucleic acid sequence (e.g., SEQ ID NO: 46, ENA accession number AF029213). SEQ ID NO: 46 is a wild-type gene sequence encoding IL1RAP protein, and is shown below:

```

10  TCTCAAAGGATGACACTTCTGTGGTGTGTAGTGAGTCTCTACTTTTATGGAATCCTGCAA
    AGTGATGCCTCAGAACGCTGCGATGACTGGGGACTAGACACCATGAGGCAAATCCAAGTG
    TTTGAAGATGAGCCAGCTCGCATCAAGTGCCCACTCTTTGAACACTTCTTGAAATTC AAC
    TACAGCACAGCCCATTCAGCTGGCCTTACTCTGATCTGGTATTGGACTAGGCAGGACCGG
    GACCTTGAGGAGCCAATTA ACTTCCGCCTCCCCGAGAACCGCATTAGTAAGGAGAAAGAT
15  GTGCTGTGGTTCCGGCCCACTCTCCTCAATGACACTGGCAACTATACCTGCATGTTAAGG
    AACACTACATATTGCAGCAAAGTTGCATTTCCCTTGGAAAGTTGTTCAAAAAGACAGCTGT
    TTCAATTCCTCCCATGAAACTCCCAGTGCATAAACTGTATATAGAATATGGCATT CAGAGG
    ATCACTTGTCCAAATGTAGATGGATATTTTCCTTCCAGTGTCAAACCGACTATCACTTGG
    TATATGGGCTGTTATAAAATACAGAATTTTAATAATGTAATACCCGAAGGTATGAACTTG
20  AGTTTCCTCATTGCCTTAATTTCAAATAATGGAAATTACACATGTGTTGTTACATATCCA
    GAAAATGGACGTACGTTTCATCTCACCAGGACTCTGACTGTAAAGGTAGTAGGCTCTCCA
    AAAAATGCAGTGCCCCCTGTGATCCATTCACCTAATGATCATGTGGTCTATGAGAAAGAA
    CCAGGAGAGGAGCTACTCATTCCCTGTACGGTCTATTTTAGTTTTCTGATGGATTCTCGC
    AATGAGGTTTGGTGGACCATTGATGGAAAAAACCTGATGACATCACTATTGATGTCACC
25  ATTAACGAAAGTATAAGTCATAGTAGAACAGAAGATGAAACAAGAACTCAGATTTTGAGC
    ATCAAGAAAGTTACCTCTGAGGATCTCAAGCGCAGCTATGTCTGTCATGCTAGAAGTGCC
    AAAGGCGAAGTTGCCAAAGCAGCCAAGGTGAAGCAGAAAGTGCCAGCTCCAAGATACACA
    GTGGAAGTGGCTTGTGGTTTTGGAGCCACAGTCCTGCTAGTGGTGATTCTCATTGTTGTT
    TACCATGTTTACTGGCTAGAGATGGTCCTATTTTACCGGGCTCATTGTTGGAACAGATGAA
30  ACCATTTTAGATGGAAAAGAGTATGATATTTATGTATCCTATGCAAGGAATGCGGAAGAA
    GAAGAATTTGTATTACTGACCCTCCGTGGAGTTTTGGAGAATGAATTTGGATACAAGCTG
    TGCATCTTTGACCGAGACAGTCTGCCTGGGGGAATTGTCACAGATGAGACTTTGAGCTTC
    ATTCAGAAAAGCAGACGCCTCCTGGTTGTTCTAAGCCCCAACTACGTGCTCCAGGGAACC
    CAAGCCCTCCTGGAGCTCAAGGCTGGCCTAGAAAATATGGCCTCTCGGGGCAACATCAAC
35  GTCATTTTAGTACAGTACAAAGCTGTGAAGGAAACGAAGGTGAAAGAGCTGAAGAGGGCT
    AAGACGGTGCTCACGGTCATTAAATGGAAAGGGGAAAAATCCAAGTATCCACAGGGCAGG
    TTCTGGAAGCAGCTGCAGGTGGCCATGCCAGTGAAGAAAAGTCCCAGGCGGTCTAGCAGT
    GATGAGCAGGGCCTCTCGTATTCATCTTTGAAAAATGTATGAAAGGAATAATGAAAAGGA
    (SEQ ID NO: 46)

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As used herein, the term "INPP5D" refers to the gene encoding Phosphatidylinositol 3,4,5-trisphosphate 5-phosphatase 1. The terms "INPP5D" and "Phosphatidylinositol 3,4,5-trisphosphate 5-

phosphatase 1" include wild-type forms of the INPP5D gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type INPP5D. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type INPP5D nucleic acid sequence (e.g., SEQ ID NO: 47, ENA accession number X98429). SEQ ID NO: 47 is a wild-type gene sequence encoding INPP5D protein, and is shown below:

```

10 GTTGCTGTGCGCGTTGCTGTGCGCCGAGGCCACCAAGAGGCAACGGGCGGCAGGTTGCAG
    TGGAGGGGCGCTCCGCTCCCCTCGGTGGTGTGTGGGTCTGGGGGTGCCTGCCGGCCCCAGC
    CGAGGAGGCCACGCCCACCATGGTCCCCTGCTGGAACCATGGCAACATCACCCGCTCCA
    AGGCGGAGGAGCTGCTTTCCAGGACAGGCAAGGACGGGAGCTTCCTCGTGCGTGCCAGCG
    AGTCCATCTCCCGGGCATAACGCGCTCTGCGTGCTGTATCGGAATTGCGTTTACACTTACA
    GAATTCTGCCCAATGAAGATGATAAATCACTGTTTCAGGCATCCGAAGGCGTCTCCATGA
15 GGTTCTTCACCAAGCTGGACCAGCTCATCGAGTTTTACAAGAAGGAAAACATGGGGCTGG
    TGACCCATCTGCAATACCCTGTGCCGCTGGAGGAAGAGGACACAGGCGACGACCCTGAGG
    AGGACACAGAAAGTGTGCTGTCTCCACCCGAGCTGCCCCCAAGAAACATCCCGCTGACTG
    CCAGCTCCTGTGAGGCCAAGGAGGTTCTTTTTTCAAACGAGAATCCCCGAGCGACCGAGA
    CCAGCCGGCCGAGCCTCTCCGAGACATTGTTCCAGCGACTGCAAAGCATGGACACCAGTG
20 GGCTTCCAGAAGAGCATCTTAAGGCCATCCAAGATTATTTAAGCACTCAGCTCGCCCAGG
    ACTCTGAATTTGTGAAGACAGGGTCCAGCAGTCTTCCTCACCTGAAGAACTGACCACAC
    TGCTCTGCAAGGAGCTCTATGGAGAAGTCATCCGACCCCTCCCATCCCTGGAGTCTCTGC
    AGAGGTTATTTGACCAGCAGCTCTCCCCGGGCCTCCGTCCACGTCCTCAGGTTCTGGTG
    AGGCCAATCCCATCAACATGGTGTCCAAGCTCAGCCAACTGACAAGCCTGTTGTGCTCCA
25 TTGAAGACAAGGTCAAGGCCTTGCTGCACGAGGGTCTGAGTCTCCGCACCGGCCCTCCC
    TTATCCCTCCAGTCACCTTTGAGGTGAAGGCAGAGTCTCTGGGGATTCTCAGAAAATGC
    AGCTCAAAGTCGACGTTGAGTCTGGGAACTGATCATTAAGAAGTCCAAGGATGGTTCTG
    AGGACAAGTTCTACAGCCACAAGAAAATCCTGCAGCTGATTAAGTCACAGAAATTTCTGA
    ATAAGTTGGTGATCTTGGTGGAAACGGAGAAGGAGAAGATCCTGCGGAAGGAATATGTTT
30 TTGCTGACTCCAAAAGAGAGAAGGCTTCTGCCAGCTCCTGCAGCAGATGAAGAACAAGC
    ACTCAGAGCAGCCGGAGCCCGACATGATCACCATCTTCATCGGCACCTGGAACATGGGTA
    ACGCCCCCCCCTCCCAAGAAGATCACGTCCTGGTTTCTCTCCAAGGGGCAGGGAAAGACGC
    GGGACGACTCTGCGGACTACATCCCCCATGACATTTACGTGATCGGCACCCAAGAGGACC
    CCCTGAGTGAGAAGGAGTGGCTGGAGATCCTCAAACACTCCCTGCAAGAAATCACCAGTG
35 TGACTTTTAAACAGTCGCCATCCACACGCTCTGGAACATCCGCATCGTGGTGCTGGCCA
    AGCCTGAGCACGAGAACCGGATCAGCCACATCTGTAAGTGAACGTAAGACAGGCATTG
    CAAACACACTGGGGAACAAGGGAGCCGTGGGGGTGTCGTTTCATGTTCAATGGAACCTCCT
    TAGGGTTTCGTCAACAGCCACTTGACTTCAGGAAGTGAAAAGAACTCAGGCGAAACCAA
    ACTATATGAACATTCTCCGGTTCTGGCCCTGGGCGACAAGAAGCTGAGTCCCTTTAACA
40 TCACTCACCGCTTCACGCACCTCTTCTGGTTTGGGGATCTTAAGTACCGTGTGGATCTGC
    CTACCTGGGAGGCAGAAACCATCATCCAGAAAATCAAGCAGCAGCAGTACGCAGACCTCC
    TGTCCCACGACCAGCTGCTCACAGAGAGGAGGGAGCAGAAGGTCTTCCTACACTTCGAGG

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AGGAAGAAATCACGTTTGCCCCAACCTACCGTTTTGAGAGACTGACTCGGGACAAATACG
CCTACACCAAGCAGAAAGCGACAGGGATGAAGTACAACTTGCCCTCCTGGTGTGACCGAG
TCCTCTGGAAGTCTTATCCCCTGGTGCACGTGGTGTGTGTCAGTCTTATGGCAGTACCAGCG
ACATCATGACGAGTGACCACAGCCCTGTCTTTGCCACATTTGAGGCAGGAGTCACTTCCC
5 AGTTTGTCTCCAAGAACGGTCCCGGGACTGTTGACAGCCAAGGACAGATTGAGTTTCTCA
GGTGCTATGCCACATTGAAGACCAAGTCCCAGACCAAATTCTACCTGGAGTTCCACTCGA
GCTGCTTGAGAGTTTTGTCAAGAGTCAGGAAGGAGAAAATGAAGAAGGAAGTGAGGGGG
AGCTGGTGGTGAAGTTTGGTGAGACTCTTCCAAAGCTGAAGCCCATTATCTCTGACCCTG
AGTACCTGCTAGACCAGCACATCCTCATCAGCATCAAGTCCTCTGACAGCGACGAATCCT
10 ATGGCGAGGGGCTGCATTGCCCTTCGTTAGAGGGCCACAGAAACGCAGCTGCCCATCTACA
CGCCTCTCACCCACCATGGGGAGTTGACAGGCCACTTCCAGGGGGAGATCAAGCTGCAGA
CCTCTCAGGGCAAGACGAGGGAGAAGCTCTATGACTTTGTGAAGACGGAGCGTGATGAAT
CCAGTGGGCCAAAGACCCTGAAGAGCCTCACCAGCCACGACCCCATGAAGCAGTGGGAAG
TCACTAGCAGGGCCCCCTCCGTGCAGTGGCTCCAGCATCACTGAAATCATCAACCCCACT
15 ACATGGGAGTGGGGCCCTTTGGGCCACCAATGCCCTGCACGTGAAGCAGACCTTGTCCC
CTGACCAGCAGCCCACAGCCTGGAGCTACGACCAGCCGCCCAAGGACTCCCCGCTGGGGC
CCTGCAGGGGAGAAAGTCTCCGACACCTCCCGGCCAGCCGCCCATATCACCCAAGAAGT
TTTTACCCTCAACAGCAAACCGGGGTCTCCCTCCCAGGACACAGGAGTCAAGGGCCAGTG
ACCTGGGGAAGAAGCGCAGGGGACACGCTGCCTCAGGAGGACCTGCCGCTGACGAAGCCCG
20 AGATGTTTGAGAACCCCTGTATGGGTCCCTGAGTTCCTTCCCTAAGCCTGCTCCCAGGA
AGGACCAGGAATCCCCAAAATGCCGCGGAAGGAACCCCGCCCTGCCCGGAACCCGGCA
TCTTGTGCGCCAGCATCGTGCTACCAAAGCCCAGGAGGCTGATCGCGGCGAGGGGCCCCG
GCAAGCAGGTGCCGCGCCCCGGCTGCGCTCCTTACGTGCTCATCCTCTGCCGAGGGCA
GGGCGGCCGCGGGGACAAGAGCCAAGGGAAGCCCAAGACCCCGGTGAGCTCCCAGGGCC
25 CGGTGCCGCGCAAGAGGCCCATCAAGCCTTCCAGATCGGAAATCAACCAGCAGACCCCGC
CCACCCCGACGCCGCGGGCCGCGCTGCCAGTCAAGAGCCCGGCGGTGCTGCACCTCCAGC
ACTCCAAGGGCCGCGACTACCGCGACAACACCGAGCTCCCGTATCACGGCAAGCACCGGC
CGGAGGAGGGGCCACCAGGGCCTCTAGGCAGGACTGCCATGCAGTGAAGCCCTCAGTGAG
CTGCCACTGAGTCGGGAGCCCAGAGGAACGGCGTGAAGCCACTGGACCCTCTCCCGGGAC
30 CTCCTGCTGGCTCCTCCTGCCAGCTTCTATGCAAGGCTTTGTGTTTTAGGAAAGGGC
CTAGCTTCTGTGTGGCCACAGAGTTCACTGCCTGTGAGACTTAGCACCAAGTGCTGAGG
CTGGAAGAAAAACGCACACCAGACGGGCAACAACAGTCTGGGTCCCAGCTCGCTCTTG
GTACTTGGGACCCCAAGTGCCTTGTTGAGGGCGCCATTCTGAAGAAAGGAAGTGCAGCGCC
GATTTGAGGGTGGAGATATAGATAATAATAATATTAATAATAATAATGGCCACATGGATC
35 GAACACTCATGGTGTGCCAAGTGCTGTGCTAAGTGCTTTACGAACATTTCGTCATATCAGG
ATGACCTCGAGAGCTGAGGCTCTAGCACCTAAAACACGTGCCCAAACCCACCAGTTTAA
AACGGTGTGTGTTCCGAGGGGTGAAAGCATTAAAGAAGCCCAGTGCCCTCCTGGAGTGAGA
CAAGGGCTCGGCCTTAAGGAGCTGAAGAGTCTGGGTAGCTTGTTTAGGGTACAAGAAGCC
TGTTCTGTCCAGCTTCAGTGACACAAGCTGCTTTAGCTAAAGTCCCGCGGGTTCCGGCAT
40 GGCTAGGCTGAGAGCAGGGATCTACCTGGCTTCTCAGTTCCTTTGGTTGGAAGGAGCAGGA
AATCAGCTCCTATTCTCCAGTGGAGAGATCTGGCCTCAGCTTGGGCTAGAGATGCCAAGG
CCTGTGCCAGGTTCCCTGTGCCCTCCTCGAGGTGGGCAGCCATCACCAGCCACAGTTAAG

CCAAGCCCCCAACATGTATTCCATCGTGCTGGTAGAAGAGTCTTTGCTGTTGCTCCCGA
 AAGCCGTGCTCTCCAGCCTGGCTGCCAGGGAGGGTGGGCCTCTTGGTTCCAGGCTCTTGA
 AATAGTGACGCTTTTCTTCTATCTCTGTGGCTTTCAGCTCTGCTTCCTTGGTTATTAG
 GAGAATAGATGGGTGATGTCTTTCCTTATGTTGCTTTTTCAACATAGCAGAATTAATGTA
 5 GGGAGCTAAATCCAGTGGTGTGTGTGAATGCAGAAGGGAATGCACCCCACATTCCCATGA
 TGGAAGTCTGCGTAACCAATAAATTGTGCCTTTCTCACTCAAACC

(SEQ ID NO: 47)

As used herein, the term "ITGAM" refers to the gene encoding Integrin Subunit Alpha M. The
 10 terms "ITGAM" and "Integrin Subunit Alpha M" include wild-type forms of the ITGAM gene, as well as
 variants (e.g., splice variants and polymorphisms) of wild-type ITGAM. Examples of such variants are
 nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%,
 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type ITGAM nucleic acid sequence (e.g., SEQ
 15 ID NO: 48, NCBI Reference Sequence: NM_000632.3). SEQ ID NO: 48 is a wild-type gene sequence
 encoding ITGAM protein, and is shown below:

TTTTCTGCCCTTCTTTGCTTTGGTGGCTTCCTTGTGGTTCTCAGTGGTGCCTGCAACCCCTGGTTCA
 CCTCCTTCCAGGTTCTGGCTCCTTCCAGCCATGGCTCTCAGAGTCCTTCTGTAAACAGCCTTGACCT
 20 TATGTCATGGGTTCAACTTGGACACTGAAAACGCAATGACCTTCCAAGAGAACGCAAGGGGCTTCGG
 GCAGAGCGTGGTCCAGCTTCAGGGATCCAGGGTGGTGGTTGGAGCCCCCAGGAGATAGTGGCTG
 CCAACCAAAGGGGAGCCTCTACCACTGCGACTACAGCACAGGCTCATGCGAGCCCATCCGCCTGC
 AGGTCCCCGTGGAGGCCGTGAACATGTCCCTGGGCCTGTCCCTGGCAGCCACCACCAGCCCCCT
 CAGCTGCTGGCCTGTGGTCCCACCGTGCACCAGACTTGCAGTGAGAACACGTATGTGAAAGGGCTC
 25 TGCTTCCTGTTTGGATCCAACCTACGGCAGCAGCCCCAGAAGTTCCAGAGGCCCTCCGAGGGTGT
 CCTCAAGAGGATAGTGACATTGCCTTCTTGATTGATGGCTCTGGTAGCATCATCCACATGACTTTCCG
 GCGGATGAAGGAGTTTGTCTCAACTGTGATGGAGCAATTAAGTCCAAAACCTTGTTCTCTTTGA
 TGCAGTACTCTGAAGAATTCCGGATTCACTTTACCTTCAAAGAGTTCCAGAACAACCCTAACCCAAGA
 TCACTGGTGAAGCCAATAACGCAGCTGCTTGGGCGGACACACAGGCCACGGGCATCCGCAAAGT
 30 GGTACGAGAGCTGTTTAACATCACCAACGGAGCCCGAAAGAATGCCTTTAAGATCCTAGTTGTCATC
 ACGGATGGAGAAAAGTTTGGCGATCCCTTGGGATATGAGGATGTCATCCCTGAGGCAGACAGAGAG
 GGAGTCATTGCTACGTCATTGGGGTGGGAGATGCCTTCCGCAGTGAGAAATCCCGCCAAGAGCTT
 AATACCATCGCATCCAAGCCGCCTCGTGATCACGTGTTCCAGGTGAATAACTTTGAGGCTCTGAAGA
 CCATTGAGAACCAGCTTCGGGAGAAGATCTTTGCGATCGAGGGTACTCAGACAGGAAGTAGCAGCT
 35 CCTTTGAGCATGAGATGTCTCAGGAAGGCTTCAGCGCTGCCATCACCTCTAATGGCCCCTTGCTGAG
 CACTGTGGGGAGCTATGACTGGGCTGGTGGAGTCTTTCTATATACATCAAAGGAGAAAAGCACCTTC
 ATCAACATGACCAGAGTGGATTCAGACATGAATGATGCTTACTTGGGTTATGCTGCCGCCATCATCTT
 ACGGAACCGGGTGCAAAGCCTGGTTCTGGGGGCACCTCGATATCAGCACATCGGCCTGGTAGCGAT
 GTTCAGGCAGAACTGGCATGTGGGAGTCCAACGCTAATGTCAAGGGCACCCAGATCGGCGCCTA
 40 CTTCCGGGGCCTCCCTCTGCTCCGTGGACGTGGACAGCAACGGCAGCACCGACCTGGTCCCTCATCG
 GGGCCCCCATTACTACGAGCAGACCCGAGGGGGCCAGGTGTCCGTGTGCCCTTGCCCAGGGGG
 AGGGCTCGGTGGCAGTGTGATGCTGTTCTCTACGGGGAGCAGGGCCAACCCTGGGGCCGCTTTGG

GGCAGCCCTAACAGTGCTGGGGGACGTAAATGGGGACAAGCTGACGGACGTGGCCATTGGGGCCC
CAGGAGAGGAGGACAACCGGGGTGCTGTTTACCTGTTTCACGGAACCTCAGGATCTGGCATCAGCC
CCTCCCATAGCCAGCGGATAGCAGGCTCCAAGCTCTCTCCCAGGCTCCAGTATTTTGGTCAGTCACT
GAGTGGGGGGCCAGGACCTCACAAATGGATGGACTGGTAGACCTGACTGTAGGAGCCCAGGGGGCAGC
5 TGCTGCTGCTCAGGTCCCAGCCAGTACTGAGAGTCAAGGCAATCATGGAGTTCAATCCCAGGGAAG
TGGCAAGGAATGTATTTGAGTGTAATGATCAGGTGGTGAAAGGCAAGGAAGCCGGAGAGGTGAGAG
TCTGCCTCCATGTCCAGAAGAGCACACGGGATCGGCTAAGAGAAGGACAGATCCAGAGTGTTGTGA
CTTATGACCTGGCTCTGGACTCCGGCCGCCACATTCCCGCGCCGTCTTCAATGAGACAAAGAACA
GCACACGCAGACAGACACAGGTCTTGGGGCTGACCCAGACTTGTGAGACCCTGAAACTACAGTTGC
10 CGAATTGCATCGAGGACCCAGTGAGCCCCATTGTGCTGCGCCTGAACTTCTCTCTGGTGGGAACGC
CATTGTCTGCTTTTCGGGAACCTCCGGCCAGTGCTGGCGGAGGATGCTCAGAGACTCTTCACAGCCT
TGTTTCCCTTTGAGAAGAATTGTGGCAATGACAACATCTGCCAGGATGACCTCAGCATCACCTTCAGT
TTCATGAGCCTGGACTGCCTCGTGGTGGGTGGGCCCCGGGAGTTCAACGTGACAGTGACTGTGAGA
AATGATGGTGAGGACTCCTACAGGACACAGGTCACCTTCTTCTTCCCGCTTGACCTGTCCTACCGGA
15 AGGTGTCCACGCTCCAGAACCAGCGCTCACAGCGATCCTGGCGCCTGGCCTGTGAGTCTGCCTCCT
CCACCGAAGTGTCTGGGGCCTTGAAGAGCACCAGCTGCAGCATAAACCACCCCATCTTCCCGGAAA
ACTCAGAGGTCACCTTTAATATCACGTTTGATGTAGACTCTAAGGCTTCCCTTGAAACAAACTGCTC
CTCAAGGCCAATGTGACCAGTGAGAACAACATGCCCAGAACCAACAAAACCGAATTCCAAGTGGAGC
TGCCGGTGAAATATGCTGTCTACATGGTGGTCAACCAGCCATGGGGTCTCCACTAAATATCTCAACTT
20 CACGGCCTCAGAGAATACCAGTCGGGTGATGCAGCATCAATATCAGGTCAGCAACCTGGGGCAGAG
GAGCCTCCCCATCAGCCTGGTGTCTTGGTGCCCGTCCGGCTGAACCAGACTGTCATATGGGACCG
CCCCCAGGTCACCTTCTCCGAGAACCTCTCGAGTACGTGCCACACCAAGGAGCGCTTGCCCTCTCA
CTCCGACTTTCTGGCTGAGCTTCGGAAGGCCCCCGTGGTGAAGTGTCCATCGCTGTCTGCCAGAG
AATCCAGTGTGACATCCCGTTCTTTGGCATCCAGGAAGAATTCAATGCTACCCTCAAAGGCAACCTC
25 TCGTTTGAAGTGGTACATCAAGACCTCGCATAACCACCTCCTGATCGTGAGCACAGCTGAGATCTTGT
TTAACGATTCCGTGTTACCCCTGCTGCCGGGACAGGGGGCGTTTGTGAGGTCCCAGACGGAGACCA
AAGTGGAGCCGTTTCGAGGTCCCCAACCCCTGCCGCTCATCGTGGGCAGCTCTGTGCGGGGACTG
CTGCTCCTGGCCCTCATCACCGCCGCGCTGTACAAGCTCGGCTTCTTCAAGCGGCAATACAAGGAC
ATGATGAGTGAAGGGGGTCCCCCGGGGGCCGAACCCAGTAGCGGCTCCTTCCCGACAGAGCTGC
30 CTCTCGGTGGCCAGCAGGACTCTGCCCAGACCACACGTAGCCCCCAGGCTGCTGGACACGTCCGA
CAGCGAAGTATCCCCGACAGGACGGGCTTGGGCTTCCATTTGTGTGTGTGCAAGTGTGTATGTGCG
TGTGTGCAAGTGTCTGTGTGCAAGTGTGTGCACATGTGTGCGTGTGCGTGCATGTGCACTTGCACG
CCCATGTGTGAGTGTGTGCAAGTATGTGAGTGTGTCCAAGTGTGTGTGCGTGTGTCCATGTGTGTGC
AAGTGTGTGCATGTGTGCGAGTGTGTGCATGTGTGTGCTCAGGGGCGTGTGGCTCACGTGTGTGAC
35 TCAGATGTCTCTGGCGTGTGGGTAGGTGACGGCAGCGTAGCCTCTCCGGCAGAAGGGAAGTGCCT
GGGCTCCCTTGTGCGTGGGTGAAGCCGCTGCTGGGTTTTCTCCGGGAGAGGGGACGGTCAATCC
TGTGGGTGAAGACAGAGGGAAACACAGCAGCTTCTCTCCACTGAAAGAAGTGGGACTTCCCGTCGC
CTGCGAGCCTGCGGCCTGCTGGAGCCTGCGCAGCTTGGATGGAGACTCCATGAGAAGCCGTGGGT
GGAACCAGGAACCTCCTCCACACCAGCGCTGATGCCCAATAAAGATGCCCACTGAGGAATGATGAA
40 GCTTCCTTTCTGGATTCAATTTATTATTTCAATGTGACTTTAATTTTTTGGATGGATAAGCTTGTCTATGG
TACAAAAATCACAAGGCATTCAAGTGTACAGTGAAAAGTCTCCCTTTCCAGATATTCAAGTCACCTCC
TTAAAGGTAGTCAAGATTGTGTTTTGAGGTTTTCTTCAGACAGATTCCAGGCGATGTGCAAGTGTATG

CACGTGTGCACACACACCACACATACACACACACAAGCTTTTTTACACAAATGGTAGCATACTTTATA
 TTGGTCTGTATCTTGCTTTTTTTCACCAATATTTCTCAGACATCGGTTTCATATTAAGACATAAATTACTT
 TTTTATTCTTTTATACCGCTGCATAGTATTCCATTGTGTGAGTGTACCATAATGTATTTAACAGTCTT
 CTTTTGATATACTATTTTCATTCTCTTGTTATTGCATCAATGCTGAGTTAATAAATCAAATATATGTCAT
 5 TTTTGCATATATGTAAGGATAA
 (SEQ ID NO: 48)

As used herein, the term "ITGAX" refers to the gene encoding Integrin alpha-X. The terms
 "ITGAX" and "Integrin alpha-X" include wild-type forms of the ITGAX gene, as well as variants (e.g.,
 10 splice variants and polymorphisms) of wild-type ITGAX. Examples of such variants are nucleic acids
 having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%,
 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,
 98%, 99%, or 99.9% identity, or more) to a wild-type ITGAX nucleic acid sequence (e.g., SEQ ID NO: 49,
 ENA accession number M81695). SEQ ID NO: 49 is a wild-type gene sequence encoding ITGAX protein,
 15 and is shown below:

GAATTCCTGCCACTCTTCCTGCAACGGCCCAGGAGCTCAGAGCTCCACATCTGACCTTCT
 AGTCATGACCAGGACCAGGGCAGCACTCCTCCTGTTACAGCCTTAGCAACTTCTCTAGG
 TTTCAACTTGGACACAGAGGAGCTGACAGCCTTCCGTGTGGACAGCGCTGGGTTTGGAGA
 20 CAGCGTGGTCCAGTATGCCAACTCCTGGGTGGTGGTTGGAGCCCCCAAAGATAACAGC
 TGCCAACCAAACGGGTGGCCTCTACCAGTGTGGCTACAGCACTGGTGCCTGTGAGCCCAT
 CGGCCTGCAGGTGCCCCCGGAGGCCGTGAACATGTCCCTGGGCCTGTCCCTGGCGTCTAC
 CACCAGCCCTTCCCAGCTGCTGGCCTGCGGCCCCACCGTGCACCACGAGTGCGGGAGGAA
 CATGTACCTCACCGGACTCTGCTTCCTCCTGGGCCCCACCCAGCTCACCCAGAGGCTCCC
 25 GGTGTCCAGGCAGGAGTGCCCAAGACAGGAGCAGGACATTGTGTTCTGATCGATGGCTC
 AGGCAGCATCTCCTCCCACCACTTTGCCACGATGATGAACTTCGTGAGAGCTGTGATAAG
 CCAGTTCCAGAGACCCAGCACCCAGTTTTCCCTGATGCAGTTCTCCAACAAATTCCAAC
 AACTTCACTTTTCGAGGAATTCAGGCGCACGTCAAACCCCTCAGCCTGTTGGCTTCTGT
 TCACCAGCTGCAAGGGTTTACATACACGGCCACCGCCATCCAAATGTCGTGCACCGATT
 30 GTTCCATGCCTCATATGGGGCCCGTAGGGATGCCACCAAAATTCTCATTGTCATCACTGA
 TGGGAAGAAAGAAGGCGACAGCCTGGATTATAAGGATGTCATCCCCATGGCTGATGCAGC
 AGGCATCATCCGCTATGCAATTGGGGTTGGATTAGCTTTTCAAACAGAAATTCTTGAA
 AGAATTAATGACATTGCATCGAAGCCCTCCCAGGAACACATATTTAAAGTGAGGACTT
 TGATGCTCTGAAAGATATTCAAACCAACTGAAGGAGAAGATCTTGCCATTGAGGGTAC
 35 GGAGACCACAAGCAGTAGCTCCTTCGAATTGGAGATGGCACAGGAGGGCTTCAGCGCTGT
 GTTACACCTGATGGCCCCGTTCTGGGGGCTGTGGGGAGCTTCACCTGGTCTGGAGGTGC
 CTTCTGTACCCCCCAAATATGAGCCCTACCTTCATCAACATGTCTCAGGAGAATGTGGA
 CATGAGGGACTCTTACCTGGGTTACTCCACCGAGCTGGCCCTCTGGAAAGGGGTGCAGAG
 CCTGGTCCTGGGGGCCCCCGCTACCAGCACACCGGGAAGGCTGTCATCTTCACCCAGGT
 40 GTCCAGGCAATGGAGGATGAAGGCCGAAGTCACGGGGACTCAGATCGGCTCCTACTTCGG
 GGCCTCCCTCTGCTCCGTGGACGTAGACACCGACGGCAGCACCGACCTGGTCCTCATCGG
 GGCCCCCATTACTACGAGCAGACCCGAGGGGGCCAGGTGTCTGTGTGTCCCTTGCCCAG

GGGGTGGAGAAGGTGGTGGTGTGATGCTGTTCTCTACGGGGAGCAGGGCCACCCCTGGGG
TCGCTTTGGGGCGGCTCTGACAGTGCTGGGGGATGTGAATGGGGACAAGCTGACAGACGT
GGTCATCGGGGCCCCAGGAGAGGAGGAGAACC GG GTGCTGTCTACCTGTTTCACGGAGT
CTTGGGACCCAGCATCAGCCCCCTCCACAGCCAGCGGATCGCGGGCTCCCAGCTCTCCTC
5 CAGGCTGCAGTATTTTGGGCAGGCACTGAGCGGGGGTCAAGACCTCACCCAGGATGGACT
GGTGGACCTGGCTGTGGGGGCCCCGGGGCCAGGTGCTCCTGCTCAGGACCAGACCTGTGCT
CTGGGTGGGGGTGAGCATGCAGTTCATACCTGCCGAGATCCCCAGGTCTGCGTTTGAGTG
TCGGGAGCAGGTGGTCTCTGAGCAGACCCTGGTACAGTCCAACATCTGCCTTTACATTGA
CAAACGTTCTAAGAACCTGCTTGGGAGCCGTGACCTCCAAAGCTCTGTGACCTTGGACCT
10 GGCCCTCGACCCTGGCCGCTGAGTCCCCGTGCCACCTTCCAGGAAACAAAGAACC GG GAG
TCTGAGCCGAGTCCGAGTCCTCGGGCTGAAGGCACACTGTGAAAACCTCAACCTGCTGCT
CCCGAGCTGCGTGGAGGACTCTGTGACCCCCATTACCTTGCGTCTGAACTTCACGCTGGT
GGGCAAGCCCCCTCCTTGCTTCAGAAACCTGCGGCCTATGCTGGCCGCACTGGCTCAGAG
ATACTTCACGGCCTCCCTACCCTTTGAGAAGAACTGTGGAGCCGACCATATCTGCCAGGA
15 CAATCTCGGCATCTCCTTCAGCTTCCCAGGCTTGAAGTCCCTGCTGGTGGGGAGTAACCT
GGAGCTGAACGCAGAAGTGATGGTGTGGAATGACGGGGAAGACTCCTACGGAACCACCAT
CACCTTCTCCCACCCCGCAGGACTGTCCTACCGCTACGTGGCAGAGGGCCAGAAACAAGG
GCAGCTGCGTTCCCTGCACCTGACATGTGACAGCGCCCCAGTTGGGAGCCAGGGCACCTG
GAGCACCAGCTGCAGAATCAACCACCTCATCTTCCGTGGCGGCGCCAGATCACCTTCTT
20 GGCTACCTTTGACGTCTCCCCAAGGCTGTCTGGGAGACCGGCTGCTTCTGACAGCCAA
TGTGAGCAGTGAGAACAACACTCCCAGGACCAGCAAGACCACCTTCCAGCTGGAGCTCCC
GGTGAAGTATGCTGTCTACACTGTGGTTAGCAGCCACGAACAATTCACCAAATACCTCAA
CTTCTCAGAGTCTGAGGAGAAGGAAAGCCATGTGGCCATGCACAGATACCAGGTCAATAA
CCTGGGACAGAGGGACCTGCCTGTCAGCATCAACTTCTGGGTGCCTGTGGAGCTGAACCA
25 GGAGGCTGTGTGGATGGATGTGGAGGTCTCCCACCCCCAGAACCCATCCCTTCGGTGCTC
CTCAGAGAAAATCGCACCCCCAGCATCTGACTTCCTGGCGCACATTCAGAAGAATCCCGT
GCTGGACTGCTCCATTGCTGGCTGCCTGCGGTTCCGCTGTGACGTCCCCTCCTTCAGCGT
CCAGGAGGAGCTGGATTTACCCCTGAAGGGCAACCTCAGCTTTGGCTGGGTCCGCCAGAT
ATTGCAGAAGAAGGTGTCGGTCGTGAGTGTGGCTGAAATTACGTTGACACATCCGTGTA
30 CTCCCAGCTTCCAGGACAGGAGGCATTTATGAGAGCTCAGACGACAACGGTGCTGGAGAA
GTACAAGGTCCACAACCCCCACCCCTCATCGTAGGCAGCTCCATTGGGGGTCTGTTGCT
GCTGGCACTCATCACAGCGGTACTGTACAAAGTTGGCTTCTTCAAGCGTCAGTACAAGGA
AATGATGGAGGAGGCAAATGGACAAATTGCCCCAGAAAACGGGACACAGACCCCCAGCCC
GCCAGTGAGAAATGATCCCTCTTTGCCTTGGACTTCTTCTCCCGCGATTTTCCCCACTT
35 ACTTACCCTCACCTGTCAGGCTGACGGGGAGGAACCACTGCACCACCGAGAGAGGCTGGG
ATGGGCCTGCTTCCTGTCTTTGGGAGAAAACGTCTTGCTTGGGAAGGGGCCTTTGTCTTG
TCAAGTTCCAACCTGGAAACCCTTAGGACAGGGTCCCTGCTGTGTTCCCCAAAAGGACTT
GACTTGCAATTTCTACCTAGAAATACATGGACAATACCCCCAGGCCTCAGTCTCCCTTCT
CCCATGAGGCACGAATGATCTTTCTTTCTTTCTTTTTTTTTTTTTTTTTCTTTCTTTTTT
40 TTTTTTTTTTGAGACGGAGTCTCGCTCTGTACCCAGGCTGGAGTGCAATGGCGTGATCTC
GGCTCGCTGCAACCTCCGCCTCCCGGGTTCAAGTAATTCTGCTGTCTCAGCCTCCTGCGT
AGCTGGGACTACAGGCACACGCCACCTCGCCCCGGCCCGATCTTTCTAAATAACAGTTCTG

AATATGCTGCTCATCCCCACCTGTCTTCAACAGCTCCCCATTACCCTCAGGACAATGTCT
 GAACTCTCCAGCTTCGCGTGAGAAGTCCCCTTCCATCCCAGAGGGTGGGCTTCAGGGCGC
 ACAGCATGAGAGCCTCTGTGCCCCCATCACCTCGTTTTCCAGTGAATTAGTGTATGTCA
 GCATCAGCTCAGGGCTTCATCGTGGGGCTCTCAGTTCCGATTCCCCAGGCTGAATTGGGA
 5 GTGAGATGCCTGCATGCTGGGTTCTGCACAGCTGGCCTCCCGCGGTTGGGTCAACATTGC
 TGGCCTGGAAGGGAGGAGCGCCCTCTAGGGAGGGACATGGCCCCGGTGC GGCTGCAGCTC
 ACCAGCCCCAGGGGCAGAAGAGACCCAACCACTTCCTATTTTTTTGAGGCTATGAATATAG
 TACCTGAAAAAATGCCAAGCACTAGATTATTTTTTTAAAAAGCGTACTTTAAATGTTTGT
 GTTAATACACATTAAAACATCGCACAAAAACGATGCATCTACCGCTCCTTGGGAAATAAT
 10 CTGAAAGGTCTAAAAATAAAAAAGCCTTCTGTGG
 (SEQ ID NO: 49)

As used herein, the term "LILRB4" refers to the gene encoding Leukocyte immunoglobulin-like
 receptor subfamily B member 4. The terms "LILRB4" and "Leukocyte immunoglobulin-like receptor
 15 subfamily B member 4" include wild-type forms of the LILRB4 gene, as well as variants (e.g., splice
 variants and polymorphisms) of wild-type LILRB4. Examples of such variants are nucleic acids having at
 least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%,
 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%,
 or 99.9% identity, or more) to a wild-type LILRB4 nucleic acid sequence (e.g., SEQ ID NO: 50, ENA
 20 accession number U91925). SEQ ID NO: 50 is a wild-type gene sequence encoding LILRB4 protein, and
 is shown below:

TGAGATGAGAGCTGCCGACAGTTGGGGTCAAGGGAGGAGACGCCATGATCCCCACCTTC
 ACGGCTCTGCTCTGCCTCGGGCTGAGTCTGGGCCCCAGGACCCACATGCAGGCAGGGCCC
 25 CTCCCCAAACCCACCCTCTGGGCTGAGCCAGGCTCTGTGATCAGCTGGGGGAACTCTGTG
 ACCATCTGGTGTGAGGGGACCCTGGAGGCTCGGGAGTACCGTCTGGATAAAGAGGAAAGC
 CCAGCACCTGGGACAGACAGAACCCACTGGAGCCCAAGAACAAGGCCAGATTCTCCATC
 CCATCCATGACAGAGGACTATGCAGGGAGATACCGCTGTTACTATCGCAGCCCTGTAGGC
 TGGTCACAGCCCAGTGACCCCCTGGAGCTGGTGTATGACAGGAGCCTACAGTAAACCCACC
 30 CTTTCAGCCCTGCCGAGTCCTCTTGTGACCTCAGGAAAGAGCGTGACCCTGCTGTGTGTCAG
 TCACGGAGCCCAATGGACACTTTCTTCTGATCAAGGAGCGGGCAGCCCATCCCCTACTG
 CATCTGAGATCAGAGCACGGAGCTCAGCAGCACCAGGCTGAATTCCCATGAGTCCTGTG
 ACCTCAGTGACGGGGGGACCTACAGGTGCTTCAGCTCACACGGCTTCTCCCACTACCTG
 CTGTCACACCCCAGTGACCCCCTGGAGCTCATAGTCTCAGGATCCTTGGAGGGTCCCAGG
 35 CCCTCACCCACAAGGTCCGTCTCAACAGCTGCAGGCCCTGAGGACCAGCCCCTCATGCCT
 ACAGGGTCAGTCCCCACAGTGGTCTGAGAAGGCACTGGGAGGTACTGATCGGGGTCTTG
 GTGGTCTCCATCCTGCTTCTCTCCCTCCTCCTCTTCTCCTCCTCCAACACTGGCGTCAG
 GGAAAACACAGGACATTGGCCCAGAGACAGGCTGATTTCCAACGTCCTCCAGGGGCTGCC
 GAGCCAGAGCCCAAGGACGGGGGCCTACAGAGGAGGTCCAGCCCAGCTGCTGACGTCCAG
 40 GGAGAAAATTCTGTGCTGCCGTGAAGAACACACAGCCTGAGGACGGGGTGGAATGGAC
 ACTCGGCAGAGCCCACACGATGAAGACCCCCAGGCAGTGACGTATGCCAAGGTGAAACAC
 TCCAGACCTAGGAGAGAAATGGCCTCTCCTCCCTCCCCACTGTCTGGGGAATTCTGGAC

ACAAAGGACAGACAGGCAGAAGAGGACAGACAGATGGACACTGAGGCTGCTGCATCTGAA
 GCCCCCAGGATGTGACCTACGCCCAGCTGCACAGCTTTACCCTCAGACAGAAGGCAACT
 GAGCCTCCTCCATCCCAGGAAGGGGCTCTCCAGCTGAGCCCAGTGTCTATGCCACTCTG
 GCCATCCACTAATCCAGGGGGGACCCAGACCCCAAGCCATGGAGACTCAGGACCCAG
 5 AAGGCATGGAAGCTGCCTCCAGTAGACATCACTGAACCCAGCCAGCCAGACCCCTGAC
 ACAGACCACTAGAAGATTCCGGGAACGTTGGGAGTCACCTGATTCTGCAAAGATAAATAA
 TATCCCTGCATTATCAAATAAAGTAGCAGACCTCTCAATTCA
 (SEQ ID NO: 50)

- 10 As used herein, the term "LPL" refers to the gene encoding Lipoprotein lipase. The terms "LPL" and "Lipoprotein lipase" include wild-type forms of the LPL gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type LPL. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9%
 15 identity, or more) to a wild-type LPL nucleic acid sequence (e.g., SEQ ID NO: 51, ENA accession number M15856). SEQ ID NO: 51 is a wild-type gene sequence encoding LPL protein, and is shown below:

CCCCTCTTCCTCCTCCTCAAGGGAAAGCTGCCCACTTCTAGCTGCCCTGCCATCCCCTTT
 AAAGGGCGACTTGCTCAGCGCCAAACCGCGGCTCCAGCCCTCTCCAGCCTCCGGCTCAGC
 20 CGGCTCATCAGTCGGTCCGCGCCTTGACAGCTCCTCCAGAGGGACGCGCCCCGAGATGGAG
 AGCAAAGCCCTGCTCGTGCTGACTCTGGCCGTGTGGCTCCAGAGTCTGACCGCCTCCCGC
 GGAGGGGTGGCCGCCGCCGACCAAGAAGAGATTTTATCGACATCGAAAGTAAATTTGCC
 CTAAGGACCCCTGAAGACACAGCTGAGGACACTTGCCACCTCATTCCCGGAGTAGCAGAG
 TCCGTGGCTACCTGTCAATTCACAGCAGCAAAACCTTCATGGTGATCCATGGCTGG
 25 ACGGTAACAGGAATGTATGAGAGTTGGGTGCCAAACTTGTGGCCGCCCTGTACAAGAGA
 GAACCAGACTCCAATGTCATTGTGGTGGACTGGCTGTCACGGGCTCAGGAGCATTACCCA
 GTGTCCGCGGGCTACACCAAACTGGTGGGACAGGATGTGGCCCGGTTTATCAACTGGATG
 GAGGAGGAGTTTAACTACCCTCTGGACAATGTCCATCTCTTGGGATACAGCCTTGAGGCC
 CATGCTGCTGGCATTGCAGGAAGTCTGACCAATAAGAAAGTCAACAGAATTACTGGCCTC
 30 GATCCAGCTGGACCTAACTTTGAGTATGCAGAAGCCCCGAGTCGTCTTCTCCTGATGAT
 GCAGATTTTGTAGACGTCTTACACACATTACCCAGAGGGTCCCCTGGTCAAGCATTGGA
 ATCCAGAAACCAGTTGGGCATGTTGACATTTACCCGAATGGAGGTACTTTTCAGCCAGGA
 TGTAAATTGGAGAAGCTATCCGCGTGATTGCAGAGAGAGGACTTGAGATGTGGACCAG
 CTAGTGAAGTGCTCCACGAGCGCTCCATTATCTCTTCATCGACTCTCTGTTGAATGAA
 35 GAAAATCCAAGTAAGGCCTACAGGTGCAGTTCCAAGGAAGCCTTTGAGAAAGGGCTCTGC
 TTGAGTTGTAGAAAGAACCCTGCAACAATCTGGGCTATGAGATCAATAAAGTCAGAGCC
 AAAAGAAGCAGCAAAATGTACCTGAAGACTCGTTCTCAGATGCCCTACAAAGTCTTCCAT
 TACCAAGTAAAGATTCATTTTTCTGGGACTGAGAGTGAAACCCATACCAATCAGGCCTTT
 GAGATTTCTCTGTATGGCACCGTGGCCGAGAGTGAGAACATCCCATTCACTCTGCCTGAA
 40 GTTTCCACAAATAAGACCTACTCCTTCTAATTTACACAGAGGTAGATATTGGAGAATA
 CTCATGTTGAAGCTCAAATGGAAGAGTGATTCATACTTTAGCTGGTCAGACTGGTGGAGC
 AGTCCCGGCTTCGCCATTGAGAAGATCAGAGTAAAAGCAGGAGAGACTCAGAAAAAGGTG

ATCTTCTGTTCTAGGGAGAAAGTGTCTCATTTGCAGAAAGGAAAGGCACCTGCGGTATTT
 GTGAAATGCCATGACAAGTCTCTGAATAAGAAGTCAGGCTGAAACTGGGCGAATCTACAG
 AACAAAGAACGGCATGTGAATTCTGTGAAGAATGAAGTGGAGGAAGTAACTTTTACAAAA
 CATACCCAGTGTTTGGGGTGTTCAAAAGTGGATTTTCCTGAATATTAATCCCAGCCCTA
 5 CCCTTGTTAGTTATTTTAGGAGACAGTCTCAAGCACTAAAAAGTGGCTAATTCAATTTAT
 GGGGTATAGTGGCCAAATAGCACATCCTCCAACGTTAAAGACAGTGGATCATGAAAAGT
 GCTGTTTTGTCCTTTGAGAAAGAAATAATTGTTTGAGCGCAGAGTAAAATAAGGCTCCTT
 CATGTGGCGTATTGGGCCATAGCCTATAATTGGTTAGAACCTCCTATTTTAATTGGAATT
 CTGGATCTTTTCGACTGAGGCCTTCTCAAACCTTACTCTAAGTCTCCAAGAATACAGAAA
 10 ATGCTTTTCCGCGGCACGAATCAGACTCATCTACACAGCAGTATGAATGATGTTTTAGAA
 TGATTCCCTCTTGCTATTGGAATGTGGTCCAGACGTCAACCAGGAACATGTAAGTTGGAG
 AGGGACGAAGAAAGGGTCTGATAAACACAGAGGTTTTAAACAGTCCCTACCATTTGGCCTG
 CATCATGACAAAGTTACAAATTCAAGGAGATATAAAATCTAGATCAATTAATTCCTTAATA
 GGCTTTATCGTTTATTGCTTAATCCCTCTCTCCCCCTTCTTTTTTGTCTCAAGATTATAT
 15 TATAATAATGTTCTCTGGGTAGGTGTTGAAAATGAGCCTGTAATCCTCAGCTGACACATA
 ATTTGAATGGTGCAGAAAAAAAAAAGATACCGTAATTTTATTATTAGATTCTCCAAATGA
 TTTTCATCAATTTAAATCATTCAATATCTGACAGTTACTCTTCAGTTTTAGGCTTACCT
 TGGTCATGCTTCAGTTGTACTTCCAGTGCGTCTCTTTTGTCTGCTGGCTTTGACATGAAAA
 GATAGGTTTGAGTTCAAAATTTGCATTGTGTGAGCTTCTACAGATTTTAGACAAGGACCG
 20 TTTTACTAAGTAAAAGGGTGGAGAGGTTCTGGGGTGGATTCTAAGCAGTGCTTGTA
 ACCATCGCGTGCAATGAGCCAGATGGAGTACCATGAGGGTTGTTATTTGTTGTTTTTAAC
 AACTAATCAAGAGTGAGTGAACAACATTTTATAAACTAGATCTCCTATTTTTCAGAATGC
 TCTTCTACGTATAAATATGAAATGATAAAGATGTCAAATATCTCAGAGGCTATAGCTGGG
 AACCCGACTGTGAAAGTATGTGATATCTGAACACATACTAGAAAGCTCTGCATGTGTGTT
 25 GTCCTTCAGCATAATTCGGAAGGGAAAACAGTCGATCAAGGGATGTATTGGAACATGTGCG
 GAGTAGAAATTGTTCTGATGTGCCAGAACTTCGACCCTTCTCTGAGAGAGATGATCGT
 GCCTATAAATAGTAGGACCAATGTTGTGATTAACATCATCAGGCTTGAATGAATTCTCT
 CTA AAAATAAAATGATGTATGATTTGTTGTTGGCATCCCCTTTATTAATTCATTAAATTT
 CTGGATTTGGGTTGTGACCCAGGGTGCATTAACCTAAAAGATTCATAAGCAGCACATA
 30 GCACTGGGAACCTCTGGCTCCGAAAACTTTGTTATATATATCAAGGATGTTCTGGCTTTA
 CATTTTATTTATTAGCTGTAAATACATGTGTGGATGTGTAAATGGAGCTTGACATATTG
 GAAAGGTCATTGTGGCTATCTGCATTTATAAATGTGTGGTGCTAACTGTATGTGTCTTTA
 TCAGTGATGGTCTCACAGAGCCAACTCACTCTTATGAAATGGGCTTTAACAAAACAAGAA
 AGAAACGTACTTAACTGTGTGAAGAAATGGAATCAGCTTTTAATAAAATTGACAACATTT
 35 TATTACCAC
 (SEQ ID NO: 51)

As used herein, the term "MEF2C" refers to the gene encoding Myocyte-specific enhancer factor
 2C. The terms "MEF2C" and "Myocyte-specific enhancer factor 2C" include wild-type forms of the
 40 MEF2C gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type MEF2C.
 Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%,
 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%,

91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type MEF2C nucleic acid sequence (e.g., SEQ ID NO: 52, ENA accession number L08895). SEQ ID NO: 52 is a wild-type gene sequence encoding MEF2C protein, and is shown below:

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5  GAATTCCCAGCTCTCTGCTCGCTCTGCTCGCAGTCACAGACACTTGAGCACACGCGTACA
   CCCAGACATCTTCGGGCTGCTATTGGATTGACTTTGAAGGTTCTGTGTGGGTCGCCGTGG
   CTGCATGTTTGAATCAGGTGGAGAAGCACTTCAACGCTGGACGAAGTAAAGATTATTGTT
   GTTATTTTTTTTTTCTCTCTCTCTCTCTTAAGAAAGGAAAATATCCCAAGGACTAATC
   TGATCGGGTCTTCCTTCATCAGGAACGAATGCAGGAATTTGGGAACTGAGCTGTGCAAGT
10  GCTGAAGAAGGAGATTTGTTTGGAGGAAACAGGAAAGAGAAAGAAAAGGAAGGAAAAAAT
   ACATAATTTCAGGGACGAGAGAGAGAAGAAAAACGGGGACTATGGGGAGAAAAAAGATTC
   AGATTACGAGGATTATGGATGAACGTAACAGACAGGTGACATTTACAAAGAGGAAATTTG
   GGTTGATGAAGAAGGCTTATGAGCTGAGCGTGCTGTGTGACTGTGAGATTGCGCTGATCA
   TCTTCAACAGCACCAACAAGCTGTTCCAGTATGCCAGCACCGACATGGACAAAGTGCTTC
15  TCAAGTACACGGAGTACAACGAGCCGCATGAGAGCCGGACAAACTCAGACATCGTGGAGA
   CGTTGAGAAAGAAGGGCCTTAATGGCTGTGACAGCCCAGACCCCGATGCGGACGATTCCG
   TAGGTCACAGCCCTGAGTCTGAGGACAAGTACAGGAAAATTAACGAAGATATTGATCTAA
   TGATCAGCAGGCAAAGATTGTGTGCTGTTCCACCTCCCAACTTCGAGATGCCAGTCTCCA
   TCCCAGTGTCCAGCCACAACAGTTTGGTGTACAGCAACCCTGTCAGCTCACTGGGAAACC
20  CCAACCTATTGCCACTGGCTCACCTTCTCTGCAGAGGAATAGTATGTCTCCTGGTGTA
   CACATCGACCTCCAAGTGCAGGTAACACAGGTGGTCTGATGGGTGGAGACCTCACGTCTG
   GTGCAGGCACCAAGTGCAGGGAACGGGTATGGCAATCCCCGAAACTCACCAGGTCTGCTGG
   TCTCACCTGGTAACTTGAACAAGAATATGCAAGCAAAATCTCCTCCCCCAATGAATTTAG
   GAATGAATAACCGTAAACCAGATCTCCGAGTTCTTATTCCACCAGGCAGCAAGAATACGA
25  TGCCATCAGTGTCTGAGGATGTGACCTGCTTTTGAATCAAAGGATAAATAACTCCCAGT
   CGGCTCAGTCATTGGCTACCCAGTGTTTTCCGTAGCAACTCCTACTTTACCAGGACAAG
   GAATGGGAGGATATCCATCAGCCATTTCAACAACATATGGTACCGAGTACTCTCTGAGTA
   GTGCAGACCTGTCATCTCTGTCTGGGTTTAACACCGCCAGCGCTCTTACCTTGGTTCAG
   TAACTGGCTGGCAACAGCAACACCTACATAACATGCCACCATCTGCCCTCAGTCAGTTGG
30  GAGCTTGCACTAGCACTCATTTATCTCAGAGTTCAAATCTCTCCCTGCCTTCTACTCAA
   GCCTCAACATCAAGTCAGAACCTGTTTCTCCTCCTAGAGACCGTACCACCACCCCTTCGA
   GATACCCACAACACACGCGCCACGAGGCGGGGAGATCTCCTGTTGACAGCTTGAGCAGCT
   GTAGCAGTTCTGACGACGGGAGCGACCGAGAGGATCACCGGAACGAATTCCACTCCCCCA
   TTGGACTCACCAGACCTTCGCCGGACGAAAGGGAAAAGTCCCTCAGTCAAGCGCATGCGAC
35  TTTCTGAAGGATGGGCAACATGATCAGATTATTACTTACTAGTTTTTTTTTTTTTTCTTGC
   AGTGTGTGTGTGTGCTATACCTTAATGGGGAAGGGGGGTCGATATGCATTATATGTGCCG
   TGTGTGGAAAAAAAAAAGTCAGGTA CTCTGTTTTGTAAAAGTACTTTTAAATTGCCTCA
   GTGATACAGTATAAAGATAAACAGAAATGCTGAGATAAGCTTAGCACTTGAGTTGTACAA
   CAGAACACTTGTACAAAATAGATTTTAAGGCTAACTTCTTTTCACTGTTGTGCTCCTTTG
40  CAAAATGTATGTTACAATAGATAGTGTGTCATGTTGCAGGTTCAACGTTATTTACATGTAA
   TAGACAAAAGGAAACATTTGCCAAAAGCGGCAGATCTTTACTGAAAGAGAGAGCAGCTGT
   TATGCAACATATAGAAAAATGTATAGATGCTTGGACAGACCCGGTAATGGGTGGCCATTG
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GTAAATGTTAGGAACACACCAGGTCACCTGACATCCCAAGAATGCTCACAAACCTGCAGG
 CATATCATTGGCGTATGGCACTCATTAAAAAGGATCAGAGACCATTAAAAGAGGACCATA
 CCTATTAATAAAAAAATGTGGAGTTGGAGGGCTAACATATTTAATTAAATAAATAAATAA
 TCTGGGTCTGCATCTCTTATTAAATAAAAAATATAAAAAATATGTACATTACATTTTGCTTA
 5 TTTTCATATAAAAGGTAAGACAGAGTTTGCAAAGCATTGTGGCTTTTTGTAGTTTACTT
 AAGCCAAAATGTGTTTTTTTCCCCTTGATAGCTTCGCTAATATTTTAAACAGTCCTGTAA
 AAAACCAAAAAGGACTTTTTGTATAGAAAGCACTACCCTAAGCCATGAAGAACTCCATGC
 TTTGCTAACCAAGATAACTGTTTTCTCTTTGTAGAAGTTTTGTTTTTGAATGTGTATTT
 CTAATTATATAAAATATTAAGAATCTTTTAAAAAATCTGTGAAATTAACATGCTTGTGT
 10 ATAGCTTTCTAATATATATAATATTATGGTAATAGCAGAAGTTTTGTTATCTTAATAGCG
 GGAGGGGGGTATATTTGTGCAGTTGCACATTTGAGTAACTATTTTCTTCTGTTTTCTTT
 TACTCTGCTTACATTTTATAAGTTTAAGGTCAGCTGTCAAAGGATAACCTGTGGGGTTA
 GAACATATCACATTGCAACACCCTAAATTGTTTTTAATACATTAGCAATCTATTGGGTCA
 ACTGACATCCATTGTATATACTAGTTTCTTTCATGCTATTTTTATTTTGTTTTTTGCATT
 15 TTTATCAAATGCAGGGCCCCCTTCTGATCTCACCATTTTACCATGCATCTTGGAAATCAG
 TAAGTGCATATCCTAACTTGCCCATATTCTAAATCATCTGGTTGGTTTTTCAAGCCTAGAAT
 TTGATACGCTTTTTAGAAATATGCCCAGAATAGAAAAGCTATGTTGGGGCACATGTCCTG
 CAAATATGGCCCTAGAAACAAGTGATATGGAATTTACTTGGTGAATAAGTTATAAATTCC
 CACAGAAGAAAAATGTGAAAGACTGGGTGCTAGACAAGAAGGAAGCAGGTAAAGGGATAG
 20 TTGCTTTGTATCCGTTTTTAATTATTTTAACTGACCCTTGACAATCTTGTGAGCAATAT
 AGGACTGTTGAACAATCCCGGTGTGTCAGGACCCCCAAATGTCACTTCTGCATAAAGCAT
 GTATGTCATCTATTTTTTCTTCAATAAAGAGATTTAATAGCCATTTCAAGAAATCCATA
 AAGAACCTCTCTATGTCCCTTTTTTTAATTTAAAAAATGACTCTTGTCTAATATTCGTC
 TATAAGGGATTAATTTTCAAGACCCTTTAATAAGTGAGTGCCATAAGAAAGTCAATATATA
 25 TTGTTTAAAAGATATTTTCACTAGTCTAGGAAAGATTTTCTTCTCTTGAATGTGAAGATCTG
 TCGATTCTCTCAATCATATGCATTGACATACACAGCAAAGAAGATATAGGCAGTAATA
 TCAACACTGCTATATCATGTGTAGGACATTTCTTATCCATTTTTTCTCTTTTACTTGCAT
 AGTTGCTATGTGTTTCTCATTGTAAAAGGCTGCCGCTGGGTGGCAGAAGCCAAGAGACCT
 TATTAAGTGGCTATATTTTTCTTAACTTGATCTGAAATCCACAATTAGACCACAATGCA
 30 CCTTTGGTTGTATCCATAAAGGATGCTAGCCTGCCTTGACTAATGTTTTATATATT
 (SEQ ID NO: 52)

As used herein, the term "MMP12" refers to the gene encoding Macrophage metalloelastase.
 The terms "MMP12" and "Macrophage metalloelastase" include wild-type forms of the MMP12 gene, as
 35 well as variants (e.g., splice variants and polymorphisms) of wild-type MMP12. Examples of such
 variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%,
 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%,
 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type MMP12 nucleic acid
 sequence (e.g., SEQ ID NO: 53, ENA accession number L23808). SEQ ID NO: 53 is a wild-type gene
 40 sequence encoding MMP12 protein, and is shown below:

TAGAAGTTTACAATGAAGTTTCTTCTAATACTGCTCCTGCAGGCCACTGCTTCTGGAGCT

CTTCCCCTGAACAGCTCTACAAGCCTGGAAAAAATAATGTGCTATTTGGTGAGAGATAC
 TTAGAAAAATTTTATGGCCTTGAGATAAACAACTTCCAGTGACAAAAATGAAATATAGT
 GGAACTTAATGAAGGAAAAAATCCAAGAAATGCAGCACTTCTTGGGTCTGAAAGTGACC
 GGGCAACTGGACACATCTACCCTGGAGATGATGCACGCACCTCGATGTGGAGTCCCCGAT
 5 CTCCATCATTTTCAGGGAAATGCCAGGGGGGCGCGTATGGAGGAAACATTATATCACCTAC
 AGAATCAATAATTACACACCTGACATGAACCGTGAGGATGTTGACTACGCAATCCGGAAA
 GCTTTCCAAGTATGGAGTAATGTTACCCCTTGAAATTCAGCAAGATTAACACAGGCATG
 GCTGACATTTTGGTGGTTTTTGGCCGTGGAGCTCATGGAGACTTCCATGCTTTTGTATGGC
 AAAGGTGGAATCCTAGCCCATGCTTTTGGACCTGGATCTGGCATTGGAGGGGATGCACAT
 10 TTCGATGAGGACGAATTCTGGACTACACATTCAGGAGGCACAACTTGTTCTCTCACTGCT
 GTTCACGAGATTGGCCATTCTTAGGTCTTGGCCATTCTAGTGATCCAAAGGCTGTAATG
 TTCCCCACCTACAAATATGTCGACATCAACACATTTGCGCTCTCTGCTGATGACATACGT
 GGCATTCACTCCCTGTATGGAGACCCAAAAGAGAACCAACGCTTGCCAAATCCTGACAA
 TCAGAACCAGCTCTCTGTGACCCCAATTTGAGTTTTGATGCTGTCACTACCGTGGGAAAT
 15 AAGATCTTTTTCTTCAAAGACAGGTTCTTCTGGCTGAAGGTTTCTGAGAGACCAAAGACC
 AGTGTTAATTTAATTTCTTCTTATGGCCAACCTTGCCATCTGGCATTGAAGCTGCTTAT
 GAAATTGAAGCCAGAAATCAAGTTTTTCTTTTTAAAGATGACAAATACTGGTTAATTAGC
 AATTTAAGACCAGAGCCAAATTATCCCAAGAGCATACATTCTTTTGGTTTTCTAACTTT
 GTGAAAAAATTGATGCAGCTGTTTTTAACCCACGTTTTTATAGGACCTACTTCTTTGTA
 20 GATAACCAGTATTGGAGGTATGATGAAAGGAGACAGATGATGGACCCTGGTTATCCCAAA
 CTGATTACCAAGAATTTCCAAGGAATCGGGCCTAAAATTGATGCAGTCTTCTATTCTAAA
 AACAAATACTACTATTTCTTCCAAGGATCTAACCAATTTGAATATGACTTCCTACTCCAA
 CGTATCACCAAAACACTGAAAAGCAATAGCTGGTTTGGTTGTTAGAAATGGTGTAAATTAA
 TGGTTTTTGTAGTTCACTTCAGCTTAATAAGTATTTATTGCATATTTGCTATGTCCTCA
 25 GTGTACCACTACTTAGAGATATGTATCATAAAAATAAAATCTGTAAACCATAGGTAATGA
 TTATATAAAATACATAATTTTTCAATTTGAAAACCTCTAATTGTCCATTCTTGCTTGA
 CTCTACTATTAAGTTTGAAAATAGTTACCTTCAAAGCAAGATAATTCTATTTGAAGCATG
 CTCTGTAAGTTGCTTCCTAACATCCTTGGACTGAGAAATTATACTTACTTCTGGCATAAC
 TAAAATTAAGTATATATATTTTGGCTCAAATAAAATTG
 30 (SEQ ID NO: 53)

As used herein, the term "MS4A4A" refers to the gene encoding Membrane Spanning 4-Domains A4A. The terms "MS4A4A" and "Membrane Spanning 4-Domains A4A" include wild-type forms of the MS4A4A gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type MS4A4A.

35 Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type MS4A4A nucleic acid sequence (e.g., SEQ ID NO: 54, NCBI Reference Sequence: NM_148975.2). SEQ ID NO: 54 is a wild-type gene sequence encoding MS4A4A protein, and is shown below:

40 ATTCTCAGCACAGCCTTTAAGGTTCCAAACATCTGCTAGAAGAGGAATGCAGATTTAACTGAGTGAG
 GTGTGGAGTGGGGGAAGTTGATTGGGTCTAGACCAAAGAACTTTGAGGAACTTGCCAGAGCCCTG

CATGCATCAGACCTACAGCAGACATTGCAGGCCTGAAGAAAGCACCTTTTCTGCTGCCATGACAACC
 ATGCAAGGAATGGAACAGGCCATGCCAGGGGCTGGCCCTGGTGTGCCCCAGCTGGGAAACATGGC
 TGTACATACATTCACATCTGTGGAAAGGATTGCAAGAGAAGTTCTTGAAGGGAGAACCCAAAGTCCTT
 GGGGTTGTGCAGATTCTGACTGCCCTGATGAGCCTTAGCATGGGAATAACAATGATGTGTATGGCAT
 5 CTAATACTTATGGAAGTAACCCTATTTCCGTGTATATCGGGTACACAATTTGGGGGTCAGTAATGTTT
 ATTATTTTCAGGATCCTTGTCAATTGCAGCAGGAATTAGAACTACAAAAGGCCTGGTCCGAGGTAGTCT
 AGGAATGAATATCACCAGCTCTGTACTGGCTGCATCAGGGATCTTAATCAACACATTTAGCTTGGCGT
 TTTATTCATTCCATCACCCCTTACTGTAATACTATGGCAACTCAAATAATTGTCATGGGACTATGTCCA
 TCTTAATGGGTCTGGATGGCATGGTGCTCCTCTTAAGTGTGCTGGAATTCTGCATTGCTGTGTCCCT
 10 CTCTGCCCTTTGGATGTAAAGTGCTCTGTTGTACCCCTGGTGGGGTTGTGTTAATTCTGCCATCACATT
 CTCACATGGCAGAAACAGCATCTCCACACCACTTAATGAGGTTTGAGGCCACCAAAAGATCAACAG
 ACAAATGCTCCAGAAATCTATGCTGACTGTGACACAAGAGCCTCACATGAGAAATTACCAGTATCCAA
 CTTGATACTGATAGACTTGTGATATTATTATTATATGTAATCCAATTATGAACTGTGTGTATAGA
 GAGATAATAAATTCAAATTATGTTCTCATTTTTTTCCCTGGAAGTCAATAACTCATTTCACTGGCTCTT
 15 TATCGAGAGTACTAGAAGTTAAATTAATAAATAATGCATTTAATGAGGCAACAGCACTTGAAAGTTTTT
 CATTATCATAAGAAGCTTTATATAAAGGCATTACATTGGCAAATAAGGTTTGAAGCAGAAGAGCAAA
 AAAAAGATATTGTTAAATGAGGCCTCCATGCAAACACATACTTCCCTCCCATTTATTTAACTTTTTTT
 TTCTCCTACCTATGGGGACCAAAGTGCTTTTTTCCTTCAGGAAGTGGAGATGCATGGCCATCTCCCCC
 TCCCTTTTTCTTCTCCTGCTTTTTCTTCCCATAGAAAGTACCTTGAAGTAGCACAGTCCGTCCTTG
 20 CATGTGCACGAGCTATCATTTGAGTAAAAGTATACATGGAGTAAAAATCATATTAAGCATCAGATTCA
 ACTTATATTTTCTATTTTCATCTTCTTCTTCCCTTCTCCACCTTCTACTGGGCATAATTATATCTTAA
 TCATATATGGAAATGTGCAACATATGGTATTTGTTAAATACGTTTGTGTTTTATTGCAGAGCAAAAATAA
 ATCAAATTAGAAGCAATAAAAAAAAAAAAAAAAAAAAAA
 (SEQ ID NO: 54)

25
 As used herein, the term "MS4A6A" refers to the gene encoding Membrane-spanning 4-domains subfamily A member 6A. The terms "MS4A6A" and "Membrane-spanning 4-domains subfamily A member 6A" include wild-type forms of the MS4A6A gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type MS4A6A. Examples of such variants are nucleic acids having at least 70%

30 sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type MS4A6A nucleic acid sequence (e.g., SEQ ID NO: 55, ENA accession number AB013104). SEQ ID NO: 55 is a wild-type gene sequence encoding MS4A6A protein, and is shown below:

35
 GAGAACCAGAGTTAAAACCTCTTTGGAGCTTCTGAGGACTCAGCTGGAACCAACGGGCAC
 AGTTGGCAACACCATCATGACATCACAACTGTTCCCAATGAGACCATCATAGTGCTCCC
 ATCAAATGTCATCAACTTCTCCCAAGCAGAGAAACCCGAACCCACCAACCAGGGGCAGGA
 TAGCCTGAAGAAACATCTACACGCAGAAATCAAAGTTATTGGGACTATCCAGATCTTGTG
 40 TGGCATGATGGTATTGAGCTTGGGGATCATTTTGGCATCTGCTTCCTTCTCTCCAAATTT
 TACCCAAGTGACTTCTACACTGTTGAACTCTGCTTACCCATTCATAGGACCCTTTTTTTTT
 TATCATCTCTGGCTCTCTATCAATCGCCACAGAGAAAAGGTTAACCAAGCTTTTGGTGCA

TAGCAGCCTGGTTGGAAGCATTCTGAGTGCTCTGTCTGCCCTGGTGGGTTTCATTATCCT
 GTCTGTCAAACAGGCCACCTTAAATCCTGCCTCACTGCAGTGGAAGTCTCTCTCTGATGC
 TGATTTGCACTCTGCTGGAATTCTGCCTAGCTGTGCTCACTGCTGTGCTGCGGTGGAAAC
 AGGCTTACTCTGACTTCCCTGGGAGTGGACTTTTCCTGCCTCACAGTTACATTGGTAATT
 5 CTGGCATGTCCTCAAAAATGACTCATGACTGTGGATATGAAGAACTATTGACTTCTTAAG
 AAAAAAGGGAGAAATATTAATCAGAAAGTTGATTCTTATGATAATATGGAAAAGTTAACC
 ATTATAGAAAAGCAAAGCTTGAGTTTCCTAAATGTAAGCTTTTAAAGTAATGAACATTAA
 AAAAAACCATTATTTCACTGTC
 (SEQ ID NO: 55)

10

As used herein, the term "NLRP3" refers to the gene encoding NACHT, LRR and PYD domains-
 containing protein 3. The terms "NLRP3" and "NACHT, LRR and PYD domains-containing protein 3"
 include wild-type forms of the NLRP3 gene, as well as variants (e.g., splice variants and polymorphisms)
 of wild-type NLRP3. Examples of such variants are nucleic acids having at least 70% sequence identity
 15 (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%,
 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to
 a wild-type NLRP3 nucleic acid sequence (e.g., SEQ ID NO: 56, ENA accession number AF410477).
 SEQ ID NO: 56 is a wild-type gene sequence encoding NLRP3 protein, and is shown below:

20 GTAGATGAGGAACTGAAGTTGAGGAATAGTGAAGAGTTTGTCCAATGTCATAGCCCCGT
 AATCAACGGGACAAAAATTTTCTTGCTGATGGGTCAAGATGGCATCGTGAAGTGGTTGTT
 CACCGTAACTGTAATACAATCCTGTTTATGGATTTGTTGCATATTTTCCCCCATAG
 GGAAACCTTTTTTCCATGGCTCAGGACACACTCCTGGATCGAGCCAACAGGAGAACTTTC
 TGGTAAGCATTTGGCTAACTTTTTTTTTTTTGGAGATGGAGTCTTGCTGTGTCGCCTAGGC
 25 TGGAGTGCAGTGGCGTGATCTTGGCTCACTGCAGCCTCCACCTCCCGGGTTCAATCAATT
 CTCCTACCTCAACTTCCTGAGTAGCTGGGATTACAGGCGCCCGCCACCACACCCGGCTCA
 TTTTGTACTTTTAGTAGAGACACAGTTTTGCCATGTTGGCCAGGCTGGTCTTGAATTCC
 TCAGCTCAGGTGATATGCCTGCCTTGGCCTCTCAAAGTGCTGGGATTACAGGCGTGAGCC
 ACTGTGCCCGGCCTTGGCTAACTTTTCAAATTAAGATTTTGACTTGTTACAGTCATGT
 30 GACATTTTTTTCTTTCTGTTTGGTGAGTTTTTGATAATTTATATCTCTCAAAGTGGAGAC
 TTTAAAAAAGACTCATCTGTGTGCCGTGTTCACTGCCTGGTATCTTAGTGTGGACCGAAG
 CCTAAGGACCCTGAAAACAGCTGCAGATGAAGATGGCAAGCACCCGCTGCAAGCTGGCCA
 GGTACCTGGAGGACCTGGAGGATGTGGACTTGAAGAAATTTAAGATGCACTTAGAGGACT
 ATCCTCCCCAGAAGGGCTGCATCCCCCTCCCGAGGGGTCAGACAGAGAAGGCAGACCATG
 35 TGGATCTAGCCACGCTAATGATCGACTTCAATGGGGAGGAGAAGGCGTGGGCCATGGCCG
 TGTGGATCTTCGCTGCGATCAACAGGAGAGACCTTTATGAGAAAGCAAAAAGAGATGAGC
 CGAAGTGGGGTTCAGATAATGCACGTGTTTGAATCCCACTGTGATATGCCAGGAAGACA
 GCATTGAAGAGGAGTGGATGGGTTTACTGGAGTACCTTTGAGAATCTCTATTTGTAAAA
 TGAAGAAAGATTACCGTAAGAAGTACAGAAAGTACGTGAGAAGCAGATTCCAGTGCATTG
 40 AAGACAGGAATGCCCGTCTGGGTGAGAGTGTGAGCCTCAACAAACGCTACACACGACTGC
 GTCTCATCAAGGAGCACCGGAGCCAGCAGGAGAGGGAGCAGGAGCTTCTGGCCATCGGCA
 AGACCAAGACGTGTGAGAGCCCCGTGAGTCCCATTAAAGATGGAGTTGCTGTTTGACCCCG

ATGATGAGCATTCTGAGCCTGTGCACACCGTGGTGTTCAGGGGGCGGCAGGGATTGGGA
AAACAATCCTGGCCAGGAAGATGATGTTGGACTGGGCGTCGGGGACACTCTACCAAGACA
GGTTTGACTATCTGTTCTATATCCACTGTCTGGGAGGTGAGCCTTGTGACACAGAGGAGCC
TGGGGGACCTGATCATGAGCTGCTGCCCCGACCCAAACCCACCCATCCACAAGATCGTGA
5 GAAAACCCTCCAGAATCCTCTTCCTCATGGACGGCTTCGATGAGCTGCAAGGTGCCTTTG
ACGAGCACATAGGACCGCTCTGCACTGACTGGCAGAAGGCCGAGCGGGGAGACATTCTCC
TGAGCAGCCTCATCAGAAAGAAGCTGCTTCCCGAGGCCTCTCTGCTCATCACCACGAGAC
CTGTGGCCCTGGAGAACTGCAGCACTTGCTGGACCATCCTCGGCATGTGGAGATCCTGG
GTTTCTCCGAGGCCAAAAGGAAAGAGTACTTCTTCAAGTACTTCTCTGATGAGGCCCAAG
10 CCAGGGCAGCCTTCAGTCTGATTGAGGAGAACGAGGTCTCTTACCATGTGCTTCATCC
CCCTGGTCTGCTGGATCGTGTGCACTGGACTGAAACAGCAGATGGAGAGTGGCAAGAGCC
TTGCCCAGACATCCAAGACCACCACCGCGGTGTACGTCTTCTTCTTCCAGTTTGCTGC
AGCCCCGGGGAGGGAGCCAGGAGCACGGCCTCTGCGCCACCTCTGGGGGCTCTGCTCTT
TGGCTGCAGATGGAATCTGGAACCAGAAAATCCTGTTTGAGGAGTCCGACCTCAGGAATC
15 ATGGAAGTGCAGAAGGCGGATGTGTCTGCTTTCCTGAGGATGAACCTGTTCCAAAAGGAAG
TGGACTGCGAGAAGTTCTACAGCTTCATCCACATGACTTTCAGGAGTCTTTGCCGCCA
TGTAATACCTGCTGGAAGAGGAAAAGGAAGGAAGGACGAACGTTCCAGGGAGTCGTTTGA
AGCTTCCCAGCCGAGACGTGACAGTCCTTCTGGAAACTATGGCAAATTCGAAAAGGGGT
ATTTGATTTTGTGTACGTTTCTTCTTGGCCTGGTAAACCAGGAGAGGACCTCCTACT
20 TGGAGAAGAAATTAAGTTGCAAGATCTCTCAGCAAATCAGGCTGGAGCTGCTGAAATGGA
TTGAAGTGAAGGCCAAAGCTAAAAAGCTGCAGATCCAGCCCAGCCAGCTGGAATTGTTCT
ACTGTTTGTACGAGATGCAGGAGGAGGACTTCGTGCAAAGGGCCATGGACTATTTCCCA
AGATTGAGATCAATCTCTCCACCAGAATGGACCACATGGTTTCTTCTTTTGCATTGAGA
ACTGTCATCGGGTGGAGTCACTGTCCCTGGGGTTTCTCCATAACATGCCCAAGGAGGAAG
25 AGGAGGAGGAAAAGGAAGGCCGACACCTTGATATGGTGCAGTGTGTCTCCCAAGCTCCT
CTCATGCTGCCTGTTCTCATGGATTGGTGAACAGCCACCTCACTTCCAGTTTTTGGCGGG
GCCTCTTTTCACTTCTGAGCACCAGCCAGAGTCTAACTGAATTGGACCTCAGTGACAATT
CTCTGGGGGACCCAGGGATGAGAGTGTGTGTGAAACGCTCCAGCATCCTGGCTGTAACA
TTCGGAGATTGTGGTTGGGGCGCTGTGGCCTCTCGCATGAGTGTGCTTCGACATCTCCT
30 TGGTCCTCAGCAGCAACCAGAAGCTGGTGGAGCTGGACCTGAGTGACAACGCCCTCGGTG
ACTTCGGAATCAGACTTCTGTGTGTGGGACTGAAGCACCTGTTGTGCAATCTGAAGAAGC
TCTGGTTGGTCAGCTGCTGCCTCACATCAGCATGTTGTGAGGATCTTGCATCAGTATTGA
GCACCAGCCATTCCCTGACCAGACTCTATGTGGGGGAGAATGCCTTGGGAGACTCAGGAG
TCGCAATTTTATGTGAAAAAGCCAAGAATCCACAGTGTAACCTGCAGAACTGGGGTTGG
35 TGAATTCTGGCCTTACGTCAGTCTGTTGTTGAGCTTTGTCTCGGTACTCAGCACTAATC
AGAATCTCACGCACCTTTACCTGCGAGGCAACACTCTCGGAGACAAGGGGATCAAATAC
TCTGTGAGGGACTCTTGACCCCCGACTGCAAGCTTCAGGTGTTGGAATTAGACAATGCA
ACCTCACGTCACACTGCTGCTGGGATCTTCCACACTTCTGACCTCCAGCCAGAGCCTGC
GAAAGCTGAGCCTGGGCAACAATGACCTGGGCGACCTGGGGGTCATGATGTTCTGTGAAG
40 TGCTGAAACAGCAGAGCTGCCTCCTGCAGAACCTGGGGTTGTCTGAAATGTATTTCAATT
ATGAGACAAAAAGTGCGTTAGAAACACTTCAAGAAGAAAAGCCTGAGCTGACCGTCGTCT
TTGAGCCTTCTTGGTAGGAGTGGAACGGGGCTGCCAGACGCCAGTGTTCTCCGGTCCCT

CCAGCTGGGGGCCCTCAGGTGGAGAGAGCTGCGATCCATCCAGGCCAAGACCACAGCTCT
 GTGATCCTTCCGGTGGAGTGTCTGGAGAAGAGAGCTTGCCGACGATGCCTTCCTGTGCAGA
 GCTTGGGCATCTCCTTTACGCCAGGGTGAGGAAGACACCAGGACAATGACAGCATCGGGT
 GTTGTGTCATCACAGCGCCTCAGTTAGAGGATGTTCTCTTGGTGACCTCATGTAATTA
 5 GCTCATTCAATAAAGCACTTTCTTTATTTT
 (SEQ ID NO: 56)

As used herein, the term "NME8" refers to the gene encoding Thioredoxin domain-containing protein 3. The terms "NME8" and "Thioredoxin domain-containing protein 3" include wild-type forms of
 10 the NME8 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type NME8. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type NME8 nucleic acid sequence (e.g., SEQ ID NO: 57, ENA accession number AF202051). SEQ ID NO: 57 is a
 15 wild-type gene sequence encoding NME8 protein, and is shown below:

CGGCCACAACGAGGGAGCCGATTTAGATCCTCTGGGCCTGTTCTTCCTTTCTTTAAAC
 GTCCCAGTCTAGCTTAGAGGAGGACCTGTTTTGTTAGATAAATGGCAAGCAAAAAACGAG
 AAGTCCAGTTACAGACAGTCATCAATAATCAAAGCCTGTGGGATGAGATGTTGCAGAACAA
 20 AAGGCTTAACAGTGATTGATGTTTACCAAGCCTGGTGTGGACCTTGACAGAGCAATGCAAC
 CTTTATTCAGAAAATTGAAAAATGAACTGAACGAAGACGAAATTCTGCATTTTGCTGTCTG
 CAGAAGCTGACAACATTGTGACTTTGCAGCCATTTAGAGATAAATGTGAACCTGTTTTTC
 TCTTTAGTGTTAATGGCAAAATTATCGAAAAGATTCAGGGTGCAAATGCACCGCTTGTTA
 ATAAAAAAGTTATTAATTTGATCGATGAGGAGAGAAAAATTGCAGCAGGTGAAATGGCTC
 25 GACCTCAGTATCCTGAAATTCCATTAGTAGACTCAGATTCAGAAGTTAGTGAAGAATCAC
 CATGTGAAAGTGTTTCAGGAATTATACAGTATTGCTATTATCAAACCGGATGCTGTGATTA
 GTAAAAAAGTTCTAGAAATTAAGAAAAATTACCAAAGCTGGATTTATTATAGAAGCAG
 AGCATAAGACAGTGCTCACTGAAGAACAAGTTGTCAACTTCTATAGTCGAATAGCAGACC
 AGTGTGACTTCGAAGAGTTTGTCTCTTTTATGACAAGTGGCTTAAGCTATATTCTAGTTG
 30 TATCTCAAGGAAGTAAACACAATCCTCCCTCTGAAGAAACCGAACCACAGACTGACACCG
 AACCTAACGAACGATCTGAGGATCAACCTGAGGTGCAAGCCAGGTTACACCTGGAATGA
 TGAAGAACAACAAGACAGTTTACAAGAATATCTGGAAAGACAACATTTAGCTCAGCTCT
 GTGACATTGAAGAGGATGCAGCTAATGTTGCTAAGTTCATGGATGCTTTCTTCCCGATT
 TTAaaaaaATGAAAAGCATGAAATTAGAAAAGACATTGGCATTACTTCGACCAAATCTCT
 35 TTCATGAAAGGAAAGATGATGTTTTGCGTATTATTAAAGATGAAGACTTCAAATACTGG
 AGCAAAGACAAGTAGTATTATCGGAAAAAGAACACAAGCACTGTGCAAGGAATATGAAA
 ATGAAGACTATTTTAATAAACTTATAGAAAACATGACCAGTGGTCCATCTCTAGCCCTTG
 TTTTATTGAGAGACAATGGCTTGCAATACTGGAAACAATTACTGGGACCAAGAAGTGTG
 AAGAAGCCATTGAATATTTTCCAGAGAGTTTATGTGCACAGTTTTCGATGGACAGTTTGC
 40 CGGTCAACCAGTTGTATGGCAGCGATTATTAGAAACCGCTGAAAGGGAAATACAGCATT
 TCTTTCTCTTCAAAGCACTTTAGGCTTGATTAAACCTCATGCAACAAGTGAACAAAGAG
 AGCAGATCCTGAAGATAGTTAAGGAGGCTGGATTTGATCTGACACAGGTGAAGAAAATGT

TCCTAACTCCTGAGCAAATAGAGAAAATTTATCCAAAAGTAACAGGAAAAGACTTTTATA
 AAGATTTATTGGAAATGTTATCTGTGGGTCCATCTATGGTCATGATTCTGACCAAGTGGA
 ATGCTGTTGCAGAATGGAGACGATTGATGGGCCCAACAGACCCAGAAGAAGCAAAATTAC
 TTTCCCCTGACTCCATCCGAGCCCAGTTTGAATAAGTAAATTGAAAAACATTGTCCATG
 5 GAGCATCTAACGCCTATGAAGCAAAAGAGGTTGTTAATAGACTCTTTGAGGATCCTGAGG
 AAAACTAAAGTATATACTGTGAAAACCTTTGAGAAGATAATACATATGTTACGTCAATAT
 ACAACCATTTGGCACAGCTTCCTGGGAGGAATAATAAGAAAAACATGCTTTGGAGGAAAA
 CTCAAGATACAAAAATGAATGGCTATGCATAATAACAATAAAAATGTATTCCCCAAAC
 (SEQ ID NO: 57)

10

As used herein, the term "NOS2" refers to the gene encoding Nitric oxide synthase, inducible. The terms "NOS2" and "Nitric oxide synthase, inducible" include wild-type forms of the NOS2 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type NOS2. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%,
 15 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type NOS2 nucleic acid sequence (e.g., SEQ ID NO: 58, ENA accession number L24553). SEQ ID NO: 58 is a wild-type gene sequence encoding NOS2 protein, and is shown below:

20 AAGCCCCACAGTGAAGAACATCTGAGCTCAAATCCAGATAAGTGACATAAGTGACCTGCT
 TTGTAAAGCCATAGAGATGGCCTGTCCTTGGAATTTCTGTTCAAGACCAAATTCCACCA
 GTATGCAATGAATGGGGAAAAAGACATCAACAACAATGTGGAGAAAGCCCCCTGTGCCAC
 CTCCAGTCCAGTGACACAGGATGACCTTCAGTATCACAACCTCAGCAAGCAGCAGAATGA
 GTCCCCGCAGCCCCTCGTGGAGACGGGAAAGAAGTCTCCAGAATCTCTGGTCAAGCTGGA
 25 TGCAACCCCATTGTCTCCCCACGGCATGTGAGGATCAAAAACCTGGGGCAGCGGGATGAC
 TTTCCAAGACACACTTCACCATAAGGCCAAAGGGATTTAACTTGCAGGTCCAAATCTTG
 CCTGGGGTCCATTATGACTCCCAAAGTTTGACCAGAGGACCCAGGGACAAGCCTACCCC
 TCCAGATGAGCTTCTACCTCAAGCTATCGAATTTGTCAACCAATATTACGGCTCCTTCAA
 AGAGGCCAAAAATAGAGGAACATCTGGCCAGGGTGAAGCGGTAACAAAGGAGATAGAAAC
 30 AACAGGAACCTACCAACTGACGGGAGATGAGCTCATCTTCGCCACCAAGCAGGCCTGGCG
 CAATGCCCCACGCTGCATTGGGAGGATCCAGTGGTCCAACCTGCAGGTCTTCGATGCCCG
 CAGCTGTTCCACTGCCCCGGGAAATGTTTGAACACATCTGCAGACACGTGCGTTACTCCAC
 CAACAATGGCAACATCAGGTTCGGCCATCACCGTGTTCCTCCAGCGGAGTGATGGCAAGCA
 CGACTTCCGGGTGTGGAATGCTCAGCTCATCCGCTATGCTGGCTACCAGATGCCAGATGG
 35 CAGCATCAGAGGGGACCCTGCCAACGTGGAATTAACCTCAGCTGTGCATCGACCTGGGCTG
 GAAGCCCCAAGTACGGCCGCTTCGATGTGGTCCCCCTGGTCTGCAGGCCAATGGCCGTGA
 CCCTGAGCTCTTCGAAATCCCACCTGACCTTGTGCTTGAGGTGGCCATGGAACATCCCAA
 ATACGAGTGGTTTCGGGAACTGGAGCTAAAGTGGTACGCCCTGCCTGCAGTGGCCAACAT
 GCTGCTTGAGGTGGGCGGCCTGGAGTTCCCAGGGTGGCCCTTCAATGGCTGGTACATGGG
 40 CACAGAGATCGGAGTCCGGGACTTCTGTGACGTCCAGCGCTACAACATCCTGGAGGAAGT
 GGGCAGGAGAATGGGCCTGGAAACGCACAAGCTGGCCTCGCTCTGGAAAGACCAGGCTGT
 CGTTGAGATCAACATTGCTGTGCTCCATAGTTTCCAGAAGCAGAATGTGACCATCATGGA

CCACCACTCGGCTGCAGAATCCTTCATGAAGTACATGCAGAATGAATACCGGTCCCGTGG
 GGGCTGCCCCGGCAGACTGGATTTGGCTGGTCCCTCCCATGTCTGGGAGCATCACCCCCGT
 GTTTCACCAGGAGATGCTGAACTACGTCTGTCCCCTTTCTACTACTATCAGGTAGAGGC
 CTGGAAAACCCATGTCTGGCAGGACGAGAAGCGGAGACCCAAGAGAAGAGAGATTCCATT
 5 GAAAGTCTTGGTCAAAGCTGTGCTCTTTGCCTGTATGCTGATGCGCAAGACAATGGCGTC
 CCGAGTCAGAGTCACCATCCTCTTTGCGACAGAGACAGGAAAATCAGAGGCGCTGGCCTG
 GGACCTGGGGGCCTTATTCAGCTGTGCCTTCAACCCCAAGGTTGTCTGCATGGATAAGTA
 CAGGCTGAGCTGCCTGGAGGAGGAACGGCTGCTGTTGGTGGTGACCACTACGTTTGGCAA
 TGGAGACTGCCCTGGCAATGGAGAGAACTGAAGAAATCGCTCTTCATGCTGAAAGAGCT
 10 CAACAACAAATTCAGGTACGCTGTGTTTGGCCTCGGCTCCAGCATGTACCCTCGGTTCTG
 CGCCTTTGCTCATGACATTGATCAGAAGCTGTCCCACCTGGGGGCCTCTCAGCTCACCCC
 GATGGGAGAAGGGGATGAGCTCAGTGGGCAGGAGGACGCCTTCCGCAGCTGGGCCGTGCA
 AACCTTCAAGGCAGCCTGTGAGACGTTTGATGTCCGAGGCAAACAGCACATTTCAGATCCC
 CAAGCTCTACACCTCCAATGTGACCTGGGACCCGCACCACTACAGGCTCGTGCAGGACTC
 15 ACAGCCTTTGGACCTCAGCAAAGCCCTCAGCAGCATGCATGCCAAGAACGTGTTCCACCAT
 GAGGCTCAAATCTCGGCAGAATCTACAAAGTCCGACATCCAGCCGTGCCACCATCCTGGT
 GGAAGTCTCCTGTGAGGATGGCCAAGGCCTGAAGTACCTGCCGGGGGAGCACCTTGGGGT
 TTGCCCAGGCAACCAGCCGGCCCTGGTCCAAGGCATCCTGGAGCGAGTGGTGGATGGCCC
 CACACCCCAACAGACAGTGCACCTGGAGGCCCTGGATGAGAGTGGCAGCTACTGGGTGAG
 20 TGACAAGAGGCTGCCCCCTGCTCACTCAGCCAGGCCCTCACCTACTTCCTGGACATCAC
 CACACCCCAACCCAGCTGCTGCTCCAAAAGCTGGCCCAGGTGGCCACAGAAGAGCCTGA
 GAGACAGAGGCTGGAGGCCCTGTGCCAGCCCTCAGAGTACAGCAAGTGGAAGTTCACCAA
 CAGCCCCACATTCTGGAGGTGCTAGAGGAGTTCCCGTCCCTGCGGGTGTCTGCTGGCTT
 CCTGCTTTCCAGCTCCCCATTCTGAAGCCCAGGTTCTACTCCATCAGCTCCTCCCGGGA
 25 TCACACGCCCACGGAGATCCACCTGACTGTGGCCGTGGTCACCTACCACACCCGAGATGG
 CCAGGGTCCCCTGCACCACGGCGTCTGCAGCACATGGCTCAACAGCCTGAAGCCCCAAGA
 CCCAGTGCCCTGCTTTGTGCGGAATGCCAGCGGCTTCCACCTCCCCGAGGATCCCTCCCA
 TCCTTGATCCTCATCGGGCCTGGCACAGGCATCGCGCCCTTCCGCAGTTTCTGGCAGCA
 ACGGCTCCATGACTCCCAGCACAAAGGAGTGCGGGGAGGCGCATGACCTTGGTGTGTTGG
 30 GTGCCGCCGCCAGATGAGGACCACATCTACCAGGAGGAGATGCTGGAGATGGCCCAGAA
 GGGGGTGTGCTGCGGTGCACACAGCCTATTCCCGCCTGCCTGGCAAGCCCCAAGGTCTA
 TGTTCAAGACATCCTGCGGCAGCAGCTGGCCAGCGAGGTGCTCCGTGTGCTCCACAAGGA
 GCCAGGCCACCTCTATGTTTGGGGGATGTGCGCATGGCCCCGGGACGTGGCCACACCCCT
 GAAGCAGCTGGTGGCTGCCAAGCTGAAATTGAATGAGGAGCAGGTGAGGACTATTTCTT
 35 TCAGCTCAAGAGCCAGAAGCGCTATCACGAAGATATCTTTGGTGTGTATTTCTTACGA
 GGCGAAGAAGGACAGGGTGGCGGTGCAGCCAGCAGCCTGGAGATGTCAGCGCTCTGAGG
 GCCTACAGGAGGGGTTAAAGCTGCCGGCACAGAACTTAAGGATGGAGCCAGCTCT
 (SEQ ID NO: 58)

40 As used herein, the term "PICALM" refers to the gene encoding Phosphatidylinositol-binding
 clathrin assembly protein. The terms "PICALM" and "Phosphatidylinositol-binding clathrin assembly
 protein" include wild-type forms of the PICALM gene, as well as variants (e.g., splice variants and

polymorphisms) of wild-type PICALM. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type PICALM nucleic acid sequence (e.g., SEQ ID NO: 59, ENA accession number U45976). SEQ ID NO: 59 is a wild-type gene sequence encoding PICALM protein, and is shown below:

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GCGCGGCCCCGAACCGCCGCCAGGCCGGCACGGGGGAAGGAGCCGGTGGGGGTAGGGGGT
GCGGTGGGGGGTGGGGACCCTCCGGCTCTTGGGGGTCCCAGTCCCCGCCGGCTGCTGAGC
10 GGGTGGGGTGGTGGAGGAGCTGCAGAGATGTCCGGCCAGAGCCTGACGGACCGAATCACT
GCCGCCCAGCACAGTGTACCGGCTCTGCCGTATCCAAGACAGTATGCAAGGCCACGACC
CACGAGATCATGGGGCCCAAGAAAAAGCACCTGGACTACTTAATTCAGTGCACAAATGAG
ATGAATGTGAACATCCACAGTTGGCAGACAGTTTATTTGAAAGAACTACTAATAGTAGT
TGGGTGGTGGTCTTCAAATCTCTCATTACAACTCATCATTTGATGGTGTATGGAAATGAG
15 CGTTTTATTTCAGTATTTGGCTTCAAGAAACACGTTGTTTAACTTAAGCAATTTTTTGGAT
AAAAGTGGATTGCAAGGATATGACATGTCTACATTTATTAGGCGGTATAGTAGATATTTA
AATGAGAAAGCAGTTTTCATACAGACAAGTTGCATTTGATTTCAAAAAGTGAAGAGAGGG
GCTGATGGAGTTATGAGAACAATGAACACAGAAAACTCCTAAAACTGTACCAATTATT
CAGAATCAAATGGATGCACTTCTTGATTTTAAATGTTAATAGCAATGAACCTACAAATGGG
20 GTAATAAATGCTGCCTTCATGCTCCTGTTCAAAGATGCCATTAGACTGTTTGCAGCATAC
CATGAAGGAATTATTAATTTGTTGGAAAAATATTTTGATATGAAAAAGAACCAATGCAAA
GAAGGTCTTGACATCTATAAGAAGTTCCTAACTAGGATGACAAGAATCTCAGAGTTCCTC
AAAGTTGCAGAGCAAGTTGGAATTGACAGAGGTGATATACCAGACCTTTCACAGGCCCTT
AGCAGTCTTCTTGATGCTTTGGAACAACATTTAGCTTCCTTGGAAGGAAAGAAAATCAAA
25 GATTCTACAGCTGCAAGCAGGGCAACTACACTTTCCAATGCAGTGTCTTCCCTGGCAAGC
ACTGGTCTATCTCTGACCAAAGTGGATGAAAGGGAAAAGCAGGCAGCATTAGAGGAAGAA
CAGGCACGTTTGAAAGCTTTAAAGGAACAGCGCCTAAAAGAACTTGCAAAGAAACCTCAT
ACCTCTTTAACAACCTGCAGCCTCTCCTGTATCCACCTCAGCAGGAGGGATAATGACTGCA
CCAGCCATTGACATATTTTCTACCCCTAGTTCTTCTAACAGCACATCAAAGCTGCCCAAT
30 GATCTGCTTGATTTGCAGCAGCCAACCTTTTACCCATCTGTACATCCTATGTCAACTGCT
TCTCAGGTAGCAAGTACATGGGGAGATCCTTTCTCTGCTACTGTAGATGCTGTTGATGAT
GCCATTCCAAGCTTAAATCCTTTCTCACAAAAAGTAGTGGTGTATGTTACCTTTCCATT
TCTTCAGATGTATCTACTTTTACTACTAGGACACCTACTCATGAAATGTTTGTTGGATTCT
ACTCCTTCTCCAGTTGCACAGCCACACCCTTCAGCTGGCCTTAATGTTGACTTTGAATCT
35 GTGTTTGGAAATAAATCTACAAATGTTATTGTAGATTCTGGGGGCTTTGATGAACTAGGT
GGACTTCTCAAACCAACAGTGGCCTCTCAGAACCAGAACCTTCCTGTTGCCAACTCCCA
CCTAGCAAGTTAGTATCTGATGACTTGGATTCATCTTTAGCCAACCTTGTTGGGCAATCTT
GGCATCGGAAATGGAACCACTAAGAATGATGTAAATTGGAGTCAACCAGGTGAAAAGAAG
TTAACTGGGGGATCTAACTGCGAACCAGGTTGCACCAACAACCGCTTGGAATGCTGCA
40 ACAATGGCACCCCTGTAAATGGCCTATCCTGCTACTACCAACAGGCATGATAGGATAT
GGAATTCCTCCACAAATGGGAAGTGTTCTGTAAATGACGCAACCAACCTTAATATACAGC
CAGCCTGTCATGAGACCTCCAAACCCCTTTGGCCCTGTATCAGGAGCACAGATACAGTTT

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ATGTAACCTTGATGGAAGAAAATGGAATTACTCCAAAAAGACAAGTGCTCAAGCAGCAAAA
 TCCTTACTTCCAGCAAAATCCAACTGCTGTCTCTTAAATCTCTTAACTCTCTTCTTCC
 ATTAGGATGCTACAAGTANCTCAGTGAAGGCCCATGAAGGGAATTGGGGACTAGTTTATA
 GGGNGAACGTATTCATTACAGTTTATAAAGGCCAGGATTGGNTTGGATTTTAGGATTANG

5 TTC

(SEQ ID NO: 59)

As used herein, the term "PILRA" refers to the gene encoding Paired Immunoglobulin Like Type 2 Receptor Alpha. The terms "PILRA" and "Paired Immunoglobulin Like Type 2 Receptor Alpha" include wild-type forms of the PILRA gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type PILRA. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type PILRA nucleic acid sequence (e.g., SEQ ID NO: 60, NCBI Reference Sequence: NM_013439.2).

15 SEQ ID NO: 60 is a wild-type gene sequence encoding PILRA protein, and is shown below:

AATAGGGGAAAATAAGCCAGATGGATAAAGGAAGTGCTGGTCACCCTGGAGGTGCACTGGTTTGGG
 GAAGGCTCCTGGCCCCACAGCCCTCTTCGAGCCTGAGCCCGGCTCTCCTCACTCACCTCAACCC
 CCAGGCGGCCCTCCACAGGGCCCTCTCCTGCCTGGACGGCTCTGCTGGTCTCCCCGTCCCCCTG
 20 GAGAAGAACAAGGCCATGGGTGCGCCCTGCTGCTGCCCTACTGCCCTTGCTGCTGCCGCCAGC
 ATTTCTGCAGCCTAGTGGCTCCACAGGATCTGGTCCAAGCTACCTTTATGGGGTCACTCAACCAAAA
 CACCTCTCAGCCTCCATGGGTGGCTCTGTGGAAATCCCCTTCTCCTTCTATTACCCCTGGGAGTTAG
 CCACAGCTCCCGACGTGAGAATATCCTGGAGACGGGGCCACTTCCACAGGCAGTCCTTCTACAGCA
 CAAGGCCGCTTCCATTACAAGGATTATGTGAACCGGCTCTTTCTGAACTGGACAGAGGGTCAGAA
 25 GAGCGGCTTCCTCAGGATCTCCAACCTGCAGAAGCAGGACCAGTCTGTGTATTTCTGCCGAGTTGA
 GCTGGACACACGGAGCTCAGGGAGGCAGCAGTGGCAGTCCATCGAGGGGACCAAACCTCTCCATCA
 CCCAGGCTGTACGACCACCACCCAGAGGCCCAGCAGCATGACTACCACCTGGAGGCTCAGTAGC
 ACAACCACCACAACCGGCCTCAGGGTCACACAGGGCAAACGACGCTCAGACTCTTGGCACATAAGT
 CTGGAGACTGCTGTGGGGGTGGCAGTGGCTGTCACTGTGCTCGGAATCATGATTTTGGGACTGATC
 30 TGCCTCCTCAGGTGGAGGAGAAGGAAAGGTCAGCAGCGGACTAAAGCCACAACCCAGCCAGGGA
 ACCCTTCCAAAACACAGAGGAGCCATATGAGAATATCAGGAATGAAGGACAAAATACAGATCCCAAG
 CTAAATCCCAAGGATGACGGCATCGTCTATGCTTCCCTTGCCCTCTCCAGCTCCACCTCACCCAGAG
 CACCTCCAGCCACCGTCCCCTCAAGAGCCCCCAGAACGAGACCCTGTACTCTGTCTTAAAGGCCT
 AACCAATGGACAGCCCTCTCAAGACTGAATGGTGAGGCCAGGTACAGTGGCGCACACCTGTAATCC
 35 CAGCTACTCTGAAGCCTGAGGCAGAATCAAGTGAGCCCAGGAGTTCAGGGCCAGCTTTGATAATGG
 AGCGAGATGCCATCTCTAGTTAAAAATATATATTAACAATAAAGTAACAAATTTAAAAAGATAAAAAAA
 (SEQ ID NO: 60)

As used herein, the term "PLCG2" refers to the gene encoding 1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-2. The terms "PLCG2" and "1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-2" include wild-type forms of the PLCG2 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type PLCG2. Examples of such variants are

nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type PLCG2 nucleic acid sequence (e.g., SEQ ID NO: 61, ENA accession number M37238). SEQ ID NO: 61 is a wild-type gene sequence

5 encoding PLCG2 protein, and is shown below:

```
GAATTCGGCGCTGAGTGACCCGAGTCGGGACGCGGGCTGCGCGCGCGGGACCCCGGAGCC
CAAACCCGGGGCAGGCGGGCAGCTGTGCCCGGGCGGCACGGCCAGCTTCCTGATTTCTCC
CGATTCCTTCTTCTCCCTGGAGCGGCCGACAATGTCCACCACGGTCAATGTAGATTCCC
10 TTGCGGAATATGAGAAGAGCCAGATCAAGAGAGCCCTGGAGCTGGGGACGGTGATGACTG
TGTTTCAGCTTCCGCAAGTCCACCCCCGAGCGGAGAACCGTCCAGGTGATCATGGAGACGC
GGCAGGTGGCCTGGAGCAAGACCGCCGACAAGATCGAGGGCTTCTTGATATCATGGAAA
TAAAAGAAATCCGCCCAGGGAAGAACTCCAAAGATTTGAGCGAGCAAAGCAGTTTCGCC
AGAAAGAAGACTGCTGCTTCACCATCCTATATGGCACTCAGTTCGTCCTCAGCACGCTCA
15 GCTTGGCAGCTGACTCTAAAGAGGATGCAGTTAACTGGCTCTCTGGCTTGAAAATCTTAC
ACCAGGAAGCGATGAATGCGTCCACGCCCACCATTATCGAGAGTTGGCTGAGAAAGCAGA
TATATTCTGTGGATCAAACCAGAAGAAACAGCATCAGTCTCCGAGAGTTGAAGACCATCT
TGCCCCTGATCAACTTTAAAGTGAGCAGTGCCAAGTTCCTTAAAGATAAGTTTGTGGAAA
TAGGAGCACACAAAGATGAGCTCAGCTTTGAACAGTTCCATCTCTTCTATAAAAACTTA
20 TGTTTGAACAGCAAAAATCGATTCTCGATGAATTCAAAAAGGATTGTCCTGTTTCATCC
TGGGGAACACTGACAGGCCGGATGCCTCTGCTGTTTACCTGCATGACTTCCAGAGGTTTC
TCATACATGAACAGCAGGAGCATTGGGCTCAGGATCTGAACAAAGTCCGTGAGCGGATGA
CAAAGTTCATTGATGACACCATGCGTGAAACTGCTGAGCCTTTCTTGTGTTGTGGATGAGT
TCCTCACGTACCTGTTTTTACGAGAAAACAGCATCTGGGATGAGAAGTATGACGCGGTGG
25 ACATGCAGGACATGAACAACCCCCTGTCTCATTACTGGATCTCCTCGTCACATAACACGT
ACCTTACAGGTGACCAGCTGCGGAGCGAGTCGTCCCCAGAAGCTTACATCCGCTGCCTGC
GCATGGGCTGTGCTGCATTGAACTGGACTGCTGGGACGGGCCCCGATGGGAAGCCGGTCA
TCTACCATGGCTGGACGCGGACTACCAAGATCAAGTTTGATGACGTCGTGCAGGCCATCA
AAGACCACGCCTTTGTTACCTCGAGCTTCCCAGTGATCCTGTCCATCGAGGAGCACTGCA
30 GCGTGGAGCAACAGCGTCACATGGCCAAGGCCTTCAAGGAAGTATTTGGCGACCTGCTGT
TGACGAAGCCCACGGAGGCCAGTGCTGACCAGCTGCCCTCGCCCAGCCAGCTGCGGGAGA
AGATCATCATCAAGCATAAGAAGCTGGGCCCCCGAGGCGATGTGGATGTCAACATGGAGG
ACAAGAAGGACGAACACAAGCAACAGGGGGAGCTGTACATGTGGGATTCCATTGACCAGA
AATGGACTCGGCACTACTGCGCCATTGCTGATGCCAAGCTGTCCTTCAGTGATGACATTG
35 AACAGACTATGGAGGAGGAAGTGCCCCAGGATATACCCCTACAGAACTACATTTTGGGG
AGAAATGGTTCCACAAGAAGGTGGAGAAGAGGACGAGTGCCGAGAAGTTGCTGCAGGAAT
ACTGCATGGAGACGGGGGGCAAGGATGGCACCTTCCTGGTTCTGGGAGAGCGAGACCTTCC
CCAATGACTACACCCTGTCTTCTGGCGGTGAGGCCGGGTCCAGCACTGCCGGATCCGCT
CCACCATGGAGGGCGGGACCCTGAAATACTACTTGACTGACAACCTGAGGTTTCAGGAGGA
40 TGTATGCCCTCATCCAGCACTACCGCGAGACGCACCTGCCGTGCGCCGAGTTCGAGCTGC
GGCTCACGGACCCTGTGCCCAACCCCAACCCCCACGAGTCCAAGCCGTGGTACTATGACA
GCCTGAGCCGCGGAGAGGCAGAGGACATGCTGATGAGGATTCCCCGGGACGGGGCCTTCC
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TGATCCGGAAGCGAGAGGGGAGCGACTCCTATGCCATCACCTTCAGGGCTAGGGGCAAGG
TAAAGCATTGTGCGATCAACCGGGACGGCCGGCACTTTGTGCTGGGGACCTCCGCCTATT
TTGAGAGTCTGGTGGAGCTCGTCAGTTACTACGAGAAGCATTCACTCTACCGAAAGATGA
GACTGCGCTACCCCGTGACCCCGAGCTCCTGGAGCGCTACAATACGAAAGAGATATAA
5 ACTCCCTCTACGACGTCAGCAGAATGTATGTGGATCCCAGTGAAATCAATCCGTCCATGC
CTCAGAGAACCGTGAAAGCTCTGTATGACTACAAAGCCAAGCGAAGCGATGAGCTGAGCT
TCTGCCGTGGTGCCCTCATCCACAATGTCTCCAAGGAGCCCGGGGGCTGGTGGAAAGGAG
ACTATGGAACCAGGATCCAGCAGTACTTCCCATCCAACCTACGTCGAGGACATCTCAACTG
CAGACTTCGAGGAGCTAGAAAAGCAGATTATTGAAGACAATCCCTTAGGGTCTCTTTGCA
10 GAGGAATATTGGACCTCAATACCTATAACGTCGTGAAAGCCCCTCAGGGAAAAAACAGA
AGTCCTTTGTCTTCATCCTGGAGCCCAAGGAGCAGGGCGATCCTCCGGTGGAGTTTGCCA
CAGACAGGGTGGAGGAGCTCTTTGAGTGGTTTCAGAGCATCCGAGAGATCACGTGGAAGA
TTGACAGCAAGGAGAACAACATGAAGTACTGGGAGAAGAACCAGTCCATCGCCATCGAGC
TCTCTGACCTGGTTGTCTACTGCAAACCAACCAGCAAAACCAAGGACAACCTTAGAAAATC
15 CTGACTTCCGAGAAATCCGCTCCTTTGTGGAGACGAAGGCTGACAGCATCATCAGACAGA
AGCCCGTCGACCTCCTGAAGTACAATCAAAAGGGCCTGACCCGCGTCTACCCAAAGGGAC
AAAGAGTTGACTCTTCAAACCTACGACCCCTTCCGCCTCTGGCTGTGCGGTTCTCAGATGG
TGGCACTCAATTTCCAGACGGCAGATAAGTACATGCAGATGAATCACGCATTGTTTTCTC
TCAACGGGCGCACGGGCTACGTTCTGCAGCCTGAGAGCATGAGGACAGAGAAATATGACC
20 CGATGCCACCCGAGTCCCAGAGGAAGATCCTGATGACGCTGACAGTCAAGGTTCTCGGTG
CTCGCCATCTCCCCAACTTGGACGAAGTATTGCCTGTCCCTTTGTAGAAGTGGAGATCT
GTGGAGCCGAGTATGGCAACAACAAGTTCAAGACGACGGTTGTGAATGATAATGGCCTCA
GCCCTATCTGGGCTCCAACACAGGAGAAGGTGACATTTGAAATTTATGACCCAAACCTGG
CATTTCTGCGCTTTGTGGTTTATGAAGAAGATATGTTTCAGCGATCCCAACTTTCTTGCTC
25 ATGCCACTTACCCCATTAAGCAGTCAAATCAGGATTCAGGTCCGTTCTCTGAAGAATG
GGTACAGCGAGGACATAGAGCTGGCTTCCCTCCTGGTTTTCTGTGAGATGCGGCCAGTCC
TGGAGAGCGAAGAGGAACTTTACTCCTCCTGTCGCCAGCTGAGGAGGCGGCAAGAAGAAC
TGAACAACCAGCTCTTTCTGTATGACACACACCAGAACTTGCGCAATGCCAACCGGGATG
CCCTGGTTAAAGAGTTCAGTGTTAATGAGAACCACTCCAGCTGTACCAGGAGAAATGCAA
30 CAAGAGGTTAAGAGAGAAGAGAGTCAGCAACAGCAAGTTTTACTCATAGAAGCTGGGGTA
TGTGTGTAAGGGTATTGTGTGTGTGCGCATGTGTGTTTGCATGTAGGAGAACGTGCCCTA
TTCACACTCTGGGAAGACGCTAATCTGTGACATCTTTTCTTCAAGCCTGCCATCAAGGAC
ATTTCTTAAGACCCAACCTGGCATGAGTTGGGGTAATTTCTTATTATTTTCATCTTGGACA
ACTTCTAACTTATATCTTTATAGAGGATTCCCCAAAATGTGCTCCTCATTTTTGGCCTCT
35 CATGTTCCAAACCTCATTGAATAAAAAGCAATGAAAACCTTG
(SEQ ID NO: 61)

As used herein, the term "PTK2B" refers to the gene encoding Protein-tyrosine kinase 2-beta. The terms "PTK2B" and "Protein-tyrosine kinase 2-beta" include wild-type forms of the PTK2B gene, as
40 well as variants (e.g., splice variants and polymorphisms) of wild-type PTK2B. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type PTK2B nucleic acid sequence (e.g., SEQ ID NO: 62, ENA accession number U33284). SEQ ID NO: 62 is a wild-type gene sequence encoding PTK2B protein, and is shown below:

```
5  CGGTACAGGTAAGTCGGCCGGGCAGGTAGGGGTGCCCCAGGAGTAGTCGCTGGAGTCCGC
   GCCTCCCTGGGACTGCAATGTGCCGGTCTTAGCTGCTGCCTGAGAGGATGTCTGGGGTGT
   CCGAGCCCCTGAGCCGAGTAAAGTTGGGCACATTACGCCGGCCTGAAGGCCCTGCAGAGC
   CCATGGTGGTGGTACCAGTAGATGTGAAAAAGGAGGACGTGCGTATCCTCAAGGTCTGCT
   TCTATAGCAACAGCTTCAATCCTGGGAAGAACTTCAAACCTGGTCAAATGCACTGTCCAGA
10  CGGAGATCCGGGAGATCATCACCTCCATCCTGCTGAGCGGGCGGATCGGGGCCAACATCC
   GGTTGGCTGAGTGCTATGGGCTGAGGCTGAAGCACATGAAGTCCGATGAGATCCACTGGC
   TGCACCCACAGATGACGGTGGGTGAGGTGCAGGACAAGTATGAGTGTCTGCACGTGGAAG
   CCGAGTGGAGGTATGACCTTCAAATCCGCTACTTGCCAGAAGACTTCATGGAGAGCCTGA
   AGGAGGACAGGACCACGCTGCTCTATTTTTACCAACAGCTCCGGAACGACTACATGCAGC
15  GCTACGCCAGCAAGGTCAGCGAGGGCATGGCCCTGCAGCTGGGCTGCCTGGAGCTCAGGC
   GGTTCTTCAAGGATATGCCCCACAATGCACTTGACAAGAAGTCCAACTTCGAGCTCCTAG
   AAAAGGAAGTGGGGCTGGACTTGTTTTTCCCAAAGCAGATGCAGGAGAACTTAAAGCCCA
   AACAGTTCGGAAGATGATCCAGCAGACCTTCCAGCAGTACGCCTCGCTCAGGGAGGAGG
   AGTGCGTCATGAAGTTCTTCAACACTCTCGCCGGCTTCGCCAACATCGACCAGGAGACCT
20  ACCGCTGTGAACTCATTCAAGGATGGAACATTACTGTGGACCTGGTCATTGGCCCTAAAG
   GGATCCGCCAGCTGACTAGTCAGGACGCAAAGCCCACCTGCCTGGCCGAGTTCAAGCAGA
   TCAGGTCCATCAGGTGCCTCCCGCTGGAGGAGGGCCAGGCAGTACTTCAGCTGGGCATTG
   AAGGTGCCCCCAGGCCTTGTCCATCAAACCTCATCCCTAGCAGAGGCTGAGAACATGG
   CTGACCTCATAGACGGCTACTGCCGGCTGCAGGGTGAGCACCAAGGCTCTCTCATCATCC
25  ATCCTAGGAAAGATGGTGAGAAGCGGAACAGCCTGCCCCAGATCCCCATGCTAAACCTGG
   AGGCCCCGGCGGTCCCACCTCTCAGAGAGCTGCAGCATAGAGTCAGACATCTACGCAGAGA
   TTCCCGACGAAACCCTGCGAAGGCCCGGAGGTCCACAGTATGGCATTGCCCCGTGAAGATG
   TGGTCCTGAATCGTATTCTTGGGGAAGGCTTTTTTGGGGAGGTCTATGAAGGTGTCTACA
   CAAATCACAAAGGGGAGAAAATCAATGTAGCTGTCAAGACCTGCAAGAAAGACTGCACTC
30  TGGACAACAAGGAGAAGTTCATGAGCGAGGCAGTGATCATGAAGAACCTCGACCACCCGC
   ACATCGTGAAGCTGATCGGCATCATTGAAGAGGAGCCCACCTGGATCATCATGGAATTGT
   ATCCCTATGGGGAGCTGGGCCACTACCTGGAGCGGAACAAGAACTCCCTGAAGGTGCTCA
   CCCTCGTGCTGTACTCACTGCAGATATGCAAAGCCATGGCCTACCTGGAGAGCATCAACT
   GCGTGACAGGGACATTGCTGTCCGGAACATCCTGGTGGCCTCCCCTGAGTGTGTGAAGC
35  TGGGGGACTTTGGTCTTTCCCGGTACATTGAGGACGAGGACTATTACAAAGCCTCTGTGA
   CTCGTCTCCCCATCAAATGGATGTCCCCAGAGTCCATTAACCTCCGACGCTTCACGACAG
   CCAGTGACGTCTGGATGTTCCCGTGTGCATGTGGGAGATCCTGAGCTTTGGGAAGCAGC
   CCTTCTTCTGGCTGGAGAACAAGGATGTCATCGGGGTGCTGGAGAAAGGAGACCGGCTGC
   CCAAGCCTGATCTCTGTCCACCGGTCCTTTATACCCTCATGACCCGCTGCTGGGACTACG
40  ACCCCAGTGACCGGCCCCCGCTTCACCGAGCTGGTGTGCAGCCTCAGTGACGTTTATCAGA
   TGGAGAAGGACATTGCCATGGAGCAAGAGAGGAATGCTCGCTACCGAACCCCCAAAATCT
   TGGAGCCCACAGCCTTCCAGGAACCCCCACCCAAGCCCAGCCGACCTAAGTACAGACCCC
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CTCCGCAAACCAACCTCCTGGCTCCAAAGCTGCAGTTCCAGGTTCTGAGGGTCTGTGTG
 CCAGCTCTCCTACGCTCACCAGCCCTATGGAGTATCCATCTCCCGTTAACTCACTGCACA
 CCCACCTCTCCACCGGCACAATGTCTTCAAACGCCACAGCATGCGGGAGGAGGACTTCA
 TCCAACCCAGCAGCCGAGAAGAGGGCCAGCAGCTGTGGGAGGCTGAAAAGGTCAAATGC
 5 GGCAAATCCTGGACAAACAGCAGAAGCAGATGGTGGAGGACTACCACTGGCTCAGGCAGG
 AGGAGAAGTCCCTGGACCCCATGGTTTATATGAATGATAAGTCCCCATTGACGCCAGAGA
 AGGAGGTGCGCTACCTGGAGTTCACAGGGCCCCCACAGAAGCCCCCGAGGCTGGGCGCAC
 AGTCCATCCAGCCCACAGCTAACCTGGACCGGACCGATGACCTGGTGTACCTCAATGTCA
 TGGAGCTGGTGCGGGCCGTGCTGGAGCTCAAGAATGAGCTCTGTCAGCTGCCCCCGAGG
 10 GCTACGTGGTGGTGGTGAAGAATGTGGGGCTGACCCTGCGGAAGCTCATCGGGAGCGTGG
 ATGATCTCCTGCCTTCCTTGCCGTCATCTTCACGGACAGAGATCGAGGGCACCCAGAAAC
 TGCTCAACAAAGACCTGGCAGAGCTCATCAACAAGATGCGGCTGGCGCAGCAGAACGCCG
 TGACCTCCCTGAGTGAGGAGTGCAAGAGGCAGATGCTGACGGCTTCACACACCCTGGCTG
 TGGACGCCAAGAACCTGCTCGACGCTGTGGACCAGGCCAAGGTTCTGGCCAATCTGGCCC
 15 ACCCACCTGCAGAGTGACGGAGGGTGGGGGCCACCTGCCTGCGTCTTCCGCCCTGCCTG
 CCATGTACCTCCCCTGCCTTGCTGTTGGTCATGTGGGTCTTCCAGGGAGAAGGCCAAGGG
 GAGTCACCTTCCCTTGCCACTTTGCACGACGCCCTCTCCCCACCCCTACCCCTGGCTGTA
 CTGCTCAGGCTGCAGCTGGACAGAGGGGACTCTGGGCTATGGACACAGGGTGACGGTGAC
 AAAGATGGCTCAGAGGGGGACTGCTGCTGCCTGGCCACTGCTCCCTAAGCCAGCCT
 20 (SEQ ID NO: 62)

As used herein, the term "SCIMP" refers to the gene encoding SLP Adaptor and CSK Interacting
 Membrane Protein. The terms "SCIMP" and "SLP Adaptor and CSK Interacting Membrane Protein"
 include wild-type forms of the SCIMP gene, as well as variants (e.g., splice variants and polymorphisms)
 25 of wild-type SCIMP. Examples of such variants are nucleic acids having at least 70% sequence identity
 (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%,
 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to
 a wild-type SCIMP nucleic acid sequence (e.g., SEQ ID NO: 63, NCBI Reference Sequence:
 NM_207103.3). SEQ ID NO: 63 is a wild-type gene sequence encoding SCIMP protein, and is shown
 30 below:

ACTGTCTCTAGCAGTGGGTGAAGGCCTGTGAGTGAGGAATGCCTCTCACCAGCTGTGCCTGAGCTG
 CAGCACTCCAGCCACTGCTGTCTCCTTAGCTGCTCACATATGGATACTTTCACAGTTCAGGATTCCAC
 TGCAATGAGCTGGTGGAGGAATAATTTCTGGATCATCTTAGCTGTGGCCATCATCGTTGTCTCTGTG
 35 GGTCTGGGCCTCATCCTGTACTGTGTCTGTAAGTGGCAGCTTAGACGAGGCAAGAAATGGGAAATT
 GCCAAGCCCCTGAAACACAAGCAAGTAGATGAAGAAAAGATGTATGAGAATGTTCTTAATGAGTCGC
 CAGTTCAATTACCGCCTCTGCCACCGAGGAATTGGCCTTCTCTAGAAGACTCTTCCCCACAGGAAGC
 CCCAAGTCAGCCGCCCGCTACATACTCACTGGTAAATAAAGTTAAAAATAAGAAGACTGTTTCCATCC
 CAAGCTACATTGAGCCTGAAGATGACTATGACGATGTTGAAATCCCTGCAAATACTGAAAAAGCATCA
 40 TTTTGAAACAGCCATTTCTTCTTTTGGCAAACTGAAGAGGGTTCACACAACCTATTTTAAACAATC
 AAGAATGGTTGAACTTCAGTAGGTCTCTGGGCCCTGAAAGCCAGTGGTGATTTTATGAAGCTCTATA
 AGATAAAGCACTTCCCAAACCTTAGATGAAGACACCCCTGCGATCGGATGACTGCAGCCAGAGGAG

ACACATGGGTGCTCGGCTCTGAGGACTTAGAGGGGTCAGCCTTGTGCTGTTGAGGAACTTTCCAT
 GGGAAGGACCACGGGGCTCCATGGCTCCCACCTGTGGGAACTACTCATTCTTGGCATTCTTTCCC
 CCTTCATTCCCTTTGGTTTGCATGGTTCTGAGTGATATTAATCTCAGCATTGGTTGTGCAGACCCT
 CCCAGGCTCCCATCCCCAGCAAGGCCCTCACCAAGCATGCTGGTCTTTACCCTCTACCCCACCCA
 5 CCTCCTGCACTGTGAGGCTGTGGGTGAGTTACAGCTGAGTGCTCTCGTGCCCAGGTTCCCACACCA
 CATCTCGCGAGTTTGAAGGGCAGGGAGTACCTTTTGTCTCGTGAACCCTCCCCACCTAGACACCC
 TGCAAACCCAGTGCCTTTATATGATGTAGGCCAAATTGACCATAGAGATTTGAGTTTTACCTAGGT
 TTTCTCCCGTGCTTGCAAGTTGTAAGTGTAAACAATGGACAAAGGACAAAAGTTACCTTCTGATTTACA
 CCTAGAAGCATCATTTTGAATAGGTGTGTTGGGGGTGCTACAGGAAAAATACATTTCCCCCAGGAC
 10 AAATCATGGGGAACAGGAAAGAAAAGGGGCATGTAACAATGGCATATACAAGATGAGAGTTCAGGG
 GGCTTAATATCCCCTGTCCATCATTTTCATCAGTACTTACTCGAGTTCTAGGAAAACAGCCTCAAGCC
 CCTTCCTTCAGATCACTGTCCCTGGGCATCTGGGAGGAGGCAGAAGGTCCACTGTGATGTGCTGC
 AGCCAATGAGATGGGCCAGGGACATGGGCAGATGTCTTGTTAAACAAGTGTCTAATGGGGTCAAC
 AAGGCCCCGAGTCAGCTTTATAGGCTCTTAGACCTCATCAATTCCTTCTAGCTGATCGCCAGAGCCCT
 15 AGGACTTGACTCATTCTAACTATACTCACAAGATGCTGGTTTCTAAGTGACCTCTGGGAAATCTGGCA
 AATGAACAGCCTTGCAAGAGAGAGCACTGTGAACCTGGAAAGGCCTGAGAGTGAAGTCAAGTTCCCT
 CAAGAGATGGGAAAATGTGTTCCCTCCCATTTTCAAGCTTTCTCCCTCAATCAACGCTGGAGCACTGG
 GGACCTGGGCTTCCTCCCTGGTTCTCTTTCCAGACTCTATGAAGGCTTCACCTTGCTATTAATAC
 CTCTTGAGGAGGCCAAGGTGGGCGGATCACCTGAGGTCGGGAGTTGAGACCCAGCCTGACCAACA
 20 TGGAGAAACCCCATTTCTACTAAAAATACAAAATTAGTCAGGCATGGTTCGCGCATGCCTGTAATCCCA
 GCTACTTGGGAGGCTGAGGCAGAAAGATCGCTTGAACTGGGAGGCGGAGGTTGCGGTGAGCCGA
 GAACATGCCATTGCACTCCAGCCTGGACAACAAGAGTGAACTCCATCTAAAAATAAATAAATAAATA
 AATAAATAAACCTCCTTATGTTAGGCCAGTAGTTATCTAACTATGGCCTTATGGGACTCTGGTATCC
 CACCAGCCAAAGAGAGGACTCTTCCCAAATTATAGAACAAAAATAAGCCAAAGGATTGGAGTGTTC
 25 AAACACATGCTTTCGTCTTATAAATGTTCTGTAAACCCTCCATGACTATGACAAAAGTTAAAAACAAAT
 GCCAGACAAA
 (SEQ ID NO: 63)

As used herein, the term "SLC24A4" refers to the gene encoding Solute Carrier Family 24
 30 Member 4. The terms "SLC24A4" and "Solute Carrier Family 24 Member 4" include wild-type forms of the
 SLC24A4 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type SLC24A4.
 Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%,
 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%,
 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type SLC24A4
 35 nucleic acid sequence (e.g., SEQ ID NO: 64, NCBI Reference Sequence: NM_153646.3). SEQ ID NO:
 64 is a wild-type gene sequence encoding SLC24A4 protein, and is shown below:

AGACGGCACCCAGGCGCTCCGGGATGGCGCTCCGCGGGACCCTCCGGCCGCTCAAAGTTCGCAG
 GAGGCGAGAGATGCTGCCGCAGCAAGTCGGCTTCGTGTGCGCGGTGCTGGCCCTGGTGTGCTGTG
 40 CGTCCGGCCTCTTCGGCAGCTTGGGGCACAAACAGCTTCTGCTAGCAAACGTGTCCTGCCAGACA
 CGTGGAGAAATAGAAAGTTGATGGCCCCAGTGAATGGGACACAGACAGCCAAGAACTGCACAGATC
 CTGCGATTACGAGTTCCCCACAGATCTGTTCTCCAATAAGGAGCGACAGCACGGAGCCGTCCTGC

TGCACATCCTTGGTGCTCTGTATATGTTCTATGCCTTGGCCATAGTGTGCGATGACTTCTTTGTTCCG
TCTCTAGAGAAGATCTGTGAGAGACTCCATCTGAGCGAAGATGTGGCTGGAGCCACCTTCATGGCT
GCAGGAAGCTCAACGCCAGAGCTGTTTGCGTCTGTTATTGGGGTGTTTCATCACCCATGGGGACGTC
GGGGTGGGCACCATCGTGGGCTCTGCTGTGTTCAACATCCTGTGCATAATTGGAGTGTGCGGACTG
5 TTTGCTGGCCAGGTGGTCCGTCTGACGTGGTGGGCCGTGTGCCGAGACTCCGTGTACTACACCATC
TCTGTCATCGTGTCTCATCGTGTTCATATATGATGAACAAATTGTGTGGTGGGAAGGCCTGGTGCTCA
TCATCTTGTATGTGTTTTATATTCTGATCATGAAGTACAATGTGAAGATGCAAGCCTTTTTTACAGTCA
AACAAAAGAGCATTGCAAACGGTAACCCGGTCAACAGTGAGCTGGAGGCTGGTAATGATTTCTATGA
CGGTAGCTATGATGACCCTTCCGTGCCATTGCTGGGGCAAGTGAAGGAGAAGCCACAGTATGGCAA
10 GAACCCCGTGGTGATGGTGGACGAGATTATGAGCTCCAGCCCTCCCAAGTTCACCTTCCCTGAAGC
AGGCTTACGAATCATGATCACCAATAAGTTTGGACCCAGGACCCGACTACGGATGGCCAGCAGGAT
CATCATTAATGAGCGGCAGAGACTGATCAACTCGGCCAATGGTGTGAGCAGTAAGCCGCTTCAAAC
GGGAGGCACGAGAACATTGAGAACGGGAATGTTCTGTGAAAACCCCGAAGACCTCAGCAGAAT
CAGGAGCAGCAGCCGCCGCCACAGCCACCACCGCCAGAGCCAGAGCCGGTGGAGGCTGACTTCCT
15 GTCCCCCTTCTCCGTGCCGGAGGCCAGAGGGGACAAGGTCAAGTGGGTGTTACCTGGCCCCCTCA
TCTTCCTCCTGTGCGTCACCATTCCCAACTGCAGCAAGCCCCGCTGGGAGAAGTTCTTCATGGTCAC
CTTCATCACCGCCACGCTGTGGATCGCTGTGTTCTCCTACATCATGGTGTGGCTGGTGACTATTATC
GGATACACACTTGGGATCCCGGATGTCATCATGGGCATTACTTTCTGTCAGCAGGGACAAGTGTTT
CAGACTGCATGGCCAGCCTAATTGTGGCGAGACAAGGCCTTGGGGACATGGCAGTCTCCAACACCA
20 TAGGAAGCAACGTGTTTGACATCCTGGTAGGACTTGGTGTACCGTGGGGCCTGCAGACCATGGTTG
TTAATTATGGATCAACAGTGAAGATCAACAGCCGGGGGCTGGTCTATTCCGTGGTCTCTGTTGCTGGG
CTCTGTGCTCTCACCGTCCTCGGCATCCACCTAAACAAGTGGCGACTGGACCGGAAGCTGGGTGT
CTACGTGCTGGTTCTCTACGCCATCTTCTTGCTTCTCCATAATGATAGAGTTTAACGTCTTTACCTT
CGTCAACTTGCCGATGTGCCGGGAAGACGATTAGCGCTGAGTCGCGGCCCTGGGAGCTGATCTG
25 GACACCCTGTGACACTGGCGTTCTCCTCTCCCCCTCCTTCCCCCACCACAGGTCTCTCCTGCATAGGC
AGCCACTGTCCGTTCTTTCACACACTGGAAGGAAGAGCCATCGTGGTCTTTGTCTGGCCACAGGCCA
GGCTGCTGGGCATCCTCCTCCTCCTTGGAGTTCGCGCCCTGCAAGGCTGGATTGGGGGCCATTAT
CTGAGCAGCTTCAAAGACCCCTGAGCTGCCAACCACGGAGATGTGCCAAGCATCTCATCTCTCCTG
CACACTTTAGTCAGAAGGACTTCTGCATGCAGTTTGTCTTTCTGTTCTGCAGGCAGCTTCAGAATTGA
30 GGTCATTTGTGAGCACAAGATCTCATAGGGCAGGTGCAAAATAGGAATGTTGTTCTCAAGTGTACC
TCCAGCCCAGAGGTGGTTCTTAGGCAGCATGTGCTCCTGGGAGCCTCTGACTTTTGCTGGAAGCA
GCCACAGTTTGAAGGGGCAAGACCTCAACCTGTTGGGGTTTAGGGCCCATGATGGCAGACATTCT
ACCCCTTTTCTGGAAGAACTGGAAGAATGAAAATAATTTTTTCTGTGGAAGAGAGAAAATGAGTGA
ATATTCTTCTCACTTTTATTGATGCATTAGAGAATAAGCAATGAAATATTAATAAATGAAACATCATAT
35 AGGTCATCATACTTGAAAATTATCATTCCATATGAAAGGATCATGATACACACCAAAAAAGTAATGATC
GTAAAGACACAAATCCTCTGTATGCCATCTTGCAATTGGCACTGAGGTGTTTGGTTTGAATAGGGAA
AAAGGTAAGAGACTAACGTGGAAAGGTGCTAACTCAGAGACTGGAGATTATAGTTTACAGCTGTACT
TTCCAGATCTTCTATGTGACACAATGCACTGTCCTTGTGGGTTTGTCAATTTATTGGTTAATGCTCTAGT
TTCAAACACCCTGTTGAAAGTTCCAGTTATTTATATGCCCAACAAATTCATAGCCTGCTGAACTGA
40 ACTGAGTGTGTCAGAAGTGCTGGTTAATGACGAGAAGAGATTGCCTGAAAAACAACAACTGCTTTC
TGGTTAGCTGAAGGCAAGTGTGAAAATCAGAATTTAGAATATTTAGAGCTAAGCTTCTGGAACCACGT
AGTTTCTACACGTGGCAGGCCAAGAATGGGAGGCTGACTCAAACTAGATAGAAAAATATAAATAAT

CTTCGACCACTTGATAGCTCTCAAATATATATTTAAAAGATTTATGAATACAAACCATTTATGGTTTATG
ATTTCTAAAAAGAAAGCACAAATTAATTTTATAGAGAGGTTTTTTATTTTTTAAATATTTCTATTGCAAAAG
TCTATCCGATTTGATGCACTTTGAATATTGAGATATTTTGCACGGATGAATGTATGGGAACCTACCCAT
GATGATGTAAGAGGAAAGAACATTTTTTTGTGATTCACCAGACATCACTTTAAACTTGGTGATGAGTTT
5 AAATCCAGTAGCTAATCCCTTCCTGAGACTCAAAGATCGTGACGCTGGTTGGAATTTCTGACTGTGC
CCTTTAGGGCCTCCTGAGTTTCAAAGGAGGAAGTGTTCTGTGCTTGTGTCCCTGAAGTTCCCTGTTG
CATGAGCCTGCGACAGGACCTCACCCCCACCACCAGGCTTCTATTTGGGATTCACATCAGTATTAGT
ATCGTAGCTACACCAAGTTCAGGCTTCTCTTTTTGTTTTTTACCTAGAAATTGGGCTCAGTGGTCTTC
AACTTGAGGACGAGGGTGATTTTCTAAGAAATCAGCAAAGAGGGAAGGCAGGGCCCCCTGTAGATT
10 CACCAGTATAAACTTCAGCTGCAGGGATTCCAGAGCCCTCGGGACCACTCTGTCACTTAATAGCCA
AGTTCTCCTGGTTCCTCCGATCTTACAGGCTCATCCAGGTTCCAAAGTGCTTCTGTCTCTGTTTTGAT
TCTCCAAACTGCTCTGTGATGTATGTAGGGATTATTCTCCCCACTTAACAGAAAGTAGTGTCTTGGAG
AGGTCAAGGGTCTCTAGTTCAATGGCCAGTCATAGCAGAAGGGAGGCCAAGCACCAGTCCATCACC
CCTCCCAGGCCAGCCTCTGTAAGTTGGCCACACTTGGGGAGTGAGTGTGGGTATGACTTTACCCTC
15 CTGGTTGGTTCTTACTGTTTGAGTCAAACCTCATCAATATATCATTGACTCCTGGGTTCCCTCAGGTC
ATTTCTAATATCTGTCCCTATCCAATGCCTCTATTTTATCTTGAAAAAGGACCAAAAATTATTTTTAG
CTATGGCAAGGCACAGGCCACATGGCCCCCTGATGGCGTCCCTGCTGGTTTTCAATTCTCTGAAGCCT
TGTGTAGCTTTTCAAGACACAGTATCCTAATTACCCTCCTCTTCCCTCAGCAGAACCATTGAGATTC
TAAATGAATACTCTTAGTCTCTAAAGTTGCAGTTAGAACTAAATAATGTTTTTAAATATGTAATATGC
20 TCCTCTTGGCTAATTTTCTTTTGACTTTAATGTGCCAATGTAACCTTCCTTTAAAGGATCTATGCATTTAT
TAAATCTGGAAAATATATGTACACTGTAGGTGGAAAATTCTCTTTTTAACTAAATATTTTTCCATCAC
AAATTTAAAGAATTGCATGATTAATTAGGCTTTCATTTTTAAATTACGCTTTCATCACTACGCAGGATTA
CTTTATTTTATTCCCAAAGCTCATTAGCATGGGATAATTACTCTGCTACAGAAATAGGCAATTTAAAAA
AATGAATTTAGCTCTTCTCATTGGGGGCAGAAAAGAAAAAAAACCATTGCACTCAGATGGAAAATG
25 CCTATAGACACAGGAGCAGGTGGTTCCTGTGGACTTCTGGTTTGAATTTTGCCTCACCAGGTCAAG
CGTGGTTAGGGTGAAGGTGTCCAGTATCTTGAAAACCTGGCCCTGGAGGAAGGTTCTGGGTCAGC
TGCAATGAGAGACTGGTGATTAAGGGCACCGTGGGCAGGACACAGTCCTCGCCTTACCACCCCAT
CCTTCCTGTTACCACAGTCTGCTGGCCTCCATGCCTCTTCCCCTTGCACTTGTGTCTCCTCCTTAT
GCACAGAGCTGCCTGCCTTTATGAATTTCTTTTCTTTTTTTTTGAGACAGCGTCTTGCTGTGTCACC
30 CAGGCTGGAGTGCAGTGGTGCCATCTTGGCTCACTGCAACCTCCGCCTCCCAGGTTCAAGCAATTC
TTGTGCCTCAGCCTCCTGAGGATTACAGGCGTGCGCCACCACACCCAGCTAATTTTTGTATTTTTAGT
AGAGACGGGTTTTACCATGTTGGCCAGGCTGGTCTCAAACCTCCTGACCTCAGGTGATCCACCCAC
CTCGGTTTCCCAAAGTGCTGGGATTACAGGTGTGAGCCACCACGCCAGCCTGCCCTTGTGAATTTT
CACCTGCTCCTTACCCTCACCTGTTAGGACTGTTTCTTGCTTTTGCCCCTGTGGTCCCCTGCCTTA
35 ACAGACCTAAGCAGCTGATAATGCACCAAGCTTCCCTGACCAGGTGGGGTGTGTCTATCACCCAAG
GGCAGTCCTACAGACCCTGACCAAAGGCCGTTCTGGGCGGCCCAAGGTCCAGGTTTCTTCCACCT
GCTCTTCCCTGTTTATGGGGATTTGCAAGCCTAATTGCATCAGCAGGAGCCCATCTCTCAGAGAACC
CGGACTCCCCAAGCAGACTGGGATTTTGGGAAGGGTGTGGGGGGTGTCAATTGCTGGATACCCGTCT
TTCTGCCTGTCCTTTCTCCTCTCTGAATCCTGGGGCCCCTCTCCCTCCTTAAAGCTGGAGTGGACAG
40 AGGGACAGGAGAGGATCAGAGTTCATCCCCCTGGGAAAGAGCAAGAGCGAATGAATCCCAGCGC
CAGCGGCTGAGGCTGCCTTCCGTGCCTTCCCTCCATGGGCGACGGGTGAGTGGGGCTTAGGAAAC
TGGAACAGGGAAGGTTCTGTTACCACACTTTGGAACCTTTCCCCTGGGATTACAGCAGTTGAGAAGCA

GAGACCTTTCTGCCCTGGGTGAATGGGTCCTTGGGGGAGGGGTTGGTCTTTTGTCTCGCATCCCCA
TCTTTCCTTTCCTTCTGGGCCATGCTCCTCCCTGGCTGGAAAAAGGTGGCTGTGCTGTCCCTGTGAT
CCACTCTCAGCAAATGCGTGTGGCTCAAATAAACAAAGAACTTACCTGTTAGAGTGAAAATCCTCAG
GAGATTGTACCCAAATGCCATGCTCTAAATATTCATGGTCTCTCTAATGCCCTCAAGACGTGATTTCC
5 ATGGGAACCATCCTCCCCTGGGGGCAGTTAGCAGGAGTACGTGGGGCACGTGAGGTGGTCCTCCT
TTCAGCACACCGTGCCCATAGAACTTCTAGAAATTTCTGAAAATGCTCTGTGGGCAGCTCTTGGGT
GGCAGTAAGTCCATCAACCCCCATCTACCCCGGGCCTGAAGCGCTGCGCTTGCTCTCTTTATGTGTG
TGCACCCGAAGGATTTCTGTCTCTGTAGCTGATCCTGTGAGCCCCTCAAGCATGAAGCCTCCCTT
GGGGCTTCTCAAAGCATGGAGAGGGGCCCTTCTGTCTTTGGGAAAATCTTCCCCACTGTGTCAGT
10 TATATGGGAACAAGAGTGATGGGGTCTTCTCTAGGCCTGTGCCACAGGACAGAGAACACGGGATT
CTGCTGTTGCTTTGAGCCACAGCCTTTACCAGCCCGGCTTGTGTGGGGGGCCCCCTTCGCCCTTGCT
GCAAAGAGCTGTTCCCCAAAGGGCATATCCACAGGGTACAGGTTTTAAAGGCTTTTTTTTTTTTTT
TTGAGACAGGGTCTCGCTCTGTGCGCTAGACTCAGTGCAGTGGCGCCATGTTGGCTGGTTGCAACC
TCCACCTCCTGGGTTCAAGTGATTCTCCACCTCAGCCTCTCTGGTAGCTGGGACTACAGGCACGC
15 GCCACCATGCCCAGCTAATTTTTGGATTTTTAGTAGAGAAGGAGTTTCACCATGCTGACCAGGCTGG
TTTCGAACTCCTGACCTCAAGTGATCCGCCCCGCTGGGCCTCCCAGAGTGCTGAGATTACAGGCGT
GAGCCACCGCACCTGGCCAAAAAAGGCATTTTGATTTAGGTTGCTGTGTTTGCTTGTTGATAAAGAA
AACTCAATCGGGACACTAGTTTTGTGCTCAGCTTTAGGCCGGGTAGCTAATGGGAGGATGTCCAGCC
TGTCAGTGTGCTCCAGCGCAAGGAAATGGGTGCCACCTGGAATCAGGAGAAGAGGCTTTTCCCT
20 CCTGTTCTGCAACCAGGGTGGAGCTATCTTCCAGGGAAGCCAGCTGAGAGGTTTTAGGGCTTTGG
TTATTTTATGGGGGTTTTAAACCTCCTAACTTTTCAATGACAAATGGCTCCCAGGTGCCATAGTCTCT
GTTAAATCCTCAAACATTACAAGCACACACTGCCAGGGGCACGGGTTGTCTTTCACCTGCATGTTT
CTAAGGCTCTTTATTCAATCTCACGGTGTGAGTGTCCAGTTGTCAAAGTTATGAATCTTCCTCCTGCT
TCTAAACAGGGCTGACAGTATACTCTCGTCTAGTCTAGGAACATGTCTGCTGCTGGGATACCCTGGT
25 ACCAGGATTTGAGGGCCACGGGTGGCATCTCTGAGAGCTGAAAATCCACAGAGTGCCTGTGGGAAA
GCCAAGCCCTTGCTGTGTGGCTTTTCTATCCCTTGATTTACAGGTCTGGGAATTGGCTGCTTCTT
AGTTATAACCCAGTGACAAATGCTGGCTTAAGCCACACCTGTTCCCACTGTTGCTAGAATTCAAACA
GTTGCTTTTTTTTTTTCTTTTTGAGAAAGGGCCTCACTCTGTTGCCAGGCTGGAGTGCAGTGGCTTG
ATCACAGCTCACGAAAGCCTCAAACCTCCTAGGCTCAAGTGATCCTCCTGAAAAGTAGGTAGGACTAC
30 AGGCACATGCCACCACATACAGCTAATTTGTTTTCAATTTTTTTTTTTTTTTAGAGACAGGATCTCGCTGT
GTTCCCCAGGTAGGTCTTGAACCTCCTGGCCTCAAGTGATCCTCCTGCCTTGACCTCCCAAAGTGCTG
GATTACAAGCGTGAGCCCCTGCACCCGGCCCAAGCAGTTGCTTCTTTTTTCTCTTTTTTTTTTTTTT
GAGATGGAGCCTCACTCTGTTGCCAGGCTGGAGTGCAGTGGCGGATCTCCACTCACTGCAAGCT
CCGCTCCCGGGTTCATGCCATTCTCCTGCCTCAGCCTCCCGAGTAGCTGGGACTACAGGCGCCTG
35 CCACCACACCCAGCTAATTTTTGTATTTTTGGTACAGACAGGGTTTACCGTGTTAGCCAGGATGGT
CTTGATCTCCTGATCTCGTGATCCGCCCCACCCCGGCTCCCAAAGTGCTGGATTACAAGCGTGAGC
CACCGCGCCCCGCCAAGCAGTTGCTTCTTATGCAACATGTTGGTTGGGACTTGTCACGGGCCAGG
CCAATAAAATTCTTAATCCTGCAGAGAGTCAGTACCCTCATCACCCCATCACTGGAAAACAAATGTTT
TAAGCTATCAAGAGAGGGAATGTGCAGCTTTTGGTTTCTAGATGCATGTTTGGTGTGATCTACCTTT
40 GTGCCTAAAGGGAATGTCCCAAACAACAGAGCCTTCTTTGCTGTCACTCCAGAATTCTCTACACAGA
ATTTCCCAAGTCCATTCAGGACAGACGCGCAGTCCTCTTTCAATGGAAGAAGAGAGGACTTTTCCCC
TCCTGAAAATGACTGGAGTGTGAACAAGGCAGCTCTGTTTTCTAAATAAGTTGTTCTTGTGAGTTT

TTTCTGGCCACTGGGCATCTCTGCCCTCACTTTTCATCCCTGCCCTCTAAGCTGCAGACCCCATGAC
 CACACTGTCTGCTTCCTTGAGCTTCCCGCACGAGGCTTGGACCTGGGGGACCTGGAGACCCTGCGG
 ACAGAACTGTGGCTGAGCCACTGTGGCCAACTCTTGGGGAGCTCCACAGTGGGGGTTGCTGGTCTG
 TGAGGCTGAGTCTCCATTTAGAGCACACACTCCCTGGCAGGGCGCCTCTGCCTGTGTCTCCTGCC
 5 CAGCAGCCGCCAGCAGGGAATAGTTGCTGGTGTCTGAGCACAAAGAGAGCTTTGATTACCTAGAGA
 GGAAAAAGGCTGTCAGCCAGATGCAGCCAGGCCAGGGGTAGATACAGGAGTTGCTAAGGAAGGG
 GCCGAGCCAGGAGAGGCCAGGCAGATCCACAAAGCCCAAGGGGATGCAGGCTGGGTGTGTTTCT
 GAGGGAACCTACCAAATAGCAGGTAGATGGAATCAGAGGACTCTTGTGTCCTGAAAGAACCTCCTTA
 AAAACAATAAAACGAAGAACTTCTGGGGCTGTTACACATTGTTCAAGTCACCCCAAGATCGTTCTG
 10 GCACGCTGAGCTGAACACCACCATCTTTGTTCACTCTCTCTAATGGGCAAAGCAGGATCATCGAG
 TTGAAAAGTTGTAAATAATGAGGATATTTATCCCGCTATTTATTTTTCAATAACTGTGACCTCCTGCA
 CTGTGAATGCTCTGTGACATGAGATTCTTAGTTTAATAAACTGTCATTAAATTTGAATGAATTGATAT
 TATTGGTTACTGAACACTGGCATGAGTTTATTTTTATTGTGAAGAAAAAATCTACAGCAATCTAACT
 AAACCTTTCTAAGAAATCTAGCAGTCAGTATTGTAATGCAATATATCAAAATCTGTACACTGTCAATAA
 15 AATAAATGAGCACAAAAA
 (SEQ ID NO: 64)

As used herein, the term "SORL1" refers to the gene encoding Sortilin-related receptor. The
 terms "SORL1" and "Sortilin-related receptor" include wild-type forms of the SORL1 gene, as well as
 20 variants (e.g., splice variants and polymorphisms) of wild-type SORL1. Examples of such variants are
 nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%,
 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type SORL1 nucleic acid sequence (e.g.,
 SEQ ID NO: 65, ENA accession number Y08110). SEQ ID NO: 65 is a wild-type gene sequence
 25 encoding SORL1 protein, and is shown below:

CCGGCCAGCGGCTCTCCTGGCCTCGCGCTGCACATTCTCTCCTGGCGGCGGCCACCT
 GCAGTAGCGTTGCCCCGAACATGGCGACACGGAGCAGCAGGAGGGAGTCGCGACTCCCGT
 TCCTATTACCCCTGGTCGCACTGCTGCCGCCGGAGCTCTCTGCGAAGTCTGGACGCAGA
 30 GGCTGCACGGCGGCAGCGCGCCCTTGCCCCAGGACCGGGGCTTCCTCGTGGTGCAGGGCG
 ACCCGCGCGAGCTGCGGCTGTGGGCGCGGGGATGCCAGGGGGGCGAGCCGCGCGGACG
 AGAAGCCGCTCCGGAGGAAACGGAGCGCTGCCCTGCAGCCCGAGCCCATCAAGGTGTACG
 GACAGGTTAGTCTGAATGATTCCACAATCAGATGGTGGTGCAGTGGGCTGGAGAGAAAA
 GCAACGTGATCGTGGCCTTGCCCCGAGATAGCCTGGCATTGGCGAGGCCCAAGAGCAGTG
 35 ATGTGTACGTGTCTTACGACTATGGAAAATCATTCAAGAAAATTTAGACAAGTTAACT
 TTGGCTTGGGAAATAGGAGTGAAGCTGTTATCGCCAGTTCTACCACAGCCCTGCGGACA
 ACAAGCGGTACATCTTTGCAGACGCTTATGCCCAGTACCTCTGGATCACGTTTGACTTCT
 GCAACACTCTTCAAGGCTTTTCCATCCCATTTGCGGCGAGCTGATCTCCTCCTACACAGTA
 AGGCCTCCAACCTTCTCTTGGGCTTTGACAGGTCCCACCCCAACAAGCAGCTGTGGAAGT
 40 CAGATGACTTTGGCCAGACCTGGATCATGATTACAGGAACATGTCAAGTCCTTTTCTTGGG
 GAATTGATCCCTATGACAAACCAATACCATCTACATTGAACGACACGAACCCTCTGGCT
 ACTCCACTGTCTTCCGAAGTACAGATTTCTCCAGTCCCGGGAAACCAGGAAGTGATCC

TTGAGGAAGTGAGAGATTTTCAGCTTCGGGACAAGTACATGTTTGCTACAAAGGTGGTGC
ATCTCTTGGGCAGTGAACAGCAGTCTTCTGTCCAGCTCTGGGTCTCCTTTGGCCGGAAGC
CCATGAGAGCAGCCCAGTTTGTCAACAAGACATCCTATTAATGAATATTACATCGCAGATG
CCTCCGAGGACCAGGTGTTTGTGTGTGTGTCAGCCACAGTAACAACCGCACCAATTTATACA
5 TCTCAGAGGCAGAGGGGCTGAAGTTCTCCCTGTCCTTGGAGAACGTGCTCTATTACAGCC
CAGGAGGGGGCCGGCAGTGACACCTTGGTGAGGTATTTTGCAAATGAACCATTTGCTGACT
TCCACCGAGTGGAAGGATTGCAAGGAGTCTACATTGCTACTCTGATTAATGGTTCTATGA
ATGAGGAGAACATGAGATCGGTCAACCTTTGACAAAGGGGGAACCTGGGAGTTTCTTC
AGGCTCCAGCCTTCACGGGATATGGAGAGAAAATCAATTGTGAGCTTTCCAGGGCTGTT
10 CCCTTCATCTGGCTCAGCGCCTCAGTCAGCTCCTCAACCTCCAGCTCCGGAGAATGCCCA
TCCTGTCCAAGGAGTCGGCTCCAGGCCTCATCATCGCCACTGGCTCAGTGGGAAAGAACT
TGGCTAGCAAGACAAACGTGTACATCTCTAGCAGTGCTGGAGCCAGGTGGCGAGAGGCAC
TTCCTGGACCTCACTACTACACATGGGGAGACCACGGCGGAATCATCACGGCCATTGCCC
AGGGCATGGAAACCAACGAGCTAAAATACAGTACCAATGAAGGGGAGACCTGGAAAACAT
15 TCATCTTCTCTGAGAAGCCAGTGTTTGTGTATGGCCTCCTCACAGAACCTGGGGAGAAGA
GCACTGTCTTCACCATCTTTGGCTCGAACAAAGAGAATGTCCACAGCTGGCTGATCCTCC
AGGTCAATGCCACGGATGCCTTGGGAGTTCCCTGCACAGAGAATGACTACAAGCTGTGGT
CACCATCTGATGAGCGGGGGAATGAGTGTTTGTGCTGGGACACAAGACTGTTTTCAAACGGC
GGACCCCCCATGCCACATGCTTCAATGGAGAGGACTTTGACAGGCCGGTGGTCTGTCCA
20 ACTGCTCCTGCACCCGGGAGGACTATGAGTGTGACTTCGGTTTCAAGATGAGTGAAGATT
TGTCATTAGAGGTTTGTGTTCCAGATCCGGAATTTTCTGGAAAGTCATACTCCCCTCCTG
TGCCTTGCCCTGTGGGTTCTACTTACAGGAGAACGAGAGGCTACCGGAAGATTTCTGGGG
ACACTTGTAGCGGAGGAGATGTTGAAGCGCGACTGGAAGGAGAGCTGGTCCCCTGTCCCC
TGGCAGAAGAGAACGAGTTCATTCTGTATGCTGTGAGGAAATCCATCTACCGCTATGACC
25 TGGCCTCGGGAGCCACCGAGCAGTTGCCTCTCACCGGGCTACGGGCAGCAGTGGCCCTGG
ACTTTGACTATGAGCACAACCTGTTTGTATTGGTCCGACCTGGCCTTGGACGTCATCCAGC
GCCTCTGTTTGAATGGAAGCACAGGGCAAGAGGTGATCATCAATTCTGGCCTGGAGACAG
TAGAAGCTTTGGCTTTTGAACCCCTCAGCCAGCTGCTTTACTGGGTAGATGCAGGCTTCA
AAAAGATTGAGGTAGCTAATCCAGATGGCGACTTCCGACTCACAATCGTCAATTCCTCTG
30 TGCTTGATCGTCCCAGGGCTCTGGTCCTCGTGCCCCAAGAGGGGGTGATGTTCTGGACAG
ACTGGGGAGACCTGAAGCCTGGGATTTATCGGAGCAATATGGATGGTTCTGCTGCCTATC
ACCTGGTGTCTGAGGATGTGAAGTGGCCCAATGGCATCTCTGTGGACGACCAGTGGATTT
ACTGGACGGATGCCTACCTGGAGTGCATAGAGCGGATCACGTTCAGTGGCCAGCAGCGCT
CTGTCAATTCTGGACAACCTCCCGCACCCCTATGCCATTGCTGTCTTTAAGAATGAAATCT
35 ACTGGGATGACTGGTCACAGCTCAGCATATTCCGAGCTTCCAAATACAGTGGGTCCCAGA
TGGAGATTCTGGCAAACCAGCTCACGGGGGCTCATGGACATGAAGATTTTCTACAAGGGGA
AGAACTGGAAGCAATGCCTGTGTGCCAGGCCATGCAGCCTGCTGTGCCTGCCCAAGG
CCAACAACAGTAGAAGCTGCAGGTGTCCAGAGGATGTGTCCAGCAGTGTGCTTCCATCAG
GGGACCTGATGTGTGACTGCCCTCAGGGCTATCAGCTCAAGAACAATACCTGTGTCAAAG
40 AAGAGAACACCTGTCTTCGCAACCAGTATCGCTGCAGCAACGGGAAGTGTATCAACAGCA
TTTGGTGGTGTGACTTTGACAACGACTGTGGAGACATGAGCGATGAGAGAACTGCCCTA
CCACCATCTGTGACCTGGACACCCAGTTTCGTTGCCAGGAGTCTGGGACTTGTATCCAC

TGTCCTATAAATGTGACCTTGAGGATGACTGTGGAGACAACAGTGATGAAAGTCATTGTG
AAATGCACCAGTGCCGGAGTGACGAGTACAACCTGCAGTTCCGGCATGTGCATCCGCTCCT
CCTGGGTATGTGACGGGGACAACGACTGCAGGGACTGGTCTGATGAAGCCAACTGTACCG
CCATCTATCACACCTGTGAGGCCTCCAACCTCCAGTGCCGAAACGGGCACTGCATCCCCC
5 AGCGGTGGGCGTGTGACGGGGATACGGAAGTACCAGGATGGTTCCGATGAGGATCCAGTCA
ACTGTGAGAAGAAGTGCAATGGATTCCGCTGCCCAAACGGCACTTGCATCCCATCCAGCA
AACATTGTGATGGTCTGCGTGATTGCTCTGATGGCTCCGATGAACAGCACTGCGAGCCCC
TCTGTACGCACTTCATGGACTTTGTGTGTAAGAACCGCCAGCAGTGCCTGTTCCACTCCA
TGGTCTGTGACGGAATCATCCAGTGCCGCGACGGGTCCGATGAGGATGCGGCGTTTGCAG
10 GATGCTCCCAAGATCCTGAGTTCCACAAGGTATGTGATGAGTTCGGTTTCCAGTGTGAGA
ATGGAGTGTGCATCAGTTTGATTTGGAAGTGCGACGGGATGGATGATTGCGGCGATTATT
CTGATGAAGCCAACTGCGAAAACCCACAGAAAGCCCCAACTGCTCCCGCTACTTCCAGT
TTCGGTGTGAGAATGGCCACTGCATCCCCAACAGATGGAAATGTGACAGGGAGAACGACT
GTGGGGACTGGTCTGATGAGAAGGATTGTGGAGATTCACATATTCTTCCCTTCTCGACTC
15 CTGGGCCCTCCACGTGTCTGCCCAATTACTACCGCTGCAGCAGTGGGACCTGCGTGATGG
ACACCTGGGTGTGCGACGGGTACCGAGATTGTGCAGATGGCTCTGACGAGGAAGCCTGCC
CCTTGCTTGCAAACGTCACTGCTGCCTCCACTCCCACCCAACTTGGGCGATGTGACCGAT
TTGAGTTCGAATGCCACCAACCGAAGACGTGTATTCCCAACTGGAAGCGCTGTGACGGCC
ACCAAGATTGCCAGGATGGCCGGGACGAGGCCAATTGCCCCACACACAGCACCTTGACTT
20 GCATGAGCAGGGAGTTCCAGTGCAGGACGGGGAGGCCTGCATTGTGCTCTCGGAGCGCT
GCGACGGCTTCCTGGACTGCTCGGACGAGAGCGATGAAAAGGCCTGCAGTGATGAGTTGA
CTGTGTACAAAGTACAGAATCTTCAGTGGACAGCTGACTTCTCTGGGGATGTGACTTTGA
CCTGGATGAGGCCCAAAAAAATGCCCTCTGCATCTTGTGTATATAATGTCTACTACAGGG
TGGTTGGAGAGAGCATATGGAAGACTCTGGAGACCCACAGCAATAAGACAAACACTGTAT
25 TAAAAGTCTTGAAACCAGATACCACGTATCAGGTTAAAGTACAGGTTCAAGTGTCTCAGCA
AGGCACACAACACCAATGACTTTGTGACCCTGAGGACCCCAGAGGGATTGCCAGATGCCC
CTCGAAATCTCCAGCTGTCACTCCCCAGGGAAGCAGAAGGTGTGATTGTAGGCCACTGGG
CTCCTCCCATCCACACCCATGGCCTCATCCGTGAGTACATTGTAGAATACAGCAGGAGTG
GTTCCAAGATGTGGGCCTCCCAGAGGGCTGCTAGTAACCTTACAGAAATCAAGAACTTAT
30 TGGTCAACACTCTATACACCGTCAGAGTGGCTGCGGTGACTAGTCGTGGAATAGGAACT
GGAGCGATTCTAAATCCATTACCACCATAAAAGGAAAAGTGATCCCACCACCAGATATCC
ACATTGACAGCTATGGTGAAAATTATCTAAGCTTCACCCTGACCATGGAGAGTGATATCA
AGGTGAATGGCTATGTGGTGAACCTTTTCTGGGCATTTGACACCCACAAGCAAGAGAGGA
GAACTTTGAACTTCCGAGGAAGCATATTGTCACACAAAGTTGGCAATCTGACAGCTCATA
35 CATCCTATGAGATTTCTGCCTGGGCCAAGACTGACTTGGGGGATAGCCCTCTGGCATTG
AGCATGTTATGACCAGAGGGGTTTCGCCACCTGCACCTAGCCTCAAGGCCAAAGCCATCA
ACCAGACTGCAGTGGAATGTACCTGGACCGGCCCCCGGAATGTGGTTTATGGTATTTTCT
ATGCCACGTCCTTTCTTGACCTCTATCGCAACCCGAAGAGCTTGACTACTTCACTCCACA
ACAAGACGGTCATTGTCAGTAAGGATGAGCAGTATTTGTTTCTGGTCCGTGTAGTGGTAC
40 CCTACCAGGGGCCATCCTCTGACTACGTTGTAGTGAAGATGATCCCGGACAGCAGGCTTC
CACCCCGTCACCTGCATGTGGTTCATACGGGCAAAACCTCCGTGGTCATCAAGTGGAAT
CACCGTATGACTCTCTGACCAGGACTTGTGTATGCAATTGCAGTCAAAGATCTCATAA

GAAAGACTGACAGGAGCTACAAAGTAAAATCCCGTAACAGCACTGTGGAATACACCCTTA
 ACAAGTTGGAGCCTGGCGGGAATACCACATCATTGTCCAACCTGGGGAACATGAGCAAAG
 ATTCCAGCATAAAAAATTACCACAGTTTTCATTATCAGCACCTGATGCCTTAAAAATCATAA
 CAGAAAATGATCATGTTCTTCTGTTTTGGAAAAGCCTGGCTTTAAAGGAAAAGCATTTTA
 5 ATGAAAGCAGGGGCTATGAGATACACATGTTTGATAGTGCCATGAATATCACAGCTTACC
 TTGGGAATACTACTGACAATTTCTTTAAAATTTCCAACCTGAAGATGGGTCATAATTACA
 CGTTCACCGTCCAAGCAAGATGCCTTTTTGGCAACCAGATCTGTGGGGAGCCTGCCATCC
 TGCTGTACGATGAGCTGGGGTCTGGTGCAGATGCATCTGCAACGCAGGCTGCCAGATCTA
 CGGATGTTGCTGCTGTGGTGGTGGCCATCTTATTCTGATACTGCTGAGCCTGGGGGTGG
 10 GGTTTGCCATCCTGTACACGAAGCACCGGAGGCTGCAGAGCAGCTTCACCGCCTTCGCCA
 ACAGCCACTACAGCTCCAGGCTGGGGTCCGCAATCTTCTCCTCTGGGGATGACCTGGGGG
 AAGATGATGAAGATGCCCCCTATGATAACTGGATTTTCAGATGACGTCCCCATGGTGATAG
 CCTGAAAGAGCTTTCCTCACTAGAAACCAAATGGTGTAATATTTTATTTGATAAAGATA
 GTTGATGGTTTATTTTAAAAGATGCACTTTGAGTTGCAATATGTTATTTTTATATGGGCC
 15 (SEQ ID NO: 65)

As used herein, the term "SPI1" refers to the gene encoding Transcription factor PU.1. The terms
 "SPI1" and "Transcription factor PU.1" include wild-type forms of the SPI1 gene, as well as variants (e.g.,
 splice variants and polymorphisms) of wild-type SPI1. Examples of such variants are nucleic acids
 20 having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%,
 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%,
 98%, 99%, or 99.9% identity, or more) to a wild-type SPI1 nucleic acid sequence (e.g., SEQ ID NO: 66,
 ENA accession number X52056). SEQ ID NO: 66 is a wild-type gene sequence encoding SPI1 protein,
 and is shown below:

25 AAAATCAGGAACTTGTGCTGGCCCTGCAATGTCAAGGGAGGGGGCTCACCCAGGGCTCCT
 GTAGCTCAGGGGGCAGGCCTGAGCCCTGCACCCGCCACGACCGTCCAGCCCCTGACGG
 GCACCCCATCCTGAGGGGCTCTGCATTGGCCCCACCGAGGCAGGGGATCTGACCGACTC
 GGAGCCCGGCTGGATGTTACAGGCGTGCAAATGGAAGGGTTTCCCCTCGTCCCCCTCC
 30 ATCAGAAGACCTGGTGCCCTATGACACGGATCTATACCAACGCCAAACGCACGAGTATTA
 CCCCTATCTCAGCAGTGATGGGGAGAGCCATAGCGACCATTACTGGGACTTCCACCCCCA
 CCACGTGCACAGCGAGTTCGAGAGCTTCGCCGAGAACAACCTTCACGGAGCTCCAGAGCGT
 GCAGCCCCCGCAGCTGCAGCAGCTCTACCGCCACATGGAGCTGGAGCAGATGCACGTCTT
 CGATACCCCATGGTGCCACCCCATCCCAGTCTTGGCCACCAGGTCTCCTACCTGCCCCG
 35 GATGTGCCTCCAGTACCCATCCCTGTCCCCAGCCCAGCCCAGCTCAGATGAGGAGGAGGG
 CGAGCGGCAGAGCCCCCACTGGAGGTGTCTGACGGCGAGGCGGATGGCCTGGAGCCCGG
 GCCTGGGCTCCTGCCTGGGGAGACAGGCAGCAAGAAGAAGATCCGCCTGTACCAGTTCCT
 GTTGGACCTGCTCCGAGCGGCGACATGAAGGACAGCATCTGGTGGGTGGACAAGGACAA
 GGGCACCTTCCAGTTCTCGTCCAAGCACAAGGAGGCGCTGGCGCACCGCTGGGGCATCCA
 40 GAAGGGCAACCGCAAGAAGATGACCTACCAGAAGATGGCGCGCGCGCTGCGCAACTACGG
 CAAGACGGGCGAGGTCAAGAAGGTGAAGAAGAAGCTCACCTACCAGTTCAGCGGCGAAGT
 GCTGGGCCGCGGGGGCCTGGCCGAGCGGCGCCACCCGCCCACTGAGCCCGCAGCCCCCG

CCGGCCCCGCCAGGCCTCCCCGCTGGCCATAGCATTAAAGCCCTCGCCCGGCCCGGACACA
 GGGAGGACGCTCCCGGGGGCCAGAGGCAGGACTGTGGCGGGCCGGGCTCCGTCACCCGCC
 CCTCCCCCCTCCAGGCCCTCCACATCCCGCTTCGCCTCCCTCCAGGACTCCACCCC
 GGCTCCCGACGCCAGCTGGGCGTCAGACCCACCGGCAACCTTGACAGAGGACGACCCGGGG
 5 TACTGCCTTGGGAGTCTCAAGTCCGTATGTAAATCAGATCTCCCCTCTACCCCTCCCAC
 CCATTAACCTCCTCCCAAAAAACAAGTAAAGTTATTCTCAATCC
 (SEQ ID NO: 66)

As used herein, the term "SPP1" refers to the gene encoding Secreted Phosphoprotein 1. The
 10 terms "SPP1" and "Secreted Phosphoprotein 1" include wild-type forms of the SPP1 gene, as well as
 variants (e.g., splice variants and polymorphisms) of wild-type SPP1. Examples of such variants are
 nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%,
 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%,
 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type SPP1 nucleic acid sequence (e.g., SEQ
 15 ID NO: 67, NCBI Reference Sequence: NM_001040058.1). SEQ ID NO: 67 is a wild-type gene sequence
 encoding SPP1 protein, and is shown below:

CTCCCTGTGTTGGTGGAGGATGTCTGCAGCAGCATTTAAATTCTGGGAGGGCTTGGTTGTCAGCAG
 CAGCAGGAGGAGGCAGAGCACAGCATCGTCGGGACCAGACTCGTCTCAGGCCAGTTGCAGCCTTC
 20 TCAGCCAAACGCCGACCAAGGAAACTCACTACCATGAGAATTGCAGTGATTTGCTTTTGCCTCCTA
 GGCATCACCTGTGCCATACCAGTTAAACAGGCTGATTCTGGAAGTTCTGAGGAAAAGCAGCTTTACA
 ACAAATACCCAGATGCTGTGGCCACATGGCTAAACCCTGACCCATCTCAGAAGCAGAATCTCCTAGC
 CCCACAGAATGCTGTGCTCTGAAGAAACCAATGACTTTAAACAAGAGACCCTTCCAAGTAAGTCC
 AACGAAAGCCATGACCACATGGATGATATGGATGATGAAGATGATGATGACCATGTGGACAGCCAG
 25 GACTCCATTGACTCGAACGACTCTGATGATGTAGATGACACTGATGATTCTCACCAGTCTGATGAGT
 CTCACCATTCTGATGAATCTGATGAACTGGTCACTGATTTTCCCACGGACCTGCCAGCAACCGAAGT
 TTCACTCCAGTTGTCCCCACAGTAGACACATATGATGGCCGAGGTGATAGTGTGGTTTATGGACTG
 AGGTCAAAATCTAAGAAGTTTCGCAGACCTGACATCCAGTACCCTGATGCTACAGACGAGGACATCA
 CCTCACACATGGAAAGCGAGGAGTTGAATGGTGCATACAAGGCCATCCCCGTTGCCAGGACCTGA
 30 ACGCGCCTTCTGATTGGGACAGCCGTGGGAAGGACAGTTATGAAACGAGTCAGCTGGATGACCAGA
 GTGCTGAAACCCACAGCCACAAGCAGTCCAGATTATATAAGCGGAAAGCCAATGATGAGAGCAATGA
 GCATTCCGATGTGATTGATAGTCAGGAACTTTCCAAAGTCAGCCGTGAATTCCACAGCCATGAATTTT
 ACAGCCATGAAGATATGCTGGTTGTAGACCCCAAAAGTAAGGAAGAAGATAAACACCTGAAATTTTCG
 TATTTCTCATGAATTAGATAGTGCATCTTCTGAGGTCAATTAAGGAGAGAAAAATACAATTTCTCACT
 35 TTGCATTTAGTCAAAAGAAAAATGCTTTATAGCAAAATGAAAGAGAACATGAAATGCTTCTTTCTCAG
 TTTATTGGTTGAATGTGTATCTATTTGAGTCTGGAAATAACTAATGTGTTTGATAATTAGTTTGT
 GGCTTCATGGAACTCCCTGTAACTAAAAGCTTCAGGGTTATGTCTATGTTTATTCTATAGAAGAAA
 TGCAAACTATCACTGTATTTTAATATTTGTTATTCTCTCATGAATAGAAATTTATGTAGAAGCAAACAAA
 ATACTTTTACCCACTTAAAAAGAGAATATAACATTTTATGTCACTATAATCTTTTGTGTTTTTAAGTTAGT
 40 GTATATTTTGTGTTGATTATCTTTTTGTGGTGTGAATAAATCTTTTATCTTGAATGTAATAAGAATTTGG
 TGGTGTCAATTGCTTATTTGTTTTCCCACGGTTGTCCAGCAATTAATAAACATAACCTTTTTTACTGC
 CTAAAAA

(SEQ ID NO: 67)

As used herein, the term "SPPL2A" refers to the gene encoding Signal Peptide Peptidase Like 2A. The terms "SPPL2A" and "Signal Peptide Peptidase Like 2A" include wild-type forms of the SPPL2A gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type SPPL2A. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type SPPL2A nucleic acid sequence (e.g., SEQ ID NO: 68, NCBI Reference Sequence: NM_001040058.1). SEQ ID NO: 68 is a wild-type gene sequence encoding SPPL2A protein, and is shown below:

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AAGAGGAAGTCGCGCTGCTGTGGCGGCCGCTGTAGCAGCGGCGGTCCAGTCGTAGCCCGGCCGC
CCGCGCCTGTCCGGTCCGGTCCGGCCACGGAGGCAGCGCAGCGGCGGGACTCCGAGCCTACCC
GCCGAGTGAGCTGCGCCGCACCGTGCCGTCCCACCCGGCACCCACCAGTCCGATGGGGCCGCAG
CGGCGGCTGTCCCCTGCCGGGGCCGCCCTACTCTGGGGCTTCCTGCTCCAGCTGACAGCCGCTCA
GGAAGCAATCTTGCATGCGTCTGGAAATGGCACAACCAAGGACTACTGCATGCTTTATAACCCTTATT
GGACAGCTCTTCCAAGTACCCTAGAAAATGCAACTTCCATTAGTTTGATGAATCTGACTTCCACACCA
CTATGCAACCTTTCTGATATTCCTCCTGTTGGCATAAAGAGCAAAGCAGTTGTGGTTCCATGGGGAA
GCTGCCATTTTCTTGAAAAAGCCAGAATTGCACAGAAAGGAGGTGCTGAAGCAATGTTAGTTGTCAA
TAACAGTGTCTATTTCTCCCTCAGGTAACAGATCTGAATTTCTGATGTGAAAATACTGATTGCATT
TATAAGCTACAAAGACTTTAGAGATATGAACCAGACTCTAGGAGATAACATTACTGTGAAAATGTATT
CTCCATCGTGGCCTAACTTTGATTATACTATGGTGGTTATTTTTGTAATTGCGGTGTTCACTGTGGCA
TTAGGTGGATACTGGAGTGGACTAGTTGAATTGGAAAACCTTGAAAGCAGTGACAACTGAAGATAGAG
AAATGAGGAAAAAGAAGGAAGAATATTTAACTTTTAGTCCTCTTACAGTTGTAATATTTGTGGTCATCT
GCTGTGTTATGATGGTCTTACTTTATTTCTTCTACAAATGGTTGGTTTATGTTATGATAGCAATTTTCTG
CATAGCATCAGCAATGAGTCTGTACAACCTGTCTTGCTGCACTAATTCATAAGATACCATATGGACAAT
GCACGATTGCATGTCGTGGCAAAAACATGGAAGTGAGACTTATTTTTCTCTCTGGACTGTGCATAGC
AGTAGCTGTTGTTTGGGCTGTGTTTCGAAATGAAGACAGGTGGGCTTGGATTTTACAGGATATCTTG
GGGATTGCTTTCTGTCTGAATTTAATTAACACTGAAGTTGCCCACTTCAAGTCATGTGTGATACTT
CTAGGCCTTCTCCTCCTCTATGATGTATTTTTGTTTTCATAACACCATTTCATCACAAGAATGGTGAG
AGTATCATGGTTGAACTCGCAGCTGGACCTTTTGAAATAATGAAAAGTTGCCAGTAGTCATCAGAGT
ACCAAACTGATCTATTTCTCAGTAATGAGTGTGTGCCTCATGCCTGTTTCAATATTGGGTTTTGGAG
ACATTATTGTACCAGGCCTGTTGATTGCATACTGTAGAAGATTTGATGTTTCACTGGTTCTTCTTACA
TATACTATGTTTCGTCTACAGTTGCCTATGCTATTGGCATGATACTTACATTTGTTGTTCTGGTGCTGA
TGAAAAAGGGGCAACCTGCTCTCCTCTATTTAGTACCTTGACACTTATTACTGCCTCAGTTGTTGCC
TGGAGACGTAAGGAAATGAAAAAGTTCTGGAAAGGTAACAGCTATCAGATGATGGACCATTGTTGATT
GTGCAACAAATGAAGAAAACCCTGTGATATCTGGTGAACAGATTGTCCAGCAATAATATTATGTGGAA
CTGCTATAATGTGTCATTGATTTTCTACAAATAGACTTCGACTTTTAAATTGACTTTTGAATTGACAAT
CTGAAAGAGTCTTCAATGATATGCTTGCAAAAATATATTTTTATGAGCTGGTACTGACAGTTACATCAT
AAATAACTAAAACGCTTTGCTTTAATGTTAAAGTTGTGCCTTCACATTAAATAAAAACATATGGTCTGT
GTAGTTTCCGAGATGTACTATATACAGTATATTTTTCTAAAAAAA

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(SEQ ID NO: 68)

As used herein, the term "TBK1" refers to the gene encoding Serine/threonine-protein kinase TBK1. The terms "TBK1" and "Serine/threonine-protein kinase TBK1" include wild-type forms of the TBK1 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type TBK1. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type TBK1 nucleic acid sequence (e.g., SEQ ID NO: 69, ENA accession number AF191838). SEQ ID NO: 69 is a wild-type gene sequence encoding TBK1 protein, and is shown below:

10

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GCCGGCGGTGGCGCGGCGGAGACCCGGCTGGTATAACAAGAGGATTGCCTGATCCAGCCA
AGATGCAGAGCACTTCTAATCATCTGTGGCTTTTATCTGATATTTTAGGCCAAGGAGCTA
CTGCAAATGTCTTTCGTGGAAGACATAAGAAAACCTGGTGATTTATTTGCTATCAAAGTAT
TTAATAACATAAGCTTCCTTCGTCCAGTGGATGTTCAAATGAGAGAATTTGAAGTGTTGA
15 AAAAACTCAATCACAAAATATTGTCAAATTATTTGCTATTGAAGAGGAGACAACAACAA
GACATAAAGTACTTATTATGGAATTTTGTCCATGTGGGAGTTTATACACTGTTTTAGAAG
AACCTTCTAATGCCTATGGACTACCAGAATCTGAATTCTTAATTGTTTTGCGAGATGTGG
TGGGTGGAATGAATCATCTACGAGAGAATGGTATAGTGCACCGTGATATCAAGCCAGGAA
ATATCATGCGTGTTATAGGGGAAGATGGACAGTCTGTGTACAACTCACAGATTTTGGTG
20 CAGCTAGAGAATTAGAAGATGATGAGCAGTTTGTCTCTGTATGGCACAGAAGAATATT
TGCACCCTGATATGTATGAGAGAGCAGTGCTAAGAAAAGATCATCAGAAGAAATATGGAG
CAACAGTTGATCTTTGGAGCATTGGGGTAACATTTTACCATGCAGCTACTGGATCACTGC
CATTTAGACCCTTTGAAGGGCCTCGTAGGAATAAAGAAGTGATGTATAAAATAATTACAG
GAAAGCCTTCTGGTGCAATATCTGGAGTACAGAAAGCAGAAAATGGACCAATTGACTGGA
25 GTGGAGACATGCCTGTTTCTTGCAAGTCTTTCTCGGGGTCTTCAGGTTCTACTTACCCCTG
TTCTTGCAAACATCCTTGAAGCAGATCAGGAAAAGTGTTGGGGTTTTGACCAGTTTTTTG
CAGAACTAGTGATATACTTCACCGAATGGTAATTCATGTTTTTTCGCTACAACAAATGA
CAGCTCATAAGATTTATATTCATAGCTATAACTGCTACTATATTTTCATGAACTGGTAT
ATAAACAAACCAAAATTATTTCTTCAAATCAAGAACTTATCTACGAAGGGCGACGCTTAG
30 TCTTAGAACCTGGAAGGCTGGCACAACATTTCCCTAAACTACTGAGGAAAACCCTATAT
TTGTAGTAAGCCGGAACCTCTGAATACCATAGGATTAATATATGAAAAATTTCCCTCC
CTAAAGTACATCCACGTTATGATTTAGACGGGGATGCTAGCATGGCTAAGGCAATAACAG
GGGTTGTGTGTTATGCCTGCAGAATTGCCAGTACCTTACTGCTTTATCAGGAATTAATGC
GAAAGGGGATACGATGGCTGATTGAATTAATTAAGATGATTACAATGAACTGTTTACA
35 AAAAGACAGAAGTTGTGATCACATTGGATTTCTGTATCAGAAACATTGAAAAAAGTGA
AAGTATATGAAAAGTTGATGAAGATCAACCTGGAAGCGGCAGAGTTAGGTGAAATTTGAG
ACATACACACCAAATTGTTGAGACTTTCCAGTTCTCAGGGAACAATAGAAACCAGTCTTC
AGGATATCGACAGCAGATTATCTCCAGGTGGATCACTGGCAGACGCATGGGCACATCAAG
AAGGCACTCATCCGAAAGACAGAAATGTAGAAAACTACAAGTCCTGTAAATTGCATGA
40 CAGAGATTTACTATCAGTTCAAAAAAGACAAAGCAGAACGTAGATTAGCTTATAATGAAG
AACAAATCCACAAATTTGATAAGCAAAAACTGTATTACCATGCCACAAAAGCTATGACGC
ACTTTACAGATGAATGTGTTAAAAAGTATGAGGCATTTTTGAATAAGTCAGAAGAATGGA
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TAAGAAAGATGCTTCATCTTAGGAAACAGTTATTATCGCTGACTAATCAGTGTTTTGATA
 TTGAAGAAGAAGTATCAAAATATCAAGAATATACTAATGAGTTACAAGAACTCTGCCTC
 AGAAAATGTTTACAGCTTCCAGTGGAATCAAACATACCATGACCCCAATTTATCCAAGTT
 CTAACACATTAGTAGAAATGACTCTTGGTATGAAGAAATTAAGGAAGAGATGGAAGGGG
 5 TGGTTAAAGAACTTGCTGAAAATAACCACATTTTAGAAAGGTTTGGCTCTTTAACCATGG
 ATGGTGGCCTTCGCAACGTTGACTGTCTTTAGCTTTCTAATAGAAGTTTAAGAAAAGTTT
 CCGTTTGCACAAGAAAATAACGCTTGGGCATTAAATGAATGCCTTTATAGATAGTCACTT
 GTTTCTACAATTCAGTATTTGATGTGGTCGTGTAATATGTACAATATTGTAAATACATA
 AAAAATATACAAATTTTTGGCTGCTGTGAAGATGTAATTTTATCTTTTAACATTTATAAT
 10 TATATGAGGAAATTTGACCTCAGTGATCACGAGAAGAAAGCCATGACCGACCAATATGTT
 GACATACTGATCCTCTACTCTGAGTGGGGCTAAATAAGTTATTTTCTCTGACCGCCTACT
 GGAAATATTTTAAAGTGAACCAAAATAGGCATCCTTACAAATCAGGAAGACTGACTTGA
 CACGTTTGTAAATGGTAGAACGGTGGCTACTGTGAGTGGGGAGCAGAACCGCACCCTGT
 TATACTGGGATAACAATTTTTTTGAGAAGGATAAAGTGGCATTATTTTATTTTACAAGGT
 15 GCCCAGATCCCAGTTATCCTTGTATCCATGTAATTTTCAAGATGAATTATTAAGCAAACATT
 TTAAAGT
 (SEQ ID NO: 69)

As used herein, the term "TNF" refers to the gene encoding Tumor necrosis factor. The terms
 20 "TNF" and "Tumor necrosis factor" include wild-type forms of the TNF gene, as well as variants (e.g.,
 splice variants and polymorphisms) of wild-type TNF. Examples of such variants are nucleic acids having
 at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%,
 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%,
 99%, or 99.9% identity, or more) to a wild-type TNF nucleic acid sequence (e.g., SEQ ID NO: 70, ENA
 25 accession number X01394). SEQ ID NO: 70 is a wild-type gene sequence encoding TNF protein, and is
 shown below:

GCAGAGGACCAGCTAAGAGGGAGAGAAGCAACTACAGACCCCCCTGAAAACAACCCTCA
 GACGCCACATCCCCTGACAAGCTGCCAGGCAGGTTCTCTTCTCTCACATACTGACCCAC
 30 GGCTCCACCCTCTCTCCCCTGGAAAGGACACCATGAGCACTGAAAGCATGATCCGGGACG
 TGGAGCTGGCCGAGGAGGCGCTCCCCAAGAAGACAGGGGGGCCCCAGGGCTCCAGGCGGT
 GCTTGTTCTCAGCCTCTTCTCCTTCTGATCGTGGCAGGCGCCACCACGCTCTTCTGCC
 TGCTGCACTTTGGAGTGATCGGCCCCCAGAGGGAAGAGTTCCCCAGGGACCTCTCTCTAA
 TCAGCCCTCTGGCCCAGGCAGTCAGATCATCTTCTCGAACCCCGAGTGACAAGCCTGTAG
 35 CCCATGTTGTAGCAAACCCTCAAGCTGAGGGGCAGCTCCAGTGGCTGAACCGCCGGGCCA
 ATGCCCTCCTGGCCAATGGCGTGGAGCTGAGAGATAACCAGCTGGTGGTGGCATCAGAGG
 GCCTGTACCTCATCTACTCCCAGGTCCTCTTCAAGGGCCAAGGCTGCCCCCTCCACCCATG
 TGCTCCTCACCCACACCATCAGCCGCATCGCCGTCTCCTACCAGACCAAGGTCAACCTCC
 TCTCTGCCATCAAGAGCCCCTGCCAGAGGGAGACCCAGAGGGGGCTGAGGCCAAGCCCT
 40 GGTATGAGCCCATCTATCTGGGAGGGGTCTTCCAGCTGGAGAAGGGTGACCGACTCAGCG
 CTGAGATCAATCGGCCCCGACTATCTCGACTTTGCCGAGTCTGGGCAGGTCTACTTTGGGA
 TCATTGCCCTGTGAGGAGGACGAACATCCAACCTTCCCAAACGCCTCCCCTGCCCAATC

CCTTTATTACCCCTCCTTCAGACACCCTCAACCTCTTCTGGCTCAAAAAGAGAATTGGG
 GGCTTAGGGTCGGAACCCAAGCTTAGAACTTTAAGCAACAAGACCACCACTTCGAAACCT
 GGGATTACAGGAATGTGTGGCCTGCACAGTGAATTGCTGGCAACCACTAAGAATTCAAACCT
 GGGGCCTCCAGAACTCACTGGGGCCTACAGCTTTGATCCCTGACATCTGGAATCTGGAGA
 5 CCAGGGAGCCTTTGGTTCTGGCCAGAATGCTGCAGGACTTGAGAAGACCTCACCTAGAAA
 TTGACACAAGTGGACCTTAGGCCTTCCTCTCTCCAGATGTTTCCAGACTTCCTTGAGACA
 CGGAGCCCAGCCCTCCCCATGGAGCCAGCTCCCTCTATTTATGTTTGCACCTGTGATTAT
 TTATTATTTATTTATTATTTATTTATTTACAGATGAATGTATTTATTTGGGAGACCGGGG
 TATCCTGGGGGACCCAATGTAGGAGCTGCCTTGGCTCAGACATGTTTTCCGTGAAAACGG
 10 AGCTGAACAATAGGCTGTTCCCATGTAGCCCCCTGGCCTCTGTGCCTTCTTTTGATTATG
 TTTTTTAAATATTTATCTGATTAAGTTGTCTAAACAATGCTGATTTGGTGACCAACTGT
 CACTCATTGCTGAGCCTCTGCTCCCCAGGGGAGTTGTGTCTGTAATCGCCCTACTATTCA
 GTGGCGAGAAATAAAGTTTGCTT
 (SEQ ID NO: 70)

15
 As used herein, the term "TREM2" refers to the gene encoding Triggering receptor expressed on myeloid cells 2. The terms "TREM2" and "Triggering receptor expressed on myeloid cells 2" include wild-type forms of the TREM2 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type TREM2. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%,
 20 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type TREM2 nucleic acid sequence (e.g., SEQ ID NO: 71, ENA accession number AF213457). SEQ ID NO: 71 is a wild-type gene sequence encoding TREM2 protein, and is shown below:

25 TGACATGCCTGATCCTCTCTTTTCTGCAGTTCAAGGGAAAGACGAGATCTTGCACAAGGC
 ACTCTGCTTCTGCCCTTGGCTGGGGAAGGGTGGCATGGAGCCTCTCCGGCTGCTCATCTT
 ACTCTTTGTACAGAGCTGTCCGGAGCCCACAACACCACAGTGTTCCAGGGCGTGGCGGG
 CCAGTCCCTGCAGGTGTCTTGCCCCTATGACTCCATGAAGCACTGGGGGAGGCGCAAGGC
 CTGGTGCCGCCAGCTGGGAGAGAAGGGCCCATGCCAGCGTGTGGTCAGCACGCACAACCT
 30 GTGGCTGCTGTCCTTCTGAGGAGGTGGAATGGGAGCACAGCCATCACAGACGATACCCT
 GGGTGGCACTCTCACCATTACGCTGCGGAATCTACAACCCCATGATGCGGGTCTCTACCA
 GTGCCAGAGCCTCCATGGCAGTGAGGCTGACACCCTCAGGAAGGTCCTGGTGGAGGTGCT
 GGCAGACCCCCTGGATCACCGGGATGCTGGAGATCTCTGGTTCCCCGGGGAGTCTGAGAG
 CTTGAGGATGCCCATGTGGAGCACAGCATCTCCAGGAGCCTCTTGAAGGAGAAATCCC
 35 CTTCCCACCCACTTCCATCCTTCTCCTCCTGGCCTGCATCTTCTCATCAAGATTCTAGC
 AGCCAGCGCCCTCTGGGCTGCAGCCTGGCATGGACAGAAGCCAGGGACACATCCACCCAG
 TGAAGTGGACTGTGGCCATGACCCAGGGTATCAGCTCCAACTCTGCCAGGGCTGAGAGA
 CACGTGAAGGAAGATGATGGGAGGAAAAGCCCAGGAGAAGTCCCACCAGGGACCAGCCCA
 GCCTGCATACTTGCCACTTGCCACCAGGACTCCTTGTTCTGCTCTGGCAAGAGACTACT
 40 CTGCCTGAACACTGCTTCTCCTGGACCCTGGAAGCAGGGACTGGTTGAGGGAGTGGGGAG
 GTGGTAAGAACACCTGACAACCTTCTGAATATTGGACATTTTAAACACTTACAAATAAATC
 CAAGACTGTCATATTTAAAAA

(SEQ ID NO: 71)

As used herein, the term "TREML2" refers to the gene encoding Triggering Receptor Expressed on Myeloid Cells Like 2. The terms "TREML2" and "Triggering Receptor Expressed on Myeloid Cells Like 2" include wild-type forms of the TREML2 gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type TREML2. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type TREML2 nucleic acid sequence (e.g., SEQ ID NO: 72, NCBI Reference Sequence: NM_024807.3). SEQ ID NO: 72 is a wild-type gene sequence encoding TREML2 protein, and is shown below:

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CAATGAATCCCTGCGGTTGGCTGGGGGCAGTGGGTCCACACTGCCTCACTTCCCTAAATGGGCAG
CTTCACTTTTAGAACCCCGGGTCCTTCCCTGGCAGGCCAGGTGGCACATCCTGTGTGCGGTGGGC
15 CCTCACCTTGATCTCCAGGCCTGACACTGCCCAGCTGGATGGAACCATGGCCCCAGCCTTCCTGC
TGCTGCTGCTGCTGTGGCCACAGGGTTGCGTCTCAGGCCCTCTGCTGACAGTGTATACACAAAAG
TGAGGCTCCTTGAAGGGGAGACTCTGTCTGTGCAGTGCTCCTATAAGGGCTACAAAACCGCGTGG
AGGGCAAGGTTTGGTGCAAAATCAGGAAGAAGAAGTGTGAGCCTGGCTTTGCCCGAGTCTGGGTGA
AAGGGCCCCGCTACTTGCTGCAGGACGATGCCAGGCCAAGGTGGTCAACATCACCATGGTGGCC
20 CTCAAGCTCCAGGACTCAGGCCGATACTGGTGCATGCGCAACACCTCTGGGATCCTGTACCCCTTG
ATGGGCTTCCAGCTGGATGTGTCTCCAGCTCCCCAACTGAGAGGAACATTCCTTTCACACATCTGG
ACAACATCCTCAAGAGTGGAAGTGTCACAACTGGCCAAGCCCCTACCTCAGGCCCTGATGCCCTTT
TACCACTGGTGTGATGGTGTTCACCCCAGGACTCATCACCTTGCCTAGGCTCTTAGCCTCCACCAGA
CCTGCCTCCAAGACAGGCTACAGCTTCACTGCTACCAGCACCACCAGCCAGGGACCCAGGAGGACC
25 ATGGGGTCCCAGACAGTGACCGCGTCTCCCAGCAATGCCAGGGACTCCTCTGCTGGCCCAGAATCC
ATCTCCACTAAGTCTGGGGACCTCAGCACCAGATCGCCCACCACAGGGCTCTGCCTCACCAGCAGA
TCTCTCCTCAACAGACTACCCTCCATGCCCTCCATCAGGCACCAGGATGTTTACTCCACTGTGCTTG
GGGTGGTGTGCTGACCCTCCTGGTGTGCTGATGCTGATCATGGTCTATGGGTTTTGGAAGAAGAGACACA
TGGAAGCTACAGCATGTGCAGCGATCCTTCTACACGTGACCCACCTGGAAGACCAGAGCCCTATG
30 TGGAAGTCTACTTGATCTGAGGCCACTTAAGCATGGGGTGGGGAGCTTCTCCCAGAGTGGCCCCAG
GGGGTTAGAGGAGGGGTGAAGATTGGGGCCAGTATCGATCTTATGAAGCTGGAGGACTTGTGCAGT
GCTGGACTCACCAGGACTTCCCAAACCCAGAGGCTGCCATCCTAAGCAGCCCCACAGCCCAGTGT
TCTCCTTGGGGGCAGGAACCTGGGGAGGGGCCAGAGCAAAGGGCATCAGGGAGAAAGTCCCGAG
GAAATGTGACCAGTGTTTTCTGCTCGGAGCTGCAGACCCAGGGCTCTTGGTGGAGGCAGGGGAA
35 CCCTGAGAGTGCTGTTTACAGAGAACCTCAGCTCCCGTCTGCCTCAGAAACCCTATTGGGCTGAGCT
GCCCTCCCCACCAGGGCCACTGTGTCTCTGCTTCCCTCCGTTCTGCTTCAGCTTCCCCTAAGGTTA
GGGAAGAAAGAATCGGGCTCACGAATGCCAGAGGCAGTGATGTCCCATCCTGGAGGAGAGGAAAC
AGTGACTAAAAGCTGGGGACCCACAGAGGGGTTGGCAGCTTCTCTTGTGCGGACAGGTGTCTTTG
CTGGGCCTCTGGATGGCCCTGCCCTGACTGGGGCTGCTCCTCCCTCCTGTCCTGGGACCGCGCAG
40 AGCCCACGCTCTCACTGCTGCCTCCTGCTGGCCGCTGCCTCCTTAGAAAGCTGTGACCAGGCAGCT
AAGAGCCTCTGGGCTGCAGGGTCAGCCTCTCCCAAGACTGAAGTGCAGAGGCTGGACTTGGGGCT
CTCTCCCCCAGCTTCTACACCTGGGCTCCAAGTCTGAGTTCCACAGGGGACCCAGCAGCCTCCAG
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GAAGTCCATACCCTGGGGTGGCTGAGACCTTGGCTCTGTATGGAGGCTGCTCACCCACAGACACT
GGTGGGGAGACCATGGCTCAGAGGAAGGGTGGAGCAACCCTCCTCCTACCCCTCAGGATAGAGAG
AGAAGACACACTTGGGACACAGTGAAGACAGTAACCTGGAAGTACCACGGCCTGGAGGACTGGCC
CAGGCAGGGGGACAGGGAAAATGGAGCCCAAGTAGCCTCTGGCCAGGGACCCAATGTCCCGAGGA
5 ATCTGCCTCCCACCCACTGACTCAGGGCTCAGACTCAGCCTCTATTGTCCAGAGCACTGGCTTGGC
GTCCAGCAATGAAGGCTGGAGAATGCAGCCTGGATTCCCCTACACACACACACACACACACACA
CACACACACACACACACACACACACAGGTGTCTACTGACCTGGAGTGACTGGAATAGCACCTGG
GGATAAATGTGACAACTGTGCATTGAACCCTGGGTGAGGGACGTTCCAATGGCCAAGAGAGTGACA
CAGCCAGGACCCTGGTGGACAGCCAGAGGGGCCACTTCAGGATGGATGTGGGGAGAGTGGAAGAG
10 GCAGGGAGTAATCCTGGGGGACAGCAGGGAGGAGGCACTTCTTCCCTATGTCCAGGAGAGGGCAA
TAGAGGGAAGACTGAGGCTGAAGAATTGACGGCTCTGGACCCAGGACAGACAGACAGACAGACAGA
CAGACAGACAGACAGACACGCACACACACCCATCTCTGTCTAGCAAGCAGCCTCCTAAGATAGCTGT
TCTCCCTATCATGACGGTGTAGCCACCATCCTGTTGTATACTAGGAGAGAACTTAACCCACCTGGGG
GAAAATAGCTCCCCAAGAGCTGGCACCAGTACCACTGATGGCCCTGCTTCTCTGAGTGAGATGCC
15 CAGGAGGAGGAGCCCTAGGGAAGAAGTCAGGGACAGGGACCAGGATACCACTCTGTCACTGTGTG
ACCCTCAGCAAGTCACTAACCCTTGGCCTCATTTTTCTGTCTTGTGAAAGAGGACAATAATTCCTAC
TTCTCAAGATTGTTTTCAAGATAAAATAACATTAGCATTGTACAATGATGCAAATGCCTCATTACCATT
ATTCCTTAAGTTGTTTTCCAGCTCTAATGTTGTTTCCAACATTACATTTAAGACCTTAGGATTCTGTTTC
TTGCTTTTGTTCATATCTCTTCCCAAGTGTTCATCACTATATGGATGTTGAGGGCCCCCGATGACAGTCC
20 CTTTGGTAAGTCTCTTTTGGAGGGGGAGGGTACAGGGTGGACTCATCTCAGTGTGAACTTGGC
AAGTCACTGTCCCTCTCTGATCTTGTTCCTCATCTGGAGAAGGAGTGAGAGAGGAGAAAGGAAGAA
ACCAGTCAGGCAGGCAGTTAGGGTGGGTCTCGGTAGAATTCTTTTAAACAAAAGAACAGCCTGAAA
AATCAAGCTGCAGGCACAGATATGGGAACCTTGACAGGGGGGCTTGCCTAAGACATGCCCACAGCC
TCATAGATAAGACAGACTACACAGGTGACTTGCCCAAACATGCCTGCAATGGAAAATTTTCATCCCCT
25 GACATGTGCAGTAAGGGGAACAAAGCAATATGGAGTAAGTAACTCAAGCCAAGGGCCCACATGTAC
ATTAGAAGGACAGCAGGGAGCTACCAGAAATTCATGCCTTATGCAGATGAGCTGCCAGTCCCTCATC
GGTTTCTTATAAAAGCCTTTACATTCAACTGTAAAAATGGCAACCCTCTTTCAGGCCTCCTCTCCACA
GCAGAGAGCTTTCTTCTCTCACTCATTAACCTTTCACTCCAACCTCAAAAAAAAAAAAAAAAAAAAA
(SEQ ID NO: 72)

30

As used herein, the term "TYROBP" refers to the gene encoding TYRO protein tyrosine kinase-binding protein. The terms "TYROBP" and "TYRO protein tyrosine kinase-binding protein" include wild-type forms of the TYROBP gene, as well as variants (e.g., splice variants and polymorphisms) of wild-type TYROBP. Examples of such variants are nucleic acids having at least 70% sequence identity (e.g.,
35 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to a wild-type TYROBP nucleic acid sequence (e.g., SEQ ID NO: 73, ENA accession number AF019562). SEQ ID NO: 73 is a wild-type gene sequence encoding TYROBP protein, and is shown below:

40 CCACGCGTCCGCGCTGCGCCACATCCCACCGGCCCTTACACTGTGGTGTCCAGCAGCATC
CGGCTTCATGGGGGGACTTGAACCCTGCAGCAGGCTCCTGCTCCTGCCTCTCCTGCTGGC
TGTAAGTGGTCTCCGTCCTGTCCAGGCCAGGCCAGAGCGATTGCAGTTGCTCTACGGT

GAGCCCGGGCGTGCTGGCAGGGATCGTGATGGGAGACCTGGTGCTGACAGTGCTCATTGC
 CCTGGCCGTGTACTTCCTGGGCCGGCTGGTCCCTCGGGGGCGAGGGGCTGCGGAGGCAGC
 GACCCGGAAACAGCGTATCACTGAGACCGAGTCGCCTTATCAGGAGCTCCAGGGTCAGAG
 GTCGGATGTCTACAGCGACCTCAACACACAGAGGCCGTATTACAAATGAGCCCGAATCAT
 5 GACAGTCAGCAACATGATACCTGGATCCAGCCATTCCCTGAAGCCCACCCTGCACCTCATT
 CCAACTCCTACCGCGATACAGACCCACAGAGTGCCATCCCTGAGAGACCAGACCGCTCCC
 CAATACTCTCCTAAAATAAACATGAAGCACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA
 (SEQ ID NO: 73)

10 As used herein, the term "ZCWPW1" refers to the gene encoding Zinc finger CW-type PWWP
 domain protein 1. The terms "ZCWPW1" and "Zinc finger CW-type PWWP domain protein 1" include
 wild-type forms of the ZCWPW1 gene, as well as variants (e.g., splice variants and polymorphisms) of
 wild-type ZCWPW1. Examples of such variants are nucleic acids having at least 70% sequence identity
 (e.g., 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%,
 15 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 99.9% identity, or more) to
 a wild-type ZCWPW1 nucleic acid sequence (e.g., SEQ ID NO: 74, ENA accession number AL136735).
 SEQ ID NO: 74 is a wild-type gene sequence encoding ZCWPW1 protein, and is shown below:

CGCCGTTTTCCCGGGGAGATGCGCCGCCCGGTCTCCCTGCCAGCGGAGTGCTGGGCCGAG
 20 GACAGGGCGGCAGGGGTGACAGTGGGGTCCAGGAGAGTCTCAAATCCTAAGCTTTCAGT
 ATTTGTTATTGTGAAAGAAGTTAATTCACCTGAAACAGAGGAGGGGCAACCTGAGTTATC
 AGAAAGTGACTTCCTGGCCTTCCCTTCTTTACTGATCAGAGGCACACAAAGCGTAGTTTC
 TAAGCTGAATGATGACAACGTTGCAGAATAAAGAAGAATGTGGAAAGGGACCAAAGAGAA
 TCTTTGCCCCACCTGCACAAAATCTTACAGCCTGTTACCTTGTAGCCCTAACTCCCCTA
 25 AGGAGGAGACCCCGGGGATCAGTTCCCCAGAGACAGAGGCCAGGATAAGCCTGCCAAAGG
 CCAGTTTAAAGAAGAAAGAGGAAAAAGCAACCATGAAGAATGTTCCAAGCAGGGAACAGG
 AGAAAAAAGAAAGGCACAAATCAACAAGCAAGCAGAGAAGAAAGAAAGGAAAAATCAA
 GTCTTACCAATGCAGAAATTTGAGGAGATTGTCCAGATTGTTCTGCAGAAGTCCCTTCAGG
 AGTGCTTGGGGATGGGATCTGGCCTTGATTTTGCAGAGACTTCTTGTGCCAGCCCGTAG
 30 TATCTACCCAATCAGACAAGGAGCCAGGAATTACTGCTTCTGCTACTGATACTGATAATG
 CTAATGGAGAGGAGGTACCACATACTCAAGAGATTTCAAGTGTCTTGGGAAGGTGAAGCTG
 CCCCTGAGATAAGGACATCTAAGTTAGGCCAGCCAGATCCTGCACCCTCTAAGAAGAAAT
 CCAATAGACTCACCTTAAGCAAAAGAAAGAAAGGAAGCTCATGAGAAGGTGGAGAAAATC
 AAGGTGGACATGAGCACAGACAGGAAGACCGACTAAAGAAAACAGTTCAGGATCATTCTC
 35 AGATCAGGGACCAGCAAAAAGGAGAGATAAGTGGTTTTGGTCAATGTCTGGTCTGGGTCC
 AGTGTTCTTCCCAAATGTGGGAAATGGAGGCGGCTGTGTGGGAACATTGACCCCTCAG
 TTCTCCAGATAATTGGTCCTGTGATCAGAACACAGATGTGCAGTATAATCGCTGTGATA
 TTCCTGAGGAGACCTGGACAGGGCTTGAGAGTGATGTGGCCTATGCCTCCTACATCCCAG
 GATCCATCATCTGGGCCAAGCAATACGGTTACCCCTGGTGGCCAGGCATGATAGAATCTG
 40 ATCCTGACTTAGGGGAATATTTTCTTTTACTTCCCATCTTGATTCCCTGCCGTCTAAGT
 ACCATGTGACGTTTTTTGGAGAAACAGTTTCTCGTGCATGGATCCCAGTCAACATGCTAA
 AGAACTCCAGGAGCTGTCCCTGGAGCTATCAGTCATGAAAAGCGCAGAAATGACTGCA

GCCAGAACTGGGGGTGGCCCTGATGATGGCTCAAGAGGCAGAACAGATCAGCATTCAGG
 AACGGGTAACTTGTGGTTTCTGGAGCCGATTCAACGGATCTAACAGTAATGGGGAAA
 GAAAAGACTTACAGCTCTCTGGTTTGAACAGCCCAGGATCCTGCTTAGAGAAAAAGGAGA
 AAGAGGAAGAGTTGGAAAAGGAGGAAGGAGAGAAAACAGACCCAATTTTGCCCATTCGTA
 5 AGCGAGTCAAAATACAGACCCAAAAAACCAAGCCAAGAGGGCTTGGGGGTGATGCAGGC
 ACAGCAGATGGCCGAGGCAGGACACTGCAGAGGAAGATAATGAAGAGATCTCTAGGCAGG
 AAATCCACAGCTCCTCCTGCACCCAGAATGGGAAGGAAAGAAGGCCAAGGGAATTCAGAT
 TCTGACCAGCCAGGCCCTAAGAAAAAATTTAAAGCTCCCCAGAGCAAGGCCTTGGCAGCC
 AGCTTTTCAGAGGGAAAAGAAGTTAGAACAGTGCCAAAGAACCTGGGCCTATCAGCGTGT
 10 AAGGGGGCCTGCCCCTCATCTGCGAAAGAAGAGCCCAGACACCGGGAACCCCTGACCCAG
 GAGGCTGGAAGTGTCCCCCTTGAGGACGAAGCCTCCAGTGACCTGGACCTGGAGCAACTC
 ATGGAAGATGTTGGGAGAGAGCTGGGGCAGAGCGGGGAGCTGCAGCACAGCAACAGTGAT
 GGCGAGGACTTCCCCGTGGCGCTGTTTGGGAAGTAGCTGGTGCTCCTCTGCTCCCTCTTT
 TTCTCCCTTCTCTGGGGCGCAGGAGGGAGAAAGTTGCTAAGTGCTGGGTCTGTTTCATTGGC
 15 TATGAGGTTCAAATGTGTGTGGTGCAGTTTCTGTGTTAATAAAGCAGGTTACAGTCGAAA
 AAAAAAAAAAAAAAAAAA
 (SEQ ID NO: 74)

DETAILED DESCRIPTION OF THE INVENTION

20 The present invention provides new forms of siRNA, including single- and double-stranded short
 interfering RNA (ds-siRNA), and methods for their use in treating a patient in need of microglial gene
 silencing (e.g., a patient having dysregulated microglial gene expression, such as a patient with, e.g.,
 Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, frontotemporal dementia,
 Huntington's disease, multiple sclerosis, or progressive supranuclear palsy). The branched siRNA in the
 25 present invention has shown a surprising ability to permeate the cell. The branched compositions
 described herein may employ a variety of modifications known and previously unknown in the art. The
 siRNA of the invention may contain an antisense strand including a region that is represented by Formula
 IX:

30
$$Z-((A-P)_n(B-P)_m)_q;$$
 (IX)

wherein Z is a 5' phosphorus stabilizing moiety; each A is, independently, a 2'-modified-ribonucleoside of
 a first type; each B is, independently, a 2'-modified-ribonucleoside of a second type; each P is,
 35 independently, an internucleoside linkage selected from a phosphodiester linkage and a
 phosphorothioate linkage; n is an integer from 1 to 5; m is an integer from 1 to 5; and q is an integer
 between 1 and 15. The embodiments of each part of Formula IX and the methods of use for the
 molecules Formula IX represents are described herein.

In some embodiments, the siRNA of the invention may have a sense strand represented by
 40 Formula X:

$$Y-((A-P)_n(B-P)_m)_qL-((B-P)_m(A-P)_n)_q;$$
 128

(X)

wherein Y is a hydrophobic moiety (e.g., cholesterol, vitamin D, or tocopherol); L is a linker; each A is, independently, a 2'-modified-ribonucleoside of a first type; each B is, independently, a 2'-modified-
 5 ribonucleoside of a second type; each P is, independently, an internucleoside linkage selected from a phosphodiester linkage and a phosphorothioate linkage; n is an integer from 1 to 5; m is an integer from 1 to 5; and q is an integer between 1 and 15. The embodiments of each part of Formula X and the methods of use for the molecules Formula X represents are described herein.

10 siRNA Structure

The simplest siRNAs consist of a ribonucleic acid comprising a single- or double-stranded structure, formed by a first strand, and in the case of a double-stranded siRNA, a second strand. The first strand comprises a stretch of contiguous nucleotides that is at least partially complementary to a target nucleic acid. The second strand also comprises a stretch of contiguous nucleotides where the second
 15 stretch is at least partially identical to a target nucleic acid. The first strand and said second strand may be hybridized to each other to form a double-stranded structure. The hybridization typically occurs by Watson Crick base pairing.

Depending on the sequence of the first and second strand, the hybridization or base pairing is not necessarily complete or perfect, which means that the first and second strand are not 100% base-paired
 20 due to mismatches. One or more mismatches may also be present within the duplex without necessarily impacting the siRNA activity.

The first strand contains a stretch of contiguous nucleotides which is essentially complementary to a target nucleic acid. Typically, the target nucleic acid sequence is, in accordance with the mode of action of interfering ribonucleic acids, a single-stranded RNA, preferably an mRNA. Such hybridization
 25 occurs most likely through Watson Crick base pairing but is not necessarily limited thereto. The extent to which the first strand has a complementary stretch of contiguous nucleotides to a target nucleic acid sequence can be between 80% and 100%, e.g., 80%, 85%, 90%, 95%, or 100% complementary.

siRNAs described herein may employ modifications to the nucleobase, phosphate backbone, ribose core, 5'- and 3'-ends, and branching, wherein multiple strands of siRNA may be covalently linked.
 30

Length of siRNA molecules

It is within the scope of the invention that any length, known and previously unknown in the art, may be employed for the current invention. As described herein, potential lengths for an antisense strand of the branched siRNA of the present invention is between 10 and 30 nucleotides (e.g., 10 nucleotides,
 35 11 nucleotides, 12 nucleotides, 13 nucleotides, 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides, 26 nucleotides, 27 nucleotides, 28 nucleotides, 29 nucleotides, or 30 nucleotides), 15 and 25 nucleotides (e.g., 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, or 25 nucleotides), or 18 and 23 nucleotides (e.g., 18 nucleotides, 19
 40 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides, 26 nucleotides, 27 nucleotides, 28 nucleotides, 29 nucleotides, or 30 nucleotides). In some

embodiments, the antisense strand is 21 nucleotides. In some embodiments, the antisense strand is 22 nucleotides. In some embodiments, the antisense strand is 23 nucleotides. In some embodiments, the antisense strand is 24 nucleotides. In some embodiments, the antisense strand is 25 nucleotides. In some embodiments, the antisense strand is 26 nucleotides. In some embodiments, the antisense strand is 27 nucleotides. In some embodiments, the antisense strand is 28 nucleotides. In some embodiments, the antisense strand is 29 nucleotides. In some embodiments, the antisense strand is 30 nucleotides.

In some embodiments, the sense strand of the branched siRNA of the present invention is between 12 and 30 nucleotides (e.g., 12 nucleotides, 13 nucleotides, 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, 18 nucleotides, 19 nucleotides, 20 nucleotides, 21 nucleotides, 22 nucleotides, 23 nucleotides, 24 nucleotides, 25 nucleotides, 26 nucleotides, 27 nucleotides, 28 nucleotides, 29 nucleotides, or 30 nucleotides), or 14 and 18 nucleotides (e.g., 14 nucleotides, 15 nucleotides, 16 nucleotides, 17 nucleotides, or 18 nucleotides). In some embodiments, the sense strand is 16 nucleotides. In some embodiments, the sense strand is 17 nucleotides. In some embodiments, the sense strand is 18 nucleotides. In some embodiments, the sense strand is 19 nucleotides. In some embodiments, the sense strand is 20 nucleotides. In some embodiments, the sense strand is 21 nucleotides. In some embodiments, the sense strand is 22 nucleotides. In some embodiments, the sense strand is 23 nucleotides. In some embodiments, the sense strand is 24 nucleotides. In some embodiments, the sense strand is 25 nucleotides. In some embodiments, the sense strand is 26 nucleotides. In some embodiments, the sense strand is 27 nucleotides. In some embodiments, the sense strand is 28 nucleotides. In some embodiments, the sense strand is 29 nucleotides. In some embodiments, the sense strand is 30 nucleotides.

2' modifications

The present invention includes single- and double-stranded compositions comprising at least one alternating motif. Alternating motifs of the present invention may have the formula $((A-P)_n(B-P)_m)_q$ where A is a nucleoside of a first type, B is a nucleoside of a second type, n is from 1 to 5, m is from 1 to 5, and q is from 1 to 15, and P is an internucleoside linkage. The result may include a regular or irregular pattern of alternating nucleosides of the first and second types. Each of the types of nucleosides may be identical with the exception that at least the 2'-substituent groups are different.

Possible 2'-modifications comprise all possible orientations of OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C1 to C10 alkyl or C2 to C10 alkenyl and alkynyl. In some embodiments, the modification includes a 2'-O-methyl (2'-O-Me) modification. Some embodiments use $O[(CH_2)_nO]_mCH_3$, $O(CH_2)_nOCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, and $O(CH_2)_nON[(CH_2)_nCH_3]_2$, where n and m are from 1 to about 10. Other potential sugar substituent groups include: C1 to C10 lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. In some embodiments, the modification includes 2' methoxyethoxy (2'-O-CH₂CH₂OCH₃, also known as 2'-O-(2-methoxyethyl) or 2'-MOE). In some embodiments, the modification includes 2'-dimethylaminoethoxy, i.e., a $O(CH_2)_2ON(CH_3)_2$ group, also

known as 2'-DMAOE, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxy-ethyl or 2'-DMAEOE), i.e., 2'-O-CH₂OCH₂N(CH₃)₂. Other potential sugar substituent groups include aminopropoxy (-OCH₂CH₂CH₂NH₂), allyl (-CH₂-CH=CH₂), -O-allyl (-O-CH₂-CH=CH₂) and fluoro (F). 2'-sugar substituent groups may be in the arabino (up) position or ribo (down) position. In some
5 embodiments, the 2'-arabino modification is 2'-F. Similar modifications may also be made at other positions on the oligomeric compound, particularly the 3' position of the sugar on the 3' terminal nucleoside or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar.

Nucleobase modifications

Oligomeric compounds may also include nucleosides or other surrogate or mimetic monomeric subunits that include a nucleobase (often referred to in the art simply as "base" or "heterocyclic base moiety"). The nucleobase is another moiety that has been extensively modified or substituted and such
15 modified and or substituted nucleobases are amenable to the present invention. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases also referred herein as heterocyclic base moieties include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl
20 derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl (-C≡C-CH₃) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and
25 cytosines, 7-methylguanine and 7-methyladenine, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine. Nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in United States Patent No. 3,687,808, those disclosed in *The*
30 *Concise Encyclopedia of Polymer Science and Engineering*, pages 858-859, Kroschwitz, J.I., ed. John Wiley & Sons, 1990, those disclosed by Englisch et al., *Angewandte Chemie*, International Edition, 1991, 30, 613, and those disclosed by Sanghvi, Y.S., Chapter 15, *Antisense Research and , Applications*, pages 289-302, Crooke, S.T. and Lebleu, B., ed., CRC Press, 1993. Oligomeric compounds of the present invention can also include polycyclic heterocyclic compounds in place of one or more heterocyclic
35 base moieties. A number of tricyclic heterocyclic compounds have been previously reported. These compounds are routinely used in antisense applications to increase the binding properties of the modified strand to a target strand.

Representative cytosine analogs that make 3 hydrogen bonds with a guanosine in a second strand include 1,3-diazaphenoxazine-2-one (Kurchavov, *et al.*, *Nucleosides and Nucleotides*, 1997, 16,
40 1837-1846), 1,3-diazaphenothiazine-2-one (Lin, K.-Y.; Jones, R. J.; Matteucci, M.J. Am. Chem. Soc. 1995, 117, 3873-3874), and 6,7,8,9-tetrafluoro-1,3-diazaphenoxazine-2-one (Wang, J.; Lin, K.-Y., Matteucci, M. Tetrahedron Lett. 1998, 39, 8385-8388). Incorporated into oligonucleotides these base

modifications were shown to hybridize with complementary guanine and the latter was also shown to hybridize with adenine and to enhance helical thermal stability by extended stacking interactions (also see U.S. Patent Application entitled "Modified Peptide Nucleic Acids" filed May 24, 2002, Serial number 10/155,920; and U.S. Patent Application entitled "Nuclease Resistant Chimeric Oligonucleotides" filed May 24, 2002, Serial number 10/013,295, both of which are herein incorporated by reference in their entirety). Further helix-stabilizing properties have been observed when a cytosine analog/substitute has an aminoethoxy moiety attached to the rigid 1,3-diazaphenoxazine-2-one scaffold (Lin, K.-Y.; Matteucci, M. J. *Am. Chem. Soc.* 1998, 120, 8531-8532).

Internucleoside linkage modifications

Another variable in the design of the present invention are the internucleoside linkages making up the phosphate backbone. Although the natural RNA phosphate backbone may be employed here, derivatives thereof, known and yet unknown in the art, may be used which enhance desirable characteristics of a siRNA. Although not limiting, of particular importance in the present invention is protecting parts, or the whole, of the siRNA from hydrolysis. One example of a modification that decreases the rate of hydrolysis is phosphorothioates. Any portion or the whole of the backbone may contain phosphate substitutions (e.g., phosphorothioates, phosphodiester, etc.). For instance, the internucleoside linkages may be between 0 and 100% phosphorothioate, e.g., between 0 and 100%, 10 and 100%, 20 and 100%, 30 and 100%, 40 and 100%, 50 and 100%, 60 and 100%, 70 and 100%, 80 and 100%, 90 and 100%, 0 and 90%, 0 and 80%, 0 and 70%, 0 and 60%, 0 and 50%, 0 and 40%, 0 and 30%, 0 and 20%, 0 and 10%, 10 and 90%, 20 and 80%, 30 and 70%, 40 and 60%, 10 and 40%, 20 and 50%, 30 and 60%, 40 and 70%, 50 and 80%, or 60 and 90% phosphorothioate linkages. Similarly, the internucleoside linkages may be between 0 and 100% phosphodiester linkages, e.g., between 0 and 100%, 10 and 100%, 20 and 100%, 30 and 100%, 40 and 100%, 50 and 100%, 60 and 100%, 70 and 100%, 80 and 100%, 90 and 100%, 0 and 90%, 0 and 80%, 0 and 70%, 0 and 60%, 0 and 50%, 0 and 40%, 0 and 30%, 0 and 20%, 0 and 10%, 10 and 90%, 20 and 80%, 30 and 70%, 40 and 60%, 10 and 40%, 20 and 50%, 30 and 60%, 40 and 70%, 50 and 80%, or 60 and 90% phosphodiester linkages.

Specific examples of some potential oligomeric compounds useful in this invention include oligonucleotides containing modified e.g. non-naturally occurring internucleoside linkages. As defined in this specification, oligonucleotides having modified internucleoside linkages include internucleoside linkages that retain a phosphorus atom and internucleoside linkages that do not have a phosphorus atom. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their internucleoside backbone can also be considered to be oligonucleosides. In the *C.elegans* system, modification of the internucleotide linkage (phosphorothioate) did not significantly interfere with RNAi activity. Based on this observation, it is suggested that some compositions of the invention can also have one or more modified internucleoside linkages. A preferred phosphorus containing modified internucleoside linkage is the phosphorothioate internucleoside linkage. In some embodiments, the modified oligonucleotide backbones containing a phosphorus atom therein include, for example, phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates, 5'-alkylene phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates,

thionoalkylphosphotriesters, selenophosphates, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein one or more internucleotide linkages is a 3' to 3', 5' to 5' or 2' to 2' linkage. In some embodiments, the modified oligonucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; riboacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₂ component parts.

siRNA Patterning

Nucleosides used in the invention tolerate a range of modifications in the nucleobase and sugar.

A complete siRNA, single-stranded or double-stranded, may have 1, 2, 3, 4, 5, or more different nucleosides that each appear in the siRNA strand or strands once or more. The nucleosides may appear in a repeating pattern (e.g., alternating between two modified nucleosides) or may be a strand of one type of nucleoside with substitutions of a second type of nucleoside. Similarly, internucleoside linkages may be of one or more type appearing in a single- or double-stranded siRNA in a repeating pattern (e.g., alternating between two internucleoside linkages) or may be a strand of one type of internucleoside linkage with substitutions of a second type of internucleoside linkage. Though the siRNAs of the invention tolerate a range of substitution patterns, the following exemplify some preferred patterns in which A and B represent nucleosides of two types, and T and P represent internucleoside linkages of two types:

Pattern 1:

A-T-B-T-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-B-T-A-T-A-T-A-T-A-T-A-T
A-T-A-T-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-T-A-T

Pattern 2:

A-T-A-T-A-P-B-P-B-P-B-P-A-P-A-P-A-P-A-P-A-P-A-P-B-T-A-T-A-T-A-T-A-T-A-T
A-T-A-T-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-T-A-T

Pattern 3:

A-T-B-T-A-P-B-P-B-P-B-P-A-P-A-P-A-P-A-P-A-P-A-P-B-T-A-T-A-T-A-T-A-T-A-T
A-T-A-T-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-T-A-T

Pattern 4:

A-T-B-T-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-B-T-A-T-A-T-A-T-A-T-A-T
A-T-A-T-A-P-A-P-A-P-A-P-B-P-A-P-A-P-B-P-B-P-A-P-A-P-A-T-A-T

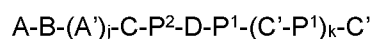
Pattern 5:

A-T-B-T-A-P-A-P-A-P-B-P-A-P-A-P-A-P-A-P-A-P-B-T-A-T-B-T-A-T-A-T-A-T-A-T
 A-T-A-T-A-P-A-P-A-P-A-P-B-P-A-P-B-P-B-P-B-P-A-P-A-P-A-T-A-T.

5 In some embodiments, T represents phosphorothioate, and P represents phosphodiester.

In some embodiments, the siRNA molecule of the disclosure features any one of the siRNA nucleotide modification patterns and/or internucleoside linkage modification patterns described in International Patent Application Publication Nos. WO 2016/161388 and WO 2020/041769, the disclosures of which are incorporated in their entirety herein.

10 In some embodiments of the disclosure, the siRNA may contain an antisense strand including a region represented by Formula A-I, wherein Formula A-I is, in the 5'-to-3' direction

**Formula A-I;**

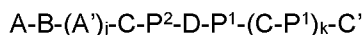
15 wherein A is represented by the formula C-P¹-D-P¹; each A' is represented by the formula C-P²-D-P²; B is represented by the formula C-P²-D-P²-D-P²-D-P²; each C is a 2'-O-methyl (2'-O-Me) ribonucleoside; each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside; each D is a 2'-F ribonucleoside; each P¹ is a phosphorothioate internucleoside linkage; each P² is a phosphodiester internucleoside linkage; j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, j is 4. In some embodiments, k is 4. In some embodiments, j is 4 and k is 4. The antisense is complementary (e.g., fully or partially complementary) to a target nucleic acid sequence.

20 In some embodiments, the antisense strand includes a structure represented by Formula A1, wherein Formula A1 is, in the 5'-to-3' direction:

**Formula A1;**

30 wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments of the disclosure, the siRNA may contain an antisense strand including a region represented by Formula A-II, wherein Formula A-II is, in the 5'-to-3' direction:



Formula A-II;

wherein A is represented by the formula C-P¹-D-P¹; each A' is represented by the formula C-P²-D-P²; B is represented by the formula C-P²-D-P²-D-P²-D-P²; each C is a 2'-O-methyl (2'-O-Me) ribonucleoside; each C', independently, is a 2'-O-Me ribonucleoside or a 2'-fluoro (2'-F) ribonucleoside; each D is a 2'-F ribonucleoside; each P¹ is a phosphorothioate internucleoside linkage; each P² is a phosphodiester internucleoside linkage; j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, j is 4. In some embodiments, k is 4. In some embodiments, j is 4 and k is 4. The antisense is complementary (e.g., fully or partially complementary) to a target nucleic acid sequence.

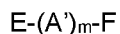
In some embodiments of the disclosure, the antisense strand includes a structure represented by Formula A2, wherein Formula A2 is, in the 5'-to-3' direction:



Formula A2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

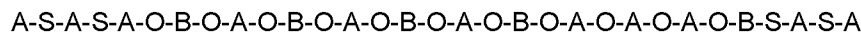
In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S-III, wherein Formula S-III is, in the 5'-to-3' direction:



Formula S-III;

wherein E is represented by the formula (C-P¹)₂; F is represented by the formula (C-P²)₃-D-P¹-C-P¹-C, (C-P²)₃-D-P²-C-P²-C, (C-P²)₃-D-P¹-C-P¹-D, or (C-P²)₃-D-P²-C-P²-D; A', C, D, P¹, and P² are as defined in Formula I; and m is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, m is 4. The sense strand is complementary (e.g., fully or partially complementary) to the antisense strand.

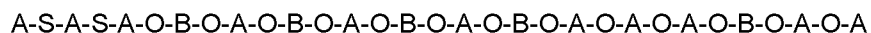
In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S1, wherein Formula S1 is, in the 5'-to-3' direction:



Formula S1;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S2, wherein Formula S2 is, in the 5'-to-3' direction:



5

Formula S2;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

10 In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S3, wherein Formula S3 is, in the 5'-to-3' direction:

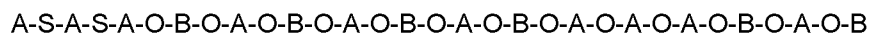


Formula S3;

15 wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S4, wherein Formula S4 is, in the 5'-to-3' direction:

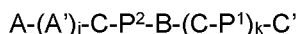
20



Formula S4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

25 In some embodiments of the disclosure, the siRNA may contain an antisense strand including a region represented by Formula A-IV, wherein Formula A-IV is, in the 5'-to-3' direction:



Formula A-IV;

30 wherein A is represented by the formula C-P¹-D-P¹; each A' is represented by the formula C-P²-D-P²; B is represented by the formula D-P¹-C-P¹-D-P¹; each C is a 2'-O-Me ribonucleoside; each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside; each D is a 2'-F ribonucleoside; each P¹ is a phosphorothioate internucleoside linkage; each P² is a phosphodiester internucleoside linkage; j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In
35 some embodiments, j is 6. In some embodiments, k is 4. In some embodiments, j is 6 and k is 4. The antisense strand is complementary (e.g., fully or partially complementary) to a target nucleic acid.

In some embodiments of the disclosure, the antisense strand includes a structure represented by Formula A3, wherein Formula A3 is, in the 5'-to-3' direction:



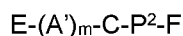
5

Formula A3;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments of the disclosure, the siRNA of the disclosure may have a sense strand represented by Formula S-V, wherein Formula S-V is, in the 5'-to-3' direction:

10



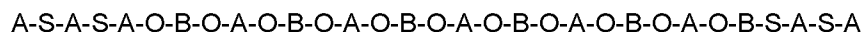
Formula S-V;

wherein E is represented by the formula $(\text{C-P}^1)_2$; F is represented by the formula $\text{D-P}^1\text{-C-P}^1\text{-C}$, $\text{D-P}^2\text{-C-P}^2\text{-C}$, $\text{D-P}^1\text{-C-P}^1\text{-D}$, or $\text{D-P}^2\text{-C-P}^2\text{-D}$; A', C, D, P¹, and P² are as defined in Formula IV; and m is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, m is 5. The sense strand is complementary (e.g., fully or partially complementary) to the antisense strand.

15

In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S5, wherein Formula S5 is, in the 5'-to-3' direction:

20



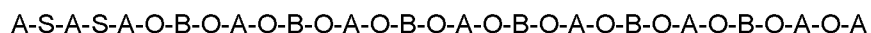
Formula S5;

25

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S6, wherein Formula S6 is, in the 5'-to-3' direction:

30



Formula S6;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

35

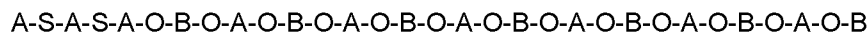
In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S7, wherein Formula S7 is, in the 5'-to-3' direction:



5 **Formula S7;**

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

10 In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S8, wherein Formula S8 is, in the 5'-to-3' direction:



Formula S8;

15 wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments of the disclosure, the siRNA may contain an antisense strand including a region represented by Formula A-VI, wherein Formula A-VI is, in the 5'-to-3' direction:



Formula A-VI;

wherein A is represented by the formula C-P¹-D-P¹; each B is represented by the formula C-P²; each C is a 2'-O-Me ribonucleoside; each C', independently, is a 2'-O-Me ribonucleoside or a 2'-F ribonucleoside; 25 each D is a 2'-F ribonucleoside; each E is represented by the formula D-P²-C-P²; F is represented by the formula D-P¹-C-P¹; each G is represented by the formula C-P¹; each P¹ is a phosphorothioate internucleoside linkage; each P² is a phosphodiester internucleoside linkage; j is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); k is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and l is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, j is 3. In some embodiments, k is 6. In some 30 embodiments, l is 2. In some embodiments, j is 3, k is 6, and l is 2. The antisense strand is complementary (e.g., fully or partially complementary) to a target nucleic acid.

In some embodiments of the disclosure, the antisense strand includes a structure represented by Formula A4, wherein Formula A4 is, in the 5'-to-3' direction:



Formula A4;

wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

40

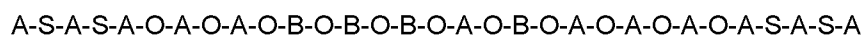
In some embodiments of the disclosure, the siRNA may contain a sense strand including a region represented by Formula S-VII, wherein Formula S-VII is, in the 5'-to-3' direction:



Formula S-VII;

wherein A' is represented by the formula C-P²-D-P²; each H is represented by the formula (C-P¹)₂; each I is represented by the formula (D-P²); B, C, D, P¹, and P² are as defined in Formula VI; m is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); n is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7); and o is an integer from 1 to 7 (e.g., 1, 2, 3, 4, 5, 6, or 7). In some embodiments, m is 3. In some embodiments, n is 3. In some embodiments, o is 3. In some embodiments, m is 3, n is 3, and o is 3. The sense strand is complementary (e.g., fully or partially complementary) to the antisense strand.

In some embodiments of the disclosure, the sense strand includes a structure represented by Formula S9, wherein Formula S9 is, in the 5'-to-3' direction:



Formula S9;

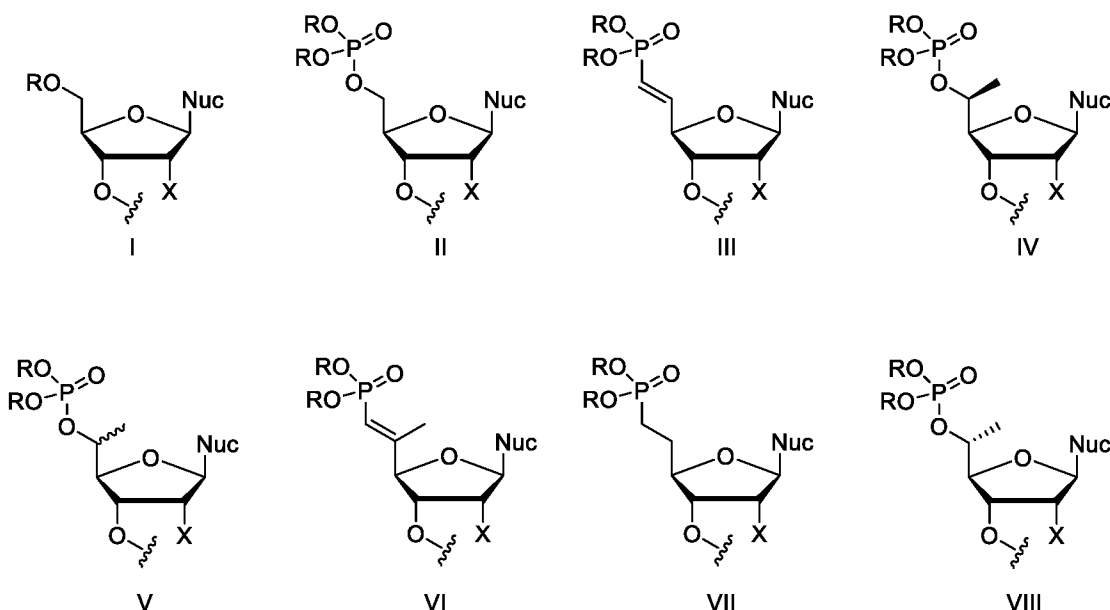
wherein A represents a 2'-O-Me ribonucleoside, B represents a 2'-F ribonucleoside, O represents a phosphodiester internucleoside linkage, and S represents a phosphorothioate internucleoside linkage.

In some embodiments of the disclosure, the siRNA may contain an antisense strand including a region that is represented by Formula VIII:

5' phosphorus stabilizing moiety

To further protect the siRNA from degradation a 5'-phosphorus stabilizing moiety may be employed. A 5'-phosphorus stabilizing moiety replaces the 5'-phosphate to prevent hydrolysis of the phosphate. Hydrolysis of the 5'-phosphate prevents binding to RISC, a necessary step in gene silencing. Any replacement for phosphate that does not impede binding to RISC is contemplated in this disclosure.

In some embodiments, the replacement for the 5'-phosphate is also stable to *in vivo* hydrolysis. Each siRNA strand may independently and optionally employ any suitable 5'-phosphorus stabilizing moiety.



5

Some exemplary endcaps are demonstrated in Formula I-VIII. Nuc in Formula I-VIII represents a nucleobase or nucleobase derivative or replacement as described herein. X in Formula I-VIII represents a 2'-modification as described herein. Some embodiments employ hydroxy as in Formula I, phosphate as in Formula II, vinylphosphonates as in Formula III, and VI, 5'-methylsubstituted phosphates as in Formula IV, VI, and VIII, or methylenephosphonates as in Formula VII, vinyl 5'-vinylphosphonate as a 5'-phosphorus stabilizing moiety as demonstrated in Formula III.

10

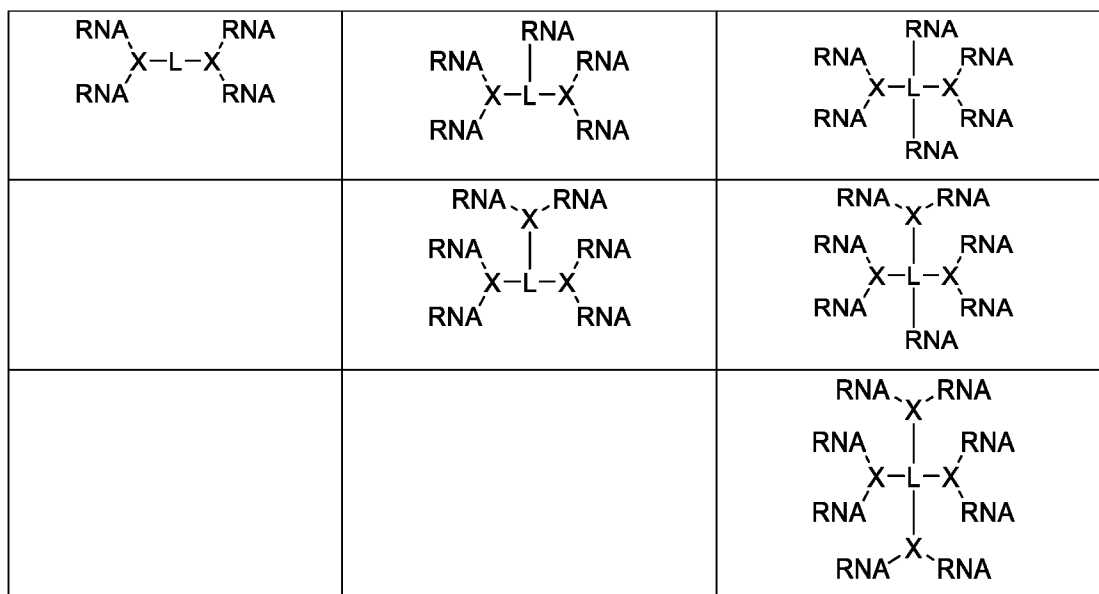
siRNA Branching

Branching of the siRNA molecules is a key feature in the present invention. The siRNA molecule may not be branched, or may be dibranched, tribranched, or tetrabranched, connected through a linker. Each main branch may be further branched to allow for 2, 3, 4, 5, 6, 7, or 8 separate RNA single- or double-strands. The branch points on the linker may stem from the same atom, or separate atoms along the linker. Some exemplary embodiments are listed in Table 1, where L represent a linker, and X represents any atom suitable to the siRNA molecule branch points:

20

Table 1: Branched siRNA structures

Dibranched	Tribranched	Tetrabranched
RNA-L-RNA	$\begin{array}{c} \text{RNA} \\ \\ \text{RNA-L-RNA} \end{array}$	$\begin{array}{c} \text{RNA} \\ \\ \text{RNA-L-RNA} \\ \\ \text{RNA} \end{array}$
$\begin{array}{c} \text{RNA} \quad \text{RNA} \\ \diagdown \quad \diagup \\ \text{X-L-X} \\ \diagup \quad \diagdown \\ \text{RNA} \quad \text{RNA} \end{array}$	$\begin{array}{c} \text{RNA} \\ \\ \text{RNA-X-L-X} \\ \quad \\ \text{RNA} \quad \text{RNA} \end{array}$	$\begin{array}{c} \text{RNA} \\ \\ \text{RNA-X-L-X} \\ \quad \quad \\ \text{RNA} \quad \text{RNA} \quad \text{RNA} \end{array}$



Linkers

Multiple strands of siRNA described herein may be covalently attached by way of a linker. The effect of this branching improves, *inter alia*, cell permeability allowing better access into microglia in the CNS. Any linking moiety may be employed which is not incompatible with the siRNAs of the present invention. Exemplary linkers include ethylene glycol chains of 2 to 10 subunits (e.g., 2, 3, 4, 5, 6, 7, 8, 9, or 10 subunits), alkyl chains, carbohydrate chains, block copolymers, peptides, RNA, DNA, and others. In some embodiments, any carbon or oxygen atom of the linker is optionally replaced with a nitrogen atom, bears a hydroxyl substituent, or bears an oxo substituent. In some embodiments, the linker is a poly-ethylene glycol (PEG) linker. The PEG linkers suitable for use with the disclosed compositions and methods include linear or non-linear PEG linkers. Examples of non-linear PEG linkers include branched PEGs, linear forked PEGs, or branched forked PEGs.

PEG linkers of various weights may be used with the disclosed compositions and methods. For example, the PEG linker may have a weight that is between 5 and 500 Daltons. In some embodiments, a PEG linker having a weight that is between 500 and 1,000 Dalton may be used. In some embodiments, a PEG linker having a weight that is between 1,000 and 10,000 Dalton may be used. In some embodiments, a PEG linker having a weight that is between 200 and 20,000 Dalton may be used. In some embodiments, the linker is covalently attached to a sense strand of the siRNA. In some embodiments, the linker is covalently attached to an antisense strand of the siRNA. In some embodiments, the PEG linker is a triethylene glycol (TrEG) linker. In some embodiments, the PEG linker is a tetraethylene linker (TEG).

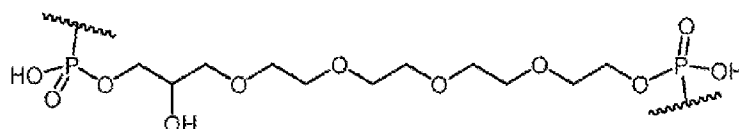
In some embodiments, the linker is an alkyl chain linker. In some embodiments, the linker is a peptide linker. In some embodiments, the linker is a RNA linker. In some embodiments, the linker is a DNA linker.

Linkers may covalently link 2, 3, 4, or 5 unique siRNA strands. The linker may covalently bind to any part of the siRNA oligomer. In some embodiments, the linker attaches to the 3' end of nucleosides of each siRNA strand. In some embodiments, the linker attaches to the 5' end of nucleosides of each siRNA strand. In some embodiments, the linker attaches to a nucleoside of an siRNA strand (e.g., sense or antisense strand) by way of a covalent bond-forming moiety. In some embodiments, the covalent-bond-

forming moiety is selected from the group consisting of an alkyl, ester, amide, carbonate, carbamate, triazole, urea, formacetal, phosphonate, phosphate, and phosphate derivative (e.g., phosphorothioate, phosphoramidate, etc.).

In some embodiments, the linker has a structure of Formula L1, as is shown below:

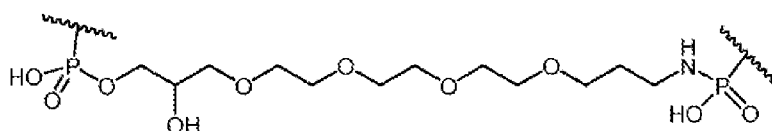
5



(Formula L1)

In some embodiments, the linker has a structure of Formula L2, as is shown below:

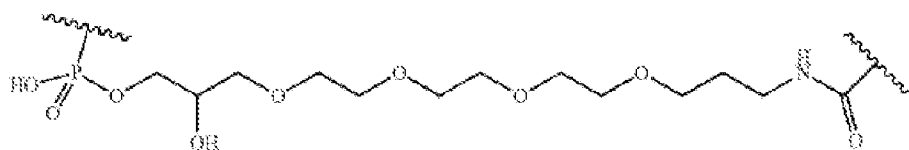
10



(Formula L2)

In some embodiments, the linker has a structure of Formula L3, as is shown below:

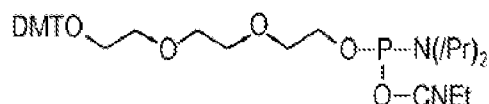
15



(Formula L3)

In some embodiments, the linker has a structure of Formula L4, as is shown below:

20



(Formula L4)

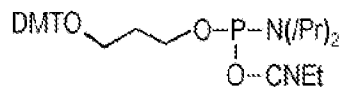
In some embodiments, the linker has a structure of Formula L5, as is shown below:

25



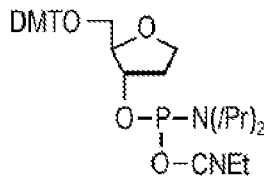
(Formula L5)

In some embodiments, the linker has a structure of Formula L6, as is shown below:



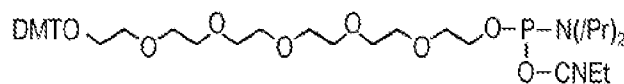
(Formula L6)

In some embodiments, the linker has a structure of Formula L7, as is shown below:



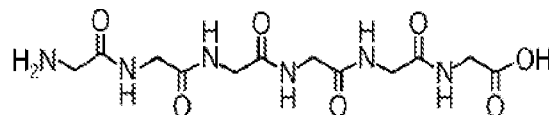
(Formula L7)

In some embodiments, the linker has a structure of Formula L8, as is shown below:



(Formula L8)

In some embodiments, the linker has a structure of Formula L9, as is shown below:



(Formula L9)

In some embodiments, the selection of a linker for use with one or more of the branched siRNA molecules disclosed herein may be based on the hydrophobicity of the linker, such that, e.g., desirable hydrophobicity is achieved for the one or more branched siRNA molecules of the disclosure. For example, a linker containing an alkyl chain may be used to increase the hydrophobicity of the branched siRNA molecule as compared to a branched siRNA molecule having a less hydrophobic linker or a hydrophilic linker.

Methods of Treatment

The invention provides methods of treating a subject in need of gene silencing. The gene silencing may be performed in order to silence defective or overactive microglial genes, silence negative regulators of microglial genes with reduced expression and/or activity, silence wild type microglial genes with an activating role in a pathway(s) that increases expression and/or activity of a disease driver gene, silence splice isoforms of a microglial gene(s) that, when selectively knocked down, may elevate total expression and/or activity of the gene(s), among other reasons, so long as the goal is to restore genetic

and biochemical pathway activity from a disease state towards a healthy state. The active compound can be administered in any suitable dose. The actual dosage amount of a composition of the present invention administered to a patient can be determined by physical and physiological factors such as body weight, severity of condition, previous or concurrent therapeutic interventions, idiopathy of the patient and on the route of administration. Depending upon the dosage and the route of administration, the number of administrations of a preferred dosage and/or an effective amount may vary according to the response of the subject. The practitioner responsible for administration will, in any event, determine the concentration of active ingredient(s) in a composition and appropriate dose(s) for the individual subject. Administration may occur any suitable number of times per day, and for as long as necessary. Subjects may be adult or pediatric humans, with or without comorbid diseases.

Diseases

The methods of the invention feature delivering a branched siRNA molecule to a microglial cell in a subject in need of microglial gene silencing. Subjects in need of microglial gene silencing may be suffering from neurodegenerative diseases in which neuroinflammation is a primary component of the disease pathology (e.g., Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, frontotemporal dementia, Huntington's disease, multiple sclerosis, or progressive supranuclear palsy).

Alzheimer's disease

Alzheimer's disease (AD) is a late-onset neurodegenerative disorder responsible for the majority of dementia cases in the elderly. AD patients suffer from a progressive cognitive decline characterized by symptoms including an insidious loss of short- and long-term memory, attention deficits, language-specific problems, disorientation, impulse control, social withdrawal, anhedonia, and other symptoms. Distinguishing neuropathological features of AD are extracellular aggregates of amyloid- β plaques and neurofibrillary tangles composed of hyperphosphorylated microtubule-associated tau proteins. Accumulation of these aggregates is associated with neuronal loss and atrophy in a number of brain regions including the frontal, temporal, and parietal lobes of the cerebral cortex as well as subcortical structures like the basal forebrain cholinergic system and the locus coeruleus within the brainstem. AD is also associated with increased neuroinflammation characterized by reactive gliosis and elevated levels of pro-inflammatory cytokines.

Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS) is a fast-progressing fatal neurodegenerative disease that affects motor neurons both in the brain and spinal cord, consequently resulting in paralysis of voluntary muscles at later stages of disease. ALS affects about 6 persons per 100,000 people and typically leads to death within 3 to 5 years after the onset of symptoms, with no cure yet available. ALS leads to muscle weakness, atrophy, and muscle spasms as a result of degeneration of upper and lower motor neurons. Cognitive and behavioral dysfunction (e.g., language dysfunction, executive dysfunction, social cognition, and verbal memory dysfunction), and frontotemporal dementia are all possible symptoms of ALS.

Parkinson's disease

PD is a progressive disorder that affects movement, and it is recognized as the second most common neurodegenerative disease after Alzheimer's disease. Common symptoms of PD include resting tremor, rigidity, and bradykinesia, and non-motor symptoms, such as depression, constipation, pain, sleep disorders, genitourinary problems, cognitive decline, and olfactory dysfunction, are also increasingly being associated with PD. A key feature of PD is the death of dopaminergic neurons in the substantia nigra pars compacta, and, for that reason, most current treatments for PD focus on increasing dopamine. Another well-known neuropathological hallmark of PD is the presence of Lewy bodies containing α -synuclein in brain regions affected by PD, which are thought to contribute to the disease.

PD is thought to result from a combination of genetic and environmental risk factors. There is no single gene responsible for all Parkinson's disease cases, and the vast majority of PD cases seem to be sporadic and not directly inherited. Mutations in the genes encoding parkin, PTEN-induced putative kinase 1 (PINK1), leucine-rich repeat kinase 2 (LRRK2), and Parkinsonism-associated deglycase (DJ-1) have been found to be associated with PD, but they represent only a small subset of the total number of PD cases. Occupational exposure to some pesticides and herbicides has also been proposed as a risk factor for PD. The synthetic neurotoxin MPTP can cause Parkinsonism, but its use is extremely rare.

Frontotemporal dementia

Frontotemporal dementia (FTD; also known as frontotemporal lobar degeneration (FTLD)) is a clinical syndrome characterized by progressive neurodegeneration in the frontal and temporal lobes of the cerebral cortex. The manifestation of FTD is complex and heterogeneous, and may present as one of three clinically distinct variants including: 1) behavioral-variant frontotemporal dementia (BVFTD), characterized by changes in behavior and personality, apathy, social withdrawal, perseverative behaviors, attentional deficits, disinhibition, and a pronounced degeneration of the frontal lobe; 2) semantic dementia (SD), characterized by fluent, anomia aphasia, progressive loss of semantic knowledge of words, objects, and concepts and a pronounced degeneration of the anterior temporal lobes. Furthermore, SD variant of FTD exhibit a flat affect, social deficits, perseverative behaviors, and disinhibition; or 3) progressive nonfluent aphasia; characterized by motor deficits in speech production, reduced language expression, and pronounced degeneration of the perisylvian cortex. Neuronal loss in brains of FTD patients is associated with one of three distinct neuropathologies: 1) the presence of tau-positive neuronal and glial inclusions; 2) ubiquitin (ub)-positive and TAR DNA-binding protein 43 (TDP43)-positive, but tau-negative inclusions; or 3) ub and fused in sarcoma (FUS)-positive, but tau and TDP-43-negative inclusions. These neuropathologies are considered to be important in the etiology of FTD.

Nearly half of FTD patients have a first-degree family member with dementia, ALS, or Parkinson's disease, suggesting a strong genetic link to the cause of the disease. A number of mutations in chromosome 17q21 have been linked to FTD presentation.

Huntington's disease

Huntington's Disease (HD) is an example of a trinucleotide repeat expansion disorder. This class of disorders involve the localized expansion of unstable repeats of sets of three nucleotides and can result in loss of function of a gene in which the expanded repeat is found, a gain of toxic function, or both. Trinucleotide repeats can be located in any part of the gene, including coding and non-coding regions.

Repeats located within coding regions typically involve a repeated glutamine encoding triplet (CAG) or an alanine encoding triplet (CGA). Expanded repeat regions within non-coding sequences can lead to aberrant expression of the gene, while expanded repeats within coding regions (also known as codon reiteration disorders) may cause protein mis-folding and aggregation. Typically, regions of wild-type genes contain a variable number of repeat sequences in the normal population, but in the afflicted populations, the number of repeats can increase from a doubling to a log order increase in the number of repeats. In HD, repeats are inserted within the N-terminal coding region of the large cytosolic protein Huntingtin (Htt). Normal Htt alleles contain 15-20 CAG repeats, while alleles containing 35 or more repeats can be considered to confer a risk for developing the disease. Alleles containing 36-39 repeats are considered incompletely penetrant, and those individuals harboring those alleles may or may not develop the disease (or exhibit delayed presentation later in life), while alleles containing 40 repeats or more are considered completely penetrant. Those individuals with juvenile onset HD (<21 years of age) are often found to have 60 or more CAG repeats.

Multiple sclerosis

Multiple sclerosis (MS) is the most common demyelinating disease of the CNS affecting young adults (disease onset between 20 to 40 years of age) and is the third leading cause for disability after trauma and rheumatic diseases in the US.

MS patients present with destruction of myelin, death of oligodendrocytes, and axonal loss. The main pathologic finding in MS is the presence of infiltrating mononuclear cells, predominantly T lymphocytes and macrophages, which breach the blood brain barrier and induce active inflammation within the CNS. The neurological symptoms that characterize MS include complete or partial vision loss, diplopia, sensory symptoms, motor weakness that can progress to complete paralysis, bladder dysfunction, and cognitive deficits. The associated inflammatory foci lead to myelin destruction, plaques of demyelination, gliosis, and axonal loss within the brain and spinal cord and are the primary drivers of the clinical manifestations of neurological disability.

The etiology of MS is not fully understood. The disease develops in genetically predisposed subjects exposed to yet undefined environmental factors and the pathogenesis involves autoimmune mechanisms associated with autoreactive T cells against myelin antigens. It is well established that not one dominant gene determines genetic susceptibility to develop MS, but rather many genes, each with different influence, are involved. The detailed molecular mechanisms underlying MS etiology are still to be elucidated.

Progressive supranuclear palsy

Progressive supranuclear palsy (PSP), a progressive and fatal tauopathy, represents ~10% of all Parkinsonian cases in the US. PSP patients have a variety of motor disorders, including postural instability, falls, abnormalities in gait, bradykinesia, vertical gaze paralysis, pseudobulbar paralysis, and axial stiffness without limb stiffness, in addition to cognitive impairments such as apathy, loss of executive function, and reduced fluency. Neuropathology of PSP is characterized by an accumulation of tau protein, which is associated with abnormal intracellular microtubules, resulting in insoluble filament deposits. The neuropathological presentation of PSP neurodegeneration is located in the subcortical

regions, including substantia nigra, globus pallidus, and subthalamic nucleus. PSP neurodegeneration is characterized by the destruction of tissues and cytokine profiles of activated microglia and astrocytes.

There are currently no disease-modifying treatments for PSP. The current standard of care is palliative. Patients in the advanced stages of the disease often have feeding tubes inserted to avoid choking hazards and to provide nutrition. Although therapies are available to decrease some symptoms of PSP, none protect the brain from neurodegeneration. Current medications to treat symptoms of PSP include dopamine agonists, tricyclic antidepressants, methysergide, onabotulinumtoxin A (to treat muscle stiffness in the face). However, as the disease progresses and symptoms worsen, medications may fail to adequately decrease symptoms.

Gene targets

The methods of the invention feature delivering a branched siRNA molecule to a microglial cell in a subject in need of microglial gene silencing. Patients in need of microglial gene silencing may have dysregulated expression and/or activity of a gene selected from the group consisting of ABCA7, ABI3, ADAM10, APOC1, APOE, AXL, BIN1, C1QA, C3, C9ORF72, CASS4, CCL5, CD2AP, CD33, CD68, CLPTM1, CLU, CR1, CSF1, CST7, CTSB, CTSD, CTSL, CXCL10, CXCL13, DSG2, ECHDC3, EPHA1, FABP5, FERMT2, FTH1, GNAS, GRN, HBEGF, HLA-DRB1, HLA-DRB5, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IGF1, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, ITGAX, LILRB4, LPL, MEF2C, MMP12, MS4A4A, MS4A6A, NLRP3, NME8, NOS2, PICALM, PILRA, PLCG2, PTK2B, SCIMP, SLC24A4, SORL1, SPI1, SPP1, SPPL2A, TBK1, TNF, TREM2, TREML2, TYROBP, and ZCWPW1 gene.

In some embodiments, the patient in need of microglial gene silencing may require silencing of any one of the genes selected from the group consisting of APOE, BIN1, C1QA, C3, C9ORF72, CCL5, CD33, CLU/APOJ, CR1, CXCL10, CXCL13, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, MEF2C, MMP12, NLRP3, NOS2, PILRA, PLCG2, PTK2B, SLC24A4, TBK1, and TNF.

Pharmaceutical compositions

The branched siRNA molecules in the present invention can be formulated into a pharmaceutical composition for administration to a subject in a biologically compatible form suitable for administration in vivo. Accordingly, in one aspect, the present invention provides a pharmaceutical composition containing a branched siRNA in admixture with a suitable diluent, carrier, or excipient. The siRNA can be administered, for example, orally or by intravenous injection.

Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington: The Science and Practice of Pharmacy (2012, 22nd ed.) and in The United States Pharmacopeia: The National Formulary (2015, USP 38 NF 33).

Under ordinary conditions of storage and use, a pharmaceutical composition may contain a preservative, e.g., to prevent the growth of microorganisms. Pharmaceutical compositions may include sterile aqueous solutions, dispersions, or powders, e.g., for the extemporaneous preparation of sterile solutions or dispersions. In all cases the form may be sterilized using techniques known in the art and may be fluidized to the extent that may be easily administered to a subject in need of treatment.

A pharmaceutical composition may be administered to a subject, e.g., a human subject, alone or in combination with pharmaceutically acceptable carriers, as noted herein, the proportion of which may

be determined by the solubility and/or chemical nature of the compound, chosen route of administration, and standard pharmaceutical practice.

Regimens

5 A physician having ordinary skill in the art can readily determine an effective amount of siRNA for administration to a mammalian subject (e.g., a human) in need thereof. For example, a physician could start prescribing doses of a siRNA of the invention at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. Alternatively, a physician may begin a treatment regimen by administering a siRNA at a high dose and
10 subsequently administer progressively lower doses until a therapeutic effect is achieved (e.g., a reduction in expression of a target gene sequence). In general, a suitable daily dose of a siRNA of the invention will be an amount of the siRNA which is the lowest dose effective to produce a therapeutic effect. A single-strand or double-strand siRNA of the invention may be administered by injection, e.g., intrathecally, intracerebroventricularly, or intrastrially. A daily dose of a therapeutic composition of a siRNA of the
15 invention may be administered as a single dose or as two, three, four, five, six or more doses administered separately at appropriate intervals throughout the day, week, month, or year, optionally, in unit dosage forms. While it is possible for a siRNA of the invention to be administered alone, it may also be administered as a pharmaceutical formulation in combination with excipients, carriers, and optionally, additional therapeutic agents.

Routes of administration

The method of the invention contemplates any route of administration tolerated by the therapeutic composition. Some embodiments of the method include injection intrathecally, intracerebroventricularly, or intrastrially.

25 Intrathecal injection is the direct injection into the spinal column or subarachnoid space. By injecting directly into the CSF of the spinal column the siRNA molecule of the invention has direct access to microglia in the spinal column and a route to access the microglia in the brain by bypassing the blood brain barrier.

Intracerebroventricular (ICV) injection is a method to directly inject into the CSF of the cerebral
30 ventricles. Similar to intrathecal injection, ICV is a method of injection which bypasses the blood brain barrier. Using ICV allows the advantage of access to the microglia of the brain and spinal column without the danger of the therapeutic being degraded in the blood.

Intrastriatal injection is the direct injection into the striatum, or corpus striatum. The striatum is an area in the subcortical basal ganglia in the brain. Injecting into the striatum bypasses the blood brain
35 barrier and the pharmacokinetic challenges of injection into the blood stream and allows for direct access to the microglia of the brain and spinal column.

EXAMPLES

Example 1. Protocol for Uptake of di-siRNA in Microglia of Non-Human Primates

40 The experiments described in this example were conducted to assess the ability of branched siRNA molecules to permeate the central nervous system and internalize within microglial cells. To this end, a branched siRNA compound targeting the huntingtin (HTT) gene and conjugated to a fluorescent

dye (Cy3) was first injected into the cerebrospinal fluid via intrathecal injection into non-human primates (NHP; cynomolgus macaque). Central nervous system tissue samples were later obtained from the animals. To assess the extent to which the branched siRNA molecules were internalized by microglial cells, the tissue samples were stained using fluorescent-labeled antibodies that are specific for markers expressed in certain cell types (e.g., microglia). Fluorescence microscopy was then utilized to determine the degree of colocalization of the Cy3-labeled branched siRNA molecules and antibody-labeled microglial cells, which served as an indicator of microglial uptake. These experiments, and their results, are described in further detail below:

Paraffin embedded CNS tissue slides were tested. A dose of fluorescent labeled branched siRNA was administered to a NHP (cynomolgus macaque) via intrathecal injection. 48 hours after injection a distribution study was done. The control was an uninjected NHP. NHP tissues for imaging were post-fixed for 48-72 hours in 4% PFA at $5\pm 3^{\circ}\text{C}$, and then transferred to PBS. All tissues were paraffin-embedded and sliced into 4 μm sections and mounted on slides for immunofluorescence staining. Subsequently, sections were deparaffinized and subjected to antigen retrieval. Samples were deparaffinized by two changes of xylene, 5 minutes each, then 50% xylene+50% ethanol (100%) for 5 minutes. Samples were hydrated by two changes of 100% ethanol for 3 minutes each, 90%, 80%, 70% and then 50% ethanol for 3 minutes each, followed by distilled water rinse. Antigen retrieval was carried out using 150 mL of Tris-EDTA buffer (pH9), placing the staining dish in a pressure cooker (containing 1200 mL DDH_2O) for 10 minutes, allowing the slides to cool to room temperature, followed by section-wise rinsing with H_2O and TBST. Sections were blocked with Background Terminator Blocking Reagent and the slides were then incubated with the primary antibody against the microglial-specific gene, Iba-1, for 1.5 hours at room temperature, followed by treatment with a secondary antibody labeled with Alexa Fluor 488 (Alexa-488). Alexa-488 was used to visualize Iba-1 antibody. DAPI was used to visualize cell nuclei. Tissues were washed three times for 5 min with TBS-Tween 20. Fluoromount-G was used to place glass coverslips, and slides were left to dry at 4°C overnight protected from light. Olympus VS200 slide scanner was used to acquire immunofluorescent images of brain and spinal cord (20 $\times$ objective). Images within each imaging channel were acquired under the same settings for light intensity and exposure times.

Colocalization of DAPI stained nuclei, Alexa-488-labeled Iba-1 antibody, and Cy3-labeled siRNA was observed across all tested brain and spinal cord tissues of cynomolgus macaques, indicating microglial cell penetration and/or uptake of the branched di-siRNA. Control experiments included uninjected NHP control (no Cy3-siRNA), non-specific primary antibody (isotype antibody control), and no secondary antibody (no Alexa Fluor 488 reagent). Robust colocalization was observed in the cortex (FIG. 1A), hippocampus (FIG. 1B), caudate nucleus (FIG. 1C), and spinal cord (FIG. 1D). Controls showed no co-localization of Cy3 and Alexa Fluor 488 signals, indicating specificity of detection of microglial uptake (not shown).

These results demonstrate that the ds-siRNA agents of the present disclosure are capable of being internalized by microglial cells of CNS tissues, including brain and spinal cord, and support the use of such agents for treatment of neurological conditions, such as Alzheimer's disease or amyotrophic lateral sclerosis.

Example 2. Method of Treating a Patient with Alzheimer's Disease

A subject diagnosed with Alzheimer's disease is treated with a dose and frequency determined by a practitioner (e.g., three times daily, twice daily, once daily, once weekly, once monthly, bi-monthly, once every 4 months, once every 5 months, once every 6 months, once every 7 months, once every 8 months, once every 9 months, once every 10 months, once every 11 months, or annually). Dosage and frequency are determined based on the subject's height, weight, age, sex, and other disorders.

The branched siRNA is selected by the practitioner for compatibility with the disease and subject. Single- or double-stranded branched siRNA are available for selection. The siRNA chosen has an antisense strand, and in the case of double-stranded siRNA, a sense strand with a sequence and RNA modifications (e.g., natural and non-natural internucleoside linkages, modified sugars, and 5'-phosphorus stabilizing moieties) best suited to the patient and the disease being targeted (e.g.,

PSM-A-T-B-T-A-P-B-P-A-P-B-P-A-P-B-P-A-P-B-P-A-P-B-T-A-T-B-T-A-T-B-T-A-T-B-T
B-T-A-T-B-P-A-P-B-P-A-P-B-P-A-P-B-P-A-P-B-P-A-P-B-P-A-T-B-T

where A and B are different nucleosides, T is phosphorothioate, P is a phosphodiester, and PSM is a 5'-phosphorus stabilizing moiety).

The branched siRNA is delivered by the route best suited the patient and condition (e.g., intrathecally, intracerebroventricularly, or intrastratially), at a rate tolerable to the patient until the subject has reached a maximum tolerated dose, or until the symptoms of the disease are ameliorated satisfactorily.

Example 3. Method of Treating a Patient with Amyotrophic Lateral Sclerosis

A subject diagnosed with Amyotrophic Lateral Sclerosis is treated with a dose and frequency determined by a practitioner (e.g., three times daily, twice daily, once daily, once weekly, once monthly bi-monthly, once every 4 months, once every 5 months, once every 6 months, once every 7 months, once every 8 months, once every 9 months, once every 10 months, once every 11 months, or annually). Dosage and frequency are determined based on the subject's height, weight, age, sex, and other disorders.

The branched siRNA is selected by the practitioner for compatibility with the disease and subject. Single- or double-stranded branched siRNA are available for selection. The siRNA chosen has an antisense strand, and in the case of double-stranded siRNA, a sense strand with a sequence and RNA modifications (e.g., natural and non-natural internucleoside linkages, modified sugars, and 5'-phosphorus stabilizing moieties) best suited to the patient and the disease being targeted (e.g.,

PSM-A-T-B-T-A-P-B-P-A-P-B-P-A-P-B-P-A-P-B-P-A-P-B-T-A-T-B-T-A-T-B-T-A-T-B-T
B-T-A-T-B-P-A-P-B-P-A-P-B-P-A-P-B-P-A-P-B-P-A-P-B-P-A-T-B-T

where A and B are different nucleosides, T is phosphorothioate, P is a phosphodiester, and PSM is a 5'-phosphorus stabilizing moiety).

The branched siRNA is delivered by the route best suited the patient and condition (e.g., intrathecally, intracerebroventricularly, or intrastratially), at a rate tolerable to the patient until the subject has reached a maximum tolerated dose, or until the symptoms of the disease are ameliorated satisfactorily.

SPECIFIC EMBODIMENTS

Some specific embodiments are listed below. The below enumerated embodiments should not be construed to limit the scope of the invention, rather, the below are presented as some examples of the utility of the invention.

- 5 E1. A method of delivering a branched small interfering RNA (siRNA) molecule to a microglial cell in a subject in need of microglial gene silencing, the method comprising administering the branched siRNA molecule to the central nervous system of the subject.
- E2. The method of E1, wherein the subject has been diagnosed as having a disease associated with expression of a dysregulated microglial gene or dysregulated microglial gene network.
- 10 E3. The method of E2, wherein the dysregulated microglial gene exhibits increased expression and/or activity in microglial cells of the subject as compared to the expression and/or activity of the microglial gene in microglial cells of a reference subject.
- E4. The method of E2, wherein the dysregulated microglial gene exhibits reduced expression and/or activity in microglial cells of the subject as compared to the expression and/or activity of the microglial gene in microglial cells of a reference subject.
- 15 E5. The method of any one of E1-E4, wherein the delivering of the branched siRNA molecule to the subject results in silencing of a gene in the subject.
- E6. The method of any one of E1-E5, wherein the siRNA includes (i) an antisense strand having complementarity to a portion of a gene encoding a positive regulator of a gene for which increased expression and/or activity (relative, e.g., to the level of expression and/or activity observed in a reference subject) is associated with a disease state.
- 20 E7. The method of any one of E1-E5, wherein the siRNA includes (i) an antisense strand having complementarity to a portion of a gene encoding a negative regulator of a gene for which decreased expression and/or activity (relative, e.g., to the level of expression and/or activity observed in a reference subject) is associated with a disease state.
- 25 E8. The method of any one of E1-E5, wherein the siRNA includes (i) an antisense strand having complementarity to a splice isoform of a gene for which overexpression of the splice isoform relative to the expression of the splice isoform in a reference subject is associated with a disease state.
- 30 E9. The method of any one of E6-E8, wherein the siRNA includes (ii) a sense strand having complementarity to the antisense strand.
- E10. The method of any one of any one of E1-E9, wherein the silencing of the microglial gene in the subject treats a disease state in the subject.
- E11. The method of any one of E1-E10, wherein the disease is a neuroinflammatory or
- 35 neurodegenerative disease.
- E12. The method of any one of E2-E10, wherein the dysregulated gene is selected from the group consisting of ABCA7, ABI3, ADAM10, APOC1, APOE, AXL, BIN1, C1QA, C3, C9ORF72, CASS4, CCL5, CD2AP, CD33, CD68, CLPTM1, CLU, CR1, CSF1, CST7, CTSB, CTSD, CTSL, CXCL10, CXCL13, DSG2, ECHDC3, EPHA1, FABP5, FERMT2, FTH1, GNAS, GRN, HBEGF, HLA-DRB1, HLA-DRB5, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IGF1, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, ITGAX, LILRB4, LPL, MEF2C, MMP12, MS4A4A, MS4A6A, NLRP3, NME8, NOS2,
- 40 PICALM, PILRA, PLCG2, PTK2B, SCIMP, SLC24A4, SORL1, SPI1, SPP1, SPPL2A, TBK1, TNF,

TREM2, TREML2, TYROBP, and ZCWPW1 or negative regulator, positive regulator, or splice isoform thereof.

E13. The method of any one of E1-E12, wherein the subject is a mammal, e.g., a human.

E14. The method of any one of E1-E13, wherein the branched siRNA is administered to the subject intrathecally, intracerebroventricularly, or intrastrially.

E15. The method of any one of E1-E14, wherein the branched siRNA is administered to the subject intrathecally.

E16. The method of any one of E1-E14, wherein the branched siRNA is administered to the subject intracerebroventricularly.

E17. The method of any one of E1-E14, wherein the branched siRNA is administered to the subject intrastrially.

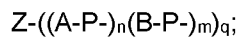
E18. The method of any one of E1-17, wherein the siRNA molecule is di-branched.

E19. The method of any one of E1-17, wherein the siRNA molecule is tri-branched.

E20. The method of any one of E1-17, wherein the siRNA molecule is tetra-branched.

E21. The method of any one of E1-20, wherein the siRNA comprises (i) an antisense strand having complementarity to one or more of genes selected from the group consisting of APOE, BIN1, C1QA, C3, C9ORF72, CCL5, CD33, CLU/APOJ, CR1, CXCL10, CXCL13, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, MEF2C, MMP12, NLRP3, NOS2, PILRA, PLCG2, PTK2B, SLC24A4, TBK1, and TNF and (ii) a sense strand having complementarity to the antisense strand.

E22. The method of E21, wherein the antisense strand has the following formula, in the 5'-to-3' direction:



wherein Z is a 5' phosphorus stabilizing moiety;

each A is, independently, a 2'-O-methyl (2'-O-Me) ribonucleoside;

each B is, independently, a 2'-fluoro-ribonucleoside;

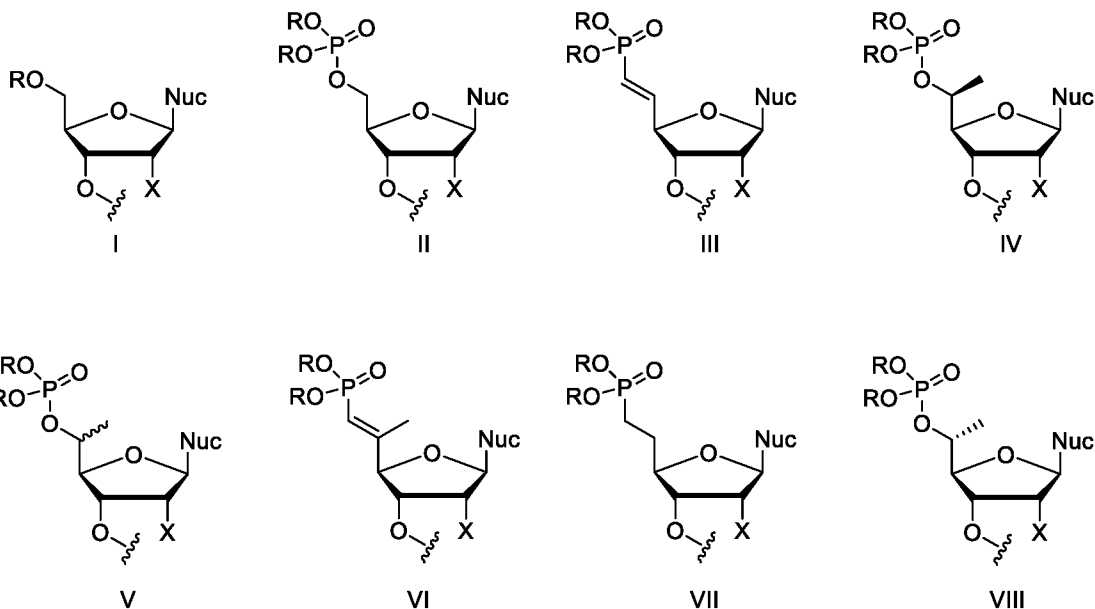
each P is, independently, an internucleoside linkage selected from a phosphodiester linkage and a phosphorothioate linkage;

n is an integer from 1 to 5;

m is an integer from 1 to 5; and

q is an integer between 1 and 15.

E23. The method of E22, wherein Z is represented in any one of Formula I-VIII:



wherein Nuc represents a nucleobase, such as adenine, uracil, guanine, thymine, or cytosine, and R represents optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl (e.g., optionally substituted C1-C6 alkyl, optionally substituted C2-C6 alkenyl, or optionally substituted C2-C6 alkynyl), phenyl, benzyl, hydroxy, or hydrogen.

E24. The method of E22 or E23, wherein Z is (E)-vinylphosphonate represented in Formula III.

E25. The method of any one of E22-E24, wherein n is from 1 to 4.

E26. The method of any one of E22-E25, wherein n is from 1 to 3.

E27. The method of any one of E22-E26, wherein n is from 1 to 2.

E28. The method of any one of E22-E27, wherein n is 1.

E29. The method of any one of E22-E28, wherein m is from 1 to 4.

E30. The method of any one of E22-E29, wherein m is from 1 to 3.

E31. The method of any one of E22-E30, wherein m is from 1 to 2.

E32. The method of any one of E22-E31, wherein m is 1.

E33. The method of any one of E22-E32, wherein n and m are each 1.

E34. The method of any one of E22-E33, wherein 10% or less of the ribonucleosides are 2'-O-Me ribonucleoside.

E35. The method of any one of E22-E34, wherein at least 10% of the ribonucleosides are 2'-O-Me ribonucleoside.

E36. The method of any one of E22-E35, wherein at least 20% of the ribonucleosides are 2'-O-Me ribonucleoside.

E37. The method of any one of E22-E36, wherein at least 30% of the ribonucleosides are 2'-O-Me ribonucleoside.

E38. The method of any one of E22-E37, wherein at least 40% of the ribonucleosides are 2'-O-Me ribonucleoside.

E39. The method of any one of E22-E38, wherein at least 50% of the ribonucleosides are 2'-O-Me ribonucleoside.

- E40. The method of any one of E22-E39, wherein at least 60% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E41. The method of any one of E22-E40, wherein at least 70% of the ribonucleosides are 2'-O-Me ribonucleoside.
- 5 E42. The method of any one of E22-E41, wherein at least 80% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E43. The method of any one of E22-E42, wherein at least 90% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E44. The method of any one of E22-E43, wherein 10% or less of the internucleoside linkages are
10 phosphodiester linkages or phosphorothioate linkages.
- E45. The method of any one of E22-E44, wherein at least 10% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- E46. The method of any one of E22-E45, wherein at least 20% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- 15 E47. The method of any one of E22-E46, wherein at least 30% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- E48. The method of any one of E22-E47, wherein at least 40% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- E49. The method of any one of E22-E48, wherein at least 50% of the internucleoside linkages are
20 phosphodiester linkages or phosphorothioate linkages.
- E50. The method of any one of E22-E49, wherein at least 60% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- E51. The method of any one of E22-E50, wherein at least 70% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- 25 E52. The method of any one of E22-E51, wherein at least 80% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- E53. The method of any one of E22-E52, wherein at least 90% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- E54. The method of any one of E22-E53, wherein 100% of the internucleoside linkages are
30 phosphodiester linkages or phosphorothioate linkages.
- E55. The method of any one of E22-E54, wherein 9 internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- E56. The method of any one of E22-E55, wherein the length of the antisense strand is between 10 and 30 nucleotides.
- 35 E57. The method of any one of E22-E56, wherein the length of the antisense strand is between 15 and 25 nucleotides.
- E58. The method of any one of E22-E57, wherein the length of the antisense strand is between 18 and 23 nucleotides.
- E59. The method of any one of E22-E58, wherein the length of the antisense strand is 18 nucleotides.
- 40 E60. The method of any one of E22-E56, wherein the length of the antisense strand is 19 nucleotides.
- E61. The method of any one of E22-E56, wherein the length of the antisense strand is 20 nucleotides.
- E62. The method of any one of E22-E56, wherein the length of the antisense strand is 21 nucleotides.

- E63. The method of any one of E22-E56, wherein the length of the antisense strand is 22 nucleotides.
 E64. The method of any one of E22-E56, wherein the length of the antisense strand is 23 nucleotides.
 E65. The method of any one of E22-E56, wherein the length of the antisense strand is 24 nucleotides.
 E66. The method of any one of E22-E56, wherein the length of the antisense strand is 25 nucleotides.
 5 E67. The method of any one of E22-E56, wherein the length of the antisense strand is 26 nucleotides.
 E68. The method of any one of E22-E56, wherein the length of the antisense strand is 27 nucleotides.
 E69. The method of any one of E22-E56, wherein the length of the antisense strand is 28 nucleotides.
 E70. The method of any one of E22-E56, wherein the length of the antisense strand is 29 nucleotides.
 E71. The method of any one of E22-E56, wherein the length of the antisense strand is 30 nucleotides.
 10 E72. The method of E22, wherein the antisense strand includes a structure of Formula A1, wherein Formula A1 is:

A-T-B-T-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-B-T-A-T-A-T-A-T-A-T-A-T

Formula A1;

15 wherein A represents a 2'-O-methyl ribonucleoside, B represents a 2'-F ribonucleoside, T represents a phosphorothioate internucleoside linkage, and P represents a phosphodiester internucleoside linkage.

- E73. The method of E22, wherein the antisense strand includes a structure of Formula A2, wherein
 20 Formula A2 is:

A-T-A-T-A-P-B-P-B-P-B-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-B-T-A-T-A-T-A-T-A-T-A-T

(Formula A2);

25 wherein A represents a 2'-O-methyl ribonucleoside, B represents a 2'-F ribonucleoside, T represents a phosphorothioate internucleoside linkage, and P represents a phosphodiester internucleoside linkage.

- E74. The method of E22, wherein the antisense strand includes a structure of Formula A3, wherein
 30 Formula A3 is:

A-T-B-T-A-P-B-P-B-P-B-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-B-T-A-T-A-T-A-T-A-T-A-T

(Formula A3)

35 wherein A represents a 2'-O-methyl ribonucleoside, B represents a 2'-F ribonucleoside, T represents a phosphorothioate internucleoside linkage, and P represents a phosphodiester internucleoside linkage.

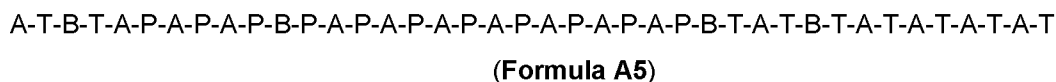
- E75. The method of E22, wherein the antisense strand includes a structure of Formula A4, wherein
 40 Formula A4 is:

A-T-B-T-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-B-T-A-T-A-T-A-T-A-T-A-T

(Formula A4)

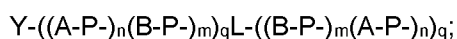
wherein A represents a 2'-O-methyl ribonucleoside, B represents a 2'-F ribonucleoside, T represents a phosphorothioate internucleoside linkage, and P represents a phosphodiester internucleoside linkage.

- E76. The method of E22, wherein the antisense strand includes a structure of Formula A5, wherein



wherein A represents a 2'-O-methyl ribonucleoside, B represents a 2'-F ribonucleoside, T represents a phosphorothioate internucleoside linkage, and P represents a phosphodiester internucleoside linkage.

- E77. The method of E22, wherein the sense strand has the following formula in the 5'-to-3' direction:



wherein Y is a hydrophobic moiety (e.g., cholesterol, vitamin D, or tocopherol) moiety;
L is a linker;

each A is, independently, a 2'-O-Me ribonucleoside;

each B is, independently, a 2'-fluoro-ribonucleoside;

each P is, independently, an internucleoside linkage selected from a phosphodiester linkage and a phosphorothioate linkage;

n is an integer from 1 to 5;

m is an integer from 1 to 5; and

each q is an integer between 1 and 15.

- E78. The method of E77, wherein Y is cholesterol.

- E79. The method of E77, wherein Y is tocopherol.

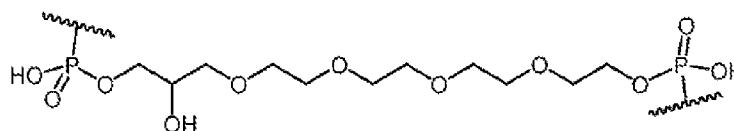
- E80. The method of any one of E77-E79, wherein L is an ethylene glycol oligomer.

- E81. The method of any one of E77-E80, wherein L is tetraethylene glycol.

- E82. The method of any one of E77-E81, wherein the linker attaches to the sense strand by way of a covalent bond-forming moiety.

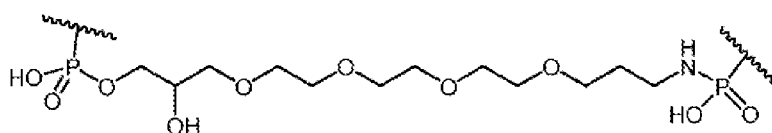
- E83. The method of E82, wherein the covalent bond-forming moiety is selected from the group consisting of an alkyl, ester, amide, carbamate, phosphonate, phosphate, phosphorothioate, phosphoroamidate, triazole, urea, and formacetal.

- E84. The method of E77, wherein L includes a structure of Formula L1, wherein Formula L1 is:



(Formula L1)

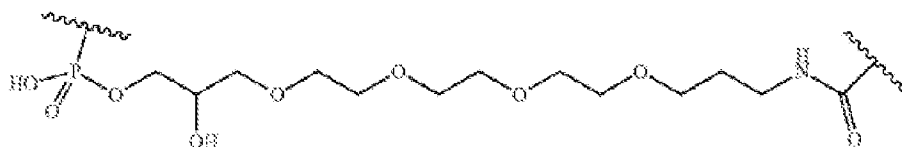
E85. The method of E77, wherein L includes a structure of Formula L2, wherein Formula L2 is:



(Formula L2)

5

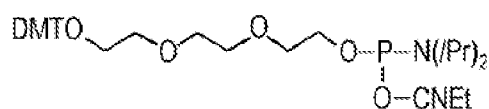
E86. The method of E77, wherein L includes a structure of Formula L3, wherein Formula L3 is:



(Formula L3)

10

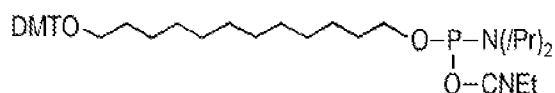
E87. The method of E77, wherein L includes a structure of Formula L4, wherein Formula L4 is:



(Formula L4)

15

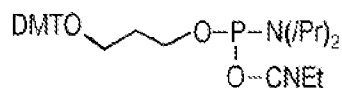
E88. The method of E77, wherein L includes a structure of Formula L5, wherein Formula L5 is:



(Formula L5)

20

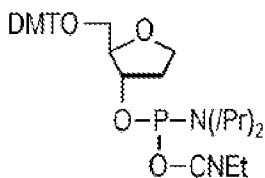
E89. The method of E77, wherein L includes a structure of Formula L6, wherein Formula L6 is:



(Formula L6)

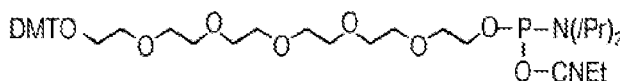
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E90. The method of E77, wherein L includes a structure of Formula L7, wherein Formula L7 is:



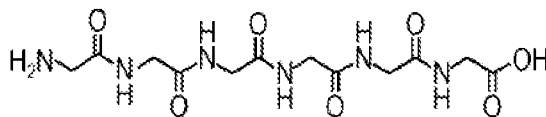
(Formula L7)

E91. The method of E77, wherein L includes a structure of Formula L8, wherein Formula L8 is:



(Formula L8)

E92. The method of E77, wherein L includes a structure of Formula L9, wherein Formula L9 is:



(Formula L9)

E93. The method of any one of E77-E92, wherein each P is independently selected from a phosphodiester linkage and a phosphorothioate linkage.

E94. The method of any one of E77-E93, wherein n is from 1 to 4.

E95. The method of any one of E77-E94, wherein n is from 1 to 3.

E96. The method of any one of E77-E95, wherein n is from 1 to 2.

E97. The method of any one of E77-E96, wherein n is 1.

E98. The method of any one of E77-E97, wherein m is from 1 to 4.

E99. The method of any one of E77-E98, wherein m is from 1 to 3.

E100. The method of any one of E77-E99, wherein m is from 1 to 2.

E101. The method of any one of E77-E100, wherein m is 1.

E102. The method of any one of E77-E101, wherein n and m are each 1.

E103. The method of any one of E77-E102, wherein 10% or less of the ribonucleosides are 2'-O-Me ribonucleoside.

E104. The method of any one of E77-E103, wherein at least 10% of the ribonucleosides are 2'-O-Me ribonucleoside.

E105. The method of any one of E77-E104, wherein at least 20% of the ribonucleosides are 2'-O-Me ribonucleoside.

E106. The method of any one of E77-E105, wherein at least 30% of the ribonucleosides are 2'-O-Me ribonucleoside.

- E107. The method of any one of E77-E106, wherein at least 40% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E108. The method of any one of E77-E107, wherein at least 50% of the ribonucleosides are 2'-O-Me ribonucleoside.
- 5 E109. The method of any one of E77-E108, wherein at least 60% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E110. The method of any one of E77-E109, wherein at least 70% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E111. The method of any one of E77-E110, wherein at least 80% of the ribonucleosides are 2'-O-Me
10 ribonucleoside.
- E112. The method of any one of E77-E111, wherein at least 90% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E113. The method of any one of E77-E112, wherein 10% or less of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- 15 E114. The method of any one of E77-E113, wherein at least 10% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- E115. The method of any one of E77-E114, wherein at least 20% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- E116. The method of any one of E77-E115, wherein at least 30% of the internucleoside linkages are
20 phosphodiester linkages or phosphorothioate.
- E117. The method of any one of E77-E116, wherein at least 40% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- E118. The method of any one of E77-E117, wherein at least 50% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- 25 E119. The method of any one of E77-E118, wherein at least 60% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- E120. The method of any one of E77-E119, wherein at least 70% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- E121. The method of any one of E77-E120, wherein at least 80% of the internucleoside linkages are
30 phosphodiester linkages or phosphorothioate.
- E122. The method of any one of E77-E121, wherein at least 90% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- E123. The method of any one of E77-E122, wherein 100% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- 35 E124. The method of any one of E77-E123, wherein the length of the sense strand is between 12 and 30 nucleotides.
- E125. The method of any one of E77-E124, wherein the length of the sense strand is between 14 and 28 nucleotides.
- E126. The method of any one of E77-E125, wherein the length of the sense strand is between 16 and 26
40 nucleotides.
- E127. The method of any one of E77-E126, wherein the length of the sense strand is between 18 and 24 nucleotides.

E128. The method of any one of E77-E125, wherein the length of the sense strand is 14 nucleotides.
 E129. The method of any one of E77-E125, wherein the length of the sense strand is 15 nucleotides.
 E130. The method of any one of E77-E125, wherein the length of the sense strand is 16 nucleotides.
 E131. The method of any one of E77-E125, wherein the length of the sense strand is 17 nucleotides.
 5 E132. The method of any one of E77-E125, wherein the length of the sense strand is 18 nucleotides.
 E133. The method of any one of E77-E125, wherein the length of the sense strand is 19 nucleotides.
 E134. The method of any one of E77-E125, wherein the length of the sense strand is 20 nucleotides.
 E135. The method of any one of E77-E125, wherein the length of the sense strand is 21 nucleotides.
 E136. The method of any one of E77-E125, wherein the length of the sense strand is 22 nucleotides.
 10 E137. The method of any one of E77-E125, wherein the length of the sense strand is 23 nucleotides.
 E138. The method of any one of E77-E125, wherein the length of the sense strand is 24 nucleotides.
 E139. The method of any one of E77-E125, wherein the length of the sense strand is 25 nucleotides.
 E140. The method of any one of E77-E125, wherein the length of the sense strand is 26 nucleotides.
 E141. The method of any one of E77-E125, wherein the length of the sense strand is 27 nucleotides.
 15 E142. The method of any one of E77-E125, wherein the length of the sense strand is 28 nucleotides.
 E143. The method of any one of E77-E125, wherein the length of the sense strand is 29 nucleotides.
 E144. The method of any one of E77-E125, wherein the length of the sense strand is 30 nucleotides.
 E145. The method of any one of E77-E144, wherein 4 internucleoside linkages are phosphorothioate linkages.

20 E146. The method of E77, wherein the sense strand includes a structure of Formula S1, wherein Formula S1 is:

A-T-A-T-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-P-A-T-A-T

Formula S1;

25 wherein A represents a 2'-O-methyl ribonucleoside, B represents a 2'-F ribonucleoside, T represents a phosphorothioate internucleoside linkage, and P represents a phosphodiester internucleoside linkage.

E147. The method of E77, wherein the sense strand includes a structure of Formula S2, wherein Formula S2 is:

30 A-T-A-T-A-P-A-P-A-P-A-P-B-P-A-P-A-P-B-P-B-P-A-P-A-P-A-T-A-T

Formula S2;

35 wherein A represents a 2'-O-methyl ribonucleoside, B represents a 2'-F ribonucleoside, T represents a phosphorothioate internucleoside linkage, and P represents a phosphodiester internucleoside linkage.

E148. The method of E77, wherein the sense strand includes a structure of Formula S3, wherein Formula S3 is:

40 A-T-A-T-A-P-A-P-A-P-A-P-B-P-A-P-B-P-B-P-B-P-A-P-A-P-A-T-A-T

Formula S3;

wherein A represents a 2'-O-methyl ribonucleoside, B represents a 2'-F ribonucleoside, T represents a phosphorothioate internucleoside linkage, and P represents a phosphodiester internucleoside linkage.

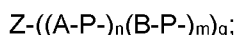
E149. A branched siRNA molecule comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region having complementarity to a segment of contiguous nucleotides within a gene selected from the group consisting of APOE, BIN1, C1QA, C3, C9ORF72, CCL5, CD33, CLU/APOJ, CR1, CXCL10, CXCL13, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, MEF2C, MMP12, NLRP3, NOS2, PILRA, PLCG2, PTK2B, SLC24A4, TBK1, and TNF or a negative regulator, positive regulator, or splice isoform thereof.

E150. The molecule of E149, wherein the siRNA molecule is di-branched.

E151. The molecule of E149, wherein the siRNA molecule is tri-branched.

E152. The molecule of any one of E149, wherein the siRNA molecule is tetra-branched.

E153. The molecule of any one of E149-E152, wherein the antisense strand of the branched siRNA has the following formula in the 5'-to-3' direction:



wherein Z is a 5' phosphorus stabilizing moiety;

each A is, independently, a 2'-O-Me ribonucleoside;

each B is, independently, a 2'-fluoro-ribonucleoside;

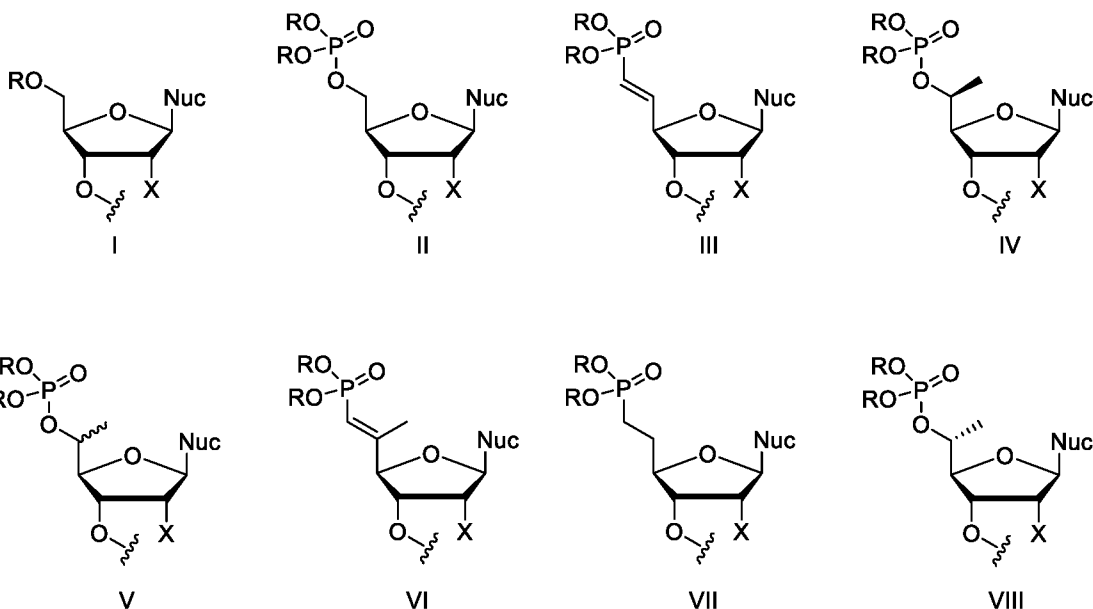
each P is, independently, an internucleoside linkage selected from a phosphodiester linkage and a phosphorothioate linkage;

n is an integer from 1 to 5;

m is an integer from 1 to 5; and

q is an integer between 1 and 15.

E154. The molecule of E153, wherein Z is represented in any one of Formula I-VIII:



wherein Nuc represents a nucleobase, such as adenine, uracil, guanine, thymine, or cytosine, and R represents optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl (e.g., optionally substituted C1-C6 alkyl, optionally substituted C2-C6 alkenyl, or optionally substituted C2-C6 alkynyl), phenyl, benzyl, hydroxy, or hydrogen.

- 5 E155. The molecule of E153 or E154, wherein Z is (E)-vinylphosphonate as represented in Formula III.
- E156. The molecule of any one of E153-E99, wherein each P is independently selected from phosphodiester and phosphorothioate.
- E157. The molecule of any one of E153-E156, wherein n is from 1 to 4.
- E158. The molecule of any one of E153-E157, wherein n is from 1 to 3.
- 10 E159. The molecule of any one of E153-E158, wherein n is from 1 to 2.
- E160. The molecule of any one of E153-E159, wherein n is 1.
- E161. The molecule of any one of E153-E160, wherein m is from 1 to 4.
- E162. The molecule of any one of E153-E161, wherein m is from 1 to 3.
- E163. The molecule of any one of E153-E162, wherein m is from 1 to 2.
- 15 E164. The molecule of any one of E153-E163, wherein m is 1.
- E165. The molecule of any one of E153-E164, wherein n and m are each 1.
- E166. The molecule of any one of E153-E165, wherein 10% or less of the ribonucleosides are 2'-O-Me ribonucleoside.
- E167. The molecule of any one of E153-E166, wherein at least 10% of the ribonucleosides are 2'-O-Me
20 ribonucleoside.
- E168. The molecule of any one of E153-E167, wherein at least 20% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E169. The molecule of any one of E153-E168, wherein at least 30% of the ribonucleosides are 2'-O-Me ribonucleoside.
- 25 E170. The molecule of any one of E153-E169, wherein at least 40% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E171. The molecule of any one of E153-E170, wherein at least 50% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E172. The molecule of any one of E153-E171, wherein at least 60% of the ribonucleosides are 2'-O-Me
30 ribonucleoside.
- E173. The molecule of any one of E153-E172, wherein at least 70% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E174. The molecule of any one of E153-E173, wherein at least 80% of the ribonucleosides are 2'-O-Me ribonucleoside.
- 35 E175. The molecule of any one of E153-E174, wherein at least 90% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E176. The molecule of any one of E153-E175, wherein 10% or less of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- E177. The molecule of any one of E153-E176, wherein at least 10% of the internucleoside linkages are
40 phosphodiester linkages or phosphorothioate.
- E178. The molecule of any one of E153-E177, wherein at least 20% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.

- E179. The molecule of any one of E153-E178, wherein at least 30% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- E180. The molecule of any one of E153-E179, wherein at least 40% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- 5 E181. The molecule of any one of E153-E180, wherein at least 50% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- E182. The molecule of any one of E153-E181, wherein at least 60% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- E183. The molecule of any one of E153-E182, wherein at least 70% of the internucleoside linkages are
10 phosphodiester linkages or phosphorothioate.
- E184. The molecule of any one of E153-E183, wherein at least 80% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- E185. The molecule of any one of E153-E184, wherein at least 90% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- 15 E186. The molecule of any one of E153-E185, wherein 100% of the internucleoside linkages are phosphodiester linkages or phosphorothioate.
- E187. The molecule of any one of E153-E186, wherein the length of the antisense strand is between 10 and 30 nucleotides.
- E188. The molecule of any one of E153-E187, wherein the length of the antisense strand is between 15
20 and 25 nucleotides.
- E189. The molecule of any one of E153-E188, wherein the length of the antisense strand is between 18 and 23 nucleotides.
- E190. The molecule of any one of E153-E187, wherein the length of the antisense strand is 18 nucleotides.
- 25 E191. The molecule of any one of E153-E187, wherein the length of the antisense strand is 19 nucleotides.
- E192. The molecule of any one of E153-E187, wherein the length of the antisense strand is 20 nucleotides.
- E193. The molecule of any one of E153-E187, wherein the length of the antisense strand is 21
30 nucleotides.
- E194. The molecule of any one of E153-E187, wherein the length of the antisense strand is 22 nucleotides.
- E195. The molecule of any one of E153-E187, wherein the length of the antisense strand is 23 nucleotides.
- 35 E196. The molecule of any one of E153-E187, wherein the length of the antisense strand is 24 nucleotides.
- E197. The molecule of any one of E153-E187, wherein the length of the antisense strand is 25 nucleotides.
- E198. The molecule of any one of E153-E187, wherein the length of the antisense strand is 26
40 nucleotides.
- E199. The molecule of any one of E153-E187, wherein the length of the antisense strand is 27 nucleotides.

E200. The molecule of any one of E153-E187, wherein the length of the antisense strand is 28 nucleotides.

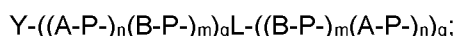
E201. The molecule of any one of E153-E187, wherein the length of the antisense strand is 29 nucleotides.

5 E202. The molecule of any one of E153-E187, wherein the length of the antisense strand is 30 nucleotides.

E203. The molecule of any one of E149-E202, wherein 9 internucleoside linkages are phosphorothioate.

E204. The molecule of any one of E149-E203, wherein the sense strand of the branched siRNA has the following formula in the 5'-to-3' direction:

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wherein Y is a hydrophobic moiety (e.g., cholesterol, vitamin D, or tocopherol);

15

L is a linker;

each A is, independently, a 2'-O-Me ribonucleoside;

each B is, independently, a 2'-fluoro-ribonucleoside;

each P is, independently, an internucleoside linkage selected from a phosphodiester linkage and a phosphorothioate linkage;

20

n is an integer from 1 to 5;

m is an integer from 1 to 5; and

q is an integer between 1 and 15.

E205. The molecule of E204, wherein Y is cholesterol.

E206. The molecule of E204, wherein Y is tocopherol.

25

E207. The molecule of any one of E204-E206, wherein L is an ethylene glycol oligomer.

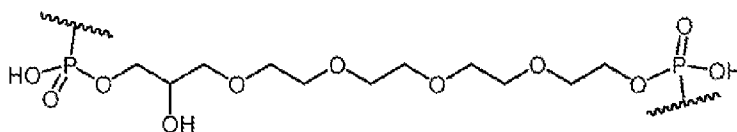
E208. The molecule of E207, wherein L is tetraethylene glycol.

E209. The molecule of any one of E204-E208, wherein L attaches to the sense strand by way of a covalent bond-forming moiety.

30

E210. The molecule of E209, wherein the covalent bond-forming moiety is selected from the group consisting of an alkyl, ester, amide, carbamate, phosphonate, phosphate, phosphorothioate, phosphoroamidate, triazole, urea, and formacetal.

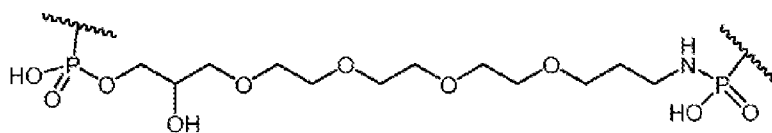
E211. The molecule of E204, wherein L includes a structure of Formula L1, wherein Formula L1 is:



35

(Formula L1)

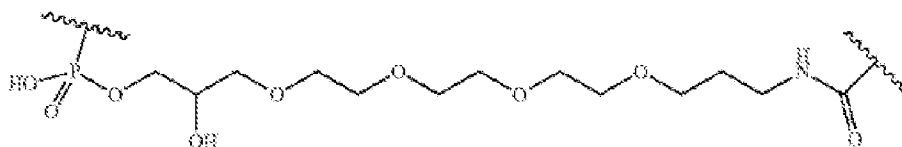
E212. The molecule of E204, wherein L includes a structure of Formula L2, wherein Formula L2 is:



(Formula L2)

E213. The molecule of E204, wherein L includes a structure of Formula L3, wherein Formula L3 is:

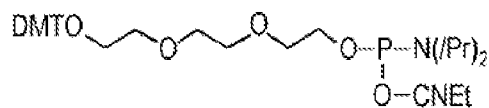
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(Formula L3)

E214. The molecule of E204, wherein L includes a structure of Formula L4, wherein Formula L4 is:

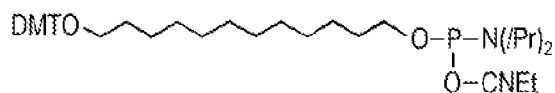
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(Formula L4)

E215. The molecule of E204, wherein L includes a structure of Formula L5, wherein Formula L5 is:

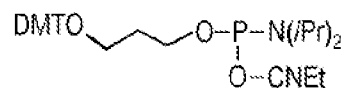
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(Formula L5)

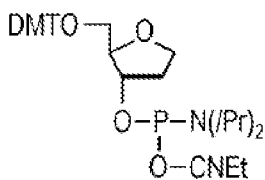
E216. The molecule of E204, wherein L includes a structure of Formula L6, wherein Formula L6 is:

20



(Formula L6)

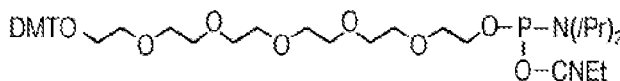
E217. The molecule of E204, wherein L includes a structure of Formula L7, wherein Formula L7 is:



(Formula L7)

5

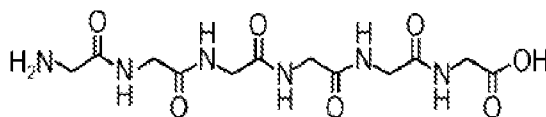
E218. The molecule of E204, wherein L includes a structure of Formula L8, wherein Formula L8 is:



(Formula L8)

10

E219. The molecule of E204, wherein L includes a structure of Formula L9, wherein Formula L9 is:



(Formula L9)

15

E220. The molecule of any one of E204-E210, wherein each P is independently selected from phosphodiester and phosphorothioate.

E221. The molecule of any one of E204-E141, wherein n is from 1 to 4.

E222. The molecule of any one of E204-E142, wherein n is from 1 to 3.

20 E223. The molecule of any one of E204-E143, wherein n is from 1 to 2.

E224. The molecule of any one of E204-E144, wherein n is 1.

E225. The molecule of any one of E204-E145, wherein m is from 1 to 4.

E226. The molecule of any one of E204-E146, wherein m is from 1 to 3.

E227. The molecule of any one of E204-E147, wherein m is from 1 to 2.

25 E228. The molecule of any one of E204-E148, wherein m is 1.

E229. The molecule of any one of E204-E149, wherein n and m are each 1.

E230. The molecule of any one of E204-E150, wherein 10% or less of the ribonucleosides are 2'-O-Me ribonucleoside.

E231. The molecule of any one of E204-E151, wherein at least 10% of the ribonucleosides are 2'-O-Me ribonucleoside.

30

E232. The molecule of any one of E204-E152, wherein at least 20% of the ribonucleosides are 2'-O-Me ribonucleoside.

E233. The molecule of any one of E204-E153, wherein at least 30% of the ribonucleosides are 2'-O-Me ribonucleoside.

- E234. The molecule of any one of E204-E154, wherein at least 40% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E235. The molecule of any one of E204-E155, wherein at least 50% of the ribonucleosides are 2'-O-Me ribonucleoside.
- 5 E236. The molecule of any one of E204-E156, wherein at least 60% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E237. The molecule of any one of E204-E157, wherein at least 70% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E238. The molecule of any one of E204-E158, wherein at least 80% of the ribonucleosides are 2'-O-Me
10 ribonucleoside.
- E239. The molecule of any one of E204-E159, wherein at least 90% of the ribonucleosides are 2'-O-Me ribonucleoside.
- E240. The molecule of any one of E204-E160, wherein 10% or less of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- 15 E241. The molecule of any one of E204-E161, wherein at least 10% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- E242. The molecule of any one of E204-E162, wherein at least 20% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- E243. The molecule of any one of E204-E163, wherein at least 30% of the internucleoside linkages are
20 phosphodiester linkages or phosphorothioate linkages.
- E244. The molecule of any one of E204-E164, wherein at least 40% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- E245. The molecule of any one of E204-E165, wherein at least 50% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- 25 E246. The molecule of any one of E204-E166, wherein at least 60% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- E247. The molecule of any one of E204-E167, wherein at least 70% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- E248. The molecule of any one of E204-E168, wherein at least 80% of the internucleoside linkages are
30 phosphodiester linkages or phosphorothioate linkages.
- E249. The molecule of any one of E204-E169, wherein at least 90% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- E250. The molecule of any one of E204-E170, wherein 100% of the internucleoside linkages are phosphodiester linkages or phosphorothioate linkages.
- 35 E251. The molecule of any one of E204-E250, wherein the length of the sense strand is between 12 and 30 nucleotides.
- E252. The molecule of any one of E204-E251, wherein the length of the sense strand is between 14 and 28 nucleotides.
- E253. The molecule of any one of E204-E252, wherein the length of the sense strand is between 16 and
40 26 nucleotides.
- E254. The molecule of any one of E204-E253, wherein the length of the sense strand is between 18 and 24 nucleotides.

- E255. The molecule of any one of E204-E251, wherein the length of the sense strand is 14 nucleotides.
- E256. The molecule of any one of E204-E251, wherein the length of the sense strand is 15 nucleotides.
- E257. The molecule of any one of E204-E251, wherein the length of the sense strand is 16 nucleotides.
- E258. The molecule of any one of E204-E251, wherein the length of the sense strand is 17 nucleotides.
- 5 E259. The molecule of any one of E204-E251, wherein the length of the sense strand is 18 nucleotides.
- E260. The molecule of any one of E204-E251, wherein the length of the sense strand is 19 nucleotides.
- E261. The molecule of any one of E204-E251, wherein the length of the sense strand is 20 nucleotides.
- E262. The molecule of any one of E204-E251, wherein the length of the sense strand is 21 nucleotides.
- E263. The molecule of any one of E204-E251, wherein the length of the sense strand is 22 nucleotides.
- 10 E264. The molecule of any one of E204-E251, wherein the length of the sense strand is 23 nucleotides.
- E265. The molecule of any one of E204-E251, wherein the length of the sense strand is 24 nucleotides.
- E266. The molecule of any one of E204-E251, wherein the length of the sense strand is 25 nucleotides.
- E267. The molecule of any one of E204-E251, wherein the length of the sense strand is 26 nucleotides.
- E268. The molecule of any one of E204-E251, wherein the length of the sense strand is 27 nucleotides.
- 15 E269. The molecule of any one of E204-E251, wherein the length of the sense strand is 28 nucleotides.
- E270. The molecule of any one of E204-E251, wherein the length of the sense strand is 29 nucleotides.
- E271. The molecule of any one of E204-E251, wherein the length of the sense strand is 30 nucleotides.
- E272. The molecule of any one of E204-E271, wherein 4 internucleoside linkages are phosphorothioate.
- E273. A method of treating a subject diagnosed as having a disease associated with expression of a
- 20 dysregulated microglial gene, the method comprising administering to the subject the branched siRNA molecule of any one of E149-E271.
- E274. The method of any one of E11-E148 or E273, wherein the disease is a neuroinflammatory disease.
- E275. The method of any one of E11-E148, E273, or E274, wherein the disease is a neurodegenerative
- 25 disease.
- E276. The method of any one of E11-E148 or E273-E275, wherein the disease is Alzheimer's disease.
- E277. The method of any one of E11-E148 or E273-E275, wherein the disease is Amyotrophic Lateral Sclerosis.
- E278. The method of any one of E11-E148 or E273-E275, wherein the disease is Parkinson's disease.
- 30 E279. The method of any one of E11-E148 or E273-E275, wherein the disease is frontotemporal dementia.
- E280. The method of any one of E11-E148 or E273-E275, wherein the disease is Huntington's disease.
- E281. The method of any one of E11-E148 or E273-E275, wherein the disease is multiple sclerosis.
- E282. The method of any one of E11-E148 or E273-E275, wherein the disease is progressive
- 35 supranuclear palsy.
- E283. The method of any one of E273, wherein the dysregulated microglial gene is selected from the group consisting of ABCA7, ABI3, ADAM10, APOC1, APOE, AXL, BIN1, C1QA, C3, C9ORF72, CASS4, CCL5, CD2AP, CD33, CD68, CLPTM1, CLU, CR1, CSF1, CST7, CTSB, CTSD, CTSL, CXCL10, CXCL13, DSG2, ECHDC3, EPHA1, FABP5, FERMT2, FTH1, GNAS, GRN, HBEGF,
- 40 HLA-DRB1, HLA-DRB5, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IGF1, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, ITGAX, LILRB4, LPL, MEF2C, MMP12, MS4A4A, MS4A6A, NLRP3,

NME8, NOS2, PICALM, PILRA, PLCG2, PTK2B, SCIMP, SLC24A4, SORL1, SPI1, SPP1, SPPL2A, TBK1, TNF, TREM2, TREML2, TYROBP, and ZCWPW1.

E284. The method of E273, wherein the administering of the branched siRNA molecule to the subject results in silencing of a microglial gene in the subject.

5 E285. The method of E284, wherein silencing of a microglial gene comprises silencing of any one of the genes selected from group consisting of APOE, BIN1, C1QA, C3, C9ORF72, CCL5, CD33, CLU/APOJ, CR1, CXCL10, CXCL13, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, MEF2C, MMP12, NLRP3, NOS2, PILRA, PLCG2, PTK2B, SLC24A4, TBK1, and TNF.

10 E286. The method of E273, wherein the microglial gene is an overactive disease driver gene (e.g., a dysregulated microglial gene).

E287. The method of E273, wherein the gene is a positive regulator of a gene for which increased expression and/or activity relative to the level of expression and/or activity observed in a reference subject is associated with a disease state.

15 E288. The method of E273, wherein the gene is a negative regulator of a gene for which decreased expression and/or activity relative to the level of expression and/or activity observed in a reference subject is associated with a disease state.

E289. The method of E273, wherein the gene is a splice isoform of a gene for which overexpression of the splice isoform relative to the expression of the splice isoform in a reference subject is
20 associated with a disease state.

E290. The method of any one of E273-E289, wherein the subject is a human.

OTHER EMBODIMENTS

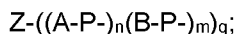
25 Various modifications and variations of the described disclosure will be apparent to those skilled in the art without departing from the scope and spirit of the disclosure. Although the disclosure has been described in connection with specific embodiments, it should be understood that the disclosure as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the disclosure that are obvious to those skilled in the art are intended to be within the scope of the disclosure.

30 Other embodiments are in the claims.

CLAIMS

1. A method of delivering a branched small interfering RNA (siRNA) molecule to a microglial cell in a subject in need of microglial gene silencing, the method comprising administering the branched siRNA molecule to the central nervous system of the subject.
2. The method of claim 1, wherein the subject has been diagnosed as having a disease associated with expression of a dysregulated microglial gene or dysregulated microglial gene pathway.
3. The method of claim 2, wherein the dysregulated microglial gene exhibits increased expression and/or activity in microglial cells of the subject as compared to the expression and/or activity of the microglial gene in microglial cells of a reference subject.
4. The method of claim 2, wherein the dysregulated microglial gene exhibits reduced expression and/or activity in microglial cells of the subject as compared to the expression and/or activity of the microglial gene in microglial cells of a reference subject.
5. The method of claim 1, wherein the microglial gene is a positive regulator of a gene for which increased expression and/or activity relative to the level of expression and/or activity observed in a reference subject is associated with a disease state.
6. The method of claim 1, wherein the microglial gene is a negative regulator of a gene for which decreased expression and/or activity relative to the level of expression and/or activity observed in a reference subject is associated with a disease state.
7. The method of claim 1, wherein the microglial gene is a splice isoform of a gene for which overexpression of the splice isoform relative to the expression of the splice isoform in a reference subject is associated with a disease state.
8. The method of any one of claims 2-7, wherein the disease is a neuroinflammatory or neurodegenerative disease.
9. The method of any one of claims 1-8, wherein the dysregulated gene is selected from the group consisting of ABCA7, ABI3, ADAM10, APOC1, APOE, AXL, BIN1, C1QA, C3, C9ORF72, CASS4, CCL5, CD2AP, CD33, CD68, CLPTM1, CLU, CR1, CSF1, CST7, CTSB, CTSD, CTSL, CXCL10, CXCL13, DSG2, ECHDC3, EPHA1, FABP5, FERMT2, FTH1, GNAS, GRN, HBEGF, HLA-DRB1, HLA-DRB5, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IGF1, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, ITGAX, LILRB4, LPL, MEF2C, MMP12, MS4A4A, MS4A6A, NLRP3, NME8, NOS2, PICALM, PILRA, PLCG2, PTK2B, SCIMP, SLC24A4, SORL1, SPI1, SPP1, SPPL2A, TBK1, TNF, TREM2, TREML2, TYROBP, and ZCWPW1.
10. The method of any one of claims 1-9, wherein the subject is a human.

11. The method of any one of claims 1-10, wherein the branched siRNA is administered to the subject intrathecally, intracerebroventricularly, or intrastratially.
12. The method of any one of claims 1-11, wherein the siRNA molecule is di-branched.
13. The method of any one of claims 1-12, wherein the siRNA comprises (i) an antisense strand having complementarity to one or more of genes selected from the group consisting of APOE, BIN1, C1QA, C3, C9ORF72, CCL5, CD33, CLU/APOJ, CR1, CXCL10, CXCL13, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, MEF2C, MMP12, NLRP3, NOS2, PILRA, PLCG2, PTK2B, SLC24A4, TBK1, and TNF, and (ii) a sense strand having complementarity to the antisense strand.
14. The method of claim 13, wherein the antisense strand has the following formula, in the 5'-to-3' direction:



wherein Z is a 5' phosphorus stabilizing moiety;

each A is, independently, a 2'-O-methyl (2'-O-Me) ribonucleoside;

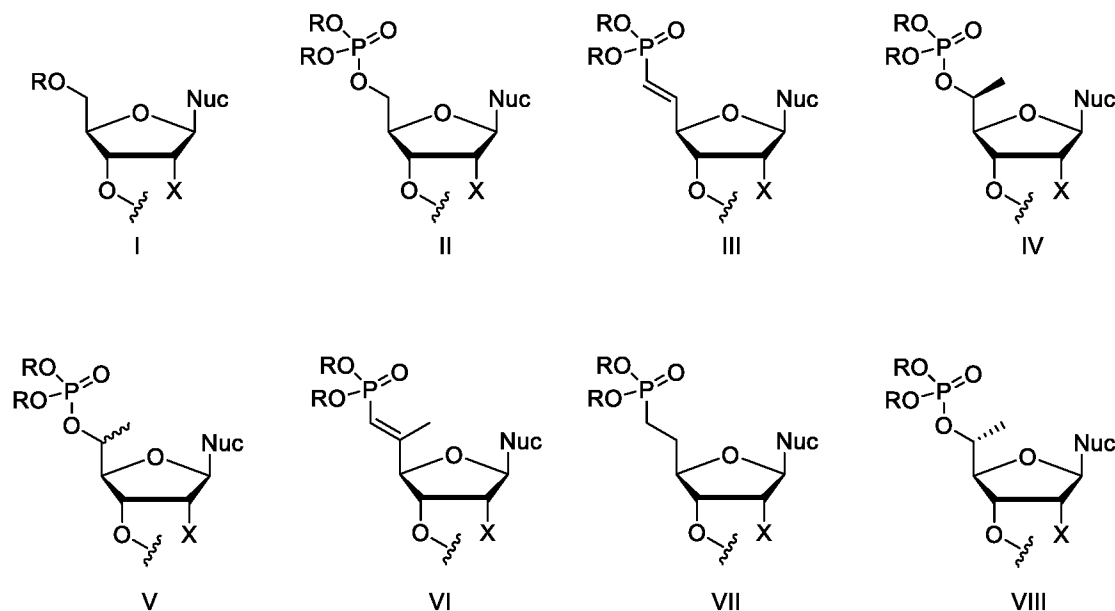
each B is, independently, a 2'-fluoro (2'-F) ribonucleoside;

each P is, independently, an internucleoside linkage selected from a phosphodiester linkage and a phosphorothioate linkage;

n is an integer from 1 to 5;

m is an integer from 1 to 5; and q is an integer between 1 and 15

15. The method of claim 14, wherein Z is represented in any one of Formula I-VIII:



wherein Nuc represents a nucleobase selected from the group consisting of adenine, uracil, guanine, thymine, and cytosine, and R represents optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, phenyl, benzyl, hydroxy, or hydrogen.

16. The method of claim 14 or 15, wherein Z is (E)-vinylphosphonate represented in Formula III.

17. The method of any one of claims 13-16, wherein at least 50% of the ribonucleosides are 2'-O-Me ribonucleoside.

18. The method of any one of claims 13-17, wherein at least 60% of the ribonucleosides are 2'-O-Me ribonucleoside.

19. The method of any one of claims 13-18, wherein at least 70% of the ribonucleosides are 2'-O-Me ribonucleoside.

20. The method of any one of claims 13-19, wherein at least 80% of the ribonucleosides are 2'-O-Me ribonucleoside.

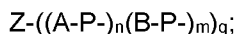
21. The method of any one of claims 13-20, wherein at least 90% of the ribonucleosides are 2'-O-Me ribonucleoside.

22. The method of any one of claims 13-21, wherein the length of the antisense strand is between 10 and 30 nucleotides.

23. The method of any one of claims 13-22, wherein the length of the antisense strand is between 15 and 25 nucleotides.

24. The method of claim 23, wherein the length of the antisense strand is 20 nucleotides.
25. The method of claim 23, wherein the length of the antisense strand is 21 nucleotides.
26. The method of claim 23, wherein the length of the antisense strand is 22 nucleotides.
27. The method of claim 23, wherein the length of the antisense strand is 23 nucleotides.
28. The method of claim 23, wherein the length of the antisense strand is 24 nucleotides.
29. The method of claim 23, wherein the length of the antisense strand is 25 nucleotides.
30. The method of claim 22, wherein the length of the antisense strand is 26 nucleotides.
31. The method of claim 22, wherein the length of the antisense strand is 27 nucleotides.
32. The method of claim 22, wherein the length of the antisense strand is 28 nucleotides.
33. The method of claim 22, wherein the length of the antisense strand is 29 nucleotides.
34. The method of claim 22, wherein the length of the antisense strand is 30 nucleotides.
35. The method of any one of claims 13-34, wherein the length of the sense strand is between 12 and 30 nucleotides.
36. The method of claim 35, wherein the length of the sense strand is 14 nucleotides.
37. The method of claim 35, wherein the length of the sense strand is 15 nucleotides.
38. The method of claim 35, wherein the length of the sense strand is 16 nucleotides
39. The method of claim 35, wherein the length of the sense strand is 17 nucleotides.
40. The method of claim 35, wherein the length of the sense strand is 18 nucleotides.
41. The method of claim 35, wherein the length of the sense strand is 19 nucleotides.
42. The method of claim 35, wherein the length of the sense strand is 20 nucleotides.
43. The method of claim 35, wherein the length of the sense strand is 21 nucleotides.
44. The method of claim 35, wherein the length of the sense strand is 22 nucleotides.

45. The method of claim 35, wherein the length of the sense strand is 23 nucleotides.
46. The method of claim 35, wherein the length of the sense strand is 24 nucleotides.
47. The method of claim 35, wherein the length of the sense strand is 25 nucleotides.
48. The method of claim 35, wherein the length of the sense strand is 26 nucleotides.
49. The method of claim 35, wherein the length of the sense strand is 27 nucleotides.
50. The method of claim 35, wherein the length of the sense strand is 28 nucleotides.
51. The method of claim 35, wherein the length of the sense strand is 29 nucleotides.
52. The method of claim 35, wherein the length of the sense strand is 30 nucleotides.
53. A branched siRNA molecule comprising a sense strand and an antisense strand, wherein the antisense strand comprises a region having complementarity to a segment of contiguous nucleotides within a gene selected from the group consisting of APOE, BIN1, C1QA, C3, C9ORF72, CCL5, CD33, CLU/APOJ, CR1, CXCL10, CXCL13, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, MEF2C, MMP12, NLRP3, NOS2, PILRA, PLCG2, PTK2B, SLC24A4, TBK1, and TNF.
54. The molecule of claim 53, wherein the antisense strand has complementarity to a portion of a gene encoding a positive regulator of a gene for which increased expression and/or activity relative to the level of expression and/or activity observed in a reference subject is associated with a disease state.
55. The molecule of claim 53, wherein the antisense strand has complementarity to a portion of a gene encoding a negative regulator of a gene for which decreased expression and/or activity relative to the level of expression and/or activity observed in a reference subject is associated with a disease state.
56. The molecule of claim 53, wherein the antisense strand has complementarity to a splice isoform of a gene for which overexpression of the splice isoform relative to the expression of the splice isoform in a reference subject is associated with a disease state.
57. The molecule of any one of claims 53-56, wherein the sense strand has complementarity to the antisense strand.
58. The molecule of any one of claims 53-57, wherein the siRNA molecule is di-branched.
59. The molecule of any one of claims 53-58, wherein the antisense strand of the branched siRNA has the following formula in the 5'-to-3' direction:



wherein Z is a 5' phosphorus stabilizing moiety;

each A is, independently, a 2'-O-Me ribonucleoside;

each B is, independently, a 2'-F ribonucleoside;

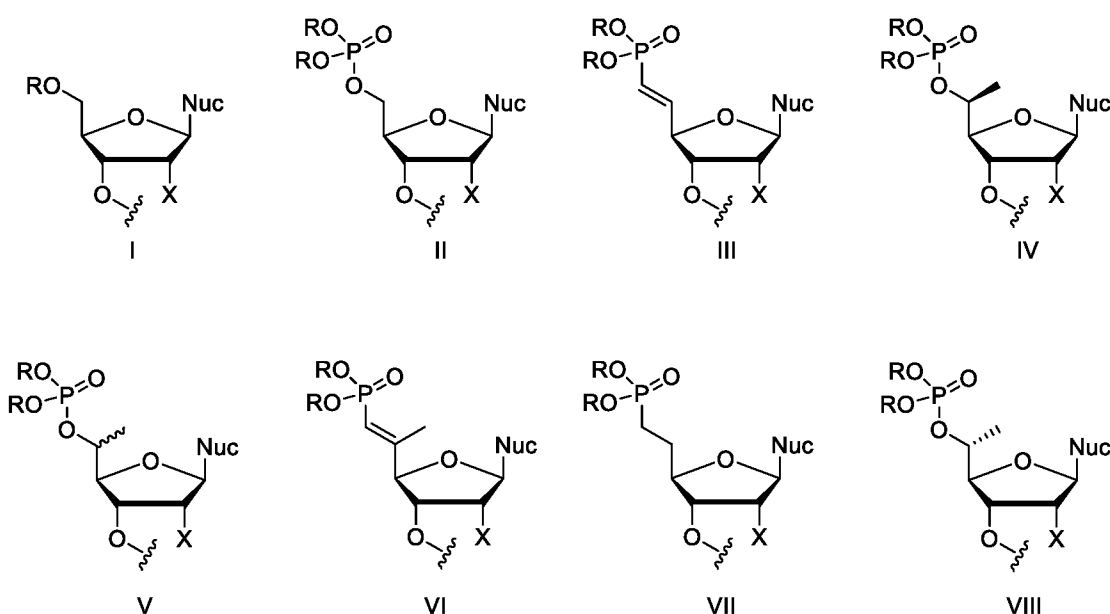
each P is, independently, an internucleoside linkage selected from a phosphodiester linkage and a phosphorothioate linkage;

n is an integer from 1 to 5;

m is an integer from 1 to 5; and

q is an integer between 1 and 15.

60. The molecule of claim 59, wherein Z is represented in any one of Formula I-VIII:



wherein Nuc represents a nucleobase selected from the group consisting of adenine, uracil, guanine, thymine, and cytosine, and R represents optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, phenyl, benzyl, hydroxy, or hydrogen.

61. The molecule of claim 59 or 60, wherein Z is (E)-vinylphosphonate as represented in Formula III.

62. The molecule of any one of claims 53-61, wherein the length of the antisense strand is between 10 and 30 nucleotides.

63. The molecule of claim 62, wherein the length of the antisense strand is between 15 and 30 nucleotides.

64. The molecule of claim 62, wherein the length of the antisense strand is 20 nucleotides.

65. The molecule of claim 62, wherein the length of the antisense strand is 21 nucleotides.
66. The molecule of claim 62, wherein the length of the antisense strand is 22 nucleotides.
67. The molecule of claim 62, wherein the length of the antisense strand is 23 nucleotides.
68. The molecule of claim 62, wherein the length of the antisense strand is 24 nucleotides.
69. The molecule of claim 62, wherein the length of the antisense strand is 25 nucleotides.
70. The molecule of claim 62, wherein the length of the antisense strand is 26 nucleotides.
71. The molecule of claim 62, wherein the length of the antisense strand is 27 nucleotides.
72. The molecule of claim 62, wherein the length of the antisense strand is 28 nucleotides.
73. The molecule of claim 62, wherein the length of the antisense strand is 29 nucleotides.
74. The molecule of claim 62, wherein the length of the antisense strand is 30 nucleotides.
75. The molecule of any one of claims 53-74, wherein the length of the sense strand is between 12 and 30 nucleotides.
76. The molecule of claim 75, wherein the length of the sense strand is 14 nucleotides.
77. The molecule of claim 75, wherein the length of the sense strand is 15 nucleotides.
78. The molecule of claim 75, wherein the length of the sense strand is 16 nucleotides
79. The molecule of claim 75, wherein the length of the sense strand is 17 nucleotides.
80. The molecule of claim 75, wherein the length of the sense strand is 18 nucleotides.
81. The molecule of claim 75, wherein the length of the sense strand is 19 nucleotides.
82. The molecule of claim 75, wherein the length of the sense strand is 20 nucleotides.
83. The molecule of claim 75, wherein the length of the sense strand is 21 nucleotides.
84. The molecule of claim 75, wherein the length of the sense strand is 22 nucleotides.
85. The molecule of claim 75, wherein the length of the sense strand is 23 nucleotides.

86. The molecule of claim 75, wherein the length of the sense strand is 24 nucleotides.
87. The molecule of claim 75, wherein the length of the sense strand is 25 nucleotides.
88. The molecule of claim 75, wherein the length of the sense strand is 26 nucleotides.
89. The molecule of claim 75, wherein the length of the sense strand is 27 nucleotides.
90. The molecule of claim 75, wherein the length of the sense strand is 28 nucleotides.
91. The molecule of claim 75, wherein the length of the sense strand is 29 nucleotides.
92. The molecule of claim 75, wherein the length of the sense strand is 30 nucleotides.
93. A method of treating a subject diagnosed as having a disease associated with expression of a dysregulated microglial gene or dysregulated microglial gene pathway, the method comprising administering to the subject the branched siRNA molecule of any one of claims 53-92.
94. The method of claim 93, wherein the dysregulated microglial gene is selected from the group consisting of ABCA7, ABI3, ADAM10, APOC1, APOE, AXL, BIN1, C1QA, C3, C9ORF72, CASS4, CCL5, CD2AP, CD33, CD68, CLPTM1, CLU, CR1, CSF1, CST7, CTSB, CTSD, CTSL, CXCL10, CXCL13, DSG2, ECHDC3, EPHA1, FABP5, FERMT2, FTH1, GNAS, GRN, HBEGF, HLA-DRB1, HLA-DRB5, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IGF1, IL10RA, IL1A, IL1B, IL1RAP, INPP5D, ITGAM, ITGAX, LILRB4, LPL, MEF2C, MMP12, MS4A4A, MS4A6A, NLRP3, NME8, NOS2, PICALM, PILRA, PLCG2, PTK2B, SCIMP, SLC24A4, SORL1, SPI1, SPP1, SPPL2A, TBK1, TNF, TREM2, TREML2, TYROBP, and ZCWPW1.
95. The method of claim 93, wherein the dysregulated microglial gene exhibits increased expression and/or activity in microglial cells of the subject as compared to the expression and/or activity of the same gene in microglial cells of a reference subject.
96. The method of claim 93, wherein the dysregulated microglial gene exhibits reduced expression and/or activity in microglial cells of the subject as compared to the expression and/or activity of the same gene in microglial cells of a reference subject.
97. The method of claim 93, wherein the administering of the branched siRNA molecule to the subject results in silencing of a gene in the subject.
98. The method of claim 97, wherein the silencing of a gene comprises silencing any one of the genes selected from the group consisting of APOE, BIN1, C1QA, C3, C9ORF72, CCL5, CD33, CLU/APOJ, CR1, CXCL10, CXCL13, IFIT1, IFIT3, IFITM3, IFNAR1, IFNAR2, IL10RA, IL1A, IL1B,

IL1RAP, INPP5D, ITGAM, MEF2C, MMP12, NLRP3, NOS2, PILRA, PLCG2, PTK2B, SLC24A4, TBK1, and TNF.

99. The method of claim 97, wherein silencing of a gene comprises silencing of a positive regulator of a gene for which increased expression and/or activity relative to the level of expression and/or activity observed in a reference subject is associated with a disease state.

100. The method of claim 97, wherein silencing of a gene comprises silencing of a gene for which decreased expression and/or activity relative to the level of expression and/or activity observed in a reference subject is associated with a disease state.

101. The method of claim 97, wherein silencing of a gene comprises silencing of a splice isoform of a gene for which overexpression of the splice isoform relative to the expression of the splice isoform in a reference subject is associated with a disease state.

102. The method of any one of claims 93-101, wherein the subject is a human.

FIG. 1A

Cortex

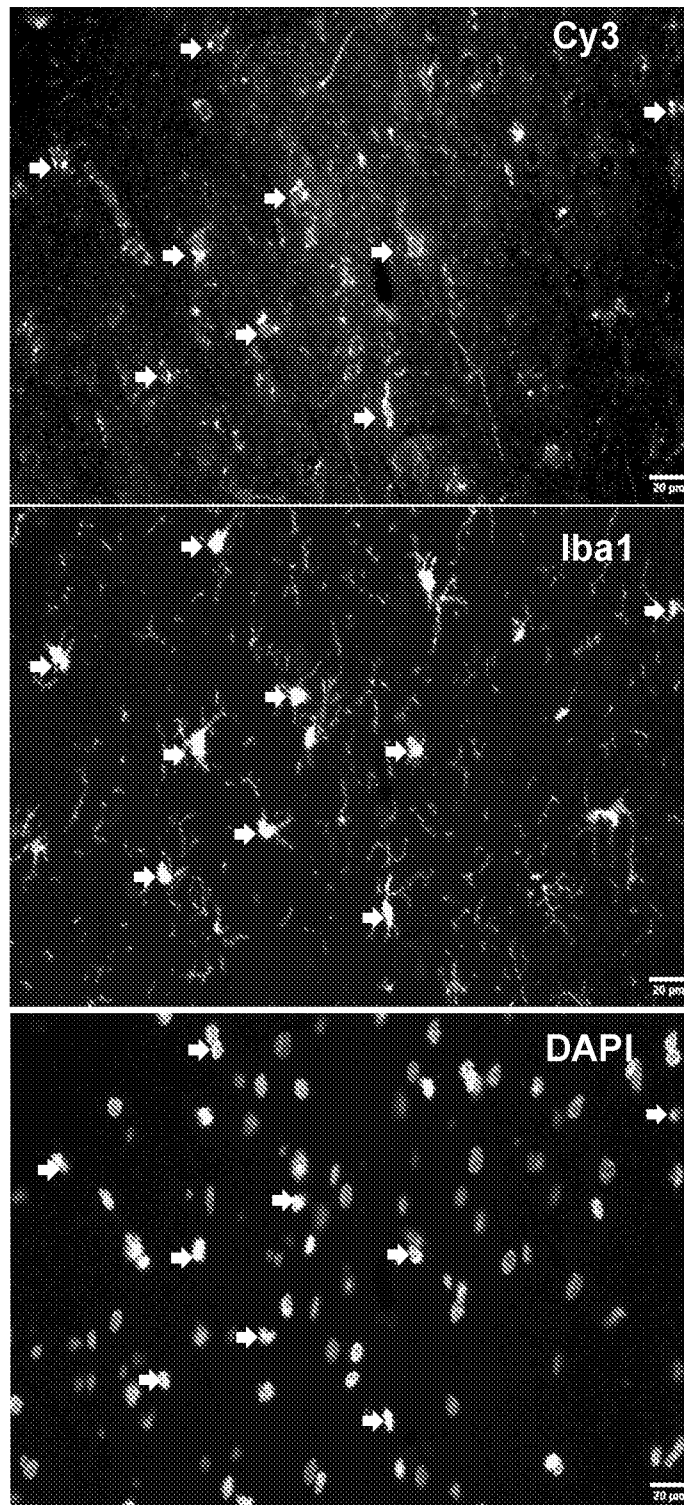


FIG. 1B

Hippocampus

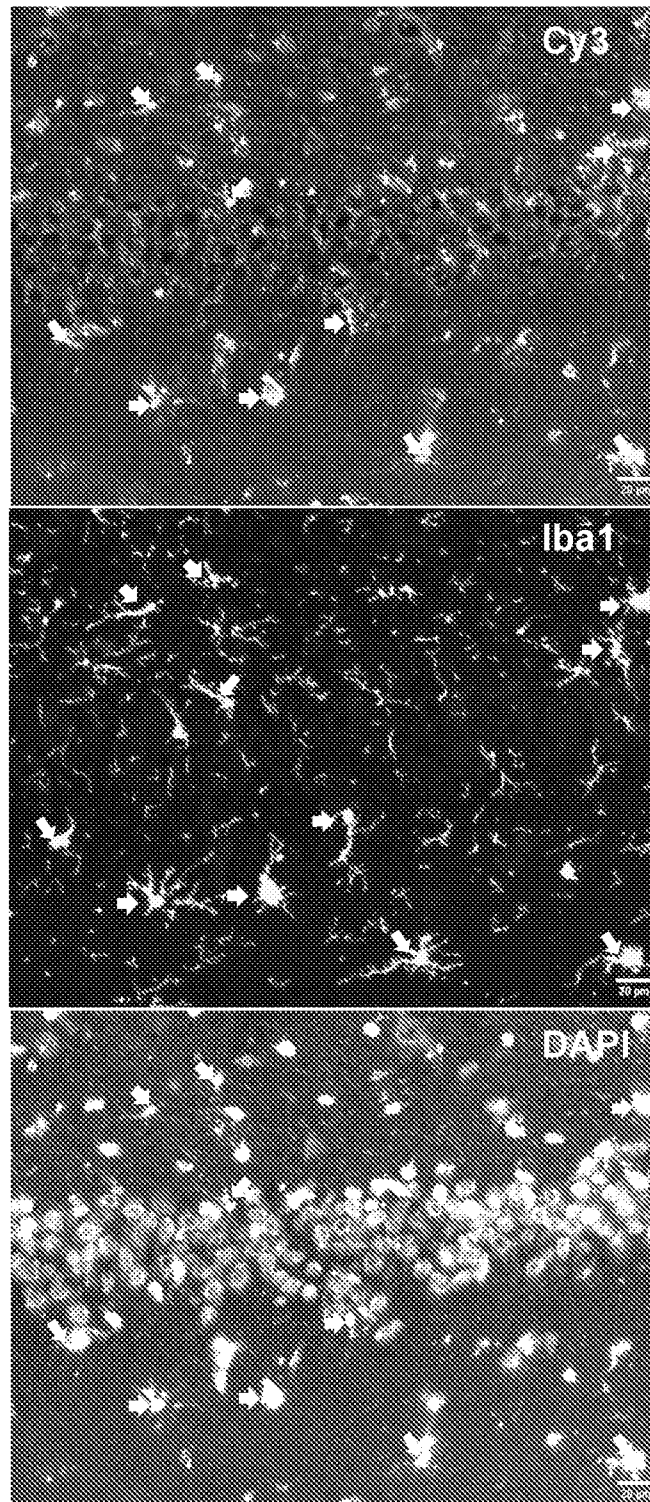


FIG. 1C

Caudate

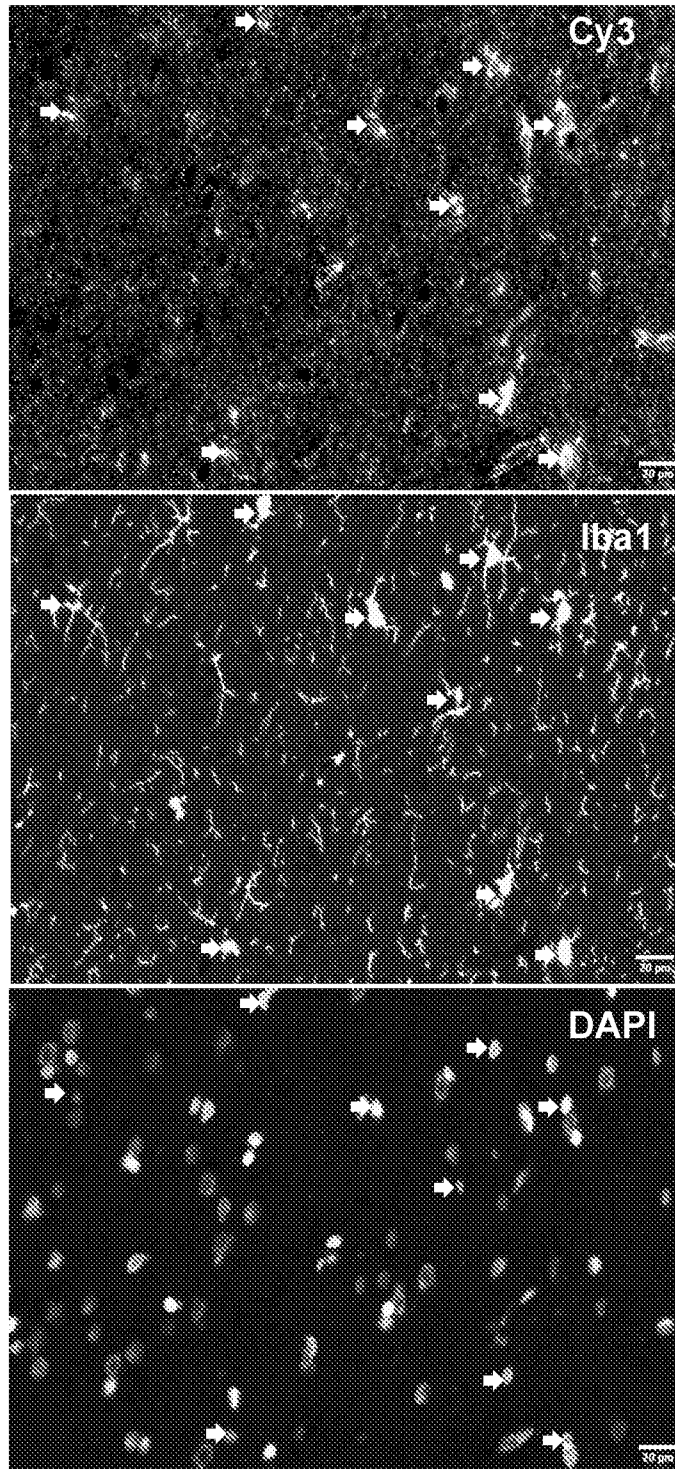
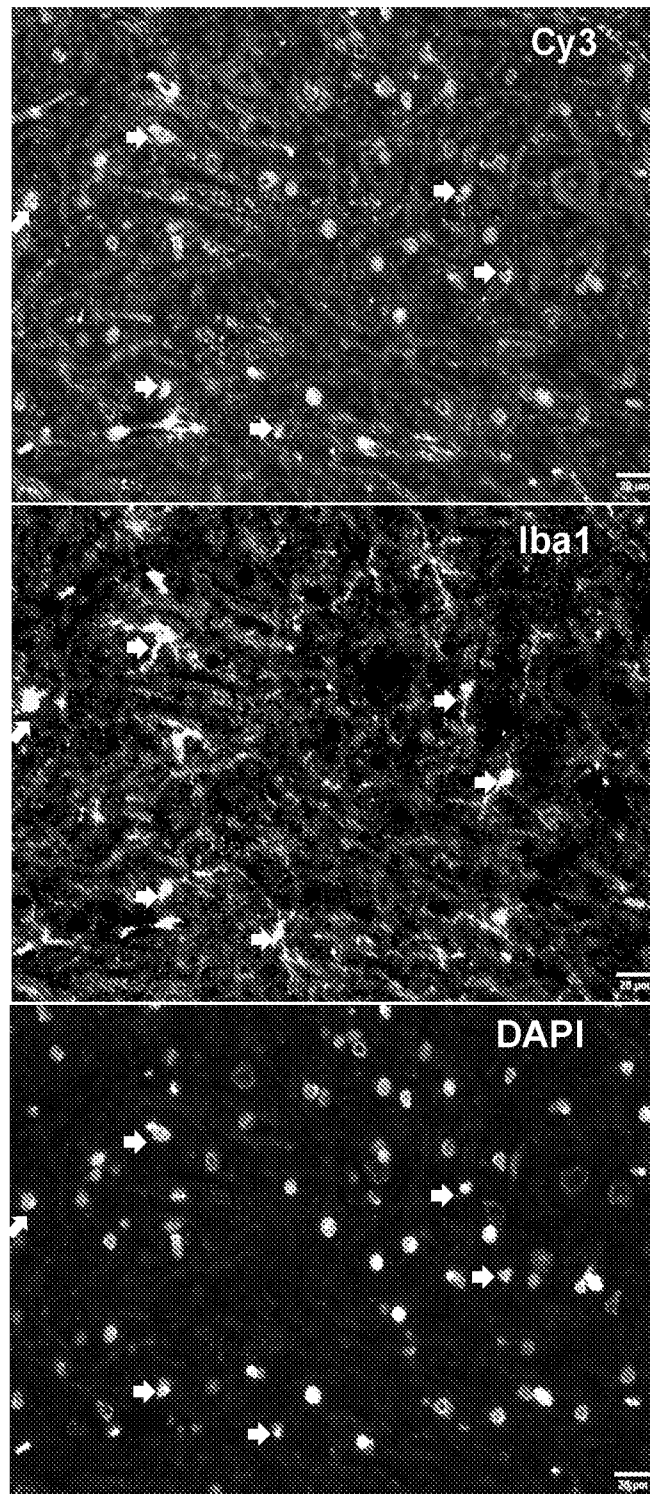


FIG. 1D

Spinal Cord



INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/021789

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/7084; A61K 31/713; A61P 25/00; A61P 25/14; A61P 43/00; C12N 15/11 (2022.01)
 CPC - A61K 31/7084; C12N 15/11; C12N 15/113; C12N 2310/11; C12N 2310/14; C12N 2310/315;
 C12N 2310/321; C12N 2310/322; C12N 2310/343; C12N 2310/344; C12N 2310/346; C12N
 2310/3513; C12N 2310/52; C12N 2320/32; C12N 2320/51 (2022.05)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 see Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
 see Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 see Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 10,799,591 B2 (UNIVERSITY OF MASSACHUSETTS) 13 October 2020 (13.10.2020) entire document	1, 2 --- 3-8, 53-57
Y	FERNANDEZ et al. The role of APOE4 in disrupting homeostatic functions of astrocytes and microglia in aging and Alzheimer's disease, Front. Aging Neurosci., 11 February 2019, Vol. 11, No. 14, Pgs. 1-18. Entire document	3, 54
Y	BONHAM et al. The transcriptional landscape of microglial genes in aging and neurodegenerative disease, Front. Immunol., 4 June 2019, Vol. 10, No. 1170, Pgs. 1-17. Entire document	4
Y	GAO et al., Transcriptional regulation of homeostatic and disease-associated-microglial genes by IRF1, LXRβ, and CEBPα, Glia, October 2019, Vol. 67, No. 10, Pgs. 1958-1975. Entire document	5, 8
Y	LEE et al. Regulator of G-protein signaling-10 negatively regulates NF-κB in microglia and neuroprotects dopaminergic neurons in hemiparkinsonian rats, J. Neurosci., 17 August 2011, Vol. 31, No. 33, Pgs. 11879-88. Entire document	6, 55
Y	MRAK et al., Interleukin-1 and the immunogenetics of Alzheimer disease, J. Neuropathol. Exp. Neurol., June 2000, Vol. 59, No. 6, Pgs. 471-6. Entire document	7, 56

☒ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"D" document cited by the applicant in the international application

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

24 May 2022

Date of mailing of the international search report

JUN 27 2022

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
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Taina Matos

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/021789

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ALTERMAN et al. A divalent siRNA chemical scaffold for potent and sustained modulation of gene expression throughout the central nervous system, Nat. Biotechnol., August 2019, Vol. 37, No. 8, Pgs. 884-894. Entire document	53-57
A	MOUMNE et al. Multiple aspects of gene dysregulation in Huntington's disease, Front. Neurol., 23 October 2013, Vol. 4, No. 127, Pgs. 1-10. Entire document	1-8, 53-57

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2022/021789

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

- a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
- b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
- c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 9-52, 58-102
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.