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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 January 2015 (15.01.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/006498 A2

(51) International Patent Classification:
A61K 48/00 (2006.01)

(21) International Application Number:
PCT/US2014/046034

(22) International Filing Date:
9 July 2014 (09.07.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/844,333 9 July 2013 (09.07.2013) US
61/869,369 23 August 2013 (23.08.2013) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,

[Continued on next page]

(54) Title: THERAPEUTIC USES OF GENOME EDITING WITH CRISPR/CAS SYSTEMS

(57) Abstract: Disclosed herein are methods, compositions, and kits for high efficiency, site-specific genomic editing of cells for treating or preventing genetic blood disorders.

1 MDKKYSIGLD IGTNSVGWAV ITDEYKVPSK KFKVLGNTDR HSIKKNLIGA LLFDSGETAE

61 ATRLKRTARR RYTRRKNRIC YLQEIFSNEM AKVDDSFFHR LEESFLVEED KKHERHPIFG

121 NIVDEVAYHE KYPTIYHLRK KLVDSTDKAD LRLIYLALAH MIKFRGHFLI EGDLNPDNSD

181 VDKLFIQLVQ TYNQLFEENP INASGVDAKA ILSARLSKSR RLENLIAQLP GEKKNGLFGN

241 LIALSLGLTP NFKSNFDLAE DAKLQLSKDT YDDDLDNLLA QIGDQYADLF LAAKNLSDAI

301 LLSDILRVNT EITKAPLSAS MIKRYDEHHQ DLTLLKALVR QQLPEKYKEI FFDQSKNGYA

361 GYIDGGASQE EFYKFIKPIL EKMDGTEELL VKLNREDLLR KQRTFDNGSI PHQIHLGELH

421 AILRRQEDFY PFLKDNREKI EKILTFRIPY YVGPLARGNS RFAWMTRKSE ETITPWNFEE

481 VVDKGASAQS FIERMTNFDK NLPNEKVLPK HSLLYEYFTV YNELTKVKYV TEGMRKPAFL

541 SGEQKKAIVD LLFKTNRKVT VKQLKEDYFK KIECFDSVEI SGVEDRFNAS LGTYHDLLKI

601 IKDKDFLDNE ENEDILEDIV LTLTLFEDRE MIEERLKTYA HLFDDKVMKQ LKRRRYTGWG

661 RLSRKLINGI RDKQSGKTIL DFLKSDGFAN RNFMQLIHDD SLTFKEDIQK AQVSGQGDSL

721 HEHIANLAGS PAIKKGILQT VKVVDELVKV MGRHKPENIV IEMARENQTT QKGQKNSRER

781 MKRIEEGIKE LGSQILKEHP VENTQLQNEK LYLYYLQNGR DMYVDQELDI NRLSDYDVDH

841 IVPQSFLKDD SIDNKVLTRS DKNRGKSDNV PSEEVVKKMK NYWRQLLNAK LITQRKFDNL

901 TKAERGGLSE LDKAGFIKRQ LVETRQITKH VAQILDSRMN TKYDENDKLI REVKVITLKS

961 KLVSDFRKDF QFYKVREINN YHHAHDAYLN AVVGTALIKK YPKLESEFVY GDYKVYDVRK

1021 MIAKSEQEIG KATAKYFFYS NIMNFFKTEI TLANGEIRKR PLIETNGETG EIVWDKGRDF

1081 ATVRKVLSMP QVNIVKKTEV QTGGFSKESI LPKRNSDKLI ARKKDWDPKK YGGFDSPTVA

1141 YSVLVVAKVE KGKSKKLKSV KELLGITIME RSSFEKNPID FLEAKGYKEV KKDLIIKLPK

1201 YSLFELENGR KRMLASAGEL QKGNELALPS KYVNFLYLAS HYEKLKGSPE DNEQKQLFVE

1261 QHKHYLDEII EQISEFSKRV ILADANLDKV LSAYNKHRDK PIREQAENII HLFTLTNLGA

1321 PAAFKYFDTT IDRKRYTSTK EVLDATLIHQ SITGLYETRI DLSQLGGD (SEQ ID NO: 298)

FIG. 16

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DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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

Published:

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

THERAPEUTIC USES OF GENOME EDITING WITH CRISPR/Cas SYSTEMS

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Nos. 61/844,333, filed on July 9, 2013, and 61/869,369, filed on August 23, 2013. The entire teachings of the above applications are incorporated herein by reference.

GOVERNMENT SUPPORT

[0002] This invention was made with government support under HL118744, HL098364, DK095384 and HL107440 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) systems are a new class of genome-editing tools that target desired genomic sites in mammalian cells. Recently published type II CRISPR/Cas systems use Cas9 nuclease that is targeted to a genomic site by complexing with a synthetic guide RNA that hybridizes to a 20-nucleotide DNA sequence and immediately preceding an NGG motif recognized by Cas9 (thus, a $(N)_{20}$NGG target DNA sequence). This results in a double-strand break three nucleotides upstream of the NGG motif. The double strand break instigates either non-homologous end-joining, which is error-prone and conducive to frameshift mutations that knock out gene alleles, or homology-directed repair, which can be exploited with the use of an exogenously introduced double-strand or

Thus, CRISPR/Cas systems could be useful tools for therapeutic applications, but unfortunately prior published reports have demonstrated an efficiency of allele targeting of only 2%-4% in human stem cells (Mali *et al.*, *Science 339*:823-826 (2013)).

SUMMARY OF THE INVENTION

[0004] Work described herein demonstrates methods of allele targeting using CRISPR/Cas systems resulting in mutant cells with efficiencies of up to 80%. These vastly improved methods permit CRISPR/Cas systems to be utilized effectively for the first time for therapeutic purposes. Methods of delivery of CRISPR/Cas systems to human stem cells are provided. In addition, methods of specifically identifying useful RNA guide sequences are provided, along with particular guide sequences useful in targeting specific genes (e.g., ADA, AK2, CD3D, DCLRE1C, IL2RG, IL7R, JAK3, LIG4, NHEJ1, PNP, PRKDC, RAG1, RAG2, ZAP70 and HBB). Moreover, methods of treatment (e.g., severe combined immunodeficiency, sickle cell disease, e.g., sickle cell anemia, beta thalassemia, etc.) utilizing the compositions and methods disclosed herein are provided. In some aspects, disclosed herein is a method for altering a target severe combined immunodeficiency (SCID)-associated polynucleotide sequence in a cell comprising contacting the SCID-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved.

[0005] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence in a subject, the method comprising (a) altering a target SCID-associated polynucleotide sequence in a cell *ex vivo* by contacting the SCID-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequence.

subject, the method comprising altering a target SCID-associated polynucleotide sequence in a cell by contacting the SCID-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, and wherein the target SCID-associated polynucleotide sequence is cleaved, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequence.

[0007] In some aspects, disclosed herein is a method for simultaneously altering multiple target SCID-associated polynucleotide sequences in a cell comprising contacting the SCID-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved.

[0008] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCID-associated polynucleotide sequences in a cell *ex vivo* by contacting the SCID-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequences.

[0009] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject, the method comprising altering target SCID-associated polynucleotide sequences in a cell by contacting the SCID-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target moieties of the target SCID-associated polynucleotide sequences, and wherein the

preventing a disorder associated with expression of the SCID-associated polynucleotide sequences.

[0010] In some aspects, disclosed herein is a method for altering a target sickle cell disease (SCD)-associated polynucleotide sequence in a cell comprising contacting the SCD-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved.

[0011] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence in a subject, the method comprising (a) altering a target SCD-associated polynucleotide sequence in a cell *ex vivo* by contacting the SCD-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequence.

[0012] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence in a subject, the method comprising altering a target SCD-associated polynucleotide sequence in a cell by contacting the SCD-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, and wherein the target SCD-associated polynucleotide sequence is cleaved, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequence.

[0013] In some aspects, disclosed herein is a method for simultaneously altering multiple target SCD-associated polynucleotide sequences in a cell comprising contacting the SCD-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the

associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved.

[0014] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCD-associated polynucleotide sequences in a cell *ex vivo* by contacting the SCD-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequences.

[0015] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject, the method comprising altering target SCD-associated polynucleotide sequences in a cell by contacting the SCD-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target moieties of the target SCD-associated polynucleotide sequences, and wherein the target SCD-associated polynucleotide sequences are cleaved, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequences.

[0016] In some aspects, disclosed herein is a method for altering a target beta thalassemia-associated polynucleotide sequence in a cell comprising contacting the beta thalassemia-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved.

[0017] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence in a subject, the method comprising (a) altering a target beta thalassemia-

palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequence.

[0018] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence in a subject, the method comprising altering a target beta thalassemia-associated polynucleotide sequence in a cell by contacting the beta thalassemia-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, and wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequence.

[0019] In some aspects, disclosed herein is a method for simultaneously altering multiple target beta thalassemia-associated polynucleotide sequences in a cell comprising contacting the beta thalassemia-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved.

[0020] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject, the method comprising (a) altering target beta thalassemia-associated polynucleotide sequences in a cell *ex vivo* by contacting the beta thalassemia-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, and (b) introducing the cell into the

[0021] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject, the method comprising altering target beta thalassemia-associated polynucleotide sequences in a cell by contacting the beta thalassemia-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target moieties of the target beta thalassemia-associated polynucleotide sequences, and wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequences.

[0022] In some embodiments, the Cas protein is *Streptococcus pyogenes* Cas9 protein or a functional portion thereof. In some embodiments, the functional portion comprises a combination of operably linked Cas9 protein functional domains selected from the group consisting of a DNA binding domain, at least one RNA binding domain, a helicase domain, and an endonuclease domain. In some embodiments, the functional domains form a complex. In some embodiments, the Cas protein is Cas9 protein from any bacterial species or functional portion thereof. In some embodiments, the functional portion comprises a combination of operably linked Cas9 protein functional domains selected from the group consisting of a DNA binding domain, at least one RNA binding domain, a helicase domain, and an endonuclease domain. In some embodiments, the functional domains form a complex.

[0023] In some embodiments, the Cas protein is complexed with the one to two ribonucleic acids. In some embodiments, the Cas protein is complexed with the multiple ribonucleic acids.

[0024] In some embodiments, the target motif is a 20-nucleotide DNA sequence. In some embodiments, each target motif is a 20-nucleotide DNA sequence. In some embodiments, the target motif is a 20-nucleotide DNA sequence beginning with G and immediately precedes an NGG motif recognized by the Cas protein. In some embodiments, each target motif is a 20-nucleotide DNA sequence beginning with G and immediately precedes an NGG motif recognized by the Cas protein. In some embodiments, the target motif is a 20-nucleotide DNA sequence and immediately precedes an NGG motif recognized by the Cas protein. In some embodiments, each

some embodiments, each target motif is $G(N)_{19}NGG$. In some embodiments, the target motif is $(N)_{20}NGG$. In some embodiments, each target motif is $(N)_{20}NGG$.

[0025] In some embodiments, the target polynucleotide sequence is cleaved such that a double-strand break results. In some embodiments, each target polynucleotide sequence is cleaved such that a double-strand break results. In some embodiments, the target polynucleotide sequence is cleaved such that a single-strand break results. In some embodiments, each target polynucleotide sequence is cleaved such that a single-strand break results.

[0026] In some embodiments, the alteration is an indel. In some embodiments, the alteration results in reduced expression of the target polynucleotide sequence. In some embodiments, the alteration results in reduced expression of the target polynucleotide sequences. In some embodiments, the alteration results in a knock out of the target polynucleotide sequence. In some embodiments, the alteration results in a knock out of the target polynucleotide sequences. In some embodiments, the alteration results in correction of the target polynucleotide sequence from an undesired sequence to a desired sequence. In some embodiments, the alteration results in correction of the target polynucleotide sequences from undesired sequences to desired sequences. In some embodiments,the alteration is a homozygous alteration. In some embodiments, each alteration is a homozygous alteration.

[0027] In some embodiments, subsequent to cleavage of the target polynucleotide sequence, homology-directed repair occurs. In some embodiments, homology-directed repair is performed using an exogenously introduced DNA repair template. In some embodiments, the exogenously introduced DNA repair template is single-stranded. In some embodiments, the exogenously introduced DNA repair template is double-stranded. In some embodiments, subsequent to cleavage of the target polynucleotide sequences, homology-directed repair occurs. In some embodiments, homology-directed repair is performed using an exogenously introduced DNA repair template. In some embodiments, the exogenously introduced DNA repair template is single-stranded. In some embodiments, the exogenously introduced DNA repair template is double-stranded.

[0028] In some embodiments, the cell is a peripheral blood cell. In some embodiments, the cell is a stem cell or a pluripotent cell. In some embodiments, the cell is a hematopoietic stem cell. In some embodiments, the cell is a $CD34^+$ cell. In some

marrow cell. In some embodiments, the cell is a $CD34^{+}CD38$-$Lineage$-$CD90^{+}CD45RA^{-}$ cell.

[0029] In some embodiments, the target polynucleotide sequence is ADA. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1 or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1 or at least a 12 nucleotide fragment thereof.

[0030] In some embodiments, the target polynucleotide sequence is AK2. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2 or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2 or at least a 12 nucleotide fragment thereof.

[0031] In some embodiments, the target polynucleotide sequence is CD3D. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3 or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3 or at least a 12 nucleotide fragment thereof.

[0032] In some embodiments, the target polynucleotide sequence is DCLRE1C. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 4 or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 4 or at least a 12 nucleotide fragment thereof.

[0033] In some embodiments, the target polynucleotide sequence is IL2RG. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence

ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6 or at least a 12 nucleotide fragment thereof.

[0034] In some embodiments, the target polynucleotide sequence is IL7R. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7 or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7 or at least a 12 nucleotide fragment thereof.

[0035] In some embodiments, the target polynucleotide sequence is JAK3. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8 or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8 or at least a 12 nucleotide fragment thereof.

[0036] In some embodiments, the target polynucleotide sequence is LIG4. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9 or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9 or at least a 12 nucleotide fragment thereof.

[0037] In some embodiments, the target polynucleotide sequence is NHEJ1. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10 or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10 or at least a 12 nucleotide fragment thereof.

[0038] In some embodiments, the target polynucleotide sequence is PNP. In

a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11 or at least a 12 nucleotide fragment thereof.

[0039] In some embodiments, the target polynucleotide sequence is PRKDC. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12 or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12 or at least a 12 nucleotide fragment thereof.

[0040] In some embodiments, the target polynucleotide sequence is RAG1. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 13 or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig.13 or at least a 12 nucleotide fragment thereof.

[0041] In some embodiments, the target polynucleotide sequence is RAG2. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 14 or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 14 or at least a 12 nucleotide fragment thereof.

[0042] In some embodiments, the target polynucleotide sequence is ZAP70. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15 or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15 or at least a 12 nucleotide fragment thereof.

selected from the group consisting of the ribonucleic acid sequences of Fig. 5 or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5 or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence of GTAACGGCAGACTTCTCCACAGG or at least a 12 nucleotide fragment thereof. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to ribonucleic acid sequence GTAACGGCAGACTTCTCCACAGG or at least a 12 nucleotide fragment thereof.

[0044] In some embodiments, the target polynucleotide sequences comprise multiple different portions of ADA. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1 or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1 or at least 12 nucleotide fragments thereof.

[0045] In some embodiments, the target polynucleotide sequences comprise multiple different portions of AK2. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2 or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2 or at least 12 nucleotide fragments thereof.

[0046] In some embodiments, the target polynucleotide sequences comprise multiple different portions of CD3D. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3 or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3 or at least 12 nucleotide fragments thereof.

[0047] In some embodiments, the target polynucleotide sequences comprise

ribonucleic acid sequences of Fig. 4 or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 4 or at least 12 nucleotide fragments thereof.

[0048] In some embodiments, the target polynucleotide sequences comprise multiple different portions of IL2RG. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6 or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6 or at least 12 nucleotide fragments thereof.

[0049] In some embodiments, the target polynucleotide sequences comprise multiple different portions of IL7R. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7 or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7 or at least 12 nucleotide fragments thereof.

[0050] In some embodiments, the target polynucleotide sequences comprise multiple different portions of JAK3. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8 or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8 or at least 12 nucleotide fragments thereof.

[0051] In some embodiments, the target polynucleotide sequences comprise multiple different portions of LIG4. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9 or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9 or at least 12 nucleotide fragments thereof.

ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10 or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10 or at least 12 nucleotide fragments thereof.

[0053] In some embodiments, the target polynucleotide sequences comprise multiple different portions of PNP. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11 or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11 or at least 12 nucleotide fragments thereof.

[0054] In some embodiments, the target polynucleotide sequences comprise multiple different portions of PRKDC. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12 or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12 or at least 12 nucleotide fragments thereof.

[0055] In some embodiments, the target polynucleotide sequences comprise multiple different portions of RAG1. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 13 or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 13 or at least 12 nucleotide fragments thereof.

[0056] In some embodiments, the target polynucleotide sequences comprise multiple different portions of RAG2. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 14 or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the

[0057] In some embodiments, the target polynucleotide sequences comprise multiple different portions of ZAP70. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15 or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15 or at least 12 nucleotide fragments thereof.

[0058] In some embodiments, the target polynucleotide sequences comprise multiple different portions of HBB. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5 or at least 12 nucleotide fragments thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5 or at least 12 nucleotide fragments thereof.

[0059] In some embodiments, the target polynucleotide sequences comprise at least a portion of any combination of target polynucleotide sequences selected from the group consisting of ADA, AK2, CD3D, DCLRE1C, IL2RG, IL7R, JAK3, LIG4, NHEJ1, PNP, PRKDC, RAG1, RAG2, and ZAP70. In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 1-15 or at least a 12 nucleotide fragment thereof. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 1-15 or at least a 12 nucleotide fragment thereof.

[0060] In some embodiments, the disorder is SCID. In some embodiments, the disorder is sickle cell disease. In some embodiments, the disorder is beta thalassemia.

[0061] In some embodiments, the one to two ribonucleic acids are designed to hybridize to a target motif immediately adjacent to a deoxyribonucleic acid motif recognized by the Cas protein. In some embodiments, each of the one to two ribonucleic acids are designed to hybridize to target motifs immediately adjacent to deoxyribonucleic acid motifs recognized by the Cas protein which flank a mutant allele located between the target motifs. In some embodiments, the multiple ribonucleic acids are designed to hybridize to target motifs immediately adjacent to deoxyribonucleic acid motifs

motifs recognized by the Cas protein which flank mutant alleles located between the target motifs. In some embodiments, the one to two ribonucleic acids are selected to minimize hybridization with nucleic acid sequences other than the target polynucleotide sequence. In some embodiments, the multiple ribonucleic acids are selected to minimize hybridization with nucleic acid sequences other than the target polynucleotide sequence. In some embodiments, the target motif is selected such that it contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell. In some embodiments, each target motif is selected such that it contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell. In some embodiments, the target motif is selected such that it contains at least one mismatch when compared with all other genomic nucleotide sequences in the cell. In some embodiments, the target motif is selected such that it contains at least one mismatch when compared with all other genomic nucleotide sequences in the cell. In some embodiments, the one to two ribonucleic acids hybridize to a target motif that it contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell. In some embodiments, each of the multiple ribonucleic acids hybridize to target motifs that contain at least two mismatches when compared with all other genomic nucleotide sequences in the cell. In some embodiments, the one to two ribonucleic acids hybridize to a target motif that contains at least one mismatch when compared with all other genomic nucleotide sequences in the cell. In some embodiments, each of the multiple ribonucleic acids hybridize to target motifs that contain at least one mismatch when compared with all other genomic nucleotide sequences in the cell.

[0062] In some embodiments, the Cas protein and the one to two ribonucleic acids are contained in a nanoparticle. In some embodiments, the Cas protein and the one to two ribonucleic acids are contained in a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid. In some embodiments, the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.Cl, DLin-TAP.Cl, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.Cl, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC,

embodiments, the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof. In some embodiments, the Cas protein and the multiple ribonucleic acids are contained in nanoparticles. In some embodiments, the Cas protein and the multiple ribonucleic acids are contained in lipid nanoparticles. In some embodiments, the lipid nanoparticles comprise at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid. In some embodiments, the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.Cl, DLin-TAP.Cl, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.Cl, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof. In some embodiments, the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof. In some embodiments, the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof.

[0063] In some embodiments, the efficiency of alteration at each loci is from about 50% to about 80%. In some embodiments, the efficiency of alteration is at least about 5%. In some embodiments, the efficiency of alteration is at least about 10%. In some embodiments, the efficiency of alteration is from about 50% to about 80%.

[0064] In some embodiments, the Cas protein is encoded by a modified nucleic acid. In some embodiments, the modified nucleic acid comprises a ribonucleic acid containing at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate. In some embodiments, at least one of the ribonucleic acids is a modified ribonucleic acid comprising one to two modified nucleotides selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

[0065] In some embodiments, any of the Cas protein or the ribonucleic acids are expressed from a plasmid. In some embodiments, any of the Cas protein or the ribonucleic acids are expressed using a promoter optimized for increased expression in

chicken beta-actin promoter, an elongation factor-1 alpha promoter, and a ubiquitin promoter.

[0066] In some embodiments, the method further comprises selecting cells that express the Cas protein. In some embodiments, selecting cells comprises FACS. In some embodiments, FACs is used to select cells which co-express Cas and a fluorescent protein selected from the group consisting of green fluorescent protein and red fluorescent protein.

[0067] In some aspects, disclosed herein is a method for altering a target SCID-associated polynucleotide sequence in a cell comprising contacting the SCID-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0068] In some aspects, disclosed herein is a method for altering a target SCD-associated polynucleotide sequence in a cell comprising contacting the SCD-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0069] In some aspects, disclosed herein is a method for altering a target beta thalassemia-associated polynucleotide sequence in a cell comprising contacting the beta thalassemia-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated

sequence is cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0070] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence in a subject, the method comprising (a) altering a target SCID-associated polynucleotide sequence in a cell *ex vivo* by contacting the SCID-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequence.

[0071] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence in a subject, the method comprising (a) altering a target SCD-associated polynucleotide sequence in a cell *ex vivo* by contacting the SCD-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequence.

[0072] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence in a subject, the method comprising (a) altering a target beta thalassemia-associated polynucleotide sequence in a cell *ex vivo* by contacting the beta thalassemia-

clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequence.

[0073] In some aspects, disclosed herein is a method for simultaneously altering multiple target SCID-associated polynucleotide sequences in a cell comprising contacting the SCID-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0074] In some aspects, disclosed herein is a method for simultaneously altering multiple target SCD-associated polynucleotide sequences in a cell comprising contacting the SCD-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0075] In some aspects, disclosed herein is a method for simultaneously altering multiple target beta thalassemia-associated polynucleotide sequences in a cell comprising contacting the beta thalassemia-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids

polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0076] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCID-associated polynucleotide sequences in a cell *ex vivo* by contacting the SCID-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequences.

[0077] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCD-associated polynucleotide sequences in a cell *ex vivo* by contacting the SCD-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequences.

[0078] In some aspects, disclosed herein is a method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject, the method comprising (a) altering target beta thalassemia-associated polynucleotide sequences in a cell *ex vivo* by contacting the beta thalassemia-

clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequences.

[0079] In some aspects, disclosed herein is a composition, comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 1-15 or at least a 12 nucleotide fragment thereof.

[0080] In some aspects, disclosed herein is a composition, comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 1-15 or at least a 12 nucleotide fragment thereof.

[0081] In some embodiments, the at least one ribonucleic acid is contained in a nanoparticle. In some embodiments, the at least one ribonucleic acid is contained in a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid. In some embodiments, the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.Cl, DLin-TAP.Cl, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.Cl, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof. In some embodiments, the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof. In some embodiments, the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof. In some embodiments, at least one of the ribonucleic acids is a modified ribonucleic acid comprising one to two modified nucleotides selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-

[0082] In some embodiments, a composition further comprises a nucleic acid sequence encoding a Cas protein.

[0083] In some embodiments, a composition further comprises a nucleic acid sequence encoding a Cas9 protein or a functional portion thereof. In some embodiments, the nucleic acid comprises a modified ribonucleic acid comprising at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

[0084] In some aspects, disclosed herein is a composition, comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 1-15 or at least a 12 nucleotide fragment thereof.

[0085] In some aspects, disclosed herein is a composition,n comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 1-15 or at least a 12 nucleotide fragment thereof.

[0086] In some embodiments, the composition further comprises a nucleic acid sequence encoding a fluorescent protein selected from the group consisting of green fluorescent protein and red fluorescent protein. In some embodiments, the composition further comprises a promoter operably linked to the chimeric nucleic acid. In some embodiments, the promoter is optimized for increased expression in human stem cells. In some embodiments, the promoter is selected from the group consisting of a Cytomegalovirus (CMV) early enhancer element and a chicken beta-actin promoter, a chicken beta-actin promoter, an elongation factor-1 alpha promoter, and a ubiquitin promoter.

[0087] In some embodiments, the chimeric nucleic acid is contained in a nanoparticle. In some embodiments, the chimeric nucleic acid is contained in a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid. In some embodiments, the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA,

DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.Cl, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof. In some embodiments, the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof. In some embodiments, the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof. In some embodiments, the chimeric nucleic acid comprises at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

[0088] In some embodiments, the Cas protein comprises a Cas9 protein or a functional portion thereof.

[0089] In some aspects, disclosed herein is a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 1-15, a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Figs. 1-15 or at least a 12 nucleotide fragment thereof.

[0090] In some embodiments, the kit further comprises one or more cell lines, cultures, or populations selected from the group consisting of human pluripotent cells, primary human cells, and non-transformed cells. In some embodiments, the kit further comprises a DNA repair template selected from the group consisting of an ADA DNA repair template, a AK2 DNA repair template, a CD3D DNA repair template, a DCLRE1C DNA repair template, a IL2RG DNA repair template, IL7R DNA repair template, a JAK3 DNA repair template, a LIG4 DNA repair template, a NHEJ1 DNA repair template, a PNP DNA repair template, a PRKDC DNA repair template, a RAG1 DNA repair template, a RAG2 DNA repair template, a ZAP70 DNA repair template, and a HBB DNA repair template.

[0091] In some aspects, the disclosure provides a composition comprising at least one ribonucleic acid having a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG or at least a 12 nucleotide fragment thereof. In some aspects, the disclosure provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a ribonucleic acid

nanoparticle. In some embodiments, the at least one ribonucleic acid is contained in a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid. In some embodiments, the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.Cl, DLin-TAP.Cl, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.Cl, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof. In some embodiments, the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof. In some embodiments, the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof. In some embodiments, at least one of the ribonucleic acids is a modified ribonucleic acid comprising one to two modified nucleotides selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate. In some embodiments, the composition includes a nucleic acid sequence encoding a Cas protein. In some embodiments, the composition includes a nucleic acid sequence encoding a Cas9 protein or a functional portion thereof. In some embodiments, the nucleic acid comprises a modified ribonucleic acid comprising at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

[0092] In some aspects, the disclosure provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a ribonucleic acid sequences of GTAACGGCAGACTTCTCCACAGG or at least a 12 nucleotide fragment thereof. In some aspects, the disclosure provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG or at least a 12 nucleotide fragment thereof. In some embodiments, the composition includes a nucleic

includes a promoter operably linked to the chimeric nucleic acid. In some embodiments, the promoter is optimized for increased expression in human stem cells. In some embodiments, the promoter is selected from the group consisting of a Cytomegalovirus (CMV) early enhancer element and a chicken beta-actin promoter, a chicken beta-actin promoter, an elongation factor-1 alpha promoter, and a ubiquitin promoter. In some embodiments, the chimeric nucleic acid is contained in a nanoparticle. In some embodiments, the chimeric nucleic acid is contained in a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid. In some embodiments, the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.Cl, DLin-TAP.Cl, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.Cl, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof. In some embodiments, the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof. In some embodiments, the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof. In some embodiments, the chimeric nucleic acid comprises at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate. In some embodiments, the Cas protein comprises a Cas9 protein or a functional portion thereof.

[0093] In some aspects, the disclosure provides a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of GTAACGGCAGACTTCTCCACAGG, a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG or at least a 12 nucleotide fragment thereof. In some embodiments, the kit includes one or more cell lines, cultures, or populations selected from the group consisting of human pluripotent cells, primary human cells, and non-transformed cells. In some embodiments, the kit includes a HBB DNA repair

BRIEF DESCRIPTION OF THE DRAWINGS

[0094] Fig. 1 shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human ADA.

[0095] Fig. 2 shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human AK2.

[0096] Fig. 3 shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human CD3D.

[0097] Fig. 4 shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human DCLRE1C.

[0098] Fig. 5 shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human HBB.

[0099] Fig. 6 shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human IL2RG.

[0100] Fig. 7 shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human IL7R.

[0101] Fig. 8 shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human JAK3.

[0102] Fig. 9 shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human LIG4.

[0103] Fig. 10 shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human NHEJ1.

[0104] Fig. 11 shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human PNP.

[0105] Fig. 12 shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human PRKDC.

[0106] Fig. 13 shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human RAG1.

[0107] Fig. 14 shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human RAG2.

[0108] Fig. 15 shows exemplary guide RNA sequences useful when the target polynucleotide sequence is human ZAP70.

[0109] Fig. 16 shows an exemplary amino acid sequence of a Cas protein. Yellow highlights indicate Ruv-C-like domain. Underlining indicates HNH nuclease domain.

DETAILED DESCRIPTION OF THE INVENTION

[0110] Work described herein demonstrates methods of allele targeting using CRISPR/Cas systems resulting in mutant cells with efficiencies of up to 80%. These vastly improved methods permit CRISPR/Cas systems to be utilized effectively for the first time for therapeutic purposes. Methods of delivery of CRISPR/Cas systems to human stem cells are provided. In addition, methods of specifically identifying useful RNA guide sequences are provided, along with particular guide sequences useful in targeting specific genes (e.g., ADA, AK2, CD3D, DCLRE1C, HBB, IL2RG, IL7R, JAK3, LIG4, NHEJ1, PNP, PRKDC, RAG1, RAG2, and ZAP70). Moreover, methods of treatment (e.g., methods of treating severe combined immunodeficiency, sickle cell disease, and beta thalassemia) utilizing the compositions and methods disclosed herein are provided.

[0111] In one aspect, the present invention provides methods for altering target polynucleotide sequences in a cell.

[0112] In certain embodiments, the target polynucleotide sequence is a severe combined immunodeficiency (SCID)-associated polynucleotide sequence. In such embodiments, a method for altering a target polynucleotide sequence in a cell comprises a method for altering a target SCID-associated polynucleotide sequence. As used herein, "severe combined immunodeficiency-associated polynucleotide sequence" and "SCID-associated polynucleotide sequence" are used interchangeably to refer to a polynucleotide sequence of a gene displaying one or more mutations associated with SCID. As used herein "severe combined immunodeficiency" and "SCID" refer to a genetic disorder characterized by dysfunctional T-lymphocytes causing a defective antibody response due to either a direct involvement with B lymphocytes or aberrant B lymphocyte activation resulting from non-functional T-helper cells. SCID encompasses dysfunctional B and T cell responses of the adaptive immune system due to mutations in one or more genes, including, but not limited to, ADA, AK2, CD3D, DCLRE1C, IL2RG, IL7R, JAK3, LIG4, NHEJ1, PNP, PRKDC, RAG1, RAG2, and ZAP70. As such, a "SCID-associated

[0113] An exemplary method for altering a target severe combined immunodeficiency (SCID)-associated polynucleotide sequence in a cell comprises contacting the SCID-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID associated polynucleotide sequence is cleaved. In some embodiments, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0114] In some embodiments, the SCID-associated polynucleotide sequence is adenosine deaminase (ADA) or a variant thereof. An exemplary ADA sequence is a human ADA sequence (NCBI Gene ID: 100). Those skilled in the art will appreciate that the guide sequences shown in Figure 1 can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human ADA.

[0115] It should also be appreciated that altering a target polynucleotide sequence of ADA can be used to treat any abnormal phenotype associated with an altered ADA polynucleotide sequence. Table 1 below shows gene phenotype relationships identified by the Online Mendelian Inheritance in Man® (OMIM®) database. Further information regarding a phenotype listed in Table 1 is publicly accessible by querying OMIM for the search term "ADA" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

[0116] Table 1 – ADA Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
20q13.12	Adenosine deaminase deficiency, partial	102700
	Severe combined immunodeficiency due to ADA deficiency	102700

[0117] In some embodiments, the SCID-associated polynucleotide sequence is adenylate kinase 2 (AK2) or a variant thereof. An exemplary AK2 sequence is a human AK2 sequence (NCBI Gene ID: 204, also known as ADK2 and AK 2). In some embodiments, the human AK2 sequence comprises all or a portion of AK2 coding

of AK2 coding sequence 2. In some embodiments, the human AK2 sequence comprises all or a portion of AK2 coding sequence 3. Those skilled in the art will appreciate that the guide sequences shown in Figures 2, 3 and 4 can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human AK2, and in particular human AK2 coding sequences 1, 2 and 3, respectively.

[0118] It should also be appreciated that altering a target polynucleotide sequence of AK2 can be used to treat any abnormal phenotype associated with an altered AK2 polynucleotide sequence. Table 2 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 2 is publicly accessible by querying OMIM for the search term "AK2" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

[0119] Table 2 – AK2 Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
1p35.1	Reticular dysgenesis	267500

[0120] In some embodiments, the SCID-associated polynucleotide sequence is CD3 antigen, delta subunit (CD3D) or a variant thereof. An exemplary CD3D sequence is a human CD3D sequence (NCBI Gene ID: 915, also known as T3D and CD3-DELTA). In some embodiments, the human CD3D sequence comprises all or a portion of CD3D coding sequence 1. In some embodiments, the human CD3D sequence comprises all or a portion of CD3D coding sequence 2. Those skilled in the art will appreciate that the guide sequences shown in Figures 5 and 6 can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human CD3D, and in particular human CD3D coding sequences 1 and 2, respectively.

[0121] It should also be appreciated that altering a target polynucleotide sequence of CD3D can be used to treat any abnormal phenotype associated with an altered CD3D polynucleotide sequence. Table 3 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 3 is

a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

[0122] Table 3 – CD3D Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
11q23.3	Severe combined immunodeficiency, T cell-negative, B-cell/natural killer-cell positive	608971

[0123] In some embodiments, the SCID-associated polynucleotide sequence is DNA cross-link repair protein 1C (DCLRE1C) or a variant thereof. An exemplary DCLRE1C sequence is a human DCLRE1C sequence (NCBI Gene ID: 64421, also known as SCIDA, SNM1C, A-SCID, hSNM1C, RS-SCID, DCLRE1C). In some embodiments, the human DCLRE1C sequence comprises all or a portion of DCLRE1C coding sequence 1. In some embodiments, the human DCLRE1C sequence comprises all or a portion of DCLRE1C coding sequence 2. In some embodiments, the human DCLRE1C sequence comprises all or a portion of DCLRE1C coding sequence 3. In some embodiments, the human DCLRE1C sequence comprises all or a portion of DCLRE1C coding sequence 4. Those skilled in the art will appreciate that the guide sequences shown in Figures 7, 8, 9, and 10 can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human DCLRE1C, and in particular human DCLRE1C coding sequences 1, 2, 3, and 4, respectively.

[0124] It should also be appreciated that altering a target polynucleotide sequence of DCLRE1C can be used to treat any abnormal phenotype associated with an altered DCLRE1C polynucleotide sequence. Table 4 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 4 is publicly accessible by querying OMIM for the search term "DCLRE1C" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

[0125] Table 4 – DCLRE1C Gene Phenotype Relationships

		MIM number
10p13	Omenn syndrome	603554
	Severe combined immunodeficiency, Athabascan type	602450

[0126] In some embodiments, the SCID-associated polynucleotide sequence is interleukin 2 receptor, gamma (IL2RG) or a variant thereof. An exemplary IL2RG sequence is a human IL2RG sequence (NCBI Gene ID: 3561, also known as P64; CIDX; IMD4; CD132; SCIDX; IL-2RG; and SCIDX1). Those skilled in the art will appreciate that the guide sequences shown in Figure 12 can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human IL2RG.

[0127] It should also be appreciated that altering a target polynucleotide sequence of IL2RG can be used to treat any abnormal phenotype associated with an altered IL2RG polynucleotide sequence. Table 5 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 5 is publicly accessible by querying OMIM for the search term "IL2RG" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

[0128] Table 5 – IL2RG Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
Xq13.1	Combined immunodeficiency, X-linked, moderate	312863
	Severe combined immunodeficiency, X-linked	300400

[0129] In some embodiments, the SCID-associated polynucleotide sequence is interleukin 7 receptor (IL7R) or a variant thereof. An exemplary IL7R sequence is a human IL7R sequence (NCBI Gene ID: 3575, also known as ILRA, CD127, IL7RA, CDW127, IL-7R-alpha). Those skilled in the art will appreciate that the guide sequences shown in Figure 13 can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human IL7R.

[0130] It should also be appreciated that altering a target polynucleotide sequence of IL7R can be used to treat any abnormal phenotype associated with an altered IL7R polynucleotide sequence. Table 6 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 6 is publicly accessible by querying OMIM for the search term "IL7R" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

[0131] Table 6 – IL7R Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
5p13.2	Severe combined immunodeficiency, T-cell negative, B-cell/natural killer cell-positive type	608971

[0132] In some embodiments, the SCID-associated polynucleotide sequence is Janus kinase 3(JAK3) or a variant thereof. An exemplary JAK3 sequence is a human JAK3 sequence (NCBI Gene ID: 3718, also known as JAKL; LJAK; JAK-3; L-JAK; JAK3_HUMAN). Those skilled in the art will appreciate that the guide sequences shown in Figure 14 can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human JAK3.

[0133] It should also be appreciated that altering a target polynucleotide sequence of JAK3 can be used to treat any abnormal phenotype associated with an altered JAK3 polynucleotide sequence. Table 7 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 7 is publicly available by querying OMIM for the search term "JAK3" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

[0134] Table 7 – JAK3 Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number

[0135] In some embodiments, the SCID-associated polynucleotide sequence is ligase IV, DNA, ATP-dependent (LIG4) or a variant thereof. An exemplary LIG4 sequence is a human LIG4 sequence (NCBI Gene ID: 3981). In some embodiments, the human LIG4 sequence comprises all or a portion of LIG4 coding sequence 1. In some embodiments, the human LIG4 sequence comprises all or a portion of LIG4 coding sequence 2. In some embodiments, the human LIG4 sequence comprises all or a portion of LIG4 coding sequence 3. Those skilled in the art will appreciate that the guide sequences shown in Figures 15, 16, and 17 can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human LIG4, and in particular human LIG4 coding sequences 1, 2, and 3, respectively.

[0136] It should also be appreciated that altering a target polynucleotide sequence of LIG4 can be used to treat any abnormal phenotype associated with an altered LIG4 polynucleotide sequence. Table 8 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 8 is publicly accessible by querying OMIM for the search term "LIG4" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

[0137] Table 8 – LIG4 Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
13q33.3	LIG4 syndrome	606593
	Severe combined immunodeficiency with sensitivity to ionizing radiation	602450
	{Multiple myeloma, resistance to}	254500

[0138] In some embodiments, the SCID-associated polynucleotide sequence is nonhomologous end-joining factor 1 (NHEJ1) or a variant thereof. An exemplary NHEJ1 sequence is the human NHEJ1 sequence (NCBI Gene ID: 79840, also known as XLF). Those skilled in the art will appreciate that the guide sequences shown in Figure 18 can

be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human NHEJ1.

[0139] It should also be appreciated that altering a target polynucleotide sequence of NHEJ1 can be used to treat any abnormal phenotype associated with an altered NHEJ1 polynucleotide sequence. Table 9 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 9 is publicly accessible by querying OMIM for the search term "NHEJ1" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

[0140] Table 9 – NHEJ1 Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
2q35	Severe combined immunodeficiency with microcephaly, growth retardation, and sensitivity to ionizing radiation	611291

[0141] In some embodiments, the SCID-associated polynucleotide sequence is a purine nucleoside phosphorylase sequence (PNP) or a variant thereof. An exemplary PNP sequence is human PNP (NCBI Gene ID: 4860, also known as NP, PUNP, and PRO1837). Those skilled in the art will appreciate that the guide sequences shown in Figure 19 can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human PNP.

[0142] It should also be appreciated that altering a target polynucleotide sequence of PNP can be used to treat any abnormal phenotype associated with an altered PNP polynucleotide sequence. Table 10 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 10 is publicly accessible by querying OMIM for the search term "PNP" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

[0143] Table 10 – PNP Gene Phenotype Relationships

		MIM number
14q11.2	Immunodeficiency due to purine nucleoside phosphorylase deficiency	613179

[0144] In some embodiments, the SCID-associated polynucleotide sequence is a protein kinase, DNA activated, catalytic polypeptide sequence (PRKDC) or a variant thereof. An exemplary PRKDC sequence is human PRKDC (NCBI Gene ID: 5591, also known as HYRC; p350; DNAPK; DNPK1; HYRC1; XRCC7; and DNA-PKcs). In some embodiments, the human PRKDC sequence comprises all or a portion of PRKDC coding sequence 1. In some embodiments, the human PRKDC sequence comprises all or a portion of PRKDC coding sequence 2. Those skilled in the art will appreciate that the guide sequences shown in Figures 20 and 21 can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human PRKDC, and in particular human PRKDC coding sequences 1 and 2, respectively.

[0145] It should also be appreciated that altering a target polynucleotide sequence of PRKDC can be used to treat any abnormal phenotype associated with an altered PRKDC polynucleotide sequence. In some embodiments, the phenotype associated with an altered PRKDC polynucleotide sequence is SCID. In some embodiments, the phenotype associated with an altered PRKDC polynucleotide sequence is radiosensitivity in xeroderma pigmentosum (Abbaszadeh *et al.*, A novel splice variant of the DNA-PKcs gene is associated with clinical and cellular radiosensitivity in a patient with xeroderma pigmentosum. J Med Genet. 2010; 47(3):176-81).

[0146] In some embodiments, the SCID-associated polynucleotide sequence is a recombination activating gene 1 sequence (RAG1) or a variant thereof. An exemplary RAG1 sequence is human RAG1 (NCBI Gene ID: 5896, also known as RAG-1 and RNF74). Those skilled in the art will appreciate that the guide sequences shown in Figure 22 can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human RAG1.

[0147] It should also be appreciated that altering a target polynucleotide sequence of RAG1 can be used to treat any abnormal phenotype associated with an altered RAG1 polynucleotide sequence. Table 11 below shows gene phenotype relationships identified

a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

[0148] Table 11 - RAG1 Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
11p12	Alpha/beta T-cell lymphopenia with gamma/delta T-cell expansion, severe cytomegalovirus infection, and autoimmunity	609889
	Combined cellular and humoral immune defects with granulomas	233650
	Omenn syndrome	603554
	Severe combined immunodeficiency, B cell-negative	601457

[0149] In some embodiments, the SCID-associated polynucleotide sequence is a recombination activating gene 2 sequence (RAG2) or a variant thereof. An exemplary RAG2 sequence is human RAG2 (NCBI Gene ID: 5897, also known as RAG-2). In some embodiments, the human RAG2 sequence comprises all or a portion of human RAG2 coding sequence 1. In some embodiments, the human RAG2 sequence comprises all or a portion of human RAG2 coding sequence 2. In some embodiments, the human RAG2 sequence comprises all or a portion of human RAG2 coding sequence 3. Those skilled in the art will appreciate that the guide sequences shown in Figures 23, 24 and 25 can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human RAG2, and in particular human RAG2 coding sequences 1, 2 and 3, respectively.

[0150] It should also be appreciated that altering a target polynucleotide sequence of RAG2 can be used to treat any abnormal phenotype associated with an altered RAG2 polynucleotide sequence. Table 12 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 12 is publicly accessible by querying OMIM for the search term "RAG2" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

[0151] Table 12 – RAG2 Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
11p12	Combined cellular and humoral immune defects with granulomas	233650
	Omenn syndrome	603554
	Severe combined immunodeficiency, B cell-negative	601457

[0152] In some embodiments, the SCID-associated polynucleotide sequence is a zeta-chain-associated protein kinase sequence (ZAP70) or a variant thereof. An exemplary ZAP70 sequence is human ZAP70 (NCBI Gene ID: 7535, also known as SRK; STD; TZK; STCD; and ZAP-70). In some embodiments, the human ZAP70 sequence comprises all or a portion of human ZAP70 coding sequence 1. In some embodiments, the human ZAP70 sequence comprises all or a portion of human ZAP70 coding sequence 2. Those skilled in the art will appreciate that the guide sequences shown in Figures 26 and 27 can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human ZAP70, and in particular human ZAP70 coding sequences 1 and 2, respectively.

[0153] It should also be appreciated that altering a target polynucleotide sequence of ZAP70 can be used to treat any abnormal phenotype associated with an altered ZAP70 polynucleotide sequence. Table 13 below shows gene phenotype relationships identified by the OMIM® database. Further information regarding a phenotype listed in Table 13 is publicly accessible by querying OMIM for the search term "ZAP70" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

[0154] Table 13 – ZAP 70 Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
2q11.2	Selective T-cell defect	269840

[0155] In some embodiments, the target polynucleotide sequence is hemoglobin beta ("HBB") (e.g., human hemoglobin beta, NCBI Gene ID: 3043) or a variant thereof. Those skilled in the art will appreciate that the guide sequences shown in Figure 11 can be used with the CRISPR/Cas systems of the present invention to alter target polynucleotide sequences of human HBB.

[0156] It should also be appreciated that altering a target polynucleotide sequence of HBB can be used to treat any abnormal phenotype associated with an altered HBB polynucleotide sequence. Table 14 below shows gene phenotype relationships as identified by the OMIM® database. Further information regarding a phenotype listed in Table 14 is publicly accessible by querying OMIM for the search term "HBB" and then clicking on a hyperlink in the "Phenotype MIM number" column corresponding to the phenotype listed.

[0157] Table 14 - HBB Gene Phenotype Relationships

Location	Phenotype	Phenotype MIM number
11p15.4	Delta-beta thalassemia	141749
	Erythremias, beta-	
	Heinz body anemias, beta-	140700
	Hereditary persistence of fetal hemoglobin	141749
	Methemoglobinemias, beta-	
	Sickle cell anemia	603903
	Thalassemia-beta, dominant inclusion-body	603902
	Thalassemias, beta-	613985
	{Malaria, resistance to}	611162

[0158] Normal adult hemoglobin is a tetramer that consists of two alpha chains and two beta chains. HBB determines the structure of the beta chains of hemoglobin. HBB mutations are associated with sickle cell diseases and/or beta thalassemia. For

results in beta-plus-thalassemia. Exemplary mutant forms of HBB involved in sickle cell disease are Hemoglobin S (Glu6Val), Hemoglobin C (Glu6Lys), Hemoglobin D (Glu121Gln), and Hemoglobin O (Glu121Lys).

[0159] Insertion of an L1 retrotransposable fragment within the IVS-II of the beta-globin gene results in beta°-thal. This represents a form of beta thalassemia in which the beta globin gene expresses full length beta-globin transcripts at levels equal to about 15% of the total beta-globin mRNA.

[0160] In some embodiments, a method for altering a target polynucleotide sequence in a cell comprises a method for altering a target sickle cell disease (SCD)-associated polynucleotide sequence. As used herein, "sickle cell disease-associated polynucleotide sequence" or "SCD-associated polynucleotide sequence" are used interchangeably to refer to a polynucleotide sequence of the HBB gene displaying one or more HBB mutations associated with SCD. As used herein, "sickle cell disease" refers to a group of symptomatic disorders involving mutations in HBB and defined by the presence of hemoglobin S (Hb S). Normal hemoglobin is a heterotetramer consisting of two alpha-hemoglobin and two beta-hemoglobin chains. Point mutations in HBB cause hemoglobin S to result, for example a point mutation changing the sixth amino acid in the beta-hemoglobin chain from glutamic acid to valine (Glu6Val). Sickle cell anemia (homogzygous HbSS) is an example of a sickle cell disease which makes up between 60-70% of reported sickle cell disease in the United States. Examples of other forms of sickle cell disease are due to coinhereitance of Hb S with various mutant beta-globin chain variants, including sickle-hemoglobin C disease (Hb SC), and two different types of sickle beta thalassemia (Hb $S\beta^+$- thalassemia and Hb S β°- thalassemia).

[0161] An exemplary method for altering a target sickle cell disease (SCD)-associated polynucleotide sequence in a cell comprises contacting the SCD-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved. In some embodiments of this and other aspects, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0162] In some embodiments, a method for altering a target polynucleotide

sequence" refers to a polynucleotide sequence of the HBB gene displaying one or more HBB mutations associated with beta thalassemia. As used herein, "beta thalassemia" refers to inherited autosomal recessive diseases characterized by decreased production of the hemoglobin subunit beta (e.g., hemoglobin beta chain) that are caused by over 200 different HBB mutations. As will be appreciated by the skilled artisan, HBB mutations resulting in beta thalassemia include non-deletional HBB mutants, deletional HBB mutants, and HBB mutants resulting from transposable elements. Table 15 below illustrates exemplary non-deletional HBB mutations.

[0163] Table 15 – Non-deletional HBB mutations associated with beta thalassemia

-101 (C->T)
-92 (C->T)
-90 (C->T)
-88 (C->A)
-88 (C->T)
-87 (C->A)
-87 (C->G)
-87 (C->T)
-86 (C->A)
-86 (C->G)
-32 (C->A)
-31 (A->C)
-31 (A->G)
-30 (T->A)
-30 (T->C)
-29 (A->G)
-28 (A->C)
-28 (A->G)
CAP +1 (A->C)
5'UTR; +10 (-T)
5'UTR; +22 (G->A)

5'UTR; +43 to +40 (-AAAC)
Initiation codon *A*TG->*G*TG
Initiation codon A*T*G->A*C*G
Initiation codon A*T*G->A*G*G
Initiation codon ATG->AT*A*
Initiation codon ATG->AT*C*
Initiation codon ATG->AT*T*
Codon 1 (-G); GTG(Val)->-TG
Codons 2/3/4 (-9 bp; +31 bp); (see below)
Codon 5 (-CT); CCT(Pro)->C--
Codon 6 (-A); GAG(Glu)->G-G
Codon 8 (-AA); AAG(Lys)->--G
Codons 8/9 (+G); AAG·TCT(Lys;Ser)->AAG·G·TCT
Codons 9/10 (+T); TCT·GCC(Ser;Ala)->TCT·T·GCC
Codon 10 (C->A); GCC(Ala)->GCA(Ala)
Codon 11 (-T); GTT(Val)->GT-
Codons 14/15 (+G);
Codon 15 (G->A); TGG(Trp)->TAG(stop codon)
Codon 15 (G->A); TGG(Trp)->TGA(stop codon)
Codon 15 (-T); TGG(Trp)->-GG
Codon 16 (-C); GGC(Gly)->GG-
Codon 17 (A->T); AAG(Lys)->TAG(stop codon)
Codon 19 (A->G); AAC(Asn)->AGC(Ser)
Codon 22 (A->C); G*A*A(Glu)->G*C*A(Ala) (not listed in Table I; this mutation is likely not associated with thalassemia)
Codon 22 (G->T); GAA(Glu)->TAA(stop codon)
Codons 22/23/24 (GAA·GTT·GGT; Glu·Val·Gly); deletion of -AAGTTGG
Codon 24; GGT(Gly); (-G; +CAC)
Codon 24 (T->A); GGT(Gly)->GGA(Gly)
Codons 24/25 (-GGT); GGT·GGT(Gly-Gly)->---·GGT(Gly)
Codons 25/26 (+T); GGT·GAG(Gly-Glu)->GGT·T·GAG(Gly-Term)
Codon 26 (*G*AG->*A*AG)

Codon 26 (+T); GAG(Glu)->GTAG
Codon 27 (G->T); GCC(Ala)->TCC(Ser)
Codons 27/28 (+C); GCC·CTG(Ala·Ser)->GCC·C·CTG
Codon 28 (-C); CTG(Leu)->-TG
Codon 28 (T->G); CTG(Leu)->CGG(Arg)
Codons 28/29 (-G); CTG·GGC(Leu·Gly)->CTG··-GC
IVS-I (-3) or codon 29 (C->T); GGC(Gly)->GGT(Gly)
IVS-I (-2) or codon 30 (A->G); *A*G^GTTGGT->*GG*^GTTGGT
IVS-I (-1) or codon 30 (G->A); A*G*^GTTGGT->A*A*^GTTGGT
IVS-I (-1) or codon 30 (G->C); A*G*^GTTGGT->A*C*^GTTGGT
IVS-I-1 (G->A); AG^*G*TTGGT->AG*A*TTGGT
IVS-I-1 (G->T); AG^*G*TTGGT->AG*T*TTGGT
IVS-I-2 (T->A); AG^G*T*TGGT->AGG*A*TGGT
IVS-I-2 (T->C); AG^G*T*TGGT->AGA*C*TGGT
IVS-I-2 (T->G); AG^G*T*TGGT->AGG*G*TGGT
IVS-I-5 (G->A)
IVS-I-5 (G->A) plus the 7,201 bp deletion involving part of the delta gene; the Corfu deletion (deltabeta-thal)
IVS-I-5 (G->C)
IVS-I-5 (G->T)
IVS-I-6 (T->C); the Portuguese type
IVS-I-110 (G->A)
IVS-I-116 (T->G)
IVS-I-128 (T->G); TTAG^GCTG->TGAG^GCTG
IVS-I-130 (G->A); TTAG^GCTG->TTAA GCTG
IVS-I-130 (G->C); TTAG^GCTG->TTAC GCTG
Codon 30 (AG*G*->AG*C*) [IVS-I-130 (+1)]
IVS-I, 3' end; -17 bp
Codon 31 (-C); CTG->-TG
Codons 31/32 (+CGG)
Codon 32 (T->A) C*T*G->C*A*G; codon 98 (G->A) *G*TG->*A*TG
Codons 33/34 (-GTG); GTG·GTC(Val-Val)->GTC·---(Val)

Codon 35 (-C); TAC(Tyr)->TA-

Codons 36/37 (-T); CCT·TGG(Pro-Trp)->CCT·-GG

Codon 37 (G->A); TGG(Trp)->TGA(stop codon)

Codons 37/38/39 (-7 nts)

Codons 38/39 (-C); ACC·CAG(Thr·Gln)->ACC·-AG

Codons 38/39 (-CC); ACC·CAG(Thr-Glu)->A--·CAG

Codon 39 (C->T); CAG(Gln)->TAG(stop codon)

Codon 40 (-G); AGG(Arg)->AG-

Codons 40/41 (+T); AGG·TTC(Arg-Phe)->AGG·T·TTC

Codon 41 (-C); TTC(Phe)->TT-

Codons 41/42 (-TTCT); TTC·TTT(Phe-Phe)->--- -TT

Codons 42/43 (+G); TTT·GAG(Phe·Glu)->TTT·G·GAG

Codons 42/43 (+T) TTT·GAG(Phe·Glu)->TTT·TGA·G(Phe;stop codon)

Codon 43 (G->T); GAG(Glu)->TAG (stop codon)

Codon 44 (-C); TCC(Ser)->TC-

Codon 45 (-T); TTT(Phe)->-TT

Codon 47 (+A); GAT(Asp)->GAA(Glu)·T

Codons 47/48 (+ATCT); GAT·CTG(Asp-Leu)->GAT·CT*ATCT*G

Codon 51 (-C); CCT(Pro)->-CT

53/54 (+G); GCT·GTT(Ala-Val)->GCT·G·GTT

Codon 54 (-T); GTT(Val)->GT-

Codons 54/55 (+A); GTT·ATG(Val·Met)->GTT·A·ATG

Codons 56/57/58/59/60 (GGC·AAC·CCT·AAG·GTG); duplication of 14 bp

Codons 57/58 (+C); AAC·CCT(Asn·Pro)->AAC·C·CCT

Codon 59 (-A); AAG(Lys)->-AG

Codon 60 (T->A); GTG(Val)->GAG(Glu)

Codon 61 (A->T); AAG(Lys)->TAG(stop codon)

Codon 64 (-G); GGC(Gly)->-GC

Codon 67 (-TG); GTG(Val)->--G

Codons 71/72 (+A); TTT·AGT(Phe·Ser)->TTT·A·AGT

Codons 71/72 (+T); TTT·AGT(Phe·Ser)->TTT·T·AGT

Codons 72/73; -AGTGA, +T; AGT·GAT(Ser-Asp)->--- -TT

Codon 76 (-C); GCT(Ala)->G-T

Codons 82/83 (-G); AAG·GGC(Lys·Gly)->AAG·-GC

Codons 84/85 (+C); ACC·TTT(Thr·Phe)->ACC·C·TTT

Codons 84/85/86 (+T); ACC·TTT·GCC(Thr·Phe·Ala)->ACC·TTT·T·GCC

Codon 88 (+T); CTG(Leu)->CTTG

Codons 89/90 (-GT); AGT·GAG(Ser·Glu)->A--·GAG

Codon 90 (G->T); GAG(Glu)->TAG(stop codon)

Codon 94 (+TG); GAC(Asp)->G*TG*AC

Codon 95 (+A); AAG(Lys)->AAAG

Codon 100; -CTT, +TCTGAGAACTT

IVS-II-1 (G->A);

IVS-II-1 (G->C);

IVS-II-2,3 (+11, -2); insertion of 11 bp (5'-ACGTTCT CTGA-3') and deletion of GA (nts 2 and 3 of IVS-II) between positions 1 and 4 of IVS-II

IVS-II-4,5 (-AG);

IVS-II-5 (G->C)

IVS-II-654 (C->T); AAGG*C*AATA->AAG^G*T*AATA

IVS-II-705 (T->G); GA*T*GTAAGA->GA*G*^GTAAGA

IVS-II-745 (C->G); CAG*C*TACCAT->CAG^*G*TACCAT

IVS-II-837 (T->G);

IVS-II-843 (T->G);

IVS-II-844 (C->G);

IVS-II-848 (C->A);

IVS-II-848 (C->G);

IVS-II-849 (A->C);

IVS-II-849 (A->G);

IVS-II-850 (-G);

IVS-II-850 (G->A);

IVS-II-850 (G->C);

IVS-II-850 (G->T);

Codons 106/107 (+G); CTG·GGC(Leu·Gly)->CTG·G·GC

Codons 108/109/110/111/112 (-12 bp);

Codon 110 (T->C); CTG(Leu)->CCG(Pro)

Codon 112 (T->A); TGT(Cys)->TGA(stop codon)

Codon 114 (T->C); CTG(Leu)->CCG(Pro)

Codon 114 (-CT; +G); CTG(Leu)->-GG

Codon 115 (C->A); GCC(Ala)->GAC(Asp)

Codons 120/121 (+A); AAA·GAA(Lys-Glu)->AAA·*A*·GAA

Codon 121 (G->T); GAA(Glu)->TAA(stop codon)

Codon 123 (-A); ACC(Thr)->-CC

Codons 123/124/125 (-ACCCCACC); ACC·CCA·CCA(Thr·Pro·Pro)->--- --- --A

Codon 124 (-A); CCA(Pro)->CC-

Codon 125 (-A); CCA(Pro)->CC-

Codons 124/125/126 (+CCA); CCA·CCA·GTG(Pro·Pro·Val)-

>CCA·CCA·CCA·GTG(Pro·Pro·Pro·Val)

Codon 126 (-T); GTG(Val)->G-G

Codon 126 (T->G); GTG(Val)->GGG(Gly)

Codons 126-131 (Val-Gln-Ala-Ala-Thr-Gln) (-17 bp);

GTG·CAG·GCT·GCC·TAT·CAG->G

Codon 127 (A->C); CAG(Gln)->CCG(Pro)

Codon 127 (A->G); CAG(Gln)->CGG(Arg)

Codon 127 (C->T); CAG(Gln)->TAG(stop codon)

Codons 127/128 (-AGG); CAG·GCT(Gln·Ala)->C-- -CT(Pro)

Codons 128/129 (-4 bp, -GCTG; +5 bp, +CCACA)

Codons 132-135 (-11 bp, -AAAGTGGTGGC)

Codons 134/135/136/137 [-(G)TGGCTGGTGT(G) and +(G)GCAG(G)];

GTG·GCT·GGT·GTG(Val-Ala-Gly-Val)->GGC·AGG(Gly-Arg)

+1480 (C->G); also known as 3' terminating codon +6 (C->G)

3'UTR (-GCATCTGGATTCT) 13 bp deletion between positions +1565 to +1577 (the numbers are relative to the Cap site)

T->C; 12 nts 5' to the poly A site or +1570 (the number is relative to the Cap site)

Poly A (T->C); AA*T*AAA->AA*C*AAA

Poly A (A->G); AAT*A*AA->AAT*G*AA

Poly A (A->G); AATA*A*A->AATA*G*A

Poly A (-AT or -TA); AATAAA->A--AAA Poly A (-AATAA); AATAAA->-----A

[0164] Those skilled in the art will also appreciate that a variety of deletional beta thalassemia alleles exist, which tend to be prevalent in certain at-risk populations. Examples of such deletional beta thalassemia alleles include, but are not limited to, a 25 bp deletion, a 44 bp deletion, a 105 bp deletion, a 290 bp deletion, a 532 bp deletion, a 619 bp deletion, a 1,393 bp deletion, a 1,605 bp deletion ("Croatian deletion"), a 3,485 bp deletion ("Thai deletion"), a 4,237 bp deletion ("Czech deletion"), a 7.6 kb deletion ("Turkish deletion"); a 10,329 bp deletion ("Asian Indian deletion"), a 12,023 bp deletion ("Australian deletion"); a 12,620 bp deletion ("Dutch deletion"), a 27 kb deletion ("Southeast Asian deletion"), a 45 kb deletion ("Filipino deletion"), and a 65 kb deletion ("Italian deletion"). Those skilled in the art will be able to retrieve the corresponding nucleic acid and protein sequences corresponding to these deletions from publicly available sources (e.g., A Syllabus of Thalassemia Mutations (1997) by Titus H.J. Huisman, et al. published by The Sickle Cell Anemia Foundation in Augusta, GA, USA, available online at http://globin.cse.psu.edu/html/huisman/thals/I-b.entries.html).

[0165] An exemplary method for altering a target beta thalassemia-associated polynucleotide sequence in a cell comprises contacting the beta thalassemia-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia associated

[0166] As used herein, the term "contacting" (i.e., contacting a polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and/or ribonucleic acids) is intended to include incubating the Cas protein and/or the ribonucleic acids in the cell together *in vitro* (e.g., adding the Cas protein or nucleic acid encoding the Cas protein to cells in culture). In some embodiments, the term "contacting" is not intended to include the *in vivo* exposure of cells to the Cas protein and/or ribonucleic acids as disclosed herein that may occur naturally in a microorganism (i.e., bacteria). The step of contacting a target polynucleotide sequence with a Cas protein and/or ribonucleic acids as disclosed herein can be conducted in any suitable manner. For example, the cells may be treated in adherent culture, or in suspension culture. It is understood that the cells contacted with a Cas protein and/or ribonucleic acids as disclosed herein can also be simultaneously or subsequently contacted with another agent, such as a growth factor or other differentiation agent or environments to stabilize the cells, or to differentiate the cells further.

[0167] In another aspect, the present invention provides a method for treating or preventing a disorder associated with expression of a polynucleotide sequence in a subject.

[0168] The terms "treat", "treating", "treatment", etc., as applied to an isolated cell, include subjecting the cell to any kind of process or condition or performing any kind of manipulation or procedure on the cell. As applied to a subject, the terms refer to providing medical or surgical attention, care, or management to an individual. The individual is usually ill or injured, or at increased risk of becoming ill relative to an average member of the population and in need of such attention, care, or management.

[0169] As used herein, the term "treating" and "treatment" refers to administering to a subject an effective amount of a composition so that the subject has a reduction in at least one symptom of the disease or an improvement in the disease, for example, beneficial or desired clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation of one or more symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total) , whether detectable or undetectable. Treating can refer to prolonging survival as compared to expected survival if not receiving treatment.

includes prophylaxis. Alternatively, treatment is "effective" if the progression of a disease is reduced or halted. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already diagnosed with a disorder associated with expression of a polynucleotide sequence, as well as those likely to develop such a disorder due to genetic susceptibility or other factors.

[0170] By "treatment", "prevention" or "amelioration" of a disease or disorder is meant delaying or preventing the onset of such a disease or disorder, reversing, alleviating, ameliorating, inhibiting, slowing down or stopping the progression, aggravation or deterioration the progression or severity of a condition associated with such a disease or disorder. In one embodiment, the symptoms of a disease or disorder are alleviated by at least 5%, at least 10%, at least 20%, at least 30%, at least 40%, or at least 50%.

[0171] In some embodiments, a method for treating or preventing a disorder associated with expression of a polynucleotide sequence comprises a method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence.

[0172] An exemplary method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence in a subject comprises (a) altering a target SCID-associated polynucleotide sequence in a cell *ex vivo* by contacting the SCID-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequence. In some embodiments of this and other aspects, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0173] An exemplary method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence in a subject comprises altering a target SCID-associated polynucleotide sequence in a cell by contacting the SCID-associated polynucleotide sequence with a clustered regularly interspaced short

target SCID-associated polynucleotide sequence, and wherein the target SCID-associated polynucleotide sequence is cleaved, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequence.

[0174] In some embodiments, a method for treating or preventing a disorder associated with expression of a polynucleotide sequence comprises a method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence.

[0175] An exemplary method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence in a subject comprises (a) altering a target SCD-associated polynucleotide sequence in a cell *ex vivo* by contacting the SCD-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequence. In some embodiments of this and other aspects, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0176] An exemplary method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence in a subject comprises altering a target SCD-associated polynucleotide sequence in a cell by contacting the SCD-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, and wherein the target SCD-associated polynucleotide sequence is cleaved, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequence.

[0177] In some embodiments, a method for treating or preventing a disorder associated with expression of a polynucleotide sequence comprises a method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence.

[0178] An exemplary method for treating or preventing a disorder associated

cell *ex vivo* by contacting the beta thalassemia-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequence. In some embodiments of this and other aspects, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0179] An exemplary method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence in a subject comprises altering a target beta thalassemia-associated polynucleotide sequence in a cell by contacting the beta thalassemia-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, and wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequence.

[0180] The present invention contemplates altering target polynucleotide sequences in any manner which is available to the skilled artisan utilizing a CRISPR/Cas system of the present invention. Any CRISPR/Cas system that is capable of altering a target polynucleotide sequence in a cell can be used. Such CRISPR-Cas systems can employ a variety of Cas proteins (Haft *et* al. *PLoS Comput Biol.* 2005;1(6)e60). The molecular machinery of such Cas proteins that allows the CRISPR/Cas system to alter target polynucleotide sequences in cells include RNA binding proteins, endo- and exo-nucleases, helicases, and polymerases. In some embodiments, the CRISPR/Cas system is a CRISPR type I system. In some embodiments, the CRISPR/Cas system is a CRISPR type II system.

[0181] The CRISPR/Cas systems of the present invention can be used to alter a target polynucleotide sequence in a cell. The present invention contemplates altering target polynucleotide sequences in a cell for any purpose. In some embodiments, the

original genotype. In some instances, a "mutant cell" exhibits a mutant phenotype, for example when a normally functioning gene is altered using the CRISPR/Cas systems of the present invention. In other instances, a "mutant cell" exhibits a wild-type phenotype, for example when a CRISPR/Cas system of the present invention is used to correct a mutant genotype. In exemplary embodiments, a mutant cell exhibits a wild-type ADA phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type AK2 phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type CD3D phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type DCLRE1C phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type IL2RG phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type IL7R phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type JAK3 phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type LIG4 phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type NHEJ1 phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type PNP phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type PRKDC phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type RAG1 phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type RAG2 phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type ZAP70 phenotype. In exemplary embodiments, a mutant cell exhibits a wild-type HBB phenotype. In some embodiments, the target polynucleotide sequence in a cell is altered to correct or repair a genetic mutation (e.g., to restore a normal phenotype to the cell). In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more ADA mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more AK2 mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more CD3D mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more DCRE1C mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more IL2RG mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is

altered to correct or repair one or more JAK3 mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more LIG4 mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more NHEJ1 mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more PNP mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more PRKDC mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more RAG1 mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more RAG2 mutations involved in SCID. In an exemplary embodiment, a target SCID-associated polynucleotide sequence in a cell is altered to correct or repair one or more ZAP70 mutations involved in SCID. In an exemplary embodiment, a target SCD-associated polynucleotide sequence in a cell is altered to correct or repair one or more HBB mutations involved in SCD. In an exemplary embodiment, a target SCD-associated polynucleotide sequence in a cell is altered to correct or repair one or more HBB mutations involved in SCD. In another exemplary embodiment, a target beta thalassemia-associated polynucleotide sequence in a cell is altered to correct or repair one or more HBB mutations involved in beta thalassemia. In some embodiments, the target polynucleotide sequence in a cell is altered to induce a genetic mutation (e.g., to disrupt the function of a gene or genomic element).

[0182] In some embodiments, the alteration is an indel. As used herein, "indel" refers to a mutation resulting from an insertion, deletion, or a combination thereof. As will be appreciated by those skilled in the art, an indel in a coding region of a genomic sequence will result in a frameshift mutation, unless the length of the indel is a multiple of three. In some embodiments, the alteration is a point mutation. As used herein, "point mutation" refers to a substitution that replaces one of the nucleotides. A CRISPR/Cas system of the present invention can be used to induce an indel of any length or a point mutation in a target polynucleotide sequence.

[0183] In some embodiments, the alteration results in a knock out of the target

useful for a variety of applications. For example, knocking out a target polynucleotide sequence in a cell can be performed *in vitro* for research purposes. For *ex vivo* or *in vivo* purposes, knocking out a target polynucleotide sequence in a cell can be useful for treating or preventing a disorder associated with expression of the target polynucleotide sequence.

[0184] As used herein, "knock out" includes deleting all or a portion of the target polynucleotide sequence in a way that interferes with the function of the target polynucleotide sequence. For example, a knock out can be achieved by altering a target polynucleotide sequence by inducing an indel in the target polynucleotide sequence in a functional domain of the target polynucleotide sequence (e.g., a DNA binding domain). Those skilled in the art will readily appreciate how to use the CRISPR/Cas systems of the present invention to knock out a target polynucleotide sequence or a portion thereof based upon the details described herein.

[0185] In some embodiments, the alteration results in reduced expression of the target polynucleotide sequence. The terms "decrease," "reduced," "reduction," and "decrease" are all used herein generally to mean a decrease by a statistically significant amount. However, for avoidance of doubt, decrease," "reduced," "reduction," "decrease" means a decrease by at least 10% as compared to a reference level, for example a decrease by at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least about 90% or up to and including a 100% decrease (i.e. absent level as compared to a reference sample), or any decrease between 10-100% as compared to a reference level.

[0186] In some embodiments, the alteration results in increased expression of the target polynucleotide sequence. The terms "increased" ,"increase" or "enhance" or "activate" are all used herein to generally mean an increase by a statically significant amount; for the avoidance of any doubt, the terms "increased", "increase" or "enhance" or "activate" means an increase of at least 10% as compared to a reference level, for example an increase of at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least about 90% or up to and including a 100% increase or any increase between 10-100% as compared to a reference level, or at least about a 2-fold, or at least about a 3-fold, or at least about a 4-fold, or at least about a 5-fold or at least about a 10-fold

[0187] The term "statistically significant" or "significantly" refers to statistical significance and generally means a two standard deviation (2SD) below normal, or lower, concentration of the marker. The term refers to statistical evidence that there is a difference. It is defined as the probability of making a decision to reject the null hypothesis when the null hypothesis is actually true. The decision is often made using the p-value.

[0188] In some embodiments, the alteration is a homozygous alteration. In some embodiments, the alteration is a heterozygous alteration.

[0189] In some embodiments, the alteration results in correction of the target polynucleotide sequence from an undesired sequence to a desired sequence. The CRISPR/Cas systems of the present invention can be used to correct any type of mutation or error in a target polynucleotide sequence. For example, the CRISPR/Cas systems of the present invention can be used to insert a nucleotide sequence that is missing from a target polynucleotide sequence due to a deletion. The CRISPR/Cas systems of the present invention can also be used to delete or excise a nucleotide sequence from a target polynucleotide sequence due to an insertion mutation. In some instances, the CRISPR/Cas systems of the present invention can be used to replace an incorrect nucleotide sequence with a correct nucleotide sequence (e.g., to restore function to a target polynucleotide sequence that is impaired due to a loss of function mutation, i.e., a SNP).

[0190] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant ADA polynucleotide sequences with wild-type ADA polynucleotide sequences.

[0191] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant AK2 polynucleotide sequences with wild-type AK2 polynucleotide sequences.

[0192] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant CD3D polynucleotide sequences with wild-type CD3D polynucleotide sequences.

[0193] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant DCLRE1C polynucleotide sequences with wild-type DCLRE1C polynucleotide sequences.

[0194] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant IL2RG polynucleotide sequences with wild-type IL2RG polynucleotide sequences.

[0195] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant IL7R polynucleotide sequences with wild-type IL7R polynucleotide sequences.

[0196] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant JAK3 polynucleotide sequences with wild-type JAK3 polynucleotide sequences.

[0197] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant LIG4 polynucleotide sequences with wild-type LIG4 polynucleotide sequences.

[0198] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant NHEJ1 polynucleotide sequences with wild-type NHEJ1 polynucleotide sequences.

[0199] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant PNP polynucleotide sequences with wild-type PNP polynucleotide sequences.

[0200] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant PRKDC polynucleotide sequences with wild-type PRKDC polynucleotide sequences.

[0201] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant RAG1 polynucleotide sequences with wild-type RAG1 polynucleotide sequences.

[0202] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant RAG2 polynucleotide sequences with wild-type RAG2 polynucleotide sequences.

[0203] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant ZAP70 polynucleotide sequences with wild-type ZAP70 polynucleotide sequences.

[0204] In exemplary embodiments, the CRISPR/Cas systems of the present invention can be used to replace mutant HBB polynucleotide sequences with wild-type

[0205] The CRISPR/Cas systems of the present invention can alter target polynucleotides with surprisingly high efficiency as compared to conventional CRISPR/Cas systems. In certain embodiments, the efficiency of alteration is at least about 5%. In certain embodiments, the efficiency of alteration is at least about 10%. In certain embodiments, the efficiency of alteration is from about 10% to about 80%. In certain embodiments, the efficiency of alteration is from about 30% to about 80%. In certain embodiments, the efficiency of alteration is from about 50% to about 80%. In some embodiments, the efficiency of alteration is greater than or equal to about 80%.

[0206] The CRISPR/Cas systems of the present invention can be used to alter any target polynucleotide sequence in a cell. Those skilled in the art will readily appreciate that desirable target polynucleotide sequences to be altered in any particular cell may correspond to any genomic sequence for which expression of the genomic sequence is associated with a disorder or otherwise facilitates entry of a pathogen into the cell. For example, a desirable target polynucleotide sequence to alter in a cell may be a polynucleotide sequence corresponding to a genomic sequence which contains a disease associated single polynucleotide polymorphism (e.g., sickle cell disease, e.g., sickle cell anemia). In such example, the CRISPR/Cas systems of the present invention can be used to correct the disease associated SNP by replacing it with a wild-type allele (e.g., replacing a Glu6Val SNP in hemoglobin S to Val6Glu, a Glu6Lys SNP in hemoglobin C to Lys6Glu, a Glu121Gln SNP in hemoglobin D to Gln121Glu, a Glu121Lys SNP in hemoglobin O to Lys121Glu). As another example, a polynucleotide sequence of a target gene which is responsible for entry or proliferation of a pathogen into a cell may be a suitable target for deletion or insertion to disrupt the function of the target gene to prevent the pathogen from entering the cell or proliferating inside the cell.

[0207] In some embodiments, the target polynucleotide sequence is a genomic sequence. In some embodiments, the target polynucleotide sequence is a human genomic sequence. In some embodiments, the target polynucleotide sequence is a mammalian genomic sequence. In some embodiments, the target polynucleotide sequence is a vertebrate genomic sequence. In some embodiments, the target sequence is a mutant or variant genomic sequence (e.g., a ADA mutant, a AK2 mutant, a CD3D mutant, a DCLRE1C mutant, a IL2RG mutant, a IL7R mutant, a JAK3 mutant, a LIG4 mutant, a NHEJ1 mutant, a PNP mutant, a PRKDC mutant, a RAG1 mutant, a RAG2 mutant, a

DCLRE1C, IL2RG, IL7R, JAK3, LIG4, NHEJ1, PNP, PRKDC, RAG1, RAG2, ZAP70, HBB). In some embodiments, the target polynucleotide sequence is a mutant or variant mammalian genomic sequence. In some embodiments, the target polynucleotide sequence is a mammalian mutant or variant genomic sequence.

[0208] In some embodiments, a target polynucleotide sequence is a pathogenic genomic sequence. Exemplary pathogenic genomic sequences include, but are not limited to a viral genomic sequence, a bacterial genomic sequence, a fungal genomic sequence, a toxin genomic sequence, or a parasitic genomic sequence. In such embodiments, the CRISPR/Cas systems of the present invention can be used to disrupt the function of a pathogen (e.g., to treat or prevent an infection by the pathogen) by cleaving a genomic sequence of the pathogen (e.g., a genomic sequence that is critical for entry into a cell, or responsible for multiplication, growth or survival once the pathogen is inside a cell).

[0209] In some embodiments, the target polynucleotide sequence is an SCID-associated polynucleotide sequence.

[0210] In some embodiments, the target polynucleotide sequence is ADA or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of ADA or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of ADA or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of ADA or a portion thereof.

[0211] In some embodiments, the target polynucleotide sequence is AK2 or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of AK2 or a portion thereof. In some embodiments, the target polynucleotide sequence is AK2 coding sequence 1 or a portion thereof. In some embodiments, the target polynucleotide sequence is AK2 coding sequence 2 or a portion thereof. In some embodiments, the target polynucleotide sequence is AK2 coding sequence 3 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of AK2 or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of AK2 or a portion thereof.

[0212] In some embodiments, the target polynucleotide sequence is CD3D or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of CD3D or a portion thereof. In some embodiments, the target polynucleotide sequence is

embodiments, the target polynucleotide sequence is a homolog of CD3D or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of CD3D or a portion thereof.

[0213] In some embodiments, the target polynucleotide sequence is DCLRE1C or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of DCLRE1C or a portion thereof. In some embodiments, the target polynucleotide sequence is DCLRE1C coding sequence 1 or a portion thereof. In some embodiments, the target polynucleotide sequence is DCLRE1C coding sequence 1 or a portion thereof. In some embodiments, the target polynucleotide sequence is DCLRE1C coding sequence 2 or a portion thereof. In some embodiments, the target polynucleotide sequence is DCLRE1C coding sequence 3 or a portion thereof. In some embodiments, the target polynucleotide sequence is DCLRE1C coding sequence 4 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of DCLRE1C or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of DCLRE1C or a portion thereof.

[0214] In some embodiments, the target polynucleotide sequence is IL2RG or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of IL2RG or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of IL2RG or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of IL2RG or a portion thereof.

[0215] In some embodiments, the target polynucleotide sequence is IL7R or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of IL7R or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of IL7R or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of IL7R or a portion thereof.

[0216] In some embodiments, the target polynucleotide sequence is JAK3 or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of JAK3 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of JAK3 or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of JAK3 or a portion thereof.

[0217] In some embodiments, the target polynucleotide sequence is LIG4 or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of

polynucleotide sequence is LIG4 coding sequence 2 or a portion thereof. In some embodiments, the target polynucleotide sequence is LIG4 coding sequence 3 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of LIG4 or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of LIG4 or a portion thereof.

[0218] In some embodiments, the target polynucleotide sequence is NHEJ1 or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of NHEJ1 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of NHEJ1 or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of NHEJ1 or a portion thereof.

[0219] In some embodiments, the target polynucleotide sequence is PNP or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of PNP or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of PNP or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of PNP or a portion thereof.

[0220] In some embodiments, the target polynucleotide sequence is PRKDC or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of PRKDC or a portion thereof. In some embodiments, the target polynucleotide sequence is PRKDC coding sequence 1 or a portion thereof. In some embodiments, the target polynucleotide sequence is PRKDC coding sequence 2 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of PRKDC or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of PRKDC or a portion thereof.

[0221] In some embodiments, the target polynucleotide sequence is RAG1 or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of RAG1 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of RAG1 or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of RAG1 or a portion thereof.

[0222] In some embodiments, the target polynucleotide sequence is RAG2 or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of RAG2 or a portion thereof. In some embodiments, the target polynucleotide sequence is RAG2 coding sequence 1 or a portion thereof. In some embodiments, the target

thereof. In some embodiments, the target polynucleotide sequence is a homolog of RAG2 or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of RAG2 or a portion thereof.

[0223] In some embodiments, the target polynucleotide sequence is ZAP70 or a portion thereof. In some embodiments, the target polynucleotide sequence is a variant of ZAP70 or a portion thereof. In some embodiments, the target polynucleotide sequence is ZAP70 coding sequence 1 or a portion thereof. In some embodiments, the target polynucleotide sequence is ZAP70 coding sequence 2 or a portion thereof. In some embodiments, the target polynucleotide sequence is a homolog of ZAP70 or a portion thereof. In some embodiments, the target polynucleotide sequence is an ortholog of ZAP70 or a portion thereof.

[0224] In some embodiments, the target polynucleotide sequence is a SCD-associated polynucleotide sequence (e.g., a mutant form of HBB; NCBI Gene ID: 3043) or a portion thereof. In some embodiments, the target polynucleotide sequence is a mutant homolog of a SCD-associated polynucleotide sequence (e.g., a mutated homolog of HBB) or a portion thereof. In some embodiments, the target polynucleotide sequence is a mutant ortholog of a SCD-associated polynucleotide sequence (e.g., a mutated ortholog of HBB) or a portion thereof.

[0225] In some embodiments, the target polynucleotide sequence is a beta thalassemia-associated polynucleotide sequence (e.g., a mutant form of HBB).

[0226] In some embodiments, the target polynucleotide sequence is a mutant homolog of a beta thalassemia-associated polynucleotide sequence (e.g., a mutated homolog of HBB) or a portion thereof. In some embodiments, the target polynucleotide sequence is a mutant ortholog of a beta thalassemia-associated polynucleotide sequence (e.g., a mutated ortholog of HBB) or a portion thereof. The relevant portions of these target polynucleotide sequences correspond to the guide sequences shown in Figures 1, 2-4, 5-6, 7-10, 12, 13, 14, 15-17, 18, 19, 20-21, 22, 23-25, 26-27, and 11, respectively.

[0227] It should be appreciated that the CRISPR/Cas systems of the present invention can cleave target polynucleotide sequences in a variety of ways. In some embodiments, the target polynucleotide sequence is cleaved such that a double-strand break results. In some embodiments, the target polynucleotide sequence is cleaved such that a single-strand break results.

contains a suitable target motif that allows at least one ribonucleic acid of the CRISPR/Cas system to direct the Cas protein to and hybridize to the target motif. Those skilled in the art will appreciate that the target motif for targeting a particular polynucleotide depends on the CRISPR/Cas system being used, and the sequence of the polynucleotide to be targeted.

[0229] In some embodiments, the target motif is at least 20 bp in length. In some embodiments, the target motif is a 20-nucleotide DNA sequence. In some embodiments, the target motif is a 20-nucleotide DNA sequence beginning with G and immediately precedes an NGG motif recognized by the Cas protein. In some embodiments, the target motif is $G(N)_{19}NGG$. In some embodiments, the target motif is a 20-nucleotide DNA sequence and immediately precedes an NGG motif recognized by the Cas protein. In some embodiments, the target motif is $(N)_{20}NGG$. It is to be understood that the type of target motif for each of the ADA, AK2, CD3D, DCLRE1C, HBB, IL2RG, IL7R, JAK3, LIG4, NHEJ1, PNP, PRKDC, RAG1, RAG2, and ZAP70 target polynucleotide sequences can be found in the "site_type" column of Figures 1, 2-4, 5-6, 7-10, 11, 12, 13, 14, 15-17, 18, 19, 20-21, 22, 23-25, and 26-27, respectively.

[0230] The target motifs of the present invention can be selected to minimize off-target effects of the CRISPR/Cas systems of the present invention. In some embodiments, the target motif is selected such that it contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell. In some embodiments, the target motif is selected such that it contains at least one mismatch when compared with all other genomic nucleotide sequences in the cell. Those skilled in the art will appreciate that a variety of techniques can be used to select suitable target motifs for minimizing off-target effects (e.g., bioinformatics analyses).

[0231] In some embodiments, the CRISPR/Cas systems of the present invention utilize homology-directed repair to correct target polynucleotide sequences. In some embodiments, subsequent to cleavage of the target polynucleotide sequence, homology-directed repair occurs. In some embodiments, homology-directed repair is performed using an exogenously introduced DNA repair template. The exogenously introduced DNA repair template can be single-stranded or double-stranded. The DNA repair template can be of any length. Those skilled in the art will appreciate that the length of any particular DNA repair template will depend on the target polynucleotide sequence

disease associated polymorphisms (e.g., SNPs). For example, homology-directed repair of a mutant allele comprising such SNPs can be achieved with a CRISPR/Cas system by selecting two target motifs which flank the mutant allele, and an designing a DNA repair template to match the wild-type allele.

[0232] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence is corrected by homology-directed repair utilizing a corresponding normal wild-type gene sequence as a DNA repair template.

[0233] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant ADA) is corrected by homology-directed repair utilizing a normal wild-type ADA sequence or portions thereof as a DNA repair template.

[0234] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant AK2) is corrected by homology-directed repair utilizing a normal wild-type AK2 sequence (e.g., wild-type AK2 coding sequence 1, AK2 coding sequence 2, and AK2 coding sequence 3 or portions thereof) as a DNA repair template.

[0235] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant CD3D) is corrected by homology-directed repair utilizing a normal wild-type CD3D sequence (e.g., wild-type CD3D coding sequence 1, and CD3D coding sequence 2 or portions thereof) as a DNA repair template.

[0236] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant DCLRE1C) is corrected by homology-directed repair utilizing a normal wild-type DCLRE1C sequence (e.g., wild-type DCLRE1C coding sequence 1, DCLRE1C coding sequence 2, DCLRE1C coding sequence 3, and DCLRE1C coding sequence 4 or portions thereof) as a DNA repair template.

[0237] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant IL2RG) is corrected by homology-directed repair utilizing a normal wild-type IL2RG sequence or portions thereof as a DNA repair template.

[0238] In an exemplary embodiment, a cleaved target SCID-associated

repair utilizing a normal wild-type IL7R sequence or portions thereof as a DNA repair template.

[0239] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant JAK3) is corrected by homology-directed repair utilizing a normal wild-type JAK3 sequence or portions thereof as a DNA repair template.

[0240] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant LIG4) is corrected by homology-directed repair utilizing a normal wild-type LIG4 sequence (e.g., wild-type LIG4 coding sequence 1, LIG4 coding sequence 2, LIG4 coding sequence 3, or portions thereof) as a DNA repair template.

[0241] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant NHEJ1) is corrected by homology-directed repair utilizing a normal wild-type NHEJ1 sequence or portions thereof as a DNA repair template.

[0242] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant PNP) is corrected by homology-directed repair utilizing a normal wild-type PNP sequence or portions thereof as a DNA repair template.

[0243] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant PRKDC) is corrected by homology-directed repair utilizing a normal wild-type PRKDC sequence (e.g., wild-type PRKDC coding sequence 1, PRKDC coding sequence 2, or portions thereof) as a DNA repair template.

[0244] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant RAG1) is corrected by homology-directed repair utilizing a normal wild-type RAG1 sequence or portions thereof as a DNA repair template.

[0245] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant RAG2) is corrected by homology-directed repair utilizing a normal wild-type RAG2 sequence (e.g., wild-type RAG2 coding sequence 1, RAG2 coding sequence 2, RAG2 coding sequence 3, or portions

[0246] In an exemplary embodiment, a cleaved target SCID-associated polynucleotide associated sequence (i.e., mutant ZAP70) is corrected by homology-directed repair utilizing a normal wild-type ZAP70 sequence (e.g., wild-type ZAP70 coding sequence 1, ZAP70 coding sequence 2, or portions thereof) as a DNA repair template.

[0247] In an exemplary embodiment, a cleaved target SCD-associated polynucleotide associated sequence is corrected by homology-directed repair utilizing a normal wild-type HBB sequence or portions thereof as a DNA repair template.

[0248] In an exemplary embodiment, a cleaved target beta thalassemia-associated polynucleotide associated sequence is corrected by homology-directed repair utilizing a normal wild-type HBB sequence or portions thereof as a DNA repair template.

[0249] In some embodiments, a CRISPR/Cas system of the present invention includes a Cas protein and at least one to two one ribonucleic acids that are capable of directing the Cas protein to and hybridizing to a target motif of a target polynucleotide sequence.

[0250] As used herein, "protein" and "polypeptide" are used interchangeably to refer to a series of amino acid residues joined by peptide bonds (i.e., a polymer of amino acids) and include modified amino acids (e.g., phosphorylated, glycated, glycosolated, etc.) and amino acid analogs. Exemplary polypeptides or proteins include gene products, naturally occurring proteins, homologs, paralogs, fragments and other equivalents, variants, and analogs of the above.

[0251] In some embodiments, a Cas protein comprises one or more amino acid substitutions or modifications. In some embodiments, the one or more amino acid substitutions comprises a conservative amino acid substitution. In some instances, substitutions and/or modifications can prevent or reduce proteolytic degradation and/or extend the half-life of the polypeptide in a cell. In some embodiments, the Cas protein can comprise a peptide bond replacement (e.g., urea, thiourea, carbamate, sulfonyl urea, etc.). In some embodiments, the Cas protein can comprise a naturally occurring amino acid. In some embodiments, the Cas protein can comprise an alternative amino acid (e.g., D-amino acids, beta-amino acids, homocysteine, phosphoserine, etc.). In some embodiments, a Cas protein can comprise a modification to include a moiety (e.g., PEGylation, glycosylation, lipidation, acetylation, end-capping, etc.).

Cas5, Cas6, Cas7, Cas8 and Cas9. In some embodiments, a Cas protein comprises a Cas protein of an *E. coli* subtype (also known as CASS2). Exemplary Cas proteins of the *E. Coli* subtype include, but are not limited to Cse1, Cse2, Cse3, Cse4, and Cas5e. In some embodiments, a Cas protein comprises a Cas protein of the Ypest subtype (also known as CASS3). Exemplary Cas proteins of the Ypest subtype include, but are not limited to Csy1, Csy2, Csy3, and Csy4. In some embodiments, a Cas protein comprises a Cas protein of the Nmeni subtype (also known as CASS4). Exemplary Cas proteins of the Nmeni subtype include, but are not limited to Csn1 and Csn2. In some embodiments, a Cas protein comprises a Cas protein of the Dvulg subtype (also known as CASS1). Exemplary Cas proteins of the Dvulg subtype include Csd1, Csd2, and Cas5d. In some embodiments, a Cas protein comprises a Cas protein of the Tneap subtype (also known as CASS7). Exemplary Cas proteins of the Tneap subtype include, but are not limited to, Cst1, Cst2, Cas5t. In some embodiments, a Cas protein comprises a Cas protein of the Hmari subtype. Exemplary Cas proteins of the Hmari subtype include, but are not limited to Csh1, Csh2, and Cas5h. In some embodiments, a Cas protein comprises a Cas protein of the Apern subtype (also known as CASS5). Exemplary Cas proteins of the Apern subtype include, but are not limited to Csa1, Csa2, Csa3, Csa4, Csa5, and Cas5a. In some embodiments, a Cas protein comprises a Cas protein of the Mtube subtype (also known as CASS6). Exemplary Cas proteins of the Mtube subtype include, but are not limited to Csm1, Csm2, Csm3, Csm4, and Csm5. In some embodiments, a Cas protein comprises a RAMP module Cas protein. Exemplary RAMP module Cas proteins include, but are not limited to, Cmr1, Cmr2, Cmr3, Cmr4, Cmr5, and Cmr6.

[0253] In some embodiments, the Cas protein is a *Streptococcus pyogenes* Cas9 protein or a functional portion thereof. In some embodiments, the Cas protein is Cas9 protein from any bacterial species or functional portion thereof. Cas9 protein is a member of the type II CRISPR systems which typically include a trans-coded small RNA (tracrRNA), endogenous ribonuclease 3 (rnc) and a Cas protein. Cas 9 protein (also known as CRISPR-associated endonuclease Cas9/Csn1) is a polypeptide comprising 1368 amino acids. An exemplary amino acid sequence of a Cas9 protein (SEQ ID NO: 298) is shown in Figure 28. Cas 9 contains 2 enconuclease domains, including an RuvC-like domain (residues 7-22, 759-766 and 982-989) which cleaves target DNA that is noncomplementary to crRNA, and an HNH nuclease domain (residues 810-872) which

[0254] As used herein, "functional portion" refers to a portion of a peptide which retains its ability to complex with at least one ribonucleic acid (e.g., guide RNA (gRNA)) and cleave a target polynucleotide sequence. In some embodiments, the functional portion comprises a combination of operably linked Cas9 protein functional domains selected from the group consisting of a DNA binding domain, at least one RNA binding domain, a helicase domain, and an endonuclease domain. In some embodiments, the functional domains form a complex.

[0255] In some embodiments, a functional portion of the Cas9 protein comprises a functional portion of a RuvC-like domain. In some embodiments, a functional portion of the Cas9 protein comprises a functional portion of the HNH nuclease domain.

[0256] It should be appreciated that the present invention contemplates various of ways of contacting a target polynucleotide sequence with a Cas protein (e.g., Cas9). In some embodiments, exogenous Cas protein can be introduced into the cell in polypeptide form. In certain embodiments, Cas proteins can be conjugated to or fused to a cell-penetrating polypeptide or cell-penetrating peptide. As used herein, "cell-penetrating polypeptide" and "cell-penetrating peptide" refers to a polypeptide or peptide, respectively, which facilitates the uptake of molecule into a cell. The cell-penetrating polypeptides can contain a detectable label.

[0257] In certain embodiments, Cas proteins can be conjugated to or fused to a charged protein (e.g., that carries a positive, negative or overall neutral electric charge). Such linkage may be covalent. In some embodiments, the Cas protein can be fused to a superpositively charged GFP to significantly increase the ability of the Cas protein to penetrate a cell (Cronican *et al. ACS Chem Biol.*2010;5(8):747-52).

[0258] In certain embodiments, the Cas protein can be fused to a protein transduction domain (PTD) to facilitate its entry into a cell. Exemplary PTDs include Tat, oligoarginine, and penetratin.

[0259] In some embodiments, the Cas9 protein comprises a Cas9 polypeptide fused to a cell-penetrating peptide. In some embodiments, the Cas9 protein comprises a Cas9 polypeptide fused to a PTD. In some embodiments, the Cas9 protein comprises a Cas9 polypeptide fused to a tat domain. In some embodiments, the Cas9 protein comprises a Cas9 polypeptide fused to an oligoarginine domain. In some embodiments, the Cas9 protein comprises a Cas9 polypeptide fused to a penetratin domain. In some

[0260] In some embodiments, the Cas protein can be introduced into a cell containing the target polynucleotide sequence in the form of a nucleic acid encoding the Cas protein (e.g., Cas9). The process of introducing the nucleic acids into cells can be achieved by any suitable technique. Suitable techniques include calcium phosphate or lipid-mediated transfection, electroporation, and transduction or infection using a viral vector. In some embodiments, the nucleic acid comprises DNA. In some embodiments, the nucleic acid comprises a modified DNA, as described herein. In some embodiments, the nucleic acid comprises mRNA. In some embodiments, the nucleic acid comprises a modified mRNA, as described herein (e.g., a synthetic, modified mRNA).

[0261] In some embodiments, the Cas protein is complexed with the one to two ribonucleic acids. In some embodiments, the Cas protein and the one to two ribonucleic acids are contained in a nanoparticle. In some embodiments, the Cas protein and the one to two ribonucleic acids are contained in a lipid nanoparticle, as described herein. In some embodiments, the Cas protein is encoded by a modified nucleic acid, as described herein (e.g., a synthetic, modified mRNA).

[0262] The methods of the present invention contemplate the use of any ribonucleic acid that is capable of directing a Cas protein to and hybridizing to a target motif of a target polynucleotide sequence. In some embodiments, at least one of the ribonucleic acids comprises tracrRNA. In some embodiments, at least one of the ribonucleic acids comprises CRISPR RNA (crRNA). In some embodiments, at least one of the ribonucleic acids comprises a guide RNA that directs the Cas protein to and hybridizes to a target motif of the target polynucleotide sequence in a cell.

[0263] The ribonucleic acids of the present invention can be selected to hybridize to a variety of different target motifs, depending on the particular CRISPR/Cas system employed, and the sequence of the target polynucleotide, as will be appreciated by those skilled in the art. The one to two ribonucleic acids can also be selected to minimize hybridization with nucleic acid sequences other than the target polynucleotide sequence. In some embodiments, the one to two ribonucleic acids hybridize to a target motif that contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell. In some embodiments, the one to two ribonucleic acids hybridize to a target motif that contains at least one mismatch when compared with all other genomic nucleotide sequences in the cell. In some embodiments, the one to two

of the one to two ribonucleic acids are designed to hybridize to target motifs immediately adjacent to deoxyribonucleic acid motifs recognized by the Cas protein which flank a mutant allele located between the target motifs.

[0264] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequence of GTAACGGCAGACTTCTCCAC. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. It should be appreciated that the former sequence is the protospacer sequence in the guide RNA, whereas the latter sequence is the protospacer plus the PAM.

[0265] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1.

[0266] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1.

[0267] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2.

[0268] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3.

[0269] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 4. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 4.

[0270] In some embodiments, at least one of the one to two ribonucleic acids

acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5.

[0271] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6.

[0272] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7.

[0273] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8.

[0274] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9.

[0275] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10.

[0276] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11.

sequences of Fig. 12. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12.

[0278] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 13. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 13.

[0279] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 14. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 14.

[0280] In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15. In some embodiments, at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15.

[0281] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above do not include the 3 nucleotide NGG sequence. For example, if the target site sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one of the one to two ribonucleic acid sequences is GATGCTCAGTACAGCCACCT. As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, a ribonucleic acid sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCT*G*AGTACAGCCACCT, with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleotide, the third nucleotide, the fourth nucleotide, the fifth nucleotide, the sixth nucleotide, the seventh nucleotide, the eighth nucleotide, the ninth nucleotide, the tenth nucleotide, the eleventh nucleotide, the twelfth nucleotide, the thirteenth nucleotide, the fourteenth nucleotide, the fifteenth nucleotide, the sixteenth

[0282] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 12 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 12 nucleotide fragment is GTACAGCCACCT.

[0283] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 13 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15 In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 13 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG . In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 13 nucleotide fragment is AGTACAGCCACCT

fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 14 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 14 nucleotide fragment is CAGTACAGCCACCT.

[0285] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 15 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 15 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 15 nucleotide fragment is TCAGTACAGCCACCT.

[0286] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 16 nucleotide

described above comprise at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 16 nucleotide fragment is CTCAGTACAGCCACCT.

[0287] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 17 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 17 nucleotide fragment of a ribonucleic acid sequence of any of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 17 nucleotide fragment is GCTCAGTACAGCCACCT.

[0288] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 18 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids

acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 18 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 18 nucleotide fragment is TGCTCAGTACAGCCACCT.

[0289] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 19 nucleotide fragment is ATGCTCAGTACAGCCACCT.

[0290] In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 20 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic

20 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequences of the at least one of the one to two ribonucleic acids described above comprise at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one of the one to two ribonucleic acids which comprises at least a 20 nucleotide fragment is GATGCTCAGTACAGCCACCT.

[0291] The present invention also contemplates multiplex genomic editing. Those skilled in the art will appreciate that the description above with respect to genomic editing of a single gene is equally applicable to the multiplex genomic editing embodiments described below.

[0292] In another aspect, the present invention provides a method for simultaneously altering multiple target polynucleotide sequences in a cell.

[0293] In some embodiments, a method for simultaneously altering multiple target polynucleotide sequences in a cell comprises a method for simultaneously altering multiple target SCID-associated polynucleotides in a cell.

[0294] An exemplary method for simultaneously altering multiple target SCID-asssociated polynucleotide sequences in a cell comprises contacting the SCID-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved. In some embodiments, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0295] In some embodiments, a method for simultaneously altering multiple target polynucleotide sequences in a cell comprises a method for simultaneously altering multiple target SCD-associated polynucleotides in a cell.

[0296] An exemplary method for simultaneously altering multiple target SCD-asssociated polynucleotide sequences in a cell comprises contacting the SCD-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic

are cleaved. In some embodiments, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0297] In some embodiments, a method for simultaneously altering multiple target polynucleotide sequences in a cell comprises a method for simultaneously altering multiple target beta thalassemia-associated polynucleotides in a cell.

[0298] An exemplary method for simultaneously altering multiple target beta thalassemia-associated polynucleotide sequences in a cell comprises contacting the polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved. In some embodiments, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%.

[0299] In yet another aspect, the present invention provides a method for treating or preventing a disorder associated with expression of polynucleotide sequences in a subject.

[0300] In some embodiments, a method for treating or preventing a disorder associated with expression of polynucleotide sequences in a subject comprises a method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject.

[0301] An exemplary method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject comprises (a) altering target SCID-associated polynucleotide sequences in a cell *ex vivo* by contacting the SCID-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequences. In some embodiments, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%. In some embodiments, the method includes the step of contacting before the step of introducing the cell into the

polynucleotide sequence, thereby allowing homology-directed repair to replace the cleaved SCID-associated polynucleotide sequence with the wild-type or normal gene sequence.

[0302] In embodiments in which the target SCID-associated polynucleotide sequences comprise ADA polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal ADA polynucleotide sequence.

[0303] In embodiments in which the target SCID-associated polynucleotide sequences comprise AK2 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal AK2 polynucleotide sequence.

[0304] In embodiments in which the target SCID-associated polynucleotide sequences comprise CD3D polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal CD3D polynucleotide sequence.

[0305] In embodiments in which the target SCID-associated polynucleotide sequences comprise DCLRE1C polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal DCLRE1C polynucleotide sequence.

[0306] In embodiments in which the target SCID-associated polynucleotide sequences comprise IL2RG polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal IL2RG polynucleotide sequence.

[0307] In embodiments in which the target SCID-associated polynucleotide sequences comprise IL7R polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal IL7R polynucleotide sequence.

[0308] In embodiments in which the target SCID-associated polynucleotide sequences comprise JAK3 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal JAK3 polynucleotide sequence.

[0309] In embodiments in which the target SCID-associated polynucleotide

repair template comprises a corresponding wild-type or normal LIG4 polynucleotide sequence.

[0310] In embodiments in which the target SCID-associated polynucleotide sequences comprise NHEJ1 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal NHEJ1 polynucleotide sequence.

[0311] In embodiments in which the target SCID-associated polynucleotide sequences comprise PNP polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal PNP polynucleotide sequence.

[0312] In embodiments in which the target SCID-associated polynucleotide sequences comprise PRKDC polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal PRKDC polynucleotide sequence.

[0313] In embodiments in which the target SCID-associated polynucleotide sequences comprise RAG1 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal RAG1 polynucleotide sequence.

[0314] In embodiments in which the target SCID-associated polynucleotide sequences comprise RAG2 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal RAG2 polynucleotide sequence.

[0315] In embodiments in which the target SCID-associated polynucleotide sequences comprise ZAP70 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal ZAP70 polynucleotide sequence.

[0316] In some embodiments, a method for treating or preventing a disorder associated with expression of polynucleotide sequences in a subject comprises a method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject.

[0317] An exemplary method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject comprises (a)

palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequences. In some embodiments, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%. In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved SCD-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the cleaved SCD-associated polynucleotide sequence with the normal HBB sequence.

[0318] In some embodiments, a method for treating or preventing a disorder associated with expression of polynucleotide sequences in a subject comprises a method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject.

[0319] An exemplary method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject comprises (a) altering target beta thalassemia-associated polynucleotide sequences in a cell *ex vivo* by contacting the beta thalassemia-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequences. In some embodiments, the efficiency of alteration of cells that express Cas protein is from about 50% to about 80%,

[0320] In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved beta thalassemia-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to

[0321] As used herein, the terms "administering," "introducing" and "transplanting" are used interchangeably in the context of the placement of cells, e.g. cells described herein comprising a target polynucleotide sequence altered according to the methods of the invention into a subject, by a method or route which results in at least partial localization of the introduced cells at a desired site. The cells can be implanted directly to the desired site, or alternatively be administered by any appropriate route which results in delivery to a desired location in the subject where at least a portion of the implanted cells or components of the cells remain viable. The period of viability of the cells after administration to a subject can be as short as a few hours, e. g. twenty-four hours, to a few days, to as long as several years. In some instances, the cells can also be administered a location other than the desired site, such as in the liver or subcutaneously, for example, in a capsule to maintain the implanted cells at the implant location and avoid migration of the implanted cells.

[0322] For *ex vivo* methods, cells can include autologous cells, i.e., a cell or cells taken from a subject who is in need of altering a target polynucleotide sequence in the cell or cells (i.e., the donor and recipient are the same individual). Autologous cells have the advantage of avoiding any immunologically-based rejection of the cells. Alternatively, the cells can be heterologous, e.g., taken from a donor. The second subject can be of the same or different species. Typically, when the cells come from a donor, they will be from a donor who is sufficiently immunologically compatible with the recipient, i.e., will not be subject to transplant rejection, to lessen or remove the need for immunosuppression. In some embodiments, the cells are taken from a xenogeneic source, i.e., a non-human mammal that has been genetically engineered to be sufficiently immunologically compatible with the recipient, or the recipient's species. Methods for determining immunological compatibility are known in the art, and include tissue typing to assess donor-recipient compatibility for HLA and ABO determinants. See, e.g., *Transplantation Immunology*, Bach and Auchincloss, Eds. (Wiley, John & Sons, Incorporated 1994).

[0323] Any suitable cell culture media can be used for *ex vivo* methods of the invention.

[0324] Another exemplary method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject comprises altering target SCID-associated polynucleotide sequences in a cell by

acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target moieties of the target SCID-associated polynucleotide sequences, and wherein the target SCID-associated polynucleotide sequences are cleaved, thereby treating or preventing a disorder associated with expression of the polynucleotide sequences.

[0325] In some embodiments, the method includes the step of contacting the cleaved SCID-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a corresponding wild-type or normal polynucleotide sequence, thereby allowing homology-directed repair to replace the cleaved SCID-associated polynucleotide sequence with the corresponding wild-type or normal polynucleotide sequence.

[0326] In embodiments in which the target SCID-associated polynucleotide sequences comprise ADA polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal ADA polynucleotide sequence.

[0327] In embodiments in which the target SCID-associated polynucleotide sequences comprise AK2 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal AK2 polynucleotide sequence.

[0328] In embodiments in which the target SCID-associated polynucleotide sequences comprise CD3D polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal CD3D polynucleotide sequence.

[0329] In embodiments in which the target SCID-associated polynucleotide sequences comprise DCLRE1C polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal DCLRE1C polynucleotide sequence.

[0330] In embodiments in which the target SCID-associated polynucleotide sequences comprise IL2RG polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal IL2RG polynucleotide sequence.

[0331] In embodiments in which the target SCID-associated polynucleotide sequences comprise IL7R polynucleotide sequences, the exogenously introduced DNA

[0332] In embodiments in which the target SCID-associated polynucleotide sequences comprise JAK3 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal JAK3 polynucleotide sequence.

[0333] In embodiments in which the target SCID-associated polynucleotide sequences comprise LIG4 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal LIG4 polynucleotide sequence.

[0334] In embodiments in which the target SCID-associated polynucleotide sequences comprise NHEJ1 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal NHEJ1 polynucleotide sequence.

[0335] In embodiments in which the target SCID-associated polynucleotide sequences comprise PNP polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal PNP polynucleotide sequence.

[0336] In embodiments in which the target SCID-associated polynucleotide sequences comprise PRKDC polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal PRKDC polynucleotide sequence.

[0337] In embodiments in which the target SCID-associated polynucleotide sequences comprise RAG1 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal RAG1 polynucleotide sequence.

[0338] In embodiments in which the target SCID-associated polynucleotide sequences comprise RAG2 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal RAG2 polynucleotide sequence.

[0339] In embodiments in which the target SCID-associated polynucleotide sequences comprise ZAP70 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal ZAP70 polynucleotide sequence.

comprises altering target SCD-associated polynucleotide sequences in a cell by contacting the SCD-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target moieties of the target SCD-associated polynucleotide sequences, and wherein the target SCD-associated polynucleotide sequences are cleaved, thereby treating or preventing a disorder associated with expression of the polynucleotide sequences.

[0341] In some embodiments, the method includes the step of contacting the cleaved SCD-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the cleaved SCD-associated polynucleotide sequence with the normal HBB sequence.

[0342] Another exemplary method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject comprises altering target beta thalassemia-associated polynucleotide sequences in a cell by contacting the beta thalassemia-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target moieties of the target beta thalassemia-associated polynucleotide sequences, and wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequences.

[0343] In some embodiments, the method includes the step of contacting the cleaved beta thalassemia-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the cleaved beta thalassemia-associated polynucleotide sequence with the normal HBB sequence.

[0344] The terms "subject" and "individual" are used interchangeably herein, and refer to an animal, for example, a human from whom cells can be obtained and/or to whom treatment, including prophylactic treatment, with the cells as described herein, is provided. For treatment of those infections, conditions or disease states which are specific for a specific animal such as a human subject, the term subject refers to that

cows, pigs, and non-human primates. The term "subject" also encompasses any vertebrate including but not limited to mammals, reptiles, amphibians and fish. However, advantageously, the subject is a mammal such as a human, or other mammals such as a domesticated mammal, e.g. dog, cat, horse, and the like, or production mammal, e.g. cow, sheep, pig, and the like.

[0345] In some embodiments, the alteration results in reduced expression of the target polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target SCID-associated polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target ADA polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target AK2 polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target CD3D polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target DCLRE1C polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target IL2RG polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target IL7R polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target JAK3 polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target LIG4 polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target NHEJ1 polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target PNP polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target PRKDC polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target RAG1 polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target RAG2 polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target ZAP70 polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target SCD-associated polynucleotide sequences. In exemplary embodiments, the alteration results in reduced expression of the target beta thalassemia-associated polynucleotide sequences. In some embodiments, the alteration results in a knock-out of the target polynucleotide sequences. In exemplary embodiments, the

polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target AK2 polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target CD3D polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target DCLRE1C polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target IL2RG polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target IL7R polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target JAK3 polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target LIG4 polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target NHEJ1 polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target PNP polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target PRKDC polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target RAG1 polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target RAG2 polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target ZAP70 polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target SCD-associated polynucleotide sequences. In exemplary embodiments, the alteration results in a knock out of the target beta thalassemia-associated polynucleotide sequences.

[0346] In some embodiments, the alteration results in correction of the target polynucleotide sequences from undesired sequences to desired sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type polynucleotide sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type ADA sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type AK2 sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type CD3D sequences. In exemplary embodiments, the alteration results in correction of the target

SCID-associated polynucleotide sequences to corresponding normal wild-type IL2RG sequences In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type IL7R sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type JAK3 sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type LIG4 sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type NHEJ1 sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type PNP sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type PRKDC sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type RAG1 sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type RAG2 sequences. In exemplary embodiments, the alteration results in correction of the target SCID-associated polynucleotide sequences to corresponding normal wild-type ZAP70 sequences. In exemplary embodiments, the alteration results in correction of the target SCD-associated polynucleotide sequences to normal wild-type HBB sequences. In exemplary embodiments, the alteration results in correction of the target beta thalassemia-associated polynucleotide sequences to normal wild-type HBB sequences. In some embodiments, each alteration is a homozygous alteration. In some embodiments, the efficiency of alteration at each loci is from about 5% to about 80%. In some embodiments, the efficiency of alteration at each loci is from about 10% to about 80%. In some embodiments, the efficiency of alteration at each loci is from about 30% to about 80%. In some embodiments, the efficiency of alteration at each loci is from about 50% to about 80%. In some embodiments, the efficiency of alteration at each loci is from greater than or equal to about 80%.

[0347] In some embodiments, each target polynucleotide sequence is cleaved such that a double-strand break results. In some embodiments, each target polynucleotide

[0348] In some embodiments, the target polynucleotide sequences comprise multiple different portions of ADA (e.g., one or more mutations in the ADA gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of ADA.

[0349] In some embodiments, the target polynucleotide sequences comprise multiple different portions of AK2 (e.g., one or more mutations in the AK2 gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of AK2.

[0350] In some embodiments, the target polynucleotide sequences comprise multiple different portions of CD3D (e.g., one or more mutations in the CD3D gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of CD3D.

[0351] In some embodiments, the target polynucleotide sequences comprise multiple different portions of DCLRE1C (e.g., one or more mutations in the DCLRE1C gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of DCLRE1C.

[0352] In some embodiments, the target polynucleotide sequences comprise multiple different portions of IL2RG (e.g., one or more mutations in the IL2RG gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of IL2RG.

[0353] In some embodiments, the target polynucleotide sequences comprise multiple different portions of IL7R (e.g., one or more mutations in the IL7R gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of IL7R.

[0354] In some embodiments, the target polynucleotide sequences comprise multiple different portions of JAK3 (e.g., one or more mutations in the JAK3 gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of JAK3.

[0355] In some embodiments, the target polynucleotide sequences comprise multiple different portions of LIG4 (e.g., one or more mutations in the LIG4 gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of LIG4.

In some embodiments, the target polynucleotide sequences comprise at least a portion of NHEJ1.

[0357] In some embodiments, the target polynucleotide sequences comprise multiple different portions of PNP (e.g., one or more mutations in the PNP gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of PNP.

[0358] In some embodiments, the target polynucleotide sequences comprise multiple different portions of PRKDC (e.g., one or more mutations in the PRKDC gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of PRKDC.

[0359] In some embodiments, the target polynucleotide sequences comprise multiple different portions of RAG1 (e.g., one or more mutations in the RAG1 gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of RAG1.

[0360] In some embodiments, the target polynucleotide sequences comprise multiple different portions of RAG2 (e.g., one or more mutations in the RAG2 gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of RAG2.

[0361] In some embodiments, the target polynucleotide sequences comprise multiple different portions of ZAP70 (e.g., one or more mutations in the ZAP70 gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of ZAP70.

[0362] In some embodiments, the target polynucleotide sequences comprise multiple different portions of HBB (e.g., one or more mutations in the HBB gene). In some embodiments, the target polynucleotide sequences comprise at least a portion of HBB.

[0363] In some embodiments, each target motif is a 20-nucleotide DNA sequence. In some embodiments, each target motif is a 20-nucleotide DNA sequence beginning with G and immediately precedes an NGG motif recognized by the Cas protein. In some embodiments, each target motif is a 20-nucleotide DNA sequence and immediately precedes an NGG motif recognized by the Cas protein. In some embodiments, each target motif is G(N)19NGG. In some embodiments, each target motif

cell. In some embodiments, each target motif is selected such that it contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell.

[0364] In some embodiments, subsequent to cleavage of the target polynucleotide sequences, homology-directed repair occurs. In some embodiments, homology-directed repair is performed using an exogenously introduced DNA repair template. In some embodiments, the exogenously introduced DNA repair template is single-stranded. In some embodiments, the exogenously introduced DNA repair template is double-stranded.

[0365] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type ADA sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type ADA sequence corresponding to the mutant ADA sequence comprising the SCID-associated polynucleotide sequence.

[0366] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type AK2 sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type AK2 sequence corresponding to the mutant AK2 sequence comprising the SCID-associated polynucleotide sequence.

[0367] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type CD3D sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type CD3D sequence corresponding to the mutant CD3D sequence comprising the SCID-associated polynucleotide sequence.

[0368] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type DCLRE1C sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type DCLRE1C sequence corresponding to the mutant DCLRE1C sequence comprising the SCID-associated polynucleotide sequence.

[0369] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type IL2RG sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type IL2RG sequence corresponding to the mutant IL2RG sequence comprising the SCID-associated polynucleotide sequence.

[0370] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type IL7R sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type IL7R sequence corresponding to the mutant IL7R sequence comprising the SCID-associated polynucleotide sequence.

introduced DNA repair template is a normal or wild-type JAK3 sequence corresponding to the mutant JAK3 sequence comprising the SCID-associated polynucleotide sequence.

[0372] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type LIG4 sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type LIG4 sequence corresponding to the mutant LIG4 sequence comprising the SCID-associated polynucleotide sequence.

[0373] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type NHEJ1 sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type NHEJ1 sequence corresponding to the mutant NHEJ1 sequence comprising the SCID-associated polynucleotide sequence.

[0374] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type PNP sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type PNP sequence corresponding to the mutant PNP sequence comprising the SCID-associated polynucleotide sequence.

[0375] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type PRKDC sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type PRKDC sequence corresponding to the mutant PRKDC sequence comprising the SCID-associated polynucleotide sequence.

[0376] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type RAG1 sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type RAG1 sequence corresponding to the mutant RAG1 sequence comprising the SCID-associated polynucleotide sequence.

[0377] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type RAG2 sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type RAG2 sequence corresponding to the mutant RAG2 sequence comprising the SCID-associated polynucleotide sequence.

[0378] In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type ZAP70 sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type ZAP70 sequence corresponding to the mutant ZAP70 sequence comprising the SCID-associated polynucleotide sequence.

[0379] In some embodiments, the exogenously introduced DNA repair template

the mutant HBB sequence comprising the SCD-associated polynucleotide sequence. In some embodiments, the exogenously introduced DNA repair template is a normal or wild-type HBB sequence corresponding to the mutant HBB sequence comprising the beta thalassemia-associated polynucleotide sequence.

[0380] In some embodiments, the Cas protein (e.g., Cas9) is complexed with the multiple ribonucleic acids. In some embodiments, the Cas protein and the multiple ribonucleic acids are contained in nanoparticles, as described herein. In some embodiments, the Cas protein and the multiple ribonucleic acids are contained in lipid nanoparticles, as described herein. In some embodiments, a nucleic acid encoding a Cas protein and the multiple ribonucleic acids are contained in nanoparticles. In some embodiments, a nucleic acid encoding a Cas protein and the multiple ribonucleic acids are contained in lipid nanoparticles, as described herein. In some embodiments, a modified, synthetic mRNA encoding a Cas protein as described herein, and multiple ribonucleic acids at least one of which comprises a modified, synthetic RNA as described herein, are contained in lipid nanoparticles. In some embodiments, a modified, synthetic mRNA encoding a Cas9 protein as described herein, and multiple ribonucleic acids at least one of which comprises a modified, synthetic RNA as described herein, are contained in lipid nanoparticles.

[0381] In some embodiments, the multiple ribonucleic acids are selected to minimize hybridization with nucleic acid sequences other than the target polynucleotide sequence (e.g., multiple alterations of a single target polynucleotide sequence). In some embodiments, the multiple ribonucleic acids are selected to minimize hybridization with nucleic acid sequences other than the target polynucleotide sequences (e.g., one or more alterations of multiple target polynucleotide sequences). In some embodiments, each of the multiple ribonucleic acids hybridize to target motifs that contain at least two mismatches when compared with all other genomic nucleotide sequences in the cell. In some embodiments, each of the multiple ribonucleic acids hybridize to target motifs that contain at least one mismatch when compared with all other genomic nucleotide sequences in the cell. In some embodiments, each of the multiple ribonucleic acids are designed to hybridize to target motifs immediately adjacent to deoxyribonucleic acid motifs recognized by the Cas protein. In some embodiments, each of the multiple ribonucleic acids are designed to hybridize to target motifs immediately adjacent to

[0382] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1.

[0383] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2.

[0384] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3.

[0385] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 4. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 4.

[0386] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5.

[0387] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6.

[0388] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of

sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7.

[0389] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8.

[0390] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9.

[0391] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9.

[0392] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10.

[0393] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11.

[0394] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12.

Fig. 13. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 13.

[0396] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 14. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 14.

[0397] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15. In some embodiments, each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15.

[0398] In some embodiments, each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 1-15 and combinations thereof. In some embodiments, the different sequences of the multiple ribonucleic acids described above do not include the 3 nucleotide NGG sequence.

[0399] For example, if a target site sequence is GATGCTCAGTACAGCCACCTTGG, a sequence of the multiple ribonucleic acids is GATGCTCAGTACAGCCACCT. As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, a sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCTGAGTACAGCCACCT, with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleotide, the third nucleotide, the fourth nucleotide, the fifth nucleotide, the sixth nucleotide, the seventh nucleotide, the eighth nucleotide, the ninth nucleotide, the tenth nucleotide, the eleventh nucleotide, the twelfth nucleotide, the thirteenth nucleotide, the fourteenth nucleotide, the fifteenth nucleotide, the sixteenth nucleotide, the seventeenth nucleotide, the eighteenth nucleotide, the nineteenth nucleotide, or the twentieth nucleotide of the ribonucleic acid.

sequence of any of Figs. 1-15. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 12 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG, a different sequence of the multiple ribonucleic acids comprising at least a 12 nucleotide fragment with single nucleotide mismatch comprises GTACAGCCACCT.

[0401] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 13 nucleotide fragments of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 13 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG, a different sequence of the multiple ribonucleic acids comprising at least a 13 nucleotide fragment with single nucleotide mismatch comprises AGTACAGCCACCT.

[0402] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 14 nucleotide fragments of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 14 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG, a different sequence of the multiple ribonucleic acids comprising at least a 14 nucleotide fragment with single nucleotide mismatch comprises CAGTACAGCCACCT.

[0403] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 15 nucleotide fragments of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 15 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG, a different sequence of the multiple

[0404] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 16 nucleotide fragments of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 16 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG, a different sequence of the multiple ribonucleic acids comprising at least a 16 nucleotide fragment with single nucleotide mismatch comprises CTCAGTACAGCCACCT.

[0405] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 17 nucleotide fragments of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 17 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG, a different sequence of the multiple ribonucleic acids comprising at least a 17 nucleotide fragment with single nucleotide mismatch comprises GCTCAGTACAGCCACCT.

[0406] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 18 nucleotide fragments of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 18 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG, a different sequence of the multiple ribonucleic acids comprising at least a 18 nucleotide fragment with single nucleotide mismatch comprises TGCTCAGTACAGCCACCT.

[0407] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 19 nucleotide fragments of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 19 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group

ribonucleic acids comprising at least a 19 nucleotide fragment with single nucleotide mismatch comprises ATGCTCAGTACAGCCACCT.

[0408] In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 20 nucleotide fragments of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the different sequences of the multiple ribonucleic acids described above comprise at least 20 nucleotide fragments sequences with single nucleotide mismatches to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if a target sequence is GATGCTCAGTACAGCCACCTTGG, a different sequence of the multiple ribonucleic acids comprising at least a 12 nucleotide fragment with single nucleotide mismatch comprises GATGCTCAGTACAGCCACCT.

[0409] It should be appreciated that any of the Cas protein or the ribonucleic acids can be expressed from a plasmid. In some embodiments, any of the Cas protein or the ribonucleic acids are expressed using a promoter optimized for increased expression in stem cells (e.g., human stem cells). In some embodiments, the promoter is selected from the group consisting of a Cytomegalovirus (CMV) early enhancer element and a chicken beta-actin promoter, a chicken beta-actin promoter, an elongation factor-1 alpha promoter, and a ubiquitin promoter.

[0410] In some embodiments, the methods of the present invention further comprise selecting cells that express the Cas protein. The present invention contemplates any suitable method for selecting cells. In some embodiments, selecting cells comprises FACS. In some embodiments, FACs is used to select cells which co-express Cas and a fluorescent protein selected from the group consisting of green fluorescent protein and red fluorescent protein.

[0411] The present invention contemplates treating and/or preventing a variety of disorders which are associated with expression of a target polynucleotide sequences. It should be appreciated that the methods and compositions described herein can be used to treat or prevent disorders associated with increased expression of a target polynucleotide sequence, as well as decreased expression of a target polynucleotide sequence in a cell. Increased and decreased expression of a target polynucleotide sequence includes circumstances where the expression levels of the target polynucleotide sequence are increased or decreased, respectively, as well as circumstances in which the function

levels. Those skilled in the art will appreciate that treating or preventing a disorder associated with increased expression of a target polynucleotide sequence can be assessed by determining whether the levels and/or activity of the target polynucleotide sequence (or an expression product thereof) are decreased in a relevant cell after employing a method or administering a composition described herein. The skilled artisan will also appreciate that treating or preventing a disorder associated with decreased expression of a target polynucleotide sequence can be assessed by determining whether the levels and/or activity of the target polynucleotide sequence (or an expression product thereof) are increased in the relevant cell after employing a method or administering a composition described herein.

[0412] In some embodiments, the disorder is a genetic disorder. In some embodiments, the disorder is a monogenic disorder. In some embodiments, the disorder is a multigenic disorder. In some embodiments, the disorder is a disorder associated with one or more SNPs. Exemplary disorders associated with one or more SNPs include a complex disease described in U.S. Patent No. 7,627,436, Alzheimer's disease as described in PCT International Application Publication No. WO/2009/112882, inflammatory diseases as described in U.S. Patent Application Publication No. 2011/0039918, polycystic ovary syndrome as described in U.S. Patent Application Publication No. 2012/0309642, cardiovascular disease as described in U.S. Patent No. 7,732,139, Huntington's disease as described in U.S. Patent Application Publication No. 2012/0136039, thromboembolic disease as described in European Patent Application Publication No. EP2535424, neurovascular diseases as described in PCT International Application Publication No. WO/2012/001613, psychosis as described in U.S. Patent Application Publication No. 2010/0292211, multiple sclerosis as described in U.S. Patent Application Publication No. 2011/0319288, schizopherenia, schizoaffective disorder, and bipolar disorder as described in PCT International Application Publication No. WO/2006/023719A2, bipolar disorder and other ailments as described in U.S. Patent Application Publication No. U.s. 2011/0104674, colorectal cancer as described in PCT International Application Publication No. WO/2006/104370A1, a disorder associated with a SNP adjacent to the AKT1 gene locus as described in U.S. Patent Application Publication No. U.S. 2006/0204969, an eating disorder as described in PCT International Application Publication No. WO/2003/012143A1, autoimmune disease as described in

disease as described in U.S. Patent No. 8,187,811, each of which is incorporated herein by reference in its entirety. Other disorders associated with one or more SNPs which can be treated or prevented according to the methods of the present invention will be apparent to the skilled artisan.

[0413] In some embodiments, the disorder is severe combined immunodeficiency. In some embodiments, the disorder is X-linked moderate combined immunodeficiency. In some embodiments, the disorder is X-linked severe combined immunodeficiency. In some embodiments, the disorder is adenosine deaminase deficiency or SCID associated with adenosine deaminase deficiency. In some embodiments, the disorder is Athabascan type SCID. In some embodiments, the disorder is T cell-negative, B-cell/natural killer cell-positive SCID. In some embodiments, the disorder is T-negative/B-positive type autosomal recessive SCID. In some embodiments, the disorder is SCID with sensitivity to ionizing radiation. In some embodiments, the disorder is SCID with microcephaly, growth retardation, and sensitivity to ionizing radiation. In some embodiments, the disorder is reticular dysgenesis. In some embodiments, the disorder is LIG4 syndrome. In some embodiments, the disorder is alpha/beta T-cell lymphopenia with gamma/delta T-cell expansion, severe cytomegalovirus infection, and autoimmunity. In some embodiments, the disorder is combined cellular and humoral immune defects with granulomas. In some embodiments, the disorder is B cell-negative SCID. In some embodiments, the disorder is a selective T-cell defect or selective T-cell defect associated with SCID. In some embodiments, the disorder is purine nucleoside phosphorylase deficiency or SCID associated with purine nucleoside phosphorylase deficiency. In some embodiments, the disorder is Omenn syndrome. In some embodiments, the disorder is bare lymphocyte syndrome. In some embodiments, the disorder is SCID associated with JAK3 mutation. In some embodiments, the disorder is SCID associated with DCLRE1C mutation. In some embodiments, the disorder is a disorder listed in any one of the Gene Phenotype Relationship tables listed herein. In some embodiments, the disorder is sickle cell anemia. In some embodiments, the disorder is sickle cell disease. In some embodiments, the disorder is sickle cell anemia. In some embodiments, the disorder is sickle beta thalassemia. In some embodiments, the disorder is beta thalassemia.

[0414] The methods of the present invention are capable of altering target

ex vivo for subsequent introduction into a subject. In some embodiments, the methods of the present invention can be used to alter target polynucleotide sequences in cells *in vivo*. In some embodiments, the cell is a peripheral blood cell. In some embodiments, the cell is a stem cell or a pluripotent cell. In some embodiments, the cell is a hematopoietic stem cell. In some embodiments, the cell is a CD34+ cell. In some embodiments, the cell is a CD34+ mobilized peripheral blood cell. In some embodiments, the cell is a CD34+ cord blood cell. In some embodiments, the cell is a CD34+ bone marrow cell. In some embodiments, the cell is a CD34+CD38-Lineage-CD90+CD45RA- cell. In some embodiments, the cell is a hepatocyte. In some embodiments, the cell is a human pluripotent cell. In some embodiments, the cell is a primary human cell. In some embodiments, the cell is a non-transformed cell. In some embodiments, the cell is not a cancer cell. In some embodiments, the cell is not a tumor cell. In some embodiments, the cell is not a transformed cell.

[0415] In some aspects, the present invention provides a method for altering a target SCID-associated polynucleotide sequence in a cell comprising contacting the SCID-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0416] In some aspects, the present invention provides a method for altering a target SCD-associated polynucleotide sequence in a cell comprising contacting the SCD-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0417] In some aspects, the present invention provides a method for altering a

the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0418] In some aspects, the present invention provides a method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence in a subject, the method comprising (a) altering a target SCID-associated polynucleotide sequence in a cell *ex vivo* by contacting the SCID-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequence.

[0419] In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved SCID-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a corresponding normal or wild-type polynucleotide sequence, thereby allowing homology-directed repair to replace the cleaved SCID-associated polynucleotide sequence with the corresponding normal or wild type polynucleotide sequence. In embodiments in which the target SCID-associated polynucleotide sequences comprise ADA polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal ADA polynucleotide sequence.

[0420] In embodiments in which the target SCID-associated polynucleotide sequences comprise AK2 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal AK2 polynucleotide

[0421] In embodiments in which the target SCID-associated polynucleotide sequences comprise CD3D polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal CD3D polynucleotide sequence.

[0422] In embodiments in which the target SCID-associated polynucleotide sequences comprise DCLRE1C polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal DCLRE1C polynucleotide sequence.

[0423] In embodiments in which the target SCID-associated polynucleotide sequences comprise IL2RG polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal IL2RG polynucleotide sequence.

[0424] In embodiments in which the target SCID-associated polynucleotide sequences comprise IL7R polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal IL7R polynucleotide sequence.

[0425] In embodiments in which the target SCID-associated polynucleotide sequences comprise JAK3 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal JAK3 polynucleotide sequence.

[0426] In embodiments in which the target SCID-associated polynucleotide sequences comprise LIG4 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal LIG4 polynucleotide sequence.

[0427] In embodiments in which the target SCID-associated polynucleotide sequences comprise NHEJ1 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal NHEJ1 polynucleotide sequence.

[0428] In embodiments in which the target SCID-associated polynucleotide sequences comprise PNP polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal PNP polynucleotide sequence.

repair template comprises a corresponding wild-type or normal PRKDC polynucleotide sequence.

[0430] In embodiments in which the target SCID-associated polynucleotide sequences comprise RAG1 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal RAG1 polynucleotide sequence.

[0431] In embodiments in which the target SCID-associated polynucleotide sequences comprise RAG2 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal RAG2 polynucleotide sequence.

[0432] In embodiments in which the target SCID-associated polynucleotide sequences comprise ZAP70 polynucleotide sequences, the exogenously introduced DNA repair template comprises a corresponding wild-type or normal ZAP70 polynucleotide sequence.

[0433] In some aspects, the present invention provides a method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence in a subject, the method comprising (a) altering a target SCD-associated polynucleotide sequence in a cell *ex vivo* by contacting the SCD-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequence.

[0434] In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved SCD-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to

[0435] In some aspects, the present invention provides a method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence in a subject, the method comprising (a) altering a target beta thalassemia-associated polynucleotide sequence in a cell *ex vivo* by contacting the beta thalassemia-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequence.

[0436] In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved beta thalassemia-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the cleaved beta thalassemia-associated polynucleotide sequence with the normal HBB sequence.

[0437] In some aspects, the present invention provides a method for simultaneously altering multiple target SCID-associated polynucleotide sequences in a cell comprising contacting the SCID-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0438] In some embodiments, the method includes the step of contacting the cleaved target SCID-associated polynucleotide sequences with an exogenously introduced

LIG4 gene, a NHEJ1 gene, a PNP gene, a PRKDC gene, a RAG1 gene, a RAG2 gene, a ZAP70 gene), thereby allowing homology-directed repair to replace the mutant portion of the cleaved SCID-associated polynucleotide sequence with the corresponding normal or wild-type sequence (e.g., of the ADA gene, the AK2 gene, the CD3D gene, the DCLRE1C gene, the IL2RG gene, the IL7R gene, the LIG4 gene, the NHEJ1 gene, the PNP gene, the PRKDC gene, the RAG1 gene, the RAG2 gene, the ZAP70 gene).

[0439] In some aspects, the present invention provides a method for simultaneously altering multiple target SCD-associated polynucleotide sequences in a cell comprising contacting the SCD-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0440] In some embodiments, the method includes the step of contacting the cleaved target SCD-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the mutant portion of the cleaved SCD-associated polynucleotide sequence with the normal HBB sequence.

[0441] In some aspects, the present invention provides a method for simultaneously altering multiple target beta thalassemia-associated polynucleotide sequences in a cell comprising contacting the beta thalassemia-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

[0442] In some embodiments, the method includes the step of contacting the

homology-directed repair to replace the mutant portion of the cleaved beta thalassemia-associated polynucleotide sequence with the normal HBB sequence.

[0443] In some aspects, the present invention provides a method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCID-associated polynucleotide sequences in a cell *ex vivo* by contacting the SCD-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequences.

[0444] In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved SCID-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a corresponding normal or wild-type sequence (e.g., of a ADA gene, a AK2 gene, a CD3D gene, a DCLRE1C gene, a IL2RG gene, a IL7R gene, a LIG4 gene, a NHEJ1 gene, a PNP gene, a PRKDC gene, a RAG1 gene, a RAG2 gene, a ZAP70 gene), thereby allowing homology-directed repair to replace the cleaved SCD-associated polynucleotide sequence with the normal or wild-type sequence (e.g., of the ADA gene, the AK2 gene, the CD3D gene, the DCLRE1C gene, the IL2RG gene, the IL7R gene, the LIG4 gene, the NHEJ1 gene, the PNP gene, the PRKDC gene, the RAG1 gene, the RAG2 gene, the ZAP70 gene).

[0445] In some aspects, the present invention provides a method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCD-associated polynucleotide sequences in a cell *ex vivo* by contacting the SCD-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a

hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequences.

[0446] In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved SCD-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the cleaved SCD-associated polynucleotide sequence with the normal HBB sequence.

[0447] In some aspects, the present invention provides a method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject, the method comprising (a) altering target beta thalassemia-associated polynucleotide sequences in a cell *ex vivo* by contacting the beta thalassemia-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequences.

[0448] In some embodiments, the method includes the step of contacting, before the step of introducing the cell into the subject, the cleaved beta thalassemia-associated polynucleotide sequences with an exogenously introduced DNA repair template comprising a normal HBB sequence, thereby allowing homology-directed repair to replace the cleaved beta thalassemia-associated polynucleotide sequence with the normal HBB sequence.

[0449] The present invention also provides compositions comprising Cas proteins

proteins or functional portions thereof, and ribonucleic acid sequences which direct Cas proteins to and hybridize to target motifs of target polynucleotides in a cell.

[0450] For administration to a subject, a composition as disclosed herein can be administered to a subject, for example in pharmaceutically acceptable compositions. Pharmaceutically acceptable compositions comprise a therapeutically-effective amount of a Cas protein of the present invention or functional portion thereof, nucleic acids encoding the Cas proteins (e.g., modified, synthetic mRNA), and ribonucleic acid sequences which direct Cas proteins to and hybridize, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents.

[0451] As described in detail below, the pharmaceutical compositions of the present invention can be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), lozenges, dragees, capsules, pills, tablets (e.g., those targeted for buccal, sublingual, and systemic absorption), boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; (8) transmucosally; or (9) nasally. Additionally, compounds can be implanted into a patient or injected using a drug delivery system. See, for example, Urquhart, et al., Ann. Rev. Pharmacol. Toxicol. 24: 199-236 (1984); Lewis, ed. "Controlled Release of Pesticides and Pharmaceuticals" (Plenum Press, New York, 1981); U.S. Pat. No. 3,773,919; and U.S. Pat. No. 35 3,270,960.

[0452] As used here, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0453] As used here, the term "pharmaceutically-acceptable carrier" means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (e.g., lubricant, talc magnesium, calcium or

organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, methylcellulose, ethyl cellulose, microcrystalline cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) lubricating agents, such as magnesium stearate, sodium lauryl sulfate and talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol (PEG); (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; (22) bulking agents, such as polypeptides and amino acids (23) serum component, such as serum albumin, HDL and LDL; (22) C2-C12 alchols, such as ethanol; and (23) other non-toxic compatible substances employed in pharmaceutical formulations. Wetting agents, coloring agents, release agents, coating agents, sweetening agents, flavoring agents, perfuming agents, preservative and antioxidants can also be present in the formulation. The terms such as "excipient", "carrier", "pharmaceutically acceptable carrier" or the like are used interchangeably herein.

[0454] The phrase "therapeutically-effective amount" as used herein in respect to a Cas protein and/or ribonucleic acids described herein means that amount of relevant protein and/or ribonucleic acid, or composition comprising the same which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment. For example, an amount administered to a subject that is sufficient to produce a statistically significant, measurable change in at least one symptom of sickle cell anemia (e.g., reduced red blood cell count.). Determination of a therapeutically effective amount is well within the capability of those skilled in the art. Generally, a therapeutically effective amount can vary with the subject's history, age, condition, sex, as well as the severity and

[0455] As used herein, the term "administer" refers to the placement of a composition into a subject by a method or route which results in at least partial localization of the composition at a desired site such that desired effect is produced. A compound or composition described herein can be administered by any appropriate route known in the art including, but not limited to, oral or parenteral routes, including intravenous, intramuscular, subcutaneous, transdermal, airway (aerosol), pulmonary, nasal, rectal, and topical (including buccal and sublingual) administration.

[0456] Exemplary modes of administration include, but are not limited to, injection, infusion, instillation, inhalation, or ingestion. "Injection" includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intraventricular, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, sub capsular, subarachnoid, intraspinal, intracerebro spinal, and intrasternal injection and infusion. In preferred embodiments, the compositions are administered by intravenous infusion or injection.

[0457] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1.

[0458] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1.

[0459] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2.

[0460] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2.

[0461] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic

ribonucleic acid sequences of Fig. 4. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 4.

[0463] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5.

[0464] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6.

[0465] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7.

[0466] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8.

[0467] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single

[0468] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10.

[0469] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11.

[0470] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12.

[0471] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 13. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 13.

[0472] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 14. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 14.

[0473] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the

nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15.

[0474] In some aspects, the present invention provides a composition comprising at least one ribonucleic acid having a ribonucleic acid sequences of GTAACGGCAGACTTCTCCACAGG. In some aspects, the present invention provides a composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to ribonucleic acid sequences of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the at least one ribonucleic acid sequences described above do not include the 3 nucleotide NGG sequence.

[0475] For example, if the target site sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid sequence is GATGCTCAGTACAGCCACCT. As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, a ribonucleic acid sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCT*G*AGTACAGCCACCT, with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleotide, the third nucleotide, the fourth nucleotide, the fifth nucleotide, the sixth nucleotide, the seventh nucleotide, the eighth nucleotide, the ninth nucleotide, the tenth nucleotide, the eleventh nucleotide, the twelfth nucleotide, the thirteenth nucleotide, the fourteenth nucleotide, the fifteenth nucleotide, the sixteenth nucleotide, the seventeenth nucleotide, the eighteenth nucleotide, the nineteenth nucleotide, or the twentieth nucleotide of the ribonucleic acid.

[0476] In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the at least one

GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 12 nucleotide fragment is GTACAGCCACCT.

[0477] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 13 nucleotide fragment is AGTACAGCCACCT.

[0478] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence

[0479] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 15 nucleotide fragment is TCAGTACAGCCACCT.

[0480] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 16 nucleotide fragment is CTCAGTACAGCCACCT.

[0481] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a

nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 17 nucleotide fragment is GCTCAGTACAGCCACCT.

[0482] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 18 nucleotide fragment is TGCTCAGTACAGCCACCT.

[0483] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In

of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 19 nucleotide fragment is ATGCTCAGTACAGCCACCT.

[0484] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 20 nucleotide fragment is GATGCTCAGTACAGCCACCT.

[0485] In some embodiments, the at least one ribonucleic acid in the composition is contained in a nanoparticle. In some embodiments, the at least one ribonucleic acid is contained in a lipid nanoparticle. In some embodiments, the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid.

[0486] In some embodiments, at least one of the ribonucleic acids in the composition is a modified ribonucleic acid as described herein (e.g., a synthetic, modified ribonucleic acid, e.g., comprising one to two modified nucleotides selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-

[0487] In some embodiments, a composition of the present invention comprises a nucleic acid sequence encoding a Cas protein. In some embodiments, a composition of the present invention comprises nucleic acid sequence encoding Cas9 protein or a functional portion thereof.

[0488] In some embodiments, the nucleic acid encoding the Cas protein (e.g., Cas9) comprises a modified ribonucleic acid as described herein (e.g., a synthetic, modified mRNA described herein, e.g., comprising at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate or any other modified nucleotides or modifications described herein).

[0489] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1.

[0490] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2.

[0491] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3.

[0492] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 4.

[0493] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5.

[0494] In some aspects, the present invention provides a composition comprising

one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6.

[0495] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7.

[0496] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8.

[0497] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9.

[0498] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10.

[0499] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11.

[0500] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12.

[0501] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 13.

[0502] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least

[0503] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15.

[0504] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG.

[0505] In some embodiments, the at least one additional ribonucleic acid sequences described above do not include the 3 nucleotide NGG sequence.

[0506] For example, if the target site sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid is GATGCTCAGTACAGCCACCT. As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, a ribonucleic acid sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCT*G*AGTACAGCCACCT, with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleotide, the third nucleotide, the fourth nucleotide, the fifth nucleotide, the sixth nucleotide, the seventh nucleotide, the eighth nucleotide, the ninth nucleotide, the tenth nucleotide, the eleventh nucleotide, the twelfth nucleotide, the thirteenth nucleotide, the fourteenth nucleotide, the fifteenth nucleotide, the sixteenth nucleotide, the seventeenth nucleotide, the eighteenth nucleotide, the nineteenth nucleotide, or the twentieth nucleotide of the ribonucleic acid.

[0507] In some embodiments, the at least one additional ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the at least one additional ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the at least one additional ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of GTAACGGCAGACTTCTCCACAGG

mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 12 nucleotide fragment is GTACAGCCACCT.

[0508] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 13 nucleotide fragment is AGTACAGCCACCT.

[0509] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of

additional ribonucleic acid which comprises at least a 14 nucleotide fragment is CAGTACAGCCACCT.

[0510] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 15 nucleotide fragment is TCAGTACAGCCACCT.

[0511] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one

[0512] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 17 nucleotide fragment is GCTCAGTACAGCCACCT.

[0513] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 18 nucleotide fragment is TGCTCAGTACAGCCACCT

a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 19 nucleotide fragment is ATGCTCAGTACAGCCACCT.

[0515] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 20 nucleotide fragment is GATGCTCAGTACAGCCACCT.

[0516] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least

mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1.

[0517] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2.

[0518] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3.

[0519] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 4.

[0520] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5.

[0521] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6.

[0522] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7.

one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8.

[0524] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9.

[0525] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10.

[0526] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11.

[0527] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12.

[0528] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 13.

[0529] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid

[0530] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15.

[0531] In some aspects, the present invention provides a composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG.

[0532] In some embodiments, the at least one additional ribonucleic acid sequences described above do not include the 3 nucleotide NGG sequence. For example, if the target site sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid is GATGCTCAGTACAGCCACCT. As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, a ribonucleic acid sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCT*G*AGTACAGCCACCT, with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleotide, the third nucleotide, the fourth nucleotide, the fifth nucleotide, the sixth nucleotide, the seventh nucleotide, the eighth nucleotide, the ninth nucleotide, the tenth nucleotide, the eleventh nucleotide, the twelfth nucleotide, the thirteenth nucleotide, the fourteenth nucleotide, the fifteenth nucleotide, the sixteenth nucleotide, the seventeenth nucleotide, the eighteenth nucleotide, the nineteenth nucleotide, or the twentieth nucleotide of the ribonucleic acid.

[0533] In some embodiments, the at least one additional ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the at least one additional ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the at least one additional ribonucleic acid described above comprises at least a 12 nucleotide

comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 12 nucleotide fragment is GTACAGCCACCT.

[0534] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 13 nucleotide fragment is AGTACAGCCACCT.

[0535] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid

GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 14 nucleotide fragment is CAGTACAGCCACCT.

[0536] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 15 nucleotide fragment is TCAGTACAGCCACCT.

[0537] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of

additional ribonucleic acid which comprises at least a 16 nucleotide fragment is CTCAGTACAGCCACCT.

[0538] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 17 nucleotide fragment is GCTCAGTACAGCCACCT.

[0539] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one

[0540] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 19 nucleotide fragment is ATGCTCAGTACAGCCACCT.

[0541] In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one additional ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one additional ribonucleic acid which comprises at least a 20 nucleotide fragment is GATGCTCAGTACAGCCACCT

of green fluorescent protein and red fluorescent protein. In some embodiments, a composition of the present invention comprises a promoter operably linked to the chimeric nucleic acid. In some embodiments, the promoter is optimized for increased expression in human stem cells. In some embodiments, the promoter is selected from the group consisting of a Cytomegalovirus (CMV) early enhancer element and a chicken beta-actin promoter, a chicken beta-actin promoter, an elongation factor-1 alpha promoter, and a ubiquitin promoter.

[0543] In some embodiments, the chimeric nucleic acid is contained in a nanoparticle. In some embodiments, the chimeric nucleic acid is contained in a lipid nanoparticle as described herein. In some embodiments, the chimeric nucleic acid comprises at least one modified nucleotide described herein. In some embodiments, the Cas protein comprises a Cas9 protein or a functional portion thereof.

[0544] For *in vivo* methods, a therapeutically effective amount of a composition described herein can be administered to a subject. Methods of administering compositions to a subject are known in the art and easily available to one of skill in the art.

[0545] In some embodiments, a composition described herein includes one or more additional pharmaceutically active agents for treating or preventing the disorder associated with expression of the target polynucleotide sequence.

[0546] The present invention also provides kits for practicing any of the methods of the present invention, as well as kits comprising the compositions of the present invention, and instructions for using the kits for altering target polynucleotide sequences in a cell.

[0547] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1.

[0548] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2.

[0549] In some aspects, the present invention comprises a kit for altering a target

the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3.

[0550] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 4.

[0551] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5.

[0552] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6.

[0553] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7.

[0554] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8.

[0555] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9.

[0556] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10.

[0557] In some aspects, the present invention comprises a kit for altering a target

[0558] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12.

[0559] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 13.

[0560] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 14.

[0561] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15.

[0562] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence having a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG.

[0563] In some embodiments, the at least one ribonucleic acid sequences described above do not include the 3 nucleotide NGG sequence. For example, if the target site sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid sequence is GATGCTCAGTACAGCCACCT. As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, a ribonucleic acid sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCT*G*AGTACAGCCACCT, with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleotide, the third nucleotide, the fourth nucleotide, the fifth nucleotide, the sixth

nucleotide, the eighteenth nucleotide, the nineteenth nucleotide, or the twentieth nucleotide of the ribonucleic acid.

[0564] In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 12 nucleotide fragment is GTACAGCCACCT.

[0565] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to f a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 13 nucleotide fragment is AGTACAGCCACCT.

[0566] In some embodiments, the ribonucleic acid sequence of the at least one

acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 14 nucleotide fragment is CAGTACAGCCACCT.

[0567] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 15 nucleotide fragment is TCAGTACAGCCACCT.

[0568] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence

described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 16 nucleotide fragment is CTCAGTACAGCCACCT.

[0569] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 17 nucleotide fragment is GCTCAGTACAGCCACCT.

[0570] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the

ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 18 nucleotide fragment is TGCTCAGTACAGCCACCT.

[0571] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 19 nucleotide fragment is ATGCTCAGTACAGCCACCT.

[0572] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence

[0573] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1, and any combination thereof.

[0574] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2, and any combination thereof.

[0575] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3, and any combination thereof.

[0576] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 4, and any combination thereof.

[0577] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5, and any combination thereof.

[0578] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6, and any combination thereof.

[0579] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding

mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7, and any combination thereof.

[0580] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8, and any combination thereof.

[0581] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9, and any combination thereof.

[0582] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10, and any combination thereof.

[0583] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11, and any combination thereof.

[0584] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12, and any combination thereof.

[0585] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 13, and any combination thereof.

the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 14, and any combination thereof.

[0587] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15, and any combination thereof.

[0588] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG.

[0589] In some embodiments, the at least one ribonucleic acid sequences with the single nucleotide mismatches described above do not include the 3 nucleotide NGG sequence. For example, if the target site sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid sequence is GATGCTCAGTACAGCCACCT. As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, a ribonucleic acid sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCT*G*AGTACAGCCACCT, with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleotide, the third nucleotide, the fourth nucleotide, the fifth nucleotide, the sixth nucleotide, the seventh nucleotide, the eighth nucleotide, the ninth nucleotide, the tenth nucleotide, the eleventh nucleotide, the twelfth nucleotide, the thirteenth nucleotide, the fourteenth nucleotide, the fifteenth nucleotide, the sixteenth nucleotide, the seventeenth nucleotide, the eighteenth nucleotide, the nineteenth nucleotide, or the twentieth nucleotide of the ribonucleic acid.

[0590] In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a

comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 12 nucleotide fragment is GTACAGCCACCT.

[0591] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 13 nucleotide fragment is AGTACAGCCACCT.

[0592] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the

ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 14 nucleotide fragment is CAGTACAGCCACCT.

[0593] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 15 nucleotide fragment is TCAGTACAGCCACCT.

[0594] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least

[0595] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 17 nucleotide fragment is GCTCAGTACAGCCACCT.

[0596] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 18 nucleotide fragment is TGCTCAGTACAGCCACCT.

[0597] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 19 nucleotide fragment of a

nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 19 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 19 nucleotide fragment is ATGCTCAGTACAGCCACCT.

[0598] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 20 nucleotide fragment is GATGCTCAGTACAGCCACCT.

[0599] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of Fig. 1 and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Fig. 1, and combinations thereof.

the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of Fig. 2 and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Fig. 2, and combinations thereof.

[0601] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of Fig. 3 and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Fig. 3, and combinations thereof.

[0602] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of Fig. 4 and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Fig. 4, and combinations thereof.

[0603] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of Fig. 5 and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Fig. 5, and combinations thereof.

[0604] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of Fig. 6 and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Fig. 6, and combinations thereof.

[0605] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of Fig. 7 and at least one ribonucleic

[0606] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of Fig. 8 and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Fig. 8, and combinations thereof.

[0607] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of Fig. 9 and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Fig. 9, and combinations thereof.

[0608] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of Fig. 10 and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Fig. 10, and combinations thereof.

[0609] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of Fig. 11 and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Fig. 11, and combinations thereof.

[0610] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of Fig. 12 and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Fig. 12, and combinations thereof.

[0611] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding

acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Fig. 13, and combinations thereof.

[0612] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of Fig. 14 and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Fig. 14, and combinations thereof.

[0613] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of Fig. 15 and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Fig. 15, and combinations thereof.

[0614] In some aspects, the present invention comprises a kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of at least one ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG and at least one ribonucleic acid sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG.

[0615] In some embodiments, the at least one ribonucleic acid sequences described above do not include the 3 nucleotide NGG sequence. For example, if the target site sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid sequence is GATGCTCAGTACAGCCACCT. As another example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, a ribonucleic acid sequence with a single nucleotide mismatch which does not include the 3 nucleotide NGG sequence is GATGCT*G*AGTACAGCCACCT, with the italicized G being the mismatched nucleotide. Those skilled in the art will appreciate, however, that the single nucleotide mismatch can comprise any nucleotide in the ribonucleic acid, e.g., the first nucleotide, the second nucleotide. the third nucleotide. the fourth nucleotide, the fifth nucleotide, the sixth

fourteenth nucleotide, the fifteenth nucleotide, the sixteenth nucleotide, the seventeenth nucleotide, the eighteenth nucleotide, the nineteenth nucleotide, or the twentieth nucleotide of the ribonucleic acid.

[0616] In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15 For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 12 nucleotide fragment is GTACAGCCACCT.

[0617] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 13 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 13 nucleotide fragment is AGTACAGCCACCT.

[0618] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 14 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 14 nucleotide fragment is CAGTACAGCCACCT.

[0619] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 15 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic

selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 15 nucleotide fragment is TCAGTACAGCCACCT.

[0620] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprise at least a 16 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 16 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 16 nucleotide fragment is CTCAGTACAGCCACCT.

[0621] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 17 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 17 nucleotide fragment is GCTCAGTACAGCCACCT.

[0622] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 18 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 18 nucleotide fragment is TGCTCAGTACAGCCACCT.

[06231 In some embodiments, the ribonucleic acid sequence of the at least one

acid sequence of the at least one ribonucleic acid described above comprises at least a 19 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 19 nucleotide fragment is ATGCTCAGTACAGCCACCT.

[0624] In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a ribonucleic acid sequence of any of Figs. 1-15. In some embodiments, the ribonucleic acid sequence of the at least one ribonucleic acid described above comprises at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of a ribonucleic acid sequence of any of Figs. 1-15. For example, if the target sequence is GATGCTCAGTACAGCCACCTTGG, the ribonucleic acid sequence of the at least one ribonucleic acid which comprises at least a 20 nucleotide fragment is GATGCTCAGTACAGCCACCT.

[0625] In some embodiments, the at least one ribonucleic acid described above comprises at least a 12 nucleotide fragment, at least a 13 nucleotide fragment, at least a 14 nucleotide fragment, at least a 15 nucleotide fragment, at least a 16 nucleotide fragment, at least a 17 nucleotide fragment, at least an 18 nucleotide fragment, at least a 19 nucleotide fragment, or at least a 20 nucleotide sequence of a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG. In some embodiments, the at least one ribonucleic acid described above comprises at least a 12, at least a 13, at least a 14, at least a 15, at least a, at least a 17, at least an 18, at least a 19, or at least a 20 nucleotide fragment of a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG.

[0626] In some embodiments, the kit comprises one or more cell lines, cultures, or populations selected from the group consisting of human pluripotent cells, primary human cells, and non-transformed cells. In some embodiments, the kit comprises a DNA repair template.

[0627] In some embodiments, the DNA repair template comprises one or more normal or wild-type ADA gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to

[0628] In some embodiments, the DNA repair template comprises one or more normal or wild-type AK2 gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant AK2 sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0629] In some embodiments, the DNA repair template comprises one or more normal or wild-type CD3D gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant CD3D sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0630] In some embodiments, the DNA repair template comprises one or more normal or wild-type DCLRE1C gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant DCLRE1C sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0631] In some embodiments, the DNA repair template comprises one or more normal or wild-type IL2RG gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant IL2RG sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0632] In some embodiments, the DNA repair template comprises one or more normal or wild-type IL7R gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant IL7R sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0633] In some embodiments, the DNA repair template comprises one or more normal or wild-type JAK3 gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant JAK3 sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0634] In some embodiments, the DNA repair template comprises one or more normal or wild-type NHEJ1 gene sequences. In some embodiments, the DNA repair

mutant NHEJ1 sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0635] In some embodiments, the DNA repair template comprises one or more normal or wild-type PNP gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant PNP sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0636] In some embodiments, the DNA repair template comprises one or more normal or wild-type PRKDC gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant PRKDC sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0637] In some embodiments, the DNA repair template comprises one or more normal or wild-type RAG1 gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant RAG1 sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0638] In some embodiments, the DNA repair template comprises one or more normal or wild-type RAG2 gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant RAG2 sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0639] In some embodiments, the DNA repair template comprises one or more normal or wild-type ZAP70 gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant ZAP70 sequences to be cleaved from target SCID-associated polynucleotide sequences.

[0640] In some embodiments, the DNA repair template comprises one or more normal or wild-type HBB gene sequences. In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant HBB sequences to be cleaved from target SCD-associated polynucleotide sequences.

[0641] In some embodiments, the DNA repair template comprises one or more normal or wild-type DNA sequences that correspond to mutant HBB sequences to be cleaved from target beta thalassemia-associated polynucleotide sequences.

[0642] It should be appreciated that the methods, compositions, and kits of the present invention may employ nanoparticles or lipid nanoparticles as a vehicle for delivering, or introducing a Cas protein and/or a ribonucleic acid of the present invention into a cell.

[0643] In some embodiments, the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid.

[0644] The cationic lipid may be, for example, N,N-dioleyl-N,N-dimethylammonium chloride (DODAC), N,N-distearyl-N,N-dimethylammonium bromide (DDAB), N-(I-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTAP), N-(I-(2,3-dioleyloxy)propyl)-N,N,N-trimethylammonium chloride (DOTMA), N,N-dimethyl-2,3-dioleyloxy)propylamine (DODMA), 1,2-DiLinoleyloxy-N,N-dimethylaminopropane (DLinDMA), 1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLenDMA), 1,2-Dilinoleylcarbamoyloxy-3-dimethylaminopropane (DLin-C-DAP), 1,2-Dilinoleyoxy-3-(dimethylamino)acetoxypropane (DLin-DAC), 1,2-Dilinoleyoxy-3-morpholinopropane (DLin-MA), 1,2-Dilinoleoyl-3-dimethylaminopropane (DLinDAP), 1,2-Dilinoleylthio-3-dimethylaminopropane (DLin-S-DMA), 1-Linoleoyl-2-linoleyloxy-3-dimethylaminopropane (DLin-2-DMAP), 1,2-Dilinoleyloxy-3-trimethylaminopropane chloride salt (DLin-TMA.Cl), 1,2-Dilinoleoyl-3-trimethylaminopropane chloride salt (DLin-TAP.Cl), 1,2-Dilinoleyloxy-3-(N-methylpiperazino)propane (DLin-MPZ), or 3-(N,N-Dilinoleylamino)-1,2-propanediol (DLinAP), 3-(N,N-Dioleylamino)-1,2-propanedio (DOAP), 1,2-Dilinoleyloxo-3-(2-N,N-dimethylamino)ethoxypropane (DLin-EG-DMA), 1,2-Dilinolenyloxy-N,N-dimethylaminopropane (DLinDMA), 2,2-Dilinoleyl-4-dimethylaminomethyl-[1,3]-dioxolane (DLin-K-DMA) or analogs thereof, (3aR,5s,6aS)-N,N-dimethyl-2,2-di((9Z,12Z)-octadeca-9,12-dienyl)tetrahydro- -3aH-cyclopenta[d][1,3]dioxol-5-amine (ALNY-100), (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (MC3), or a mixture thereof.

[0645] Other cationic lipids, which carry a net positive charge at about physiological pH, in addition to those specifically described above, may also be included in lipid particles of the invention. Such cationic lipids include, but are not limited to, N,N-

bromide ("DDAB"); N-(2,3-dioleoyloxy)propyl)-N,N,N-trimethylammonium chloride ("DOTAP"); 1,2-Dioleyloxy-3-trimethylaminopropane chloride salt ("DOTAP.Cl"); 3.beta.-(N-(N',N'-dimethylaminoethane)-carbamoyl)cholesterol ("DC-Chol"), N-(1-(2,3-dioleyloxy)propyl)-N-2-(sperminecarboxamido)ethyl)-N,N-dimethyl- ammonium trifluoracetate ("DOSPA"), dioctadecylamidoglycyl carboxyspermine ("DOGS"), 1,2-dileoyl-sn-3-phosphoethanolamine ("DOPE"), 1,2-dioleoyl-3-dimethylammonium propane ("DODAP"), N,N-dimethyl-2,3-dioleyloxy)propylamine ("DODMA"), and N-(1,2-dimyristyloxyprop-3-yl)-N,N-dimethyl-N-hydroxyethyl ammonium bromide ("DMRIE"), and mixtures thereof. Additionally, a number of commercial preparations of cationic lipids can be used, such as, e.g., LIPOFECTIN (including DOTMA and DOPE, available from GIBCO/BRL), and LIPOFECTAMINE (comprising DOSPA and DOPE, available from GIBCO/BRL). In particular embodiments, a cationic lipid is an amino lipid.

[0646] As used herein, the term "amino lipid" is meant to include those lipids having one or two fatty acid or fatty alkyl chains and an amino head group (including an alkylamino or dialkylamino group) that may be protonated to form a cationic lipid at physiological pH.

[0647] Other amino lipids would include those having alternative fatty acid groups and other dialkylamino groups, including those in which the alkyl substituents are different (e.g., N-ethyl-N-methylamino-, N-propyl-N-ethylamino- and the like). For those embodiments in which R^{11} and R^{12} are both long chain alkyl or acyl groups, they can be the same or different. In general, amino lipids having less saturated acyl chains are more easily sized, particularly when the complexes must be sized below about 0.3 microns, for purposes of filter sterilization. Amino lipids containing unsaturated fatty acids with carbon chain lengths in the range of C_{14} to C_{22} are preferred. Other scaffolds can also be used to separate the amino group and the fatty acid or fatty alkyl portion of the amino lipid. Suitable scaffolds are known to those of skill in the art.

[0648] Specific examples of PEG-modified lipids (or lipid-polyoxyethylene conjugates) that are useful in the present invention can have a variety of "anchoring" lipid portions to secure the PEG portion to the surface of the lipid vesicle. Examples of suitable PEG-modified lipids include PEG-modified phosphatidylethanolamine and phosphatidic acid, PEG-ceramide conjugates (e.g., PEG-CerC14 or PEG-CerC20) which are described

dialkylamines and PEG-modified 1,2-diacyloxypropan-3-amines. Particularly preferred are PEG-modified diacylglycerols and dialkylglycerols.

[0649] Examples of suitable neutral lipid include DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof.

[0650] As used herein "nucleic acid," in its broadest sense, includes any compound and/or substance that comprise a polymer of nucleotides linked via a phosphodiester bond. Exemplary nucleic acids include ribonucleic acids (RNAs), deoxyribonucleic acids (DNAs), threose nucleic acids (TNAs), glycol nucleic acids (GNAs), peptide nucleic acids (PNAs), locked nucleic acids (LNAs) or hybrids thereof. They may also include RNAi-inducing agents, RNAi agents, siRNAs, shRNAs, miRNAs, antisense RNAs, ribozymes, catalytic DNA, tRNA, RNAs that induce triple helix formation, aptamers, vectors, etc. In some embodiments, the nucleic acid encoding the Cas protein is an mRNA. In some embodiments, the Cas protein is encoded by a modified nucleic acid (e.g., a synthetic, modified mRNA described herein).

[0651] The present invention contemplates the use of any nucleic acid modification available to the skilled artisan. The nucleic acids of the present invention can include any number of modifications. In some embodiments, the nucleic acid comprises one or more modifications selected from the group consisting of pyridin-4-one ribonucleoside, 5-aza-uridine, 2-thio-5-aza-uridine, 2-thiouridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxyuridine, 3-methyluridine, 5-carboxymethyl-uridine, 1-carboxymethyl-pseudouridine, 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyluridine, 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine, 1-taurinomethyl-4-thio-uridine, 5-methyl-uridine, 1-methyl-pseudouridine, 4-thio-1-methyl-pseudouridine, 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine, dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, 5-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5-hydroxymethylcytidine, 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-

pseudoisocytidine, 2-aminopurine, 2,6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7-deaza-8-aza-2-aminopurine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl)adenosine, N6-glycinylcarbamoyladenosine, N6-threonylcarbamoyladenosine, 2-methylthio-N6-threonyl carbamoyladenosine, N6,N6-dimethyladenosine, 7-methyladenine, 2-methylthio-adenine, and 2-methoxy-adenine, inosine, 1-methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methylinosine, 6-methoxy-guanosine, 1-methylguanosine, N2-methylguanosine, N2,N2-dimethylguanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, and N2,N2-dimethyl-6-thio-guanosine, and combinations thereof.

[0652] Preparation of modified nucleosides and nucleotides used in the manufacture or synthesis of modified RNAs of the present invention can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art.

[0653] The chemistry of protecting groups can be found, for example, in Greene, et al., Protective Groups in Organic Synthesis, 2d. Ed., Wiley & Sons, 1991, which is incorporated herein by reference in its entirety.

[0654] Modified nucleosides and nucleotides can be prepared according to the synthetic methods described in Ogata et al. Journal of Organic Chemistry 74:2585-2588, 2009; Purmal et al. Nucleic Acids Research 22(1): 72-78, 1994; Fukuhara et al. Biochemistry 1(4): 563-568, 1962; and Xu et al. Tetrahedron 48(9): 1729-1740, 1992, each of which are incorporated by reference in their entirety.

[0655] Modified nucleic acids (e.g., ribonucleic acids) need not be uniformly modified along the entire length of the molecule. Different nucleotide modifications and/or backbone structures may exist at various positions in the nucleic acid. One of ordinary skill in the art will appreciate that the nucleotide analogs or other modification(s) may be located at any position(s) of a nucleic acid such that the function of the nucleic acid is not substantially decreased. A modification may also be a 5′ or 3′ terminal

modified nucleotides, or any intervening percentage, such as at least 50% modified nucleotides, at least 80% modified nucleotides, or at least 90% modified nucleotides.

[0656] In some embodiments, at least one of the one to two ribonucleic acids is a modified ribonucleic acid. In some embodiments, each of the one to two ribonucleic acids is a modified ribonucleic acid. In some embodiments, at least one of the multiple ribonucleic acids is a modified ribonucleic acid. In some embodiments, a plurality of the multiple ribonucleic acids are modified. In some embodiments, each of the multiple ribonucleic acids are modified. Those skilled in the art will appreciate that the modified ribonucleic acids can include one or more of the nucleic acid modification described herein.

[0657] In some aspects, provided herein are synthetic, modified RNA molecules encoding polypeptides, where the synthetic, modified RNA molecules comprise one or more modifications, such that introducing the synthetic, modified RNA molecules to a cell results in a reduced innate immune response relative to a cell contacted with synthetic RNA molecules encoding the polypeptides not comprising the one or more modifications. In some embodiments, the Cas protein comprises a synthetic, modified RNA molecule encoding a Cas protein. In some embodiments, the Cas protein comprises a synthetic, modified RNA molecule encoding a Cas9 protein.

[0658] The synthetic, modified RNAs described herein include modifications to prevent rapid degradation by endo- and exo-nucleases and to avoid or reduce the cell's innate immune or interferon response to the RNA. Modifications include, but are not limited to, for example, (a) end modifications, e.g., 5′ end modifications (phosphorylation dephosphorylation, conjugation, inverted linkages, etc.), 3′ end modifications (conjugation, DNA nucleotides, inverted linkages, etc.), (b) base modifications, e.g., replacement with modified bases, stabilizing bases, destabilizing bases, or bases that base pair with an expanded repertoire of partners, or conjugated bases, (c) sugar modifications (e.g., at the 2′ position or 4′ position) or replacement of the sugar, as well as (d) internucleoside linkage modifications, including modification or replacement of the phosphodiester linkages. To the extent that such modifications interfere with translation (i.e., results in a reduction of 50% or more in translation relative to the lack of the modification—e.g., in a rabbit reticulocyte in vitro translation assay), the modification is not suitable for the methods and compositions described herein. Specific examples of

linkages. Synthetic, modified RNAs having modified internucleoside linkages include, among others, those that do not have a phosphorus atom in the internucleoside linkage. In other embodiments, the synthetic, modified RNA has a phosphorus atom in its internucleoside linkage(s).

[0659] Non-limiting examples of modified internucleoside linkages include phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3′-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3′-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3′-5′ linkages, 2′-5′ linked analogs of these, and those) having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3′-5′ to 5′-3′ or 2′-5′ to 5′-2′. Various salts, mixed salts and free acid forms are also included.

[0660] Representative U.S. patents that teach the preparation of the above phosphorus-containing linkages include, but are not limited to, U.S. Pat. Nos. 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,195; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,316; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,625,050; 6,028,188; 6,124,445; 6,160,109; 6,169,170; 6,172,209; 6,239,265; 6,277,603; 6,326,199; 6,346,614; 6,444,423; 6,531,590; 6,534,639; 6,608,035; 6,683,167; 6,858,715; 6,867,294; 6,878,805; 7,015,315; 7,041,816; 7,273,933; 7,321,029; and U.S. Pat. RE39464, each of which is herein incorporated by reference in its entirety.

[0661] Modified internucleoside linkages that do not include a phosphorus atom therein have internucleoside linkages that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatoms 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; 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.

5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,64,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; and 5,677,439, each of which is herein incorporated by reference in its entirety.

[0663] Some embodiments of the synthetic, modified RNAs described herein include nucleic acids with phosphorothioate internucleoside linkages and oligonucleosides with heteroatom internucleoside linkage, and in particular —CH2-NH—CH2-, —CH2-N(CH3)-O—CH2-[known as a methylene (methylimino) or MMI], —CH2-O—N(CH3)-CH2-, —CH2-N(CH3)-N(CH3)-CH2- and —N(CH3)-CH2-CH2-[wherein the native phosphodiester internucleoside linkage is represented as —O—P—O—CH2-] of the above-referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above-referenced U.S. Pat. No. 5,602,240, both of which are herein incorporated by reference in their entirety. In some embodiments, the nucleic acid sequences featured herein have morpholino backbone structures of the above-referenced U.S. Pat. No. 5,034,506, herein incorporated by reference in its entirety.

[0664] Synthetic, modified RNAs described herein can also contain one or more substituted sugar moieties. The nucleic acids featured herein can include one of the following at the 2′ position: H (deoxyribose); OH (ribose); 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 can be substituted or unsubstituted C1 to C10 alkyl or C2 to C10 alkenyl and alkynyl. Exemplary modifications include O[(CH2)nO]mCH3, O(CH2).nOCH3, O(CH2)nNH2, O(CH2)nCH3, O(CH2)nONH2, and O(CH2)nON[(CH2)nCH3)]2, where n and m are from 1 to about 10. In some embodiments, synthetic, modified RNAs include one of the following at the 2′ position: C1 to C10 lower alkyl, substituted lower alkyl, 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 reporter group, an intercalator, a group for improving the pharmacokinetic properties of an RNA, or a group for improving the pharmacodynamic properties of a synthetic, modified RNA, and other substituents having similar properties. In some embodiments, the modification includes a 2′ methoxyethoxy (2′-O—CH2CH2OCH3, also known as 2′-O-(2-methoxyethyl) or 2′-MOE) (Martin et al., Helv. Chim. Acta, 1995, 78:486-504) i.e., an alkoxy-alkoxy group.

dimethylaminoethoxyethoxy (also known in the art as 2′-O-dimethylaminoethoxyethyl or 2′-DMAEOE), i.e., 2′-O—CH2-O—CH2-N(CH2)2.

[0665] Other modifications include 2′-methoxy (2′-OCH3), 2′-aminopropoxy (2′-OCH2CH2CH2NH2) and 2′-fluoro (2′-F). Similar modifications can also be made at other positions on the nucleic acid sequence, particularly the 3′ position of the sugar on the 3′ terminal nucleotide or in 2′-5′ linked nucleotides and the 5′ position of 5′ terminal nucleotide. A synthetic, modified RNA can also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative U.S. patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference in its entirety.

[0666] As non-limiting examples, synthetic, modified RNAs described herein can include at least one modified nucleoside including a 2′-O-methyl modified nucleoside, a nucleoside comprising a 5′ phosphorothioate group, a 2′-amino-modified nucleoside, 2′-alkyl-modified nucleoside, morpholino nucleoside, a phosphoramidate or a non-natural base comprising nucleoside, or any combination thereof.

[0667] In some embodiments of this aspect and all other such aspects described herein, the at least one modified nucleoside is selected from the group consisting of 5-methylcytidine (5mC), N6-methyladenosine (m6A), 3,2′-O-dimethyluridine (m4U), 2-thiouridine (s2U), 2′ fluorouridine, pseudouridine, 2′-O-methyluridine (Um), 2′ deoxyuridine (2′ dU), 4-thiouridine (s4U), 5-methyluridine (m5U), 2′-O-methyladenosine (m6A), N6,2′-O-dimethyladenosine (m6Am), N6,N6,2′-O-trimethyladenosine (m62Am), 2′-O-methylcytidine (Cm), 7-methylguanosine (m7G), 2′-O-methylguanosine (Gm), N2,7-dimethylguanosine (m2,7G), N2,N2,7-trimethylguanosine (m2,2,7G), and inosine (I).

[0668] Alternatively, a synthetic, modified RNA can comprise at least two modified nucleosides, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, at least 10, at least 15, at least 20 or more, up to the entire length of the nucleotide. At a minimum, a synthetic, modified RNA molecule comprising at least one

uniformly modified, and in fact more than one of the aforementioned modifications can be incorporated in a single synthetic, modified RNA or even at a single nucleoside within a synthetic, modified RNA. However, it is preferred, but not absolutely necessary, that each occurrence of a given nucleoside in a molecule is modified (e.g., each cytosine is a modified cytosine e.g., 5mC). However, it is also contemplated that different occurrences of the same nucleoside can be modified in a different way in a given synthetic, modified RNA molecule (e.g., some cytosines modified as 5mC, others modified as 2′-O-methylcytidine or other cytosine analog). The modifications need not be the same for each of a plurality of modified nucleosides in a synthetic, modified RNA. Furthermore, in some embodiments of the aspects described herein, a synthetic, modified RNA comprises at least two different modified nucleosides. In some such preferred embodiments of the aspects described herein, the at least two different modified nucleosides are 5-methylcytidine and pseudouridine. A synthetic, modified RNA can also contain a mixture of both modified and unmodified nucleosides.

[0669] As used herein, "unmodified" or "natural" nucleosides or nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). In some embodiments, a synthetic, modified RNA comprises at least one nucleoside ("base") modification or substitution. Modified nucleosides include other synthetic and natural nucleobases such as inosine, xanthine, hypoxanthine, nubularine, isoguanisine, tubercidine, 2-(halo)adenine, 2-(alkyl)adenine, 2-(propyl)adenine, 2 (amino)adenine, 2-(aminoalkyl)adenine, 2 (aminopropyl)adenine, 2 (methylthio) N6 (isopentenyl)adenine, 6 (alkyl)adenine, 6 (methyl)adenine, 7 (deaza)adenine, 8 (alkenyl)adenine, 8-(alkyl)adenine, 8 (alkynyl)adenine, 8 (amino)adenine, 8-(halo)adenine, 8-(hydroxyl)adenine, 8 (thioalkyl)adenine, 8-(thiol)adenine, N6-(isopentyl)adenine, N6 (methyl)adenine, N6, N6 (dimethyl)adenine, 2-(alkyl)guanine, 2 (propyl)guanine, 6-(alkyl)guanine, 6 (methyl)guanine, 7 (alkyl)guanine, 7 (methyl)guanine, 7 (deaza)guanine, 8 (alkyl)guanine, 8-(alkenyl)guanine, 8 (alkynyl)guanine, 8-(amino)guanine, 8 (halo)guanine, 8-(hydroxyl)guanine, 8 (thioalkyl)guanine, 8-(thiol)guanine, N (methyl)guanine, 2-(thio)cytosine, 3 (deaza) 5 (aza)cytosine, 3-(alkyl)cytosine, 3 (methyl)cytosine, 5-(alkyl)cytosine, 5-(alkynyl)cytosine, 5 (halo)cytosine, 5 (methyl)cytosine, 5 (propynyl)cytosine, 5 (propynyl)cytosine, 5 (trifluoromethyl)cytosine, 6-(azo)cytosine, N4 (acetyl)cytosine, 3

(methylaminomethyl)-4 (thio)uracil, 5 (methyl) 2,4 (dithio)uracil, 5 (methylaminomethyl)-2,4 (dithio)uracil, 5 (2-aminopropyl)uracil, 5-(alkyl)uracil, 5-(alkynyl)uracil, 5-(allylamino)uracil, 5 (aminoallyl)uracil, 5 (aminoalkyl)uracil, 5 (guanidiniumalkyl)uracil, 5 (1,3-diazole-1-alkyl)uracil, 5-(cyanoalkyl)uracil, 5-(dialkylaminoalkyl)uracil, 5 (dimethylaminoalkyl)uracil, 5-(halo)uracil, 5-(methoxy)uracil, uracil-5 oxyacetic acid, 5 (methoxycarbonylmethyl)-2-(thio)uracil, 5 (methoxycarbonyl-methyl)uracil, 5 (propynyl)uracil, 5 (propynyl)uracil, 5 (trifluoromethyl)uracil, 6 (azo)uracil, dihydrouracil, N3 (methyl)uracil, 5-uracil (i.e., pseudouracil), 2 (thio)pseudouracil,4 (thio)pseudouracil,2,4-(dithio)psuedouracil,5-(alkyl)pseudouracil, 5-(methyl)pseudouracil, 5-(alkyl)-2-(thio)pseudouracil, 5-(methyl)-2-(thio)pseudouracil, 5-(alkyl)-4 (thio)pseudouracil, 5-(methyl)-4 (thio)pseudouracil, 5-(alkyl)-2,4 (dithio)pseudouracil, 5-(methyl)-2,4 (dithio)pseudouracil, 1 substituted pseudouracil, 1 substituted 2(thio)-pseudouracil, 1 substituted 4 (thio)pseudouracil, 1 substituted 2,4-(dithio)pseudouracil, 1 (aminocarbonylethylenyl)-pseudouracil, 1 (aminocarbonylethylenyl)-2(thio)-pseudouracil, 1 (aminocarbonylethylenyl)-4 (thio)pseudouracil, 1 (aminocarbonylethylenyl)-2,4-(dithio)pseudouracil, 1 (aminoalkylaminocarbonylethylenyl)-pseudouracil, 1 (aminoalkylamino-carbonylethylenyl)-2(thio)-pseudouracil, 1 (aminoalkylaminocarbonylethylenyl)-4 (thio)pseudouracil, 1 (aminoalkylaminocarbonylethylenyl)-2,4-(dithio)pseudouracil, 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-substituted 1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 7-substituted 1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 7-substituted 1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 7-(aminoalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 7-(aminoalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenoxazin-1-yl, 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenoxazin-1-yl, 7-(guanidiniumalkylhydroxy)-1,3-(diaza)-2-(oxo)-phenthiazin-1-yl, 7-(guanidiniumalkylhydroxy)-1-(aza)-2-(thio)-3-(aza)-phenthiazin-1-yl, 1,3,5-(triaza)-2,6-(dioxa)-naphthalene, inosine, xanthine, hypoxanthine, nubularine, tubercidine, isoguanisine, inosinyl, 2-aza-inosinyl, 7-deaza-inosinyl, nitroimidazolyl, nitropyrazolyl,

(propynyl)isocarbostyrilyl, 7-(aza)indolyl, 6-(methyl)-7-(aza)indolyl, imidizopyridinyl, 9-(methyl)-imidizopyridinyl, pyrrolopyrizinyl, isocarbostyrilyl, 7-(propynyl)isocarbostyrilyl, propynyl-7-(aza)indolyl, 2,4,5-(trimethyl)phenyl, 4-(methyl)indolyl, 4,6-(dimethyl)indolyl, phenyl, napthalenyl, anthracenyl, phenanthracenyl, pyrenyl, stilbenzyl, tetracenyl, pentacenyl, difluorotolyl, 4-(fluoro)-6-(methyl)benzimidazole, 4-(methyl)benzimidazole, 6-(azo)thymine, 2-pyridinone, 5 nitroindole, 3 nitropyrrole, 6-(aza)pyrimidine, 2 (amino)purine, 2,6-(diamino)purine, 5 substituted pyrimidines, N2-substituted purines, N6-substituted purines, 06-substituted purines, substituted 1,2,4-triazoles, pyrrolo-pyrimidin-2-on-3-yl, 6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, para-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, bis-ortho-substituted-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, para-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, bis-ortho-(aminoalkylhydroxy)-6-phenyl-pyrrolo-pyrimidin-2-on-3-yl, pyridopyrimidin-3-yl, 2-oxo-7-amino-pyridopyrimidin-3-yl, 2-oxo-pyridopyrimidine-3-yl, or any O-alkylated or N-alkylated derivatives thereof. Modified nucleosides also include natural bases that comprise conjugated moieties, e.g. a ligand. As discussed herein above, the RNA containing the modified nucleosides must be translatable in a host cell (i.e., does not prevent translation of the polypeptide encoded by the modified RNA). For example, transcripts containing s2U and m6A are translated poorly in rabbit reticulocyte lysates, while pseudouridine, m5U, and m5C are compatible with efficient translation. In addition, it is known in the art that 2'-fluoro-modified bases useful for increasing nuclease resistance of a transcript, leads to very inefficient translation. Translation can be assayed by one of ordinary skill in the art using e.g., a rabbit reticulocyte lysate translation assay.

[0670] Further modified nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in Modified Nucleosides in Biochemistry, Biotechnology and Medicine, Herdewijn, P. ed. Wiley-VCH, 2008; those disclosed in Int. Appl. No. PCT/US09/038,425, filed Mar. 26, 2009; those disclosed in The Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. L, ed. John Wiley & Sons, 1990, and those disclosed by Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613.

[0671] Representative U.S. patents that teach the preparation of certain of the

4,845,205; 5,130,30; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,457,191; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,681,941; 6,015,886; 6,147,200; 6,166,197; 6,222,025; 6,235,887; 6,380,368; 6,528,640; 6,639,062; 6,617,438; 7,045,610; 7,427,672; and 7,495,088, each of which is herein incorporated by reference in its entirety, and U.S. Pat. No. 5,750,692, also herein incorporated by reference in its entirety.

[0672] Another modification for use with the synthetic, modified RNAs described herein involves chemically linking to the RNA one or more ligands, moieties or conjugates that enhance the activity, cellular distribution or cellular uptake of the RNA. Ligands can be particularly useful where, for example, a synthetic, modified RNA is administered *in vivo*. Such moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger et al., Proc. Natl. Acid. Sci. USA, 1989, 86: 6553-6556, herein incorporated by reference in its entirety), cholic acid (Manoharan et al., Biorg. Med. Chem. Let., 1994, 4:1053-1060, herein incorporated by reference in its entirety), a thioether, e.g., beryl-S-tritylthiol (Manoharan et al., Ann. N.Y. Acad. Sci., 1992, 660:306-309; Manoharan et al., Biorg. Med. Chem. Let., 1993, 3:2765-2770, each of which is herein incorporated by reference in its entirety), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20:533-538, herein incorporated by reference in its entirety), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al., EMBO J, 1991, 10:1111-1118; Kabanov et al., FEBS Lett., 1990, 259:327-330; Svinarchuk et al., Biochimie, 1993, 75:49-54, each of which is herein incorporated by reference in its entirety), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36:3651-3654; Shea et al., Nucl. Acids Res., 1990, 18:3777-3783, each of which is herein incorporated by reference in its entirety), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14:969-973, herein incorporated by reference in its entirety), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36:3651-3654, herein incorporated by reference in its entirety), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264:229-237, herein incorporated by reference in its entirety), or an octadecylamine or hexylamino-carbonyloxycholesterol moiety (Crooke et al., J. Pharmacol. Exp. Ther., 1996, 277:923-937, herein incorporated by reference in its entirety).

comprise a 5′ cap comprising a modified guanine nucleotide that is linked to the 5′ end of an RNA molecule using a 5′-5′ triphosphate linkage. As used herein, the term "5′ cap" is also intended to encompass other 5′ cap analogs including, e.g., 5′ diguanosine cap, tetraphosphate cap analogs having a methylene-bis(phosphonate) moiety (see e.g., Rydzik, A M et al., (2009) Org Biomol Chem 7(22):4763-76), dinucleotide cap analogs having a phosphorothioate modification (see e.g., Kowalska, J. et al., (2008) RNA 14(6):1119-1131), cap analogs having a sulfur substitution for a non-bridging oxygen (see e.g., Grudzien-Nogalska, E. et al., (2007) RNA 13(10): 1745-1755), N7-benzylated dinucleoside tetraphosphate analogs (see e.g., Grudzien, E. et al., (2004) RNA 10(9):1479-1487), or anti-reverse cap analogs (see e.g., Jemielity, J. et al., (2003) RNA 9(9): 1108-1122 and Stepinski, J. et al., (2001) RNA 7(10):1486-1495). In one such embodiment, the 5′ cap analog is a 5′ diguanosine cap. In some embodiments, the synthetic, modified RNA does not comprise a 5′ triphosphate.

[0674] The 5′ cap is important for recognition and attachment of an mRNA to a ribosome to initiate translation. The 5′ cap also protects the synthetic, modified RNA from 5′ exonuclease mediated degradation. It is not an absolute requirement that a synthetic, modified RNA comprise a 5′ cap, and thus in other embodiments the synthetic, modified RNAs lack a 5′ cap. However, due to the longer half-life of synthetic, modified RNAs comprising a 5′ cap and the increased efficiency of translation, synthetic, modified RNAs comprising a 5′ cap are preferred herein.

[0675] The synthetic, modified RNAs described herein can further comprise a 5′ and/or 3′ untranslated region (UTR). Untranslated regions are regions of the RNA before the start codon (5′) and after the stop codon (3′), and are therefore not translated by the translation machinery. Modification of an RNA molecule with one or more untranslated regions can improve the stability of an mRNA, since the untranslated regions can interfere with ribonucleases and other proteins involved in RNA degradation. In addition, modification of an RNA with a 5′ and/or 3′ untranslated region can enhance translational efficiency by binding proteins that alter ribosome binding to an mRNA. Modification of an RNA with a 3′ UTR can be used to maintain a cytoplasmic localization of the RNA, permitting translation to occur in the cytoplasm of the cell. In one embodiment, the synthetic, modified RNAs described herein do not comprise a 5′ or 3′ UTR. In another embodiment, the synthetic, modified RNAs comprise either a 5′ or 3′ UTR. In another

high stability in the cell (e.g., a murine alpha-globin 3′ UTR). In some embodiments, the 5′ UTR, the 3′ UTR, or both comprise one or more modified nucleosides.

[0676] In some embodiments, the synthetic, modified RNAs described herein further comprise a Kozak sequence. The "Kozak sequence" refers to a sequence on eukaryotic mRNA having the consensus (gcc)gccRccAUGG SEQ ID NO: 1481, where R is a purine (adenine or guanine) three bases upstream of the start codon (AUG), which is followed by another 'G'. The Kozak consensus sequence is recognized by the ribosome to initiate translation of a polypeptide. Typically, initiation occurs at the first AUG codon encountered by the translation machinery that is proximal to the 5′ end of the transcript. However, in some cases, this AUG codon can be bypassed in a process called leaky scanning. The presence of a Kozak sequence near the AUG codon will strengthen that codon as the initiating site of translation, such that translation of the correct polypeptide occurs. Furthermore, addition of a Kozak sequence to a synthetic, modified RNA will promote more efficient translation, even if there is no ambiguity regarding the start codon. Thus, in some embodiments, the synthetic, modified RNAs described herein further comprise a Kozak consensus sequence at the desired site for initiation of translation to produce the correct length polypeptide. In some such embodiments, the Kozak sequence comprises one or more modified nucleosides.

[0677] In some embodiments, the synthetic, modified RNAs described herein further comprise a "poly (A) tail", which refers to a 3′ homopolymeric tail of adenine nucleotides, which can vary in length (e.g., at least 5 adenine nucleotides) and can be up to several hundred adenine nucleotides). The inclusion of a 3′ poly(A) tail can protect the synthetic, modified RNA from degradation in the cell, and also facilitates extra-nuclear localization to enhance translation efficiency. In some embodiments, the poly(A) tail comprises between 1 and 500 adenine nucleotides; in other embodiments the poly(A) tail comprises at least 5, at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90, at least 100, at least 110, at least 120, at least 130, at least 140, at least 150, at least 160, at least 170, at least 180, at least 190, at least 200, at least 225, at least 250, at least 275, at least 300, at least 325, at least 350, at least 375, at least 400, at least 425, at least 450, at least 475, at least 500 adenine nucleotides or more. In one embodiment, the poly(A) tail comprises between 1 and 150 adenine nucleotides. In another embodiment, the poly(A) tail comprises between 90 and 120 adenine nucleotides.

[0678] It is contemplated that one or more modifications to the synthetic, modified RNAs described herein permit greater stability of the synthetic, modified RNA in a cell. To the extent that such modifications permit translation and either reduce or do not exacerbate a cell's innate immune or interferon response to the synthetic, modified RNA with the modification, such modifications are specifically contemplated for use herein. Generally, the greater the stability of a synthetic, modified RNA, the more protein can be produced from that synthetic, modified RNA. Typically, the presence of AU-rich regions in mammalian mRNAs tend to destabilize transcripts, as cellular proteins are recruited to AU-rich regions to stimulate removal of the poly(A) tail of the transcript. Loss of a poly(A) tail of a synthetic, modified RNA can result in increased RNA degradation. Thus, in one embodiment, a synthetic, modified RNA as described herein does not comprise an AU-rich region. In particular, it is preferred that the 3′ UTR substantially lacks AUUUA sequence elements.

[0679] In one embodiment, a ligand alters the cellular uptake, intracellular targeting or half-life of a synthetic, modified RNA into which it is incorporated. In some embodiments a ligand provides an enhanced affinity for a selected target, e.g., molecule, cell or cell type, intracellular compartment, e.g., mitochondria, cytoplasm, peroxisome, lysosome, as, e.g., compared to a composition absent such a ligand. Preferred ligands do not interfere with expression of a polypeptide from the synthetic, modified RNA.

[0680] Ligands can include a naturally occurring substance, such as a protein (e.g., human serum albumin (HSA), low-density lipoprotein (LDL), or globulin); carbohydrate (e.g., a dextran, pullulan, chitin, chitosan, inulin, cyclodextrin or hyaluronic acid); or a lipid. The ligand can also be a recombinant or synthetic molecule, such as a synthetic polymer, e.g., a synthetic polyamino acid. Examples of polyamino acids include polylysine (PLL), poly L aspartic acid, poly L-glutamic acid, styrene-maleic acid anhydride copolymer, poly(L-lactide-co-glycolied) copolymer, divinyl ether-maleic anhydride copolymer, N-(2-hydroxypropyl)methacrylamide copolymer (HMPA), polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyurethane, poly(2-ethylacryllic acid), N-isopropylacrylamide polymers, or polyphosphazine. Example of polyamines include: polyethylenimine, polylysine (PLL), spermine, spermidine, polyamine, pseudopeptide-polyamine, peptidomimetic polyamine, dendrimer polyamine, arginine, amidine, protamine, cationic lipid, cationic porphyrin, quaternary salt of a polyamine, or

[0681] Ligands can also include targeting groups, e.g., a cell targeting agent, (e.g., a lectin, glycoprotein, lipid or protein), or an antibody, that binds to a specified cell type such as a fibroblast cell. A targeting group can be, for example, a thyrotropin, melanotropin, lectin, glycoprotein, surfactant protein A, Mucin carbohydrate, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, multivalent fucose, glycosylated polyaminoacids, multivalent galactose, transferrin, bisphosphonate, polyglutamate, polyaspartate, a lipid, cholesterol, a steroid, bile acid, folate, vitamin B12, biotin, or an RGD peptide or RGD peptide mimetic, among others.

[0682] Other examples of ligands include dyes, intercalating agents (e.g. acridines), cross-linkers (e.g. psoralene, mitomycin C), porphyrins (TPPC4, texaphyrin, Sapphyrin), polycyclic aromatic hydrocarbons (e.g., phenazine, dihydrophenazine), artificial endonucleases (e.g. EDTA), lipophilic molecules, e.g., cholesterol, cholic acid, adamantane acetic acid, 1-pyrene butyric acid, dihydrotestosterone, 1,3-Bis-O(hexadecyl)glycerol, geranyloxyhexyl group, hexadecylglycerol, borneol, menthol, 1,3-propanediol, heptadecyl group, palmitic acid, myristic acid,O3-(oleoyl)lithocholic acid, O3-(oleoyl)cholenic acid, dimethoxytrityl, or phenoxazine) and peptide conjugates (e.g., antennapedia peptide, Tat peptide), alkylating agents, amino, mercapto, PEG (e.g., PEG-40K), MPEG, [MPEG]2, polyamino, alkyl, substituted alkyl, radiolabeled markers, enzymes, haptens (e.g. biotin), and transport/absorption facilitators (e.g., aspirin, vitamin E, folic acid).

[0683] Ligands can be proteins, e.g., glycoproteins, or peptides, e.g., molecules having a specific affinity for a co-ligand, or antibodies e.g., an antibody, that binds to a specified cell type such as a fibroblast cell, or other cell useful in the production of polypeptides. Ligands can also include hormones and hormone receptors. They can also include non-peptidic species, such as lipids, lectins, carbohydrates, vitamins, cofactors, multivalent lactose, multivalent galactose, N-acetyl-galactosamine, N-acetyl-glucosamine multivalent mannose, or multivalent fucose.

[0684] The ligand can be a substance, e.g., a drug, which can increase the uptake of the synthetic, modified RNA or a composition thereof into the cell, for example, by disrupting the cell's cytoskeleton, e.g., by disrupting the cell's microtubules, microfilaments, and/or intermediate filaments. The drug can be, for example, taxol,

[0685] One exemplary ligand is a lipid or lipid-based molecule. A lipid or lipid-based ligand can (a) increase resistance to degradation, and/or (b) increase targeting or transport into a target cell or cell membrane. A lipid based ligand can be used to modulate, e.g., binding of the modified RNA composition to a target cell.

[0686] In another aspect, the ligand is a moiety, e.g., a vitamin, which is taken up by a host cell. Exemplary vitamins include vitamin A, E, and K. Other exemplary vitamins include B vitamin, e.g., folic acid, B12, riboflavin, biotin, pyridoxal or other vitamins or nutrients taken up, for example, by cancer cells. Also included are HSA and low density lipoprotein (LDL).

[0687] In another aspect, the ligand is a cell-permeation agent, preferably a helical cell-permeation agent. Preferably, the agent is amphipathic. An exemplary agent is a peptide such as tat or antennopedia. If the agent is a peptide, it can be modified, including a peptidylmimetic, invertomers, non-peptide or pseudo-peptide linkages, and use of D-amino acids. The helical agent is preferably an alpha-helical agent, which preferably has a lipophilic and a lipophobic phase.

[0688] A "cell permeation peptide" is capable of permeating a cell, e.g., a microbial cell, such as a bacterial or fungal cell, or a mammalian cell, such as a human cell. A microbial cell-permeating peptide can be, for example, an α-helical linear peptide (e.g., LL-37 or Ceropin P1), a disulfide bond-containing peptide (e.g., α-defensin, β-defensin or bactenecin), or a peptide containing only one or two dominating amino acids (e.g., PR-39 or indolicidin). For example, a cell permeation peptide can be a bipartite amphipathic peptide, such as MPG, which is derived from the fusion peptide domain of HIV-1 gp41 and the NLS of SV40 large T antigen (Simeoni et al., Nucl. Acids Res. 31:2717-2724, 2003).

[0689] The synthetic, modified RNAs described herein can be synthesized and/or modified by methods well established in the art, such as those described in "Current Protocols in Nucleic Acid Chemistry," Beaucage, S. L. et al. (Edrs.), John Wiley & Sons, Inc., New York, N.Y., USA, which is hereby incorporated herein by reference in its entirety. Transcription methods are described further herein in the Examples.

[0690] In one embodiment of the aspects described herein, a template for a synthetic, modified RNA is synthesized using "splint-mediated ligation," which allows for the rapid synthesis of DNA constructs by controlled concatenation of long oligos

sequences of genes during T7 template generation. Splint mediated ligation can also be used to add nuclear localization sequences to an open reading frame, and to make dominant-negative constructs with point mutations starting from a wild-type open reading frame. Briefly, single-stranded and/or denatured dsDNA components are annealed to splint oligos which bring the desired ends into conjunction, the ends are ligated by a thermostable DNA ligase and the desired constructs amplified by PCR. A synthetic, modified RNA is then synthesized from the template using an RNA polymerase in vitro. After synthesis of a synthetic, modified RNA is complete, the DNA template is removed from the transcription reaction prior to use with the methods described herein.

[0691] In some embodiments of these aspects, the synthetic, modified RNAs are further treated with an alkaline phosphatase.

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[0692] One skilled in the art readily appreciates that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The details of the description and the examples herein are representative of certain embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Modifications therein and other uses will occur to those skilled in the art. These modifications are encompassed within the spirit of the invention. It will be readily apparent to a person skilled in the art that varying substitutions and modifications may be made to the invention disclosed herein without departing from the scope and spirit of the invention.

[0693] The articles "a" and "an" as used herein in the specification and in the claims, unless clearly indicated to the contrary, should be understood to include the plural referents. Claims or descriptions that include "or" between one or more members of a group are considered satisfied if one, more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process unless indicated to the contrary or otherwise evident from the context. The invention includes embodiments in which exactly one member of the group is present in, employed in, or otherwise relevant to a given product or process. The invention also includes embodiments in which more than one, or all of the group members are present in, employed in, or otherwise relevant to a given product or process. Furthermore, it is to be

more of the listed claims is introduced into another claim dependent on the same base claim (or, as relevant, any other claim) unless otherwise indicated or unless it would be evident to one of ordinary skill in the art that a contradiction or inconsistency would arise. It is contemplated that all embodiments described herein are applicable to all different aspects of the invention where appropriate. It is also contemplated that any of the embodiments or aspects can be freely combined with one or more other such embodiments or aspects whenever appropriate. Where elements are presented as lists, e.g., in Markush group or similar format, it is to be understood that each subgroup of the elements is also disclosed, and any element(s) can be removed from the group. It should be understood that, in general, where the invention, or aspects of the invention, is/are referred to as comprising particular elements, features, etc., certain embodiments of the invention or aspects of the invention consist, or consist essentially of, such elements, features, etc. For purposes of simplicity those embodiments have not in every case been specifically set forth in so many words herein. It should also be understood that any embodiment or aspect of the invention can be explicitly excluded from the claims, regardless of whether the specific exclusion is recited in the specification. For example, any one or more active agents, additives, ingredients, optional agents, types of organism, disorders, subjects, or combinations thereof, can be excluded.

[0694] Where the claims or description relate to a composition of matter, it is to be understood that methods of making or using the composition of matter according to any of the methods disclosed herein, and methods of using the composition of matter for any of the purposes disclosed herein are aspects of the invention, unless otherwise indicated or unless it would be evident to one of ordinary skill in the art that a contradiction or inconsistency would arise. Where the claims or description relate to a method, e.g., it is to be understood that methods of making compositions useful for performing the method, and products produced according to the method, are aspects of the invention, unless otherwise indicated or unless it would be evident to one of ordinary skill in the art that a contradiction or inconsistency would arise.

[0695] Where ranges are given herein, the invention includes embodiments in which the endpoints are included, embodiments in which both endpoints are excluded, and embodiments in which one endpoint is included and the other is excluded. It should be assumed that both endpoints are included unless indicated otherwise. Furthermore, it

can assume any specific value or subrange within the stated ranges in different embodiments of the invention, to the tenth of the unit of the lower limit of the range, unless the context clearly dictates otherwise. It is also understood that where a series of numerical values is stated herein, the invention includes embodiments that relate analogously to any intervening value or range defined by any two values in the series, and that the lowest value may be taken as a minimum and the greatest value may be taken as a maximum. Numerical values, as used herein, include values expressed as percentages. For any embodiment of the invention in which a numerical value is prefaced by "about" or "approximately", the invention includes an embodiment in which the exact value is recited. For any embodiment of the invention in which a numerical value is not prefaced by "about" or "approximately", the invention includes an embodiment in which the value is prefaced by "about" or "approximately".

[0696] Approximately" or "about" generally includes numbers that fall within a range of 1% or in some embodiments within a range of 5% of a number or in some embodiments within a range of 10% of a number in either direction (greater than or less than the number) unless otherwise stated or otherwise evident from the context (except where such number would impermissibly exceed 100% of a possible value). It should be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one act, the order of the acts of the method is not necessarily limited to the order in which the acts of the method are recited, but the invention includes embodiments in which the order is so limited. It should also be understood that unless otherwise indicated or evident from the context, any product or composition described herein may be considered "isolated".

[0697] As used herein the term "comprising" or "comprises" is used in reference to compositions, methods, and respective component(s) thereof, that are essential to the invention, yet open to the inclusion of unspecified elements, whether essential or not.

[0698] As used herein the term "consisting essentially of" refers to those elements required for a given embodiment. The term permits the presence of additional elements that do not materially affect the basic and novel or functional characteristic(s) of that embodiment of the invention.

[0699] The term "consisting of" refers to compositions, methods, and respective components thereof as described herein, which are exclusive of any element not recited in

Examples

[0700] Transcription activator-like effector nucleases (TALENs) bind as a pair around a genomic site, in which a double-strand break (DSB) is introduced by a dimer of FokI nuclease domains. The use of a TALEN genome-editing system to rapidly and efficiently generate mutant alleles of 15 different genes in human pluripotent stem cells (hPSCs) as a means of performing rigorous disease modeling was recently reported (Ding et al., Cell Stem Cell 12:238-251 (2013)); the proportions of clones bearing at least one mutant allele ranged from 2%-34%.

[0701] As described below, the relative efficacies of CRISPRs and TALENs targeting the same genomic sites in the same hPSC lines was assessed with the use of the same delivery platform described previously (Ding et al., Cell Stem Cell 12:238-251 (2013)). In the TALEN genome-editing system, the CAG promoter was used to co-translate (via a viral 2A peptide) each TALEN with green fluorescent protein (GFP) or red fluorescent protein (RFP). For CRISPRs, a human codon-optimized Cas9 gene was subcloned with a C-terminal nuclear localization signal (Mali et al., Science 339:823-826 (2013)) into the same CAG expression plasmid with GFP, and the guide RNA (gRNA) was separately expressed from a plasmid with the human U6 polymerase III promoter (Mali et al., Science 339:823-826 (2013)). The 20-nucleotide protospacer sequence for each gRNA was introduced using polymerase chain reaction (PCR)-based methods. Whether using TALENs or CRISPRs, equal amounts of the two plasmids were co-electroporated into hPSCs (either 25 μg of each plasmid, or 12.5 μg of each plasmid along with 25 μg of a DNA repair template if attempting knock-in) followed by fluorescence-activated cell sorting (FACS) after 24-48 hours, clonal expansion of single cells, and screening for mutations at the genomic target site via PCR.

[0702] gRNAs were designed matching G(N)19NGG sequences in seven loci in six genes (AKT2, CELSR2, CIITA, GLUT4, LINC00116, and SORT1) previously successfully targeted with TALENs (Ding et al., Cell Stem Cell 12:238-251 (2013)) and one additional locus in LDLR. In this system, CRISPRs consistently and substantially outperformed TALENs across loci and hPSC lines (see Table S1). The TALENs yielded clones with at least one mutant allele at efficiencies of 0%-34%, but matched CRISPRs

dozen nucleotides in size, centered on the predicted cleavage sites, suggesting that non-homologous end-joining mutagenesis occurs in the same way regardless of whether CRISPRs or TALENs are used. Moreover, CRISPRs readily generated homozygous mutant clones (7%-25% of all clones; Table S1) as discerned by sequencing.

[0703] Knock-in of E17K mutations into AKT2 was also attempted using a 67-nucleotide single-stranded DNA oligonucleotide as previously described (Ding et al., Cell Stem Cell 12:238-251 (2013)). Although the predicted CRISPR cleavage site lay 11 and 13 nucleotides from the point mutations, respectively, the CRISPR yielded knock-in clones at a rate of 11%, whereas TALENs yielded only 1.6% (Table S1).

ırgeting Efficiency of CRISPRs Versus TALENs in Human Pluripotent Stem Cells

Chromosome: Position (Start of Target Sequence)	Target Sequence[a]	Cell Line[b]	TALENs	CRISPRs	
			Efficiency (Mutants/Clones Screened)[c]	Efficiency (Mutants/Clones Screened)[c]	Efficiency of Homozygous Mutants
chr19:40762982	TCCCTTCCTGCCTCATTTCAGGTGAATACATCAAGACCTGGAGGCCA	HUES 9	8.9% (17/192)		
chr19:40762982	TCCCTTCCTGCCTCATTTCAGGTGAATACATCAAGACCTGGAGGCCA	HUES 9		60.5% (86/142)	12.7% (18/142)
chr1:109817568	TGCTGGCTCGGCTGCCCTGAGGTTGCTCAATCAAGCACAGGTTTCAA	HUES 1	3.5% (18/506)		
chr1:109817568	TGCTGGCTCGGCTGCCCTGAGGTTGCTCAATCAAGCACAGGTTTCAA	HUES 1		66.2% (45/68)	7.4% (5/68)
chr16:10989200	TAACAGCGATGCTGACCCCCTGTGCCTCTACCACTTCTATGACCAGA	BJ-RiPS	12.7% (37/292)		
chr16:10989205	CGATGCTGACCCCCTGTGCCTCTACCACTTCTATGACCAGATGGACC	BJ-RiPS		78.7% (96/122)	11.5% (14/122)
chr17:7186601	TGGTCCTTGCTGTGTTCTCTGCCGTGCTTGGCTCCCTGCAGTTTGGGTA	HUES 9	33.5% (52/155)		
chr17:7186601	TGGTCCTTGCTGTGTTCTCTGCGGTGCTTGGCTCCCTGCAGTTTGGGTA	HUES 9		66.5% (123/185)	24.9% (46/185)
chr19:11210899	TGGGCGACAGATGCGAAAGAAACGAGTTCCAGTGCCAAGAGCGGAAA	HUES 9	0% (0/568)		
chr19:11210917	GAAACGAGTTCCAGTGCCAAGACGGGAAATGCATCTCCTACIAAGTGG	HUES 9		51.1% (90/176)	8.0% (14/176)
chr2:110970090	TCAGAGAGGACACTGCAGTTGTCCGTGCTAGTAGCCTTCGCTTCTGGA	HUES 9	29.5% (26/88)		
chr2:110970090	TCAGAGAGGACACTGCAGTTGTCCGTGCTAGTAGCCTTCGCTTCTGGA	HUES 9		57.4% (93/162)	8.6% (14/162)
chr1:109912203	TGATGATCTCAGAGGCTCAGTATCCTTGTCCTGGGTTGGAGATAGCA	HUES 1	22.2% (128/576)		
chr1:109912203	TGATGATCTCAGAGGCTCAGTATCCTTGTCCTGGGTTGGAGATAGCA	HUES 1		68.5% (100/146)	13.0% (19/146)
chr1:109910069	TGGTAATTATGACTTTTGGACAGTCCAAGCTATATCGAAGGTGAGATCA	HUES 9	10.9% (21/192)		
chr1:109910069	TGGTAATTATGACTTTTGGACAGTCCAAGCTATATCGAAGGTGAGATCA	HUES 9		75.9% (148/195)	10.3% (20/195)
chr19:40762982	TCCCTTCCTGCCTCATTTCAGGTGAATACATCAAGACCTGGAGGCCA	HUES 9	1.6% (3/192)[d]		
chr19:40762982	TCCCTTCCTGCCTCATTTCAGGTGAATACATCAAGACCTGGAGGCCA	HUES 9		10.6% (10/94)[d]	1.1% (1/94)[d]
chr5:22683972	CTATGCCCTGCCTCATTTCAGGTCAAGATGAAATCCCTGGAGCTTGG	HUES 9		0% (0/142)	0% (0/142)

e binding sites are indicated with underlines, with the cleavage site predicted to be midway between the binding sites; for CRISPRs, the protospacer is underlined, the NGG ıay be on the antisense strand), and the predicted cleavage site is indicated with "|"; for the *AKT2* E17K target sequence, the sites of the knock-in mutations are indicated in e *AKT2* off-target site, the two mismatches in the protospacer are indicated in bold/italics

JES 9 are human embryonic stem cell lines; BJ-RiPS is an induced pluripotent stem cell line

: single heterozygotes, compound heterozygotes, and homozygous mutants; TALEN data is from Table 1 of Ding et al. (2013), with the exception of *LDLR*

serted E17K knock-in mutations into an *AKT2* allele(s) using single-stranded DNA oligonucleotide (refer to Figure 3 of Ding et al., 2013)

[0705] It is worth noting that the requirement for a G(N)19NGG target sequence somewhat limits site selection. Because either DNA strand can be targeted, a target sequence occurs on average every 32 basepairs. This is no barrier for gene knockout, where any coding sequence can be targeted, but it may present difficulties when trying to knock in or correct a mutation at a specific location. However, the requirement for a G at the start of the protospacer is dictated by the use of the U6 promoter to express the gRNA, and alternative CRISPR/Cas systems can relieve this requirement (Cong et al., Science 339:819-823 (2013)). This allows for the use of (N)20NGG target sequences, which are found on average every 8 basepairs.

[0706] In addition, the extent of CRISPR off-target effects remains to be defined and is highly sequence-dependent. Previous analyses have suggested that one-nucleotide mismatches in the first half of the protospacer are better tolerated than mismatches in second half (Jinek et al., Science 337:816-821 (2012); Cong et al., Science 339:819-823 (2013)). For the AKT2 sequence, there is a two-mismatch sequence differing at nucleotides 1 and 3, in the more "tolerant" half of the protospacer. Zero clones were obtained with mutations at this potential off-target site, as compared to 61% at the on-target site (Table S1). For one of the SORT1 sequences, use of a different human pluripotent stem cell line in which a single nucleotide polymorphism results in a one-nucleotide mismatch at the target site yielded mutant clones at an efficiency of 42%, compared to 66% in the original cell line. Thus, judicious selection of target sites is necessary to minimize systematic off-target effects; target sites with perfect-match or single-nucleotide-mismatch sequences elsewhere in the genome should be avoided.

[0707] From a practical standpoint, CRISPRs are easier to implement than TALENs. Each TALEN pair must be constructed de novo, whereas for CRISPRs the Cas9 component is fixed and the gRNA requires only swapping of the 20-nucleotide protospacer. Given this consideration and the demonstration herein of substantially increased efficiency as a result of replacing TALENs with CRISPRs in an otherwise identical system, CRISPRs appear to be a very powerful and broadly applicable tool for genome editing, particularly in a therapeutic context.

CLAIMS

What is claimed is:

1. A method for altering a target severe combined immunodeficiency (SCID)-associated polynucleotide sequence in a cell comprising contacting the SCID-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved.

2. A method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence in a subject, the method comprising (a) altering a target SCID-associated polynucleotide sequence in a cell *ex vivo* by contacting the SCID-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequence.

3. A method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence in a subject, the method comprising altering a target SCID-associated polynucleotide sequence in a cell by contacting the SCID-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, and wherein the target SCID-associated polynucleotide sequence is cleaved,

thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequence.

4. A method for simultaneously altering multiple target SCID-associated polynucleotide sequences in a cell comprising contacting the SCID-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved.

5. A method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCID-associated polynucleotide sequences in a cell *ex vivo* by contacting the SCID-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequences.

6. A method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject, the method comprising altering target SCID-associated polynucleotide sequences in a cell by contacting the SCID-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target moieties of the target SCID-associated polynucleotide sequences, and wherein the target SCID-associated polynucleotide sequences are cleaved, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequences.

7. A method for altering a target sickle cell disease (SCD)-associated polynucleotide sequence in a cell comprising contacting the SCD-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved.

8. A method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence in a subject, the method comprising (a) altering a target SCD-associated polynucleotide sequence in a cell *ex vivo* by contacting the SCD-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequence.

9. A method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence in a subject, the method comprising altering a target SCD-associated polynucleotide sequence in a cell by contacting the SCD-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, and wherein the target SCD-associated polynucleotide sequence is cleaved, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequence.

10. A method for simultaneously altering multiple target SCD-associated polynucleotide sequences in a cell comprising contacting the SCD-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the

ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved.

11. A method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCD-associated polynucleotide sequences in a cell *ex vivo* by contacting the SCD-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequences.

12. A method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject, the method comprising altering target SCD-associated polynucleotide sequences in a cell by contacting the SCD-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target moieties of the target SCD-associated polynucleotide sequences, and wherein the target SCD-associated polynucleotide sequences are cleaved, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequences.

13. A method for altering a target beta thalassemia-associated polynucleotide sequence in a cell comprising contacting the beta thalassemia-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved.

14. A method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence in a subject, the method comprising (a) altering a target beta thalassemia-associated polynucleotide sequence in a cell *ex vivo* by contacting the beta thalassemia-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequence.

15. A method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence in a subject, the method comprising altering a target beta thalassemia-associated polynucleotide sequence in a cell by contacting the beta thalassemia-associated polynucleotide sequence with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, and wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequence.

16. A method for simultaneously altering multiple target beta thalassemia-associated polynucleotide sequences in a cell comprising contacting the beta thalassemia-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved.

17. A method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject, the method comprising (a) altering target beta thalassemia-associated polynucleotide sequences in a cell *ex vivo* by contacting the beta thalassemia-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequences.

18. A method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject, the method comprising altering target beta thalassemia-associated polynucleotide sequences in a cell by contacting the beta thalassemia-associated polynucleotide sequences with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target moieties of the target beta thalassemia-associated polynucleotide sequences, and wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequences.

19. A method according to any one of claims 1-18, wherein the Cas protein is *Streptococcus pyogenes* Cas9 protein or a functional portion thereof.

20. The method according to claim 19, wherein the functional portion comprises a combination of operably linked Cas9 protein functional domains selected from the group consisting of a DNA binding domain, at least one RNA binding domain, a helicase domain, and an endonuclease domain.

21. The method according to claim 20, wherein the functional domains form a complex.

22. A method according to any one of claims 1-18, wherein the Cas protein is Cas9 protein from any bacterial species or functional portion thereof.

23. The method according to claim 22, wherein the functional portion comprises a combination of operably linked Cas9 protein functional domains selected from the group consisting of a DNA binding domain, at least one RNA binding domain, a helicase domain, and an endonuclease domain.

24. The method according to claim 22, wherein the functional domains form a complex.

25. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the Cas protein is complexed with the one to two ribonucleic acids.

26. A method according to any one of claims 4-6, 10-12, or 16-18, wherein the Cas protein is complexed with the multiple ribonucleic acids.

27. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the target motif is a 20-nucleotide DNA sequence.

28. A method according to any one of claims 4-6, 10-12, or 16-18, wherein each target motif is a 20-nucleotide DNA sequence.

29. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the target motif is a 20-nucleotide DNA sequence beginning with G and immediately precedes an NGG motif recognized by the Cas protein.

30. A method according to any one of claims 4-6, 10-12, or 16-18, wherein each target motif is a 20-nucleotide DNA sequence beginning with G and immediately precedes an NGG motif recognized by the Cas protein.

31. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the target motif is a 20-nucleotide DNA sequence and immediately precedes an NGG motif recognized by the Cas protein.

32. A method according to any one of claims 4-6, 10-12, or 16-18, wherein each target motif is a 20-nucleotide DNA sequence and immediately precedes an NGG motif recognized by the Cas protein.

33. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the target motif is $G(N)_{19}NGG$.

34. A method according to any one of claims 4-6, 10-12, or 16-18, wherein each target motif is $G(N)_{19}NGG$.

35. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the target motif is $(N)_{20}NGG$.

36. A method according to any one of claims 4-6, 10-12, or 16-18, wherein each target motif is $(N)_{20}NGG$.

37. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the target polynucleotide sequence is cleaved such that a double-strand break results.

38. A method according to any one of claims 4-6, 10-12, or 16-18, wherein each target polynucleotide sequence is cleaved such that a double-strand break results.

39. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the target polynucleotide sequence is cleaved such that a single-strand break results.

40. A method according to any one of claims 4-6, 10-12, or 16-18, wherein each target polynucleotide sequence is cleaved such that a single-strand break results.

41. A method according to any one of claims 1-18, wherein the alteration is an indel.

42. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the alteration results in reduced expression of the target polynucleotide sequence.

43. A method according to any one of claims 4-6, 10-12, or 16-18, wherein the alteration results in reduced expression of the target polynucleotide sequences.

44. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the alteration results in a knock out of the target polynucleotide sequence.

45. A method according to any one of claims 4-6, 10-12, or 16-18, wherein the alteration results in a knock out of the target polynucleotide sequences.

46. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the alteration results in correction of the target polynucleotide sequence from an undesired sequence to a desired sequence.

47. A method according to any one of claims 4-6, 10-12, or 16-18, wherein the alteration results in correction of the target polynucleotide sequences from undesired sequences to desired sequences.

48. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the alteration is a homozygous alteration.

49. A method according to any one of claims 4-6, 10-12, or 16-18, wherein each alteration is a homozygous alteration.

50. A method according to any one of claims 1-3, 7-9, or 13-15, wherein subsequent to cleavage of the target polynucleotide sequence, homology-directed repair occurs.

51. A method according to claim 50, wherein homology-directed repair is performed using an exogenously introduced DNA repair template.

52. A method according to claim 51, wherein the exogenously introduced DNA repair template is single-stranded.

53. A method according to claim 51, wherein the exogenously introduced DNA repair template is double-stranded.

54. A method according to any one of claims 4-6, 10-12, or 16-18, wherein subsequent to cleavage of the target polynucleotide sequences, homology-directed repair occurs.

55. A method according to claim 54, wherein homology-directed repair is performed using an exogenously introduced DNA repair template.

56. A method according to claim 55, wherein the exogenously introduced DNA repair template is single-stranded.

57. A method according to claim 55, wherein the exogenously introduced DNA repair template is double-stranded.

58. A method according to any one of claims 1-57, wherein the cell is a peripheral blood cell.

59. A method according to any one of claims 1-58, wherein the cell is a stem cell or a pluripotent cell.

60. A method according to any one of claims 1-59, wherein the cell is a hematopoietic stem cell.

61. A method according to any one of claims 1-60, wherein the cell is a $CD34^+$ cell.

62. A method according to any one of claims 1-61, wherein the cell is a $CD34^+$ mobilized peripheral blood cell.

63. A method according to any one of claims 1-62, wherein the cell is a $CD34^+$ cord blood cell.

64. A method according to any one of claims 1-63, wherein the cell is a $CD34^+$ bone marrow cell.

65. A method according to any one of claims 1-64, wherein the cell is a $CD34^+CD38^-$ Lineage-$CD90^+CD45RA^-$ cell.

66. A method according to any one of claims 1-3, wherein the target polynucleotide sequence is ADA.

67. A method according to claim 66, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1 or at least a 12 nucleotide fragment thereof.

68. A method according to claim 66, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1 or at least a 12 nucleotide fragment thereof.

69. A method according to any one of claims 1-3, wherein the target polynucleotide sequence is AK2.

70. A method according to claim 69, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2 or at least a 12 nucleotide fragment thereof.

71. A method according to claim 69, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2 or at least a 12 nucleotide fragment thereof.

72. A method according to any one of claims 1-3, wherein the target polynucleotide sequence is CD3D.

73. A method according to claim 72, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3 or at least a 12 nucleotide fragment thereof.

74. A method according to claim 72, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3 or at least a 12 nucleotide fragment thereof.

75. A method according to any one of claims 1-3, wherein the target polynucleotide sequence is DCLRE1C.

76. A method according to claim 75, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 4 or at least a 12 nucleotide fragment thereof.

77. A method according to claim 75, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 4 or at least a 12 nucleotide fragment thereof.

78. A method according to any one of claims 1-3, wherein the target polynucleotide sequence is IL2RG.

79. A method according to claim 78, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6 or at least a 12 nucleotide fragment thereof.

80. A method according to claim 78, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a

sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6 or at least a 12 nucleotide fragment thereof.

81. A method according to any one of claims 1-3, wherein the target polynucleotide sequence is IL7R.

82. A method according to claim 81, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7 or at least a 12 nucleotide fragment thereof.

83. A method according to claim 81, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7 or at least a 12 nucleotide fragment thereof.

84. A method according to any one of claims 1-3, wherein the target polynucleotide sequence is JAK3.

85. A method according to claim 84, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8 or at least a 12 nucleotide fragment thereof.

86. A method according to claim 84, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8 or at least a 12 nucleotide fragment thereof.

87. A method according to any one of claims 1-3, wherein the target polynucleotide sequence is LIG4.

88. A method according to claim 87, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9 or at least a 12 nucleotide fragment thereof.

89. A method according to claim 87, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9 or at least a 12 nucleotide fragment thereof.

90. A method according to any one of claims 1-3, wherein the target polynucleotide sequence is NHEJ1.

91. A method according to claim 90, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10 or at least a 12 nucleotide fragment thereof.

92. A method according to claim 90, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10 or at least a 12 nucleotide fragment thereof.

93. A method according to any one of claims 1-3, wherein the target polynucleotide sequence is PNP.

94. A method according to claim 93, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11 or at least a 12 nucleotide fragment thereof.

95. A method according to claim 93, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11 or at least a 12 nucleotide fragment thereof.

96. A method according to any one of claims 1-3, wherein the target polynucleotide sequence is PRKDC.

97. A method according to claim 96, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12 or at least a 12 nucleotide fragment thereof.

98. A method according to claim 96, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12 or at least a 12 nucleotide fragment thereof.

99. A method according to any one of claims 1-3, wherein the target polynucleotide sequence is RAG1.

100. A method according to claim 99, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 13 or at least a 12 nucleotide fragment thereof.

101. A method according to claim 99, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig.13 or at least a 12 nucleotide fragment thereof.

102. A method according to any one of claims 1-3, wherein the target polynucleotide sequence is RAG2.

103. A method according to claim 102, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 14 or at least a 12 nucleotide fragment thereof.

104. A method according to claim 102, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 14 or at least a 12 nucleotide fragment thereof.

105. A method according to any one of claims 1-3, wherein the target polynucleotide sequence is ZAP70.

106. A method according to claim 105, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15 or at least a 12 nucleotide fragment thereof.

107. A method according to claim 105, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15 or at least a 12 nucleotide fragment thereof.

108. A method according to any one of claims 6-9 or 13-15, wherein the target polynucleotide sequence is HBB.

109. A method according to claim 108, wherein at least one of the one to two ribonucleic acids comprises a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5 or at least a 12 nucleotide fragment thereof.

110. A method according to claim 108, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5 or at least a 12 nucleotide fragment thereof.

111. A method according to any one of claims 4-6, wherein the target polynucleotide sequences comprise multiple different portions of ADA.

112. A method according to claim 111, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 1 or at least 12 nucleotide fragments thereof.

113. A method according to claim 111, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence

selected from the group consisting of the ribonucleic acid sequences of Fig. 1 or at least 12 nucleotide fragments thereof.

114. A method according to any one of claims 4-6, wherein the target polynucleotide sequences comprise multiple different portions of AK2.

115. A method according to claim 114, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2 or at least 12 nucleotide fragments thereof.

116. A method according to claim 114, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 2 or at least 12 nucleotide fragments thereof.

117. A method according to any one of claims 4-6, wherein the target polynucleotide sequences comprise multiple different portions of CD3D.

118. A method according to claim 117, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3 or at least 12 nucleotide fragments thereof.

119. A method according to claim 117, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 3 or at least 12 nucleotide fragments thereof.

120. A method according to any one of claims 4-6, wherein the target polynucleotide sequences comprise multiple different portions of DCLRE1C.

121. A method according to claim 120, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 4 or at least 12 nucleotide fragments thereof.

122. A method according to claim 120, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 4 or at least 12 nucleotide fragments thereof.

123. A method according to any one of claims 4-6, wherein the target polynucleotide sequences comprise multiple different portions of IL2RG.

124. A method according to claim 123, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6 or at least 12 nucleotide fragments thereof.

125. A method according to claim 123, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 6 or at least 12 nucleotide fragments thereof.

126. A method according to any one of claims 4-6, wherein the target polynucleotide sequences comprise multiple different portions of IL7R.

127. A method according to claim 126, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7 or at least 12 nucleotide fragments thereof.

128. A method according to claim 126, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 7 or at least 12 nucleotide fragments thereof.

129. A method according to any one of claims 4-6, wherein the target polynucleotide sequences comprise multiple different portions of JAK3.

130. A method according to claim 129, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8 or at least 12 nucleotide fragments thereof.

131. A method according to claim 129, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 8 or at least 12 nucleotide fragments thereof.

132. A method according to any one of claims 4-6, wherein the target polynucleotide sequences comprise multiple different portions of LIG4.

133. A method according to claim 132, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9 or at least 12 nucleotide fragments thereof.

134. A method according to claim 132, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 9 or at least 12 nucleotide fragments thereof.

135. A method according to any one of claims 4-6, wherein the target polynucleotide sequences comprise multiple different portions of NHEJ1.

136. A method according to claim 135, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10 or at least 12 nucleotide fragments thereof.

137. A method according to claim 135, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 10 or at least 12 nucleotide fragments thereof.

138. A method according to any one of claims 4-6, wherein the target polynucleotide sequences comprise multiple different portions of PNP.

139. A method according to claim 138, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11 or at least 12 nucleotide fragments thereof.

140. A method according to claim 138, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 11 or at least 12 nucleotide fragments thereof.

141. A method according to any one of claims 4-6, wherein the target polynucleotide sequences comprise multiple different portions of PRKDC.

142. A method according to claim 141, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12 or at least 12 nucleotide fragments thereof.

143. A method according to claim 141, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 12 or at least 12 nucleotide fragments thereof.

144. A method according to any one of claims 4-6, wherein the target polynucleotide sequences comprise multiple different portions of RAG1.

145. A method according to claim 144, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 13 or at least 12 nucleotide fragments thereof.

146. A method according to claim 144, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence

selected from the group consisting of the ribonucleic acid sequences of Fig. 13 or at least 12 nucleotide fragments thereof.

147. A method according to any one of claims 4-6, wherein the target polynucleotide sequences comprise multiple different portions of RAG2.

148. A method according to claim 147, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 14 or at least 12 nucleotide fragments thereof.

149. A method according to claim 147, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 14 or at least 12 nucleotide fragments thereof.

150. A method according to any one of claims 4-6, wherein the target polynucleotide sequences comprise multiple different portions of ZAP70.

151. A method according to claim 150, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15 or at least 12 nucleotide fragments thereof.

152. A method according to claim 150, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 15 or at least 12 nucleotide fragments thereof.

153. A method according to any one of claims 10-12 or 16-18, wherein the target polynucleotide sequences comprise multiple different portions of HBB.

154. A method according to claim 153, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5 or at least 12 nucleotide fragments thereof.

155. A method according to claim 153, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Fig. 5 or at least 12 nucleotide fragments thereof.

156. A method according to any one of claims 4-6, wherein the target polynucleotide sequences comprise at least a portion of any combination of target polynucleotide sequences selected from the group consisting of ADA, AK2, CD3D, DCLRE1C, IL2RG, IL7R, JAK3, LIG4, NHEJ1, PNP, PRKDC, RAG1, RAG2, and ZAP70.

157. A method according to claim 156, wherein each of the multiple ribonucleic acids comprises a different sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 1-15 or at least a 12 nucleotide fragment thereof.

158. A method according to claim 156, wherein each of the multiple ribonucleic acids comprises a sequence with a single nucleotide mismatch to a different sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 1-15 or at least a 12 nucleotide fragment thereof.

159. A method according to any one of claims 2-3 and 5-6, wherein the disorder is SCID.

160. A method according to any one of claims 8-9, 11-12, wherein the disorder is sickle cell disease.

161. A method according to any one of claims 14-15, or 17-18, wherein the disorder is beta thalassemia.

162. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the one to two ribonucleic acids are designed to hybridize to a target motif immediately adjacent to a deoxyribonucleic acid motif recognized by the Cas protein.

163. A method according to any one of claims 1-3, 7-9, or 13-15, wherein each of the one to two ribonucleic acids are designed to hybridize to target motifs immediately adjacent to deoxyribonucleic acid motifs recognized by the Cas protein which flank a mutant allele located between the target motifs.

164. A method according to any one of claims 4-6, 10-12, or 16-18, wherein the multiple ribonucleic acids are designed to hybridize to target motifs immediately adjacent to deoxyribonucleic acid motifs recognized by the Cas protein.

165. A method according to any one of claims 4-6, 10-12, or 16-18, wherein the multiple ribonucleic acids are designed to hybridize to target motifs immediately adjacent to deoxyribonucleic acid motifs recognized by the Cas protein which flank mutant alleles located between the target motifs.

166. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the one to two ribonucleic acids are selected to minimize hybridization with nucleic acid sequences other than the target polynucleotide sequence.

167. A method according to any one of claims 4-6, 10-12, or 16-18, wherein the multiple ribonucleic acids are selected to minimize hybridization with nucleic acid sequences other than the target polynucleotide sequence.

168. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the target motif is selected such that it contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell.

169. A method according to any one of claims 4-6, 10-12, or 16-18, wherein each target motif is selected such that it contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell.

170. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the target motif is selected such that it contains at least one mismatch when compared with all other genomic nucleotide sequences in the cell.

171. A method according to any one of claims 4-6, 10-12, or 16-18, wherein the target motif is selected such that it contains at least one mismatch when compared with all other genomic nucleotide sequences in the cell.

172. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the one to two ribonucleic acids hybridize to a target motif that it contains at least two mismatches when compared with all other genomic nucleotide sequences in the cell.

173. A method according to any one of claims 4-6, 10-12, or 16-18, wherein each of the multiple ribonucleic acids hybridize to target motifs that contain at least two mismatches when compared with all other genomic nucleotide sequences in the cell.

174. A method according to any one of claims 1-3, 7-9, or 13-15, wherein the one to two ribonucleic acids hybridize to a target motif that contains at least one mismatch when compared with all other genomic nucleotide sequences in the cell.

175. A method according to any one of claims 4-6, 10-12, or 16-18, wherein each of the multiple ribonucleic acids hybridize to target motifs that contain at least one mismatch when compared with all other genomic nucleotide sequences in the cell.

176. A method according to any one of claims 3, 9, or 15, wherein the Cas protein and the one to two ribonucleic acids are contained in a nanoparticle.

177. A method according to any one of claims 3, 9, or 15, wherein the Cas protein and the one to two ribonucleic acids are contained in a lipid nanoparticle.

178. A method according to claim 177, wherein the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid.

179. A method according to claim 178, wherein the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA,

DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.Cl, DLin-TAP.Cl, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.Cl, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof.

180. A method according to claim 178, wherein the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof.

181. A method according to claim 178, wherein the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof.

182. A method according to any one of claims 6, 12, or 18, wherein the Cas protein and the multiple ribonucleic acids are contained in nanoparticles.

183. A method according to to any one of claims 6, 12, or 18, wherein the Cas protein and the multiple ribonucleic acids are contained in lipid nanoparticles.

184. A method according to claim 183, wherein the lipid nanoparticles comprise at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid.

185. A method according to claim 184, wherein the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.Cl, DLin-TAP.Cl, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.Cl, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof.

186. A method according to claim 184, wherein the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof.

187. A method according to claim 184 wherein the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof.

188. A method according to any one of claims 1-18, wherein the efficiency of alteration at each loci is from about 50% to about 80%.

189. A method according to any one of claims 1-18, wherein the efficiency of alteration is at least about 5%.

190. A method according to any one of claims 1-18, wherein the efficiency of alteration is at least about 10%.

191. A method according to any one of claims 1-18, wherein the efficiency of alteration is from about 50% to about 80%.

192. A method according to any one of claims 1-18, wherein the Cas protein is encoded by a modified nucleic acid.

193. A method according to claim 192, wherein the modified nucleic acid comprises a ribonucleic acid containing at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

194. A method according to any one of claims 1-193, wherein at least one of the ribonucleic acids is a modified ribonucleic acid comprising one to two modified nucleotides selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

195. A method according to any one of claims 1-194, wherein any of the Cas protein or the ribonucleic acids are expressed from a plasmid.

196. A method according to any one of claims 1-195, wherein any of the Cas protein or the ribonucleic acids are expressed using a promoter optimized for increased expression in stem cells.

197. A method according to claim 196, wherein the promoter is selected from the group consisting of a Cytomegalovirus (CMV) early enhancer element and a chicken beta-actin promoter, a chicken beta-actin promoter, an elongation factor-1 alpha promoter, and a ubiquitin promoter.

198. A method according to any one of claims 1-2, 4-5, 7-8, 10-11, 13-14, or 16-17, further comprising selecting cells that express the Cas protein.

199. A method according to claim 198, wherein selecting cells comprises FACS.

200. A method according to claim 199, wherein FACs is used to select cells which co-express Cas and a fluorescent protein selected from the group consisting of green fluorescent protein and red fluorescent protein.

201. A method for altering a target SCID-associated polynucleotide sequence in a cell comprising contacting the SCID-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

202. A method for altering a target SCD-associated polynucleotide sequence in a cell comprising contacting the SCD-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced

short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

203. A method for altering a target beta thalassemia-associated polynucleotide sequence in a cell comprising contacting the beta thalassemia-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

204. A method for treating or preventing a disorder associated with expression of a SCID-associated polynucleotide sequence in a subject, the method comprising (a) altering a target SCID-associated polynucleotide sequence in a cell *ex vivo* by contacting the SCID-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCID-associated polynucleotide sequence, wherein the target SCID-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequence.

205. A method for treating or preventing a disorder associated with expression of a SCD-associated polynucleotide sequence in a subject, the method comprising (a)

altering a target SCD-associated polynucleotide sequence in a cell *ex vivo* by contacting the SCD-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target SCD-associated polynucleotide sequence, wherein the target SCD-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequence.

206. A method for treating or preventing a disorder associated with expression of a beta thalassemia-associated polynucleotide sequence in a subject, the method comprising (a) altering a target beta thalassemia-associated polynucleotide sequence in a cell *ex vivo* by contacting the beta thalassemia-associated polynucleotide sequence in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and from one to two ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to a target motif of the target beta thalassemia-associated polynucleotide sequence, wherein the target beta thalassemia-associated polynucleotide sequence is cleaved, and wherein the efficiency of alteration is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequence.

207. A method for simultaneously altering multiple target SCID-associated polynucleotide sequences in a cell comprising contacting the SCID-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide

sequences, wherein the target SCID-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

208. A method for simultaneously altering multiple target SCD-associated polynucleotide sequences in a cell comprising contacting the SCD-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

209. A method for simultaneously altering multiple target beta thalassemia-associated polynucleotide sequences in a cell comprising contacting the beta thalassemia-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target beta thalassemia-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%.

210. A method for treating or preventing a disorder associated with expression of SCID-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCID-associated polynucleotide sequences in a cell *ex vivo* by contacting the SCID-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target

SCID-associated polynucleotide sequences, wherein the target SCID-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCID-associated polynucleotide sequences.

211. A method for treating or preventing a disorder associated with expression of SCD-associated polynucleotide sequences in a subject, the method comprising (a) altering target SCD-associated polynucleotide sequences in a cell *ex vivo* by contacting the SCD-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCD-associated polynucleotide sequences, wherein the target SCD-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the SCD-associated polynucleotide sequences.

212. A method for treating or preventing a disorder associated with expression of beta thalassemia-associated polynucleotide sequences in a subject, the method comprising (a) altering target beta thalassemia-associated polynucleotide sequences in a cell *ex vivo* by contacting the beta thalassemia-associated polynucleotide sequences in a cell selected from the group consisting of a human pluripotent cell, a primary human cell, and a non-transformed human cell, with a clustered regularly interspaced short palindromic repeats-associated (Cas) protein and multiple ribonucleic acids, wherein the ribonucleic acids direct Cas protein to and hybridize to target motifs of the target SCID-associated polynucleotide sequences, wherein the target beta thalassemia-associated polynucleotide sequences are cleaved, and wherein the efficiency of alteration of cells that express Cas protein is from about 8% to about 80%, and (b) introducing the cell into the subject, thereby treating or preventing a disorder associated with expression of the beta thalassemia-associated polynucleotide sequences.

213. A composition comprising at least one ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 1-15 or at least a 12 nucleotide fragment thereof.

214. A composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 1-15 or at least a 12 nucleotide fragment thereof.

215. A composition according to claims 213 or 214, wherein the at least one ribonucleic acid is contained in a nanoparticle.

216. A composition according to any one of claims 213-215, wherein the at least one ribonucleic acid is contained in a lipid nanoparticle.

217. A composition according to claim 216, wherein the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid.

218. A composition according to claim 217, wherein the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.Cl, DLin-TAP.Cl, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.Cl, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof.

219. A composition according to claim 217, wherein the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof.

220. A composition according to claim 217, wherein the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof.

221. A composition according to any one of claims 213-220, wherein at least one of the ribonucleic acids is a modified ribonucleic acid comprising one to two modified nucleotides selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

222. A composition according to any one of claims 213-221, further comprising a nucleic acid sequence encoding a Cas protein.

223. A composition according to any one of claims 213-221, further comprising a nucleic acid sequence encoding a Cas9 protein or a functional portion thereof.

224. A composition according to any one of claims 221-223, wherein the nucleic acid comprises a modified ribonucleic acid comprising at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

225. A composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 1-15 or at least a 12 nucleotide fragment thereof.

226. A composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 1-15 or at least a 12 nucleotide fragment thereof.

227. A composition according to claims 225 or 226, further comprising a nucleic acid sequence encoding a fluorescent protein selected from the group consisting of green fluorescent protein and red fluorescent protein.

228. A composition according to any one of claims 225-227, further comprising a promoter operably linked to the chimeric nucleic acid.

229. A composition according to claim 228, wherein the promoter is optimized for increased expression in human stem cells.

230. A composition according to claim 229, wherein the promoter is selected from the group consisting of a Cytomegalovirus (CMV) early enhancer element and a chicken beta-actin promoter, a chicken beta-actin promoter, an elongation factor-1 alpha promoter, and a ubiquitin promoter.

231. A composition according to any one of claims 225-230, wherein the chimeric nucleic acid is contained in a nanoparticle.

232. A composition according to any one of claims 225-231, wherein the chimeric nucleic acid is contained in a lipid nanoparticle.

233. A composition according to claim 232, wherein the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid.

234. A composition according to claim 233, wherein the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.Cl, DLin-TAP.Cl, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.Cl, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof.

235. A composition according to claim 233, wherein the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof.

236. A composition according to claim 233, wherein the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof.

237. A composition according to any one of claims 225-236, wherein the chimeric nucleic acid comprises at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

238. A composition according to any one of claims 225-237, wherein the Cas protein comprises a Cas9 protein or a functional portion thereof.

239. A kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of Figs. 1-15, a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of Figs. 1-15 or at least a 12 nucleotide fragment thereof.

240. A kit according to claim 236, further comprising one or more cell lines, cultures, or populations selected from the group consisting of human pluripotent cells, primary human cells, and non-transformed cells.

241. A kit according to claim 236, further comprising a DNA repair template selected from the group consisting of an ADA DNA repair template, a AK2 DNA repair template, a CD3D DNA repair template, a DCLRE1C DNA repair template, a IL2RG DNA repair template, IL7R DNA repair template, a JAK3 DNA repair template, a LIG4 DNA repair template, a NHEJ1 DNA repair template, a PNP DNA repair template, a PRKDC DNA repair template, a RAG1 DNA repair

template, a RAG2 DNA repair template, a ZAP70 DNA repair template, and a HBB DNA repair template.

242. A method according to claim 108, wherein at least one of the one to two ribonucleic acids comprises a sequence of GTAACGGCAGACTTCTCCACAGG or at least a 12 nucleotide fragment thereof.

243. A method according to claim 108, wherein at least one of the one to two ribonucleic acids comprises a sequence with a single nucleotide mismatch to ribonucleic acid sequence GTAACGGCAGACTTCTCCACAGG or at least a 12 nucleotide fragment thereof.

244. A composition comprising at least one ribonucleic acid having a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG or at least a 12 nucleotide fragment thereof.

245. A composition comprising at least one ribonucleic acid comprising a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG or at least a 12 nucleotide fragment thereof.

246. A composition according to claims 244 or 245, wherein the at least one ribonucleic acid is contained in a nanoparticle.

247. A composition according to any one of claims 244-246, wherein the at least one ribonucleic acid is contained in a lipid nanoparticle.

248. A composition according to claim 247, wherein the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid.

249. A composition according to claim 248, wherein the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.Cl, DLin-TAP.Cl,

DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.Cl, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof.

250. A composition according to claim 247, wherein the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof.

251. A composition according to claim 247, wherein the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof.

252. A composition according to any one of claims 244-251, wherein at least one of the ribonucleic acids is a modified ribonucleic acid comprising one to two modified nucleotides selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

253. A composition according to any one of claims 244-252, further comprising a nucleic acid sequence encoding a Cas protein.

254. A composition according to any one of claims 244-253, further comprising a nucleic acid sequence encoding a Cas9 protein or a functional portion thereof.

255. A composition according to any one of claims 244-254, wherein the nucleic acid comprises a modified ribonucleic acid comprising at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

256. A composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid having a

ribonucleic acid sequences of GTAACGGCAGACTTCTCCACAGG or at least a 12 nucleotide fragment thereof.

257. A composition comprising a chimeric nucleic acid comprising a ribonucleic acid encoding a Cas protein and at least one additional ribonucleic acid sequence comprising a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG or at least a 12 nucleotide fragment thereof.

258. A composition according to claims 256 or 257, further comprising a nucleic acid sequence encoding a fluorescent protein selected from the group consisting of green fluorescent protein and red fluorescent protein.

259. A composition according to any one of claims 256-258, further comprising a promoter operably linked to the chimeric nucleic acid.

260. A composition according to claim 259, wherein the promoter is optimized for increased expression in human stem cells.

261. A composition according to claims 259 or 260, wherein the promoter is selected from the group consisting of a Cytomegalovirus (CMV) early enhancer element and a chicken beta-actin promoter, a chicken beta-actin promoter, an elongation factor-1 alpha promoter, and a ubiquitin promoter.

262. A composition according to any one of claims 256-261, wherein the chimeric nucleic acid is contained in a nanoparticle.

263. A composition according to any one of claims 256-262, wherein the chimeric nucleic acid is contained in a lipid nanoparticle.

264. A composition according to claim 263, wherein the lipid nanoparticle comprises at least one of a cationic lipid, a neutral lipid, an amino lipid, a sterol, and a PEG or PEG-modified lipid.

265. A composition according to claim 264, wherein the cationic lipid is selected from the group consisting of ALNY-100, C12-200, DODAC, DDAB, DOTAP, DOTMA, DODMA, DLinDMA, DLenDMA, DLin-C-DAP, DLin-DAC, DLin-MA, DLinDAP, DLin-S-DMA, DLin-2-DMAP, DLin-TMA.Cl, DLin-TAP.Cl, DLin-MPZ, DLinAP, DOAP, DLin-EG-DMA, DLinDMA, DLin-K-DMA, DLin-KC2-DMA, DLin-M-C3-DMA, KC2, MC3, DOTAP.Cl, DOSPA, DOGS, DOPE, DODAP, DMRIE, XTC, and mixtures thereof.

266. A composition according to claim 264, wherein the neutral lipid is selected from the group consisting of DPSC, DPPC, POPC, DOPE, SM, and mixtures thereof.

267. A composition according to claim 264, wherein the PEG-modified lipid is selected from the group consisting of PEG-DMG, PEG-CerC14, PEG-CerC20, and mixtures thereof.

268. A composition according to any one of claims 256-267, wherein the chimeric nucleic acid comprises at least one modified nucleotide selected from the group consisting of pseudouridine, 5-methylcytodine, 2-thio-uridine, 5-methyluridine-5'-triphosphate, 4-thiouridine-5'-triphosphate, 5,6-dihydrouridine-5'-triphosphate, and 5-azauridine-5'-triphosphate.

269. A composition according to any one of claims 256-268, wherein the Cas protein comprises a Cas9 protein or a functional portion thereof.

270. A kit for altering a target polynucleotide sequence in a cell comprising a Cas9 protein or a nucleic acid encoding the Cas9 protein, and at least one ribonucleic acid sequence selected from the group consisting of the ribonucleic acid sequences of GTAACGGCAGACTTCTCCACAGG, a sequence with a single nucleotide mismatch to a ribonucleic acid sequence of GTAACGGCAGACTTCTCCACAGG or at least a 12 nucleotide fragment thereof.

271. A kit according to claim 270, further comprising one or more cell lines, cultures, or populations selected from the group consisting of human pluripotent cells, primary human cells, and non-transformed cells.

272. A kit according to claims 270 or 271, further comprising a HBB DNA repair template.

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	20	43248474	+	GCTTCTCTGAACCAACGAGCAGG	1	2	17
(N20)NGG	20	43248475	+	CTTCTCTGAACCAACGAGCAGGG	2	3	21
(N20)NGG	20	43248463	-	AGAGGTTCTGCCCTGCTCGTTGG	1	2	19
(N20)NGG	20	43248481	-	TGGAGGAGTGGCGTCTTCAGAGG	1	3	36
(N20)NGG	20	43248951	+	GCCTTTCCAGAACATCAATGCGG	1	3	35
(N20)NGG	20	43248986	+	TCCTCCCAGAAGATGAAAAGAGG	1	8	88
(N20)NGG	20	43248987	+	CCTCCCAGAAGATGAAAAGAGGG	1	8	120
(N20)NGG	20	43249018	+	GACCTGCTCTATAAAGCCTATGG	1	3	20
(N20)NGG	20	43249019	+	ACCTGCTCTATAAAGCCTATGGG	1	5	24
(N20)NGG	20	43249042	+	ATGCCACCTTCAGCCTCTGCAGG	2	6	74
(N20)NGG	20	43249046	+	CACCTTCAGCCTCTGCAGGTAGG	1	5	86
(N20)NGG	20	43249057	+	TCTGCAGGTAGGTTCCTGTCTGG	1	2	32
(N20)NGG	20	43249058	+	CTGCAGGTAGGTTCCTGTCTGGG	3	10	82
(N20)NGG	20	43249065	+	TAGGTTCCTGTCTGGGCTTCTGG	1	1	40
(N20)NGG	20	43249066	+	AGGTTCCTGTCTGGGCTTCTGGG	1	5	66
(N20)NGG	20	43248921	-	ATGTTCTGGAAAGGCCAGAATGG	1	2	78
(N20)NGG	20	43248930	-	GCCGCATTGATGTTCTGGAAAGG	1	2	17
(N20)NGG	20	43248935	-	ATTTGGCCGCATTGATGTTCTGG	1	1	9
(N20)NGG	20	43248952	-	TTCTGGGAGGAAACTAGATTTGG	1	6	76
(N20)NGG	20	43248965	-	CCCTCTTTTCATCTTCTGGGAGG	3	7	75
(N20)NGG	20	43248968	-	GCTCCCTCTTTTCATCTTCTGGG	2	10	106
(N20)NGG	20	43248969	-	AGCTCCCTCTTTTCATCTTCTGG	1	6	99
(N20)NGG	20	43248998	-	TCCCATAGGCTTTATAGAGCAGG	1	2	13
(N20)NGG	20	43249012	-	GGCTGAAGGTGGCATCCCATAGG	1	2	34

FIG. 1

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	20	43249023	-	CTACCTGCAGAGGCTGAAGGTGG	1	7	86
(N20)NGG	20	43249026	-	AACCTACCTGCAGAGGCTGAAGG	1	4	42
(N20)NGG	20	43249033	-	AGACAGGAACCTACCTGCAGAGG	2	9	79
(N20)NGG	20	43249658	+	TCTCCTCCTCCCTCTTCTGCAGG	4	24	329
(N20)NGG	20	43249674	+	CTGCAGGCTCAAAAATGACCAGG	1	5	39
(N20)NGG	20	43249725	+	GCTCATCTTCAAGTCCACCCTGG	1	1	26
(N20)NGG	20	43249751	+	CTGATTACCAGATGACCAAACGG	1	4	33
(N20)NGG	20	43249752	+	TGATTACCAGATGACCAAACGGG	1	2	21
(N20)NGG	20	43249758	+	CCAGATGACCAAACGGGACATGG	1	1	20
(N20)NGG	20	43249759	+	CAGATGACCAAACGGGACATGGG	1	2	14
(N20)NGG	20	43249773	+	GGACATGGGCTTTACTGAAGAGG	1	3	29
(N20)NGG	20	43249784	+	TTACTGAAGAGGAGTTTAAAAGG	1	4	74
(N20)NGG	20	43249788	+	TGAAGAGGAGTTTAAAAGGCTGG	1	6	79
(N20)NGG	20	43249795	+	GAGTTTAAAAGGCTGGTGAGTGG	3	6	46
(N20)NGG	20	43249796	+	AGTTTAAAAGGCTGGTGAGTGGG	1	6	48
(N20)NGG	20	43249811	+	TGAGTGGGTGTGAGCCATACTGG	1	1	16
(N20)NGG	20	43249639	-	GAGCCTGCAGAAGAGGGAGGAGG	4	21	222
(N20)NGG	20	43249642	-	TTTGAGCCTGCAGAAGAGGGAGG	1	6	78
(N20)NGG	20	43249645	-	ATTTTTGAGCCTGCAGAAGAGGG	1	10	102
(N20)NGG	20	43249646	-	CATTTTTGAGCCTGCAGAAGAGG	1	8	72
(N20)NGG	20	43249670	-	TGTTGAGCGAGTAGTTAGCCTGG	1	1	4
(N20)NGG	20	43249700	-	GGGTGGACTTGAAGATGAGCGGG	1	4	28
(N20)NGG	20	43249701	-	AGGGTGGACTTGAAGATGAGCGG	2	7	80
(N20)NGG	20	43249717	-	CTGGTAATCAGTGTCCAGGGTGG	1	4	27

FIG. 1

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	20	43249720	-	CATCTGGTAATCAGTGTCCAGGG	1	2	30
(N20)NGG	20	43249721	-	TCATCTGGTAATCAGTGTCCAGG	1	2	25
(N20)NGG	20	43249736	-	CCATGTCCCGTTTGGTCATCTGG	1	1	8
(N20)NGG	20	43249744	-	AGTAAAGCCCATGTCCCGTTTGG	1	1	6
(N20)NGG	20	43251239	+	TGCTCTTCCAGATCTGCCCCTGG	2	5	61
(N20)NGG	20	43251256	+	CCCTGGTCCAGCTACCTCACTGG	2	5	30
(N20)NGG	20	43251263	+	CCAGCTACCTCACTGGTGCCTGG	1	5	42
(N20)NGG	20	43251270	+	CCTCACTGGTGCCTGGAAGCCGG	1	8	72
(N20)NGG	20	43251276	+	TGGTGCCTGGAAGCCGGACACGG	1	3	32
(N20)NGG	20	43251293	+	ACACGGAGCATGCAGTCATTCGG	1	1	25
(N20)NGG	20	43251311	+	TTCGGTGAGCTCTGTTCCCCTGG	1	2	25
(N20)NGG	20	43251312	+	TCGGTGAGCTCTGTTCCCCTGGG	1	1	18
(N20)NGG	20	43251204	-	TGGAAGAGCAGGTGTGTGGCTGG	1	6	147
(N20)NGG	20	43251208	-	GATCTGGAAGAGCAGGTGTGTGG	1	11	97
(N20)NGG	20	43251215	-	AGGGGCAGATCTGGAAGAGCAGG	1	8	82
(N20)NGG	20	43251224	-	AGCTGGACCAGGGGCAGATCTGG	1	4	62
(N20)NGG	20	43251233	-	CAGTGAGGTAGCTGGACCAGGGG	1	4	65
(N20)NGG	20	43251234	-	CCAGTGAGGTAGCTGGACCAGGG	1	2	47
(N20)NGG	20	43251235	-	ACCAGTGAGGTAGCTGGACCAGG	1	4	35
(N20)NGG	20	43251241	-	CCAGGCACCAGTGAGGTAGCTGG	1	5	53
(N20)NGG	20	43251248	-	CCGGCTTCCAGGCACCAGTGAGG	1	2	49
(N20)NGG	20	43251259	-	ATGCTCCGTGTCCGGCTTCCAGG	1	1	10
(N20)NGG	20	43251267	-	ATGACTGCATGCTCCGTGTCCGG	2	3	36
(N20)NGG	20	43251469	+	GCTCTATTCTGCTTCTCTACAGG	1	4	34

FIG. 1

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	20	43251475	+	TTCTGCTTCTCTACAGGCTGTGG	1	11	100
(N20)NGG	20	43251495	+	TGGACATACTCAAGACAGAGCGG	1	2	48
(N20)NGG	20	43251499	+	CATACTCAAGACAGAGCGGCTGG	1	3	14
(N20)NGG	20	43251500	+	ATACTCAAGACAGAGCGGCTGGG	1	1	16
(N20)NGG	20	43251506	+	AAGACAGAGCGGCTGGGACACGG	1	9	81
(N20)NGG	20	43251520	+	GGGACACGGCTACCACACCCTGG	1	1	15
(N20)NGG	20	43251529	+	CTACCACACCCTGGAAGACCAGG	1	3	42
(N20)NGG	20	43251543	+	AAGACCAGGCCCTTTATAACAGG	1	3	34
(N20)NGG	20	43251549	+	AGGCCCTTTATAACAGGCTGCGG	1	2	25
(N20)NGG	20	43251553	+	CCTTTATAACAGGCTGCGGCAGG	1	2	16
(N20)NGG	20	43251571	+	GCAGGAAAACATGCACTTCGAGG	1	4	26
(N20)NGG	20	43251578	+	AACATGCACTTCGAGGTAAGCGG	1	1	14
(N20)NGG	20	43251579	+	ACATGCACTTCGAGGTAAGCGGG	1	1	10
(N20)NGG	20	43251584	+	CACTTCGAGGTAAGCGGGCCAGG	1	1	7
(N20)NGG	20	43251585	+	ACTTCGAGGTAAGCGGGCCAGGG	1	1	9
(N20)NGG	20	43251590	+	GAGGTAAGCGGGCCAGGGAGTGG	2	6	85
(N20)NGG	20	43251591	+	AGGTAAGCGGGCCAGGGAGTGGG	1	2	38
(N20)NGG	20	43251592	+	GGTAAGCGGGCCAGGGAGTGGGG	1	3	47
(N20)NGG	20	43251595	+	AAGCGGGCCAGGGAGTGGGGAGG	2	10	143
(N20)NGG	20	43251510	-	GGGCCTGGTCTTCCAGGGTGTGG	1	5	82
(N20)NGG	20	43251515	-	ATAAAGGGCCTGGTCTTCCAGGG	2	5	38
(N20)NGG	20	43251516	-	TATAAAGGGCCTGGTCTTCCAGG	1	3	20
(N20)NGG	20	43251525	-	GCAGCCTGTTATAAAGGGCCTGG	1	4	23
(N20)NGG	20	43251530	-	CTGCCGCAGCCTGTTATAAAGGG	1	1	13

FIG. 1

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	20	43251531	-	CCTGCCGCAGCCTGTTATAAAGG	1	1	7
(N20)NGG	20	43251647	+	GACCTGGCTCTCCCCCTTCCAGG	1	5	127
(N20)NGG	20	43251650	+	CTGGCTCTCCCCCTTCCAGGAGG	1	4	116
(N20)NGG	20	43251663	+	TTCCAGGAGGCTGTGAAGAGCGG	3	7	125
(N20)NGG	20	43251687	+	ATTCACCGTACTGTCCACGCCGG	1	2	47
(N20)NGG	20	43251688	+	TTCACCGTACTGTCCACGCCGGG	1	1	11
(N20)NGG	20	43251689	+	TCACCGTACTGTCCACGCCGGGG	1	1	2
(N20)NGG	20	43251692	+	CCGTACTGTCCACGCCGGGGAGG	1	1	3
(N20)NGG	20	43251695	+	TACTGTCCACGCCGGGGAGGTGG	1	1	4
(N20)NGG	20	43251696	+	ACTGTCCACGCCGGGGAGGTGGG	1	1	11
(N20)NGG	20	43251701	+	CCACGCCGGGGAGGTGGGCTCGG	1	6	45
(N20)NGG	20	43251719	+	CTCGGCCGAAGTAGTAAAAGAGG	1	2	6
(N20)NGG	20	43251724	+	CCGAAGTAGTAAAAGAGGTGAGG	1	1	13
(N20)NGG	20	43251725	+	CGAAGTAGTAAAAGAGGTGAGGG	1	2	51
(N20)NGG	20	43251730	+	TAGTAAAAGAGGTGAGGGCCTGG	1	3	44
(N20)NGG	20	43251731	+	AGTAAAAGAGGTGAGGGCCTGGG	1	2	55
(N20)NGG	20	43251735	+	AAAGAGGTGAGGGCCTGGGCTGG	2	15	136
(N20)NGG	20	43251741	+	GTGAGGGCCTGGGCTGGCCATGG	3	11	158
(N20)NGG	20	43251742	+	TGAGGGCCTGGGCTGGCCATGGG	2	10	99
(N20)NGG	20	43251743	+	GAGGGCCTGGGCTGGCCATGGGG	1	17	142
(N20)NGG	20	43251627	-	CTCCTGGAAGGGGGAGAGCCAGG	2	7	106
(N20)NGG	20	43251636	-	CTTCACAGCCTCCTGGAAGGGGG	1	7	115
(N20)NGG	20	43251637	-	TCTTCACAGCCTCCTGGAAGGGG	1	7	86
(N20)NGG	20	43251638	-	CTCTTCACAGCCTCCTGGAAGGG	1	9	79

FIG. 1

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	20	43251639	-	GCTCTTCACAGCCTCCTGGAAGG	1	5	96
(N20)NGG	20	43251643	-	TGCCGCTCTTCACAGCCTCCTGG	1	3	39
(N20)NGG	20	43251670	-	CCTCCCCGGCGTGGACAGTACGG	1	1	6
(N20)NGG	20	43251679	-	CCGAGCCCACCTCCCCGGCGTGG	1	5	37
(N20)NGG	20	43251684	-	TTCGGCCGAGCCCACCTCCCCGG	1	3	19
(N20)NGG	20	43251702	-	CCTCACCTCTTTTACTACTTCGG	1	4	46
(N20)NGG	20	43252846	+	TGGGCATCTCGCCCACAGACTGG	1	2	13
(N20)NGG	20	43252856	+	GCCCACAGACTGGTCCCCCAAGG	1	6	43
(N20)NGG	20	43252859	+	CACAGACTGGTCCCCCAAGGTGG	1	1	37
(N20)NGG	20	43252862	+	AGACTGGTCCCCCAAGGTGGTGG	1	2	36
(N20)NGG	20	43252895	+	GAAGTACCAGCAGCAGACCGTGG	1	1	34
(N20)NGG	20	43252910	+	GACCGTGGTAGCCATTGACCTGG	1	1	10
(N20)NGG	20	43252914	+	GTGGTAGCCATTGACCTGGCTGG	1	2	21
(N20)NGG	20	43252932	+	GCTGGAGATGAGACCATCCCAGG	1	4	44
(N20)NGG	20	43252950	+	CCAGGAAGCAGCCTCTTGCCTGG	2	11	127
(N20)NGG	20	43252961	+	CCTCTTGCCTGGACATGTCCAGG	1	4	42
(N20)NGG	20	43252970	+	TGGACATGTCCAGGCCTACCAGG	1	3	18
(N20)NGG	20	43252973	+	ACATGTCCAGGCCTACCAGGTGG	1	6	45
(N20)NGG	20	43252974	+	CATGTCCAGGCCTACCAGGTGGG	1	4	24
(N20)NGG	20	43252987	+	ACCAGGTGGGTCCTGTGAGAAGG	1	6	35
(N20)NGG	20	43252992	+	GTGGGTCCTGTGAGAAGGAATGG	1	14	148
(N20)NGG	20	43252818	-	TGTGGGCGAGATGCCCACCCAGG	1	3	19
(N20)NGG	20	43252835	-	ACCTTGGGGGACCAGTCTGTGGG	1	2	23
(N20)NGG	20	43252836	-	CACCTTGGGGGACCAGTCTGTGG	1	3	29

FIG. 1

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	20	43252848	-	ACACAGCTCCACCACCTTGGGGG	1	5	37
(N20)NGG	20	43252849	-	TACACAGCTCCACCACCTTGGGG	1	2	24
(N20)NGG	20	43252850	-	TTACACAGCTCCACCACCTTGGG	1	1	34
(N20)NGG	20	43252851	-	CTTACACAGCTCCACCACCTTGG	1	3	29
(N20)NGG	20	43252879	-	TGGCTACCACGGTCTGCTGCTGG	1	3	22
(N20)NGG	20	43252890	-	AGCCAGGTCAATGGCTACCACGG	1	2	24
(N20)NGG	20	43252899	-	CTCATCTCCAGCCAGGTCAATGG	1	7	131
(N20)NGG	20	43252906	-	GGATGGTCTCATCTCCAGCCAGG	1	2	44
(N20)NGG	20	43252923	-	CAAGAGGCTGCTTCCTGGGATGG	3	8	86
(N20)NGG	20	43252927	-	CAGGCAAGAGGCTGCTTCCTGGG	2	7	85
(N20)NGG	20	43252928	-	CCAGGCAAGAGGCTGCTTCCTGG	1	7	113
(N20)NGG	20	43252939	-	CCTGGACATGTCCAGGCAAGAGG	1	2	50
(N20)NGG	20	43252946	-	TGGTAGGCCTGGACATGTCCAGG	1	2	17
(N20)NGG	20	43252957	-	CAGGACCCACCTGGTAGGCCTGG	1	3	33
(N20)NGG	20	43252962	-	TCTCACAGGACCCACCTGGTAGG	1	2	28
(N20)NGG	20	43252966	-	TCCTTCTCACAGGACCCACCTGG	1	6	55
(N20)NGG	20	43254211	+	CTACTCCTCTCCTCACACAGAGG	1	5	119
(N20)NGG	20	43254212	+	TACTCCTCTCCTCACACAGAGGG	1	10	105
(N20)NGG	20	43254213	+	ACTCCTCTCCTCACACAGAGGGG	1	6	66
(N20)NGG	20	43254231	+	AGGGGACCTCACCCCAGACGAGG	1	1	26
(N20)NGG	20	43254234	+	GGACCTCACCCCAGACGAGGTGG	1	1	21
(N20)NGG	20	43254237	+	CCTCACCCCAGACGAGGTGGTGG	1	2	40
(N20)NGG	20	43254246	+	AGACGAGGTGGTGGCCCTAGTGG	1	2	24
(N20)NGG	20	43254247	+	GACGAGGTGGTGGCCCTAGTGGG	1	2	13

FIG. 1

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	20	43254252	+	GGTGGTGGCCCTAGTGGGCCAGG	1	2	48
(N20)NGG	20	43254253	+	GTGGTGGCCCTAGTGGGCCAGGG	1	3	40
(N20)NGG	20	43254261	+	CCTAGTGGGCCAGGGCCTGCAGG	1	4	43
(N20)NGG	20	43254264	+	AGTGGGCCAGGGCCTGCAGGAGG	3	14	163
(N20)NGG	20	43254265	+	GTGGGCCAGGGCCTGCAGGAGGG	1	14	225
(N20)NGG	20	43254266	+	TGGGCCAGGGCCTGCAGGAGGGG	2	18	238
(N20)NGG	20	43254267	+	GGGCCAGGGCCTGCAGGAGGGGG	2	32	318
(N20)NGG	20	43254280	+	CAGGAGGGGGAGCGAGACTTCGG	1	2	39
(N20)NGG	20	43254281	+	AGGAGGGGGAGCGAGACTTCGGG	1	2	35
(N20)NGG	20	43254282	+	GGAGGGGGAGCGAGACTTCGGGG	1	1	29
(N20)NGG	20	43254288	+	GGAGCGAGACTTCGGGGTCAAGG	1	2	20
(N20)NGG	20	43254293	+	GAGACTTCGGGGTCAAGGCCCGG	1	2	18
(N20)NGG	20	43254333	+	GCGCCACCAGCCCAGTGAGTAGG	1	1	15
(N20)NGG	20	43254187	-	TCTGTGTGAGGAGAGGAGTAGGG	1	10	104
(N20)NGG	20	43254188	-	CTCTGTGTGAGGAGAGGAGTAGG	2	11	148
(N20)NGG	20	43254194	-	GGTCCCCTCTGTGTGAGGAGAGG	1	4	52
(N20)NGG	20	43254199	-	GGTGAGGTCCCCTCTGTGTGAGG	1	3	51
(N20)NGG	20	43254215	-	CCACCACCTCGTCTGGGGTGAGG	1	4	100
(N20)NGG	20	43254220	-	TAGGGCCACCACCTCGTCTGGGG	1	1	11
(N20)NGG	20	43254221	-	CTAGGGCCACCACCTCGTCTGGG	1	2	16
(N20)NGG	20	43254222	-	ACTAGGGCCACCACCTCGTCTGG	1	1	17
(N20)NGG	20	43254238	-	CTGCAGGCCCTGGCCCACTAGGG	1	7	54
(N20)NGG	20	43254239	-	CCTGCAGGCCCTGGCCCACTAGG	3	5	89
(N20)NGG	20	43254248	-	GCTCCCCCTCCTGCAGGCCCTGG	1	17	186

FIG. 1

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	20	43254254	-	AGTCTCGCTCCCCCTCCTGCAGG	1	4	38
(N20)NGG	20	43254289	-	CATGCAGCACAGGATGGACCGGG	1	3	34
(N20)NGG	20	43254290	-	GCATGCAGCACAGGATGGACCGG	1	3	42
(N20)NGG	20	43254295	-	GTGGCGCATGCAGCACAGGATGG	1	3	62
(N20)NGG	20	43254299	-	GCTGGTGGCGCATGCAGCACAGG	1	1	22
(N20)NGG	20	43254314	-	GATCCTACTCACTGGGCTGGTGG	1	2	32
(N20)NGG	20	43254317	-	GGTGATCCTACTCACTGGGCTGG	1	2	13
(N20)NGG	20	43254321	-	GGGCGGTGATCCTACTCACTGGG	1	1	10
(N20)NGG	20	43254322	-	AGGGCGGTGATCCTACTCACTGG	1	1	14
(N20)NGG	20	43255096	+	AACCCCTTTCTTCCCTTCCCAGG	1	11	148
(N20)NGG	20	43255097	+	ACCCCTTTCTTCCCTTCCCAGGG	5	16	156
(N20)NGG	20	43255098	+	CCCCTTTCTTCCCTTCCCAGGGG	1	18	215
(N20)NGG	20	43255105	+	CTTCCCTTCCCAGGGGCTGCCGG	1	15	150
(N20)NGG	20	43255106	+	TTCCCTTCCCAGGGGCTGCCGGG	2	11	144
(N20)NGG	20	43255109	+	CCTTCCCAGGGGCTGCCGGGAGG	2	15	134
(N20)NGG	20	43255120	+	GCTGCCGGGAGGCTATCAAAAGG	1	2	9
(N20)NGG	20	43255148	+	CTATGAGTTTGTAGAGATGAAGG	1	2	59
(N20)NGG	20	43255157	+	TGTAGAGATGAAGGCCAAAGAGG	1	7	68
(N20)NGG	20	43255158	+	GTAGAGATGAAGGCCAAAGAGGG	1	10	86
(N20)NGG	20	43255163	+	GATGAAGGCCAAAGAGGGCGTGG	1	1	33
(N20)NGG	20	43255172	+	CAAAGAGGGCGTGGTGTATGTGG	1	3	17
(N20)NGG	20	43255175	+	AGAGGGCGTGGTGTATGTGGAGG	1	3	39
(N20)NGG	20	43255180	+	GCGTGGTGTATGTGGAGGTGCGG	1	3	88
(N20)NGG	20	43255199	+	GCGGTACAGTCCGCACCTGCTGG	1	1	2

FIG. 1

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	20	43255214	+	CCTGCTGGCCAACTCCAAAGTGG	1	3	32
(N20)NGG	20	43255228	+	CCAAAGTGGAGCCAATCCCCTGG	2	5	22
(N20)NGG	20	43255235	+	GGAGCCAATCCCCTGGAACCAGG	1	1	30
(N20)NGG	20	43255250	+	GAACCAGGCTGAGTGAGTGATGG	1	4	65
(N20)NGG	20	43255251	+	AACCAGGCTGAGTGAGTGATGGG	1	3	48
(N20)NGG	20	43255256	+	GGCTGAGTGAGTGATGGGCCTGG	1	2	70
(N20)NGG	20	43255260	+	GAGTGAGTGATGGGCCTGGAAGG	1	7	91
(N20)NGG	20	43255261	+	AGTGAGTGATGGGCCTGGAAGGG	2	8	97
(N20)NGG	20	43255262	+	GTGAGTGATGGGCCTGGAAGGGG	1	9	107
(N20)NGG	20	43255071	-	GGGAAGGGAAGAAAGGGGTTGGG	2	22	449
(N20)NGG	20	43255072	-	TGGGAAGGGAAGAAAGGGGTTGG	3	32	451
(N20)NGG	20	43255076	-	CCCCTGGGAAGGGAAGAAAGGGG	2	23	175
(N20)NGG	20	43255077	-	GCCCCTGGGAAGGGAAGAAAGGG	2	13	169
(N20)NGG	20	43255078	-	AGCCCCTGGGAAGGGAAGAAAGG	1	22	197
(N20)NGG	20	43255086	-	CTCCCGGCAGCCCCTGGGAAGGG	2	7	127
(N20)NGG	20	43255087	-	CCTCCCGGCAGCCCCTGGGAAGG	2	11	137
(N20)NGG	20	43255091	-	ATAGCCTCCCGGCAGCCCCTGGG	1	2	20
(N20)NGG	20	43255092	-	GATAGCCTCCCGGCAGCCCCTGG	1	1	15
(N20)NGG	20	43255102	-	CGATCCTTTTGATAGCCTCCCGG	1	1	11
(N20)NGG	20	43255125	-	CTTCATCTCTACAAACTCATAGG	3	5	67
(N20)NGG	20	43255149	-	CACATACACCACGCCCTCTTTGG	1	1	15
(N20)NGG	20	43255187	-	TTGGAGTTGGCCAGCAGGTGCGG	1	5	56
(N20)NGG	20	43255192	-	CCACTTTGGAGTTGGCCAGCAGG	1	3	26
(N20)NGG	20	43255200	-	GATTGGCTCCACTTTGGAGTTGG	1	5	22

FIG. 1

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	20	43255206	-	CCAGGGGATTGGCTCCACTTTGG	1	2	18
(N20)NGG	20	43255217	-	TCAGCCTGGTTCCAGGGGATTGG	1	4	79
(N20)NGG	20	43255222	-	CTCACTCAGCCTGGTTCCAGGGG	1	5	69
(N20)NGG	20	43255223	-	ACTCACTCAGCCTGGTTCCAGGG	1	7	79
(N20)NGG	20	43255224	-	CACTCACTCAGCCTGGTTCCAGG	1	3	62
(N20)NGG	20	43255231	-	GGCCCATCACTCACTCAGCCTGG	1	2	39
(N20)NGG	20	43257687	+	CCACTCACTGTTTTGTTTCCAGG	1	5	76
(N20)NGG	20	43257690	+	CTCACTGTTTTGTTTCCAGGAGG	1	6	88
(N20)NGG	20	43257695	+	TGTTTTGTTTCCAGGAGGAGAGG	1	7	117
(N20)NGG	20	43257696	+	GTTTTGTTTCCAGGAGGAGAGGG	1	11	95
(N20)NGG	20	43257724	+	CCTCCCAGCTAACACAGCAGAGG	1	5	52
(N20)NGG	20	43257725	+	CTCCCAGCTAACACAGCAGAGGG	1	5	66
(N20)NGG	20	43257726	+	TCCCAGCTAACACAGCAGAGGGG	1	7	53
(N20)NGG	20	43257743	+	GAGGGGCTGCTGAACGTCATTGG	1	1	28
(N20)NGG	20	43257748	+	GCTGCTGAACGTCATTGGCATGG	1	2	26
(N20)NGG	20	43257778	+	GCTCACCCTTCCAGACTTCCTGG	2	5	47
(N20)NGG	20	43257832	+	GTGAGTTGCCCCCAACCCACAGG	1	2	28
(N20)NGG	20	43257662	-	GGAAACAAAACAGTGAGTGGTGG	2	9	97
(N20)NGG	20	43257665	-	CCTGGAAACAAAACAGTGAGTGG	1	5	106
(N20)NGG	20	43257683	-	GAGGGCGATCCCTCTCCTCCTGG	2	4	21
(N20)NGG	20	43257701	-	CTCTGCTGTGTTAGCTGGGAGGG	1	7	73
(N20)NGG	20	43257702	-	CCTCTGCTGTGTTAGCTGGGAGG	1	4	56
(N20)NGG	20	43257705	-	GCCCCTCTGCTGTGTTAGCTGGG	1	3	34
(N20)NGG	20	43257706	-	AGCCCCTCTGCTGTGTTAGCTGG	1	4	32

FIG. 1

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	20	43257754	-	AGGAAGTCTGGAAGGGTGAGCGG	1	8	158
(N20)NGG	20	43257761	-	CTTGGCCAGGAAGTCTGGAAGGG	1	2	37
(N20)NGG	20	43257762	-	ACTTGGCCAGGAAGTCTGGAAGG	1	4	48
(N20)NGG	20	43257766	-	TCAAACTTGGCCAGGAAGTCTGG	1	4	39
(N20)NGG	20	43257774	-	TGTAGTAGTCAAACTTGGCCAGG	1	1	16
(N20)NGG	20	43257779	-	AGGCATGTAGTAGTCAAACTTGG	1	3	33
(N20)NGG	20	43257799	-	GGGGCAACTCACGCGATAGCAGG	1	1	2
(N20)NGG	20	43264867	+	TCTTCCCCCTGCCCCCTTGCAGG	1	11	106
(N20)NGG	20	43264870	+	TCCCCCTGCCCCCTTGCAGGTGG	1	5	90
(N20)NGG	20	43264892	+	GAACTGCATGTCCACCTAGACGG	1	1	25
(N20)NGG	20	43264925	+	CCTGAAACCATCTTATACTATGG	1	5	49
(N20)NGG	20	43264929	+	AAACCATCTTATACTATGGCAGG	1	2	23
(N20)NGG	20	43264849	-	TCCACCTGCAAGGGGGCAGGGGG	1	12	174
(N20)NGG	20	43264850	-	TTCCACCTGCAAGGGGGCAGGGG	1	5	64
(N20)NGG	20	43264851	-	GTTCCACCTGCAAGGGGGCAGGG	1	6	42
(N20)NGG	20	43264852	-	AGTTCCACCTGCAAGGGGGCAGG	1	1	41
(N20)NGG	20	43264856	-	ATGCAGTTCCACCTGCAAGGGGG	1	4	33
(N20)NGG	20	43264857	-	CATGCAGTTCCACCTGCAAGGGG	1	2	29
(N20)NGG	20	43264858	-	ACATGCAGTTCCACCTGCAAGGG	1	1	38
(N20)NGG	20	43264859	-	GACATGCAGTTCCACCTGCAAGG	1	2	51
(N20)NGG	20	43264881	-	GCTTGATGGATCCGTCTAGGTGG	1	2	5
(N20)NGG	20	43264884	-	CAGGCTTGATGGATCCGTCTAGG	1	1	5
(N20)NGG	20	43264895	-	TAAGATGGTTTCAGGCTTGATGG	1	1	26
(N20)NGG	20	43264903	-	CCATAGTATAAGATGGTTTCAGG	1	1	23

FIG. 1

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	20	43264910	-	TTACCTGCCATAGTATAAGATGG	1	5	28
(N20)NGG	20	43280218	+	CGGGGCGCACGAGGGCACCATGG	1	1	14
(N20)NGG	20	43280261	+	AAGCCCAAAGTGAGCGCGCCGG	1	1	7
(N20)NGG	20	43280262	+	AGCCCAAAGTGAGCGCGCCGGGG	1	1	4
(N20)NGG	20	43280263	+	GCCCAAAGTGAGCGCGCCGGGGG	1	1	8
(N20)NGG	20	43280264	+	CCCAAAGTGAGCGCGCCGGGGG	1	1	11
(N20)NGG	20	43280270	+	GTGAGCGCGCCGGGGGCTCCGG	1	3	41
(N20)NGG	20	43280271	+	TGAGCGCGCCGGGGGCTCCGGG	1	3	24
(N20)NGG	20	43280272	+	GAGCGCGCCGGGGGCTCCGGGG	1	3	44
(N20)NGG	20	43280195	-	CATGGTGCCCTCGTGCGCCCGG	1	2	15
(N20)NGG	20	43280213	-	GAAGGCGGGCGTCTGGGCCATGG	1	2	26
(N20)NGG	20	43280219	-	CTTGTCGAAGGCGGGCGTCTGGG	1	1	6
(N20)NGG	20	43280220	-	GCTTGTCGAAGGCGGGCGTCTGG	1	1	9
(N20)NGG	20	43280227	-	ACTTTGGGCTTGTCGAAGGCGGG	1	2	17
(N20)NGG	20	43280228	-	CACTTTGGGCTTGTCGAAGGCGG	1	2	18
(N20)NGG	20	43280231	-	GCTCACTTTGGGCTTGTCGAAGG	1	1	21
(N20)NGG	20	43280242	-	CCCCCGCGCGCTCACTTTGGG	1	1	9
(N20)NGG	20	43280243	-	GCCCCCGCGCGCTCACTTTGG	2	6	11

FIG. 1

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	1	33476443	+	TATTTCAGCCTAGTATCAGAAGG	1	2	38
(N20)NGG	1	33476448	+	CAGCCTAGTATCAGAAGGCCAGG	2	4	49
(N20)NGG	1	33476415	-	GATACTAGGCTGAAATAGAGAGG	1	2	28
(N20)NGG	1	33476429	-	TCGCCTGGCCTTCTGATACTAGG	2	3	20
(N20)NGG	1	33478814	+	TCTTCCTGTTCTCAGATCACCGG	4	452	2834
(N20)NGG	1	33478815	+	CTTCCTGTTCTCAGATCACCGGG	2	5	408
(N20)NGG	1	33478816	+	TTCCTGTTCTCAGATCACCGGGG	1	1	25
(N20)NGG	1	33478852	+	TCGATCAGATGATAATGAAAAGG	2	3	34
(N20)NGG	1	33478914	+	CCCCACTCATAGAGTACTACAGG	2	2	8
(N20)NGG	1	33478920	+	TCATAGAGTACTACAGGAAACGG	2	2	44
(N20)NGG	1	33478921	+	CATAGAGTACTACAGGAAACGGG	2	2	35
(N20)NGG	1	33478922	+	ATAGAGTACTACAGGAAACGGGG	2	2	26
(N20)NGG	1	33478923	+	TAGAGTACTACAGGAAACGGGGG	2	3	11
(N20)NGG	1	33479014	+	CAAAGCCACATGTAAAGACTTGG	1	6	64
(N20)NGG	1	33478796	-	TTCCCCGGTGATCTGAGAACAGG	1	1	13
(N20)NGG	1	33478811	-	TCGACGGATCAAGGGTTCCCCGG	2	2	2
(N20)NGG	1	33478819	-	TCATCTGATCGACGGATCAAGGG	2	2	4
(N20)NGG	1	33478820	-	ATCATCTGATCGACGGATCAAGG	2	3	9
(N20)NGG	1	33478827	-	TTTCATTATCATCTGATCGACGG	2	3	41
(N20)NGG	1	33478853	-	GGCTTGCAGGCGGATTTTCAAGG	1	3	16
(N20)NGG	1	33478863	-	GAGTGTGGTAGGCTTGCAGGCGG	2	4	44
(N20)NGG	1	33478866	-	TTTGAGTGTGGTAGGCTTGCAGG	2	2	17
(N20)NGG	1	33478874	-	TGGGGTGGTTTGAGTGTGGTAGG	2	6	77
(N20)NGG	1	33478878	-	TGAGTGGGGTGGTTTGAGTGTGG	2	5	86
(N20)NGG	1	33478889	-	GTAGTACTCTATGAGTGGGGTGG	2	2	15
(N20)NGG	1	33478892	-	CCTGTAGTACTCTATGAGTGGGG	2	2	16
(N20)NGG	1	33478893	-	TCCTGTAGTACTCTATGAGTGGG	2	2	16

FIG. 2

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	1	33478894	-	TTCCTGTAGTACTCTATGAGTGG	2	3	23
(N20)NGG	1	33478926	-	GGGATGCATCGATGGCGGAGTGG	1	2	11
(N20)NGG	1	33478931	-	GGTCTGGGATGCATCGATGGCGG	2	2	43
(N20)NGG	1	33478934	-	GGGGGTCTGGGATGCATCGATGG	1	4	26
(N20)NGG	1	33478946	-	GAACACGACATCGGGGGTCTGGG	2	2	3
(N20)NGG	1	33478947	-	CGAACACGACATCGGGGGTCTGG	2	2	3
(N20)NGG	1	33478952	-	GCTTGCGAACACGACATCGGGGG	2	2	3
(N20)NGG	1	33478953	-	TGCTTGCGAACACGACATCGGGG	2	3	4
(N20)NGG	1	33478954	-	ATGCTTGCGAACACGACATCGGG	2	2	37
(N20)NGG	1	33478955	-	GATGCTTGCGAACACGACATCGG	2	2	5
(N20)NGG	1	33478977	-	TGGCTTTGGAGAAGGCTGCTAGG	3	9	93
(N20)NGG	1	33478985	-	TTTACATGTGGCTTTGGAGAAGG	2	4	94
(N20)NGG	1	33478991	-	CAAGTCTTTACATGTGGCTTTGG	2	3	39
(N20)NGG	1	33478997	-	CATAACCAAGTCTTTACATGTGG	1	1	29
(N20)NGG	1	33480122	+	ATATTCATTTGCTGTCTTTCAGG	1	3	129
(N20)NGG	1	33480142	+	AGGCTGATTCACCCCAAGAGTGG	1	1	23
(N20)NGG	1	33480159	+	GAGTGGCCGTTCCTACCACGAGG	2	2	6
(N20)NGG	1	33480209	+	AAGATGACGTATGTAAACTCAGG	1	1	11
(N20)NGG	1	33480131	-	GGTAGGAACGGCCACTCTTGGGG	2	2	15
(N20)NGG	1	33480132	-	TGGTAGGAACGGCCACTCTTGGG	2	2	13
(N20)NGG	1	33480133	-	GTGGTAGGAACGGCCACTCTTGG	2	2	62
(N20)NGG	1	33480143	-	TGAACTCCTCGTGGTAGGAACGG	2	3	20
(N20)NGG	1	33480148	-	AGGGTTGAACTCCTCGTGGTAGG	2	2	10
(N20)NGG	1	33480152	-	TTGGAGGGTTGAACTCCTCGTGG	2	2	11
(N20)NGG	1	33480167	-	CTTTCATGGGCTCTTTTGGAGGG	2	6	59
(N20)NGG	1	33480168	-	TCTTTCATGGGCTCTTTTGGAGG	2	4	62
(N20)NGG	1	33480171	-	TCATCTTTCATGGGCTCTTTTGG	2	4	61

FIG. 2

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	1	33480180	-	TTACATACGTCATCTTTCATGGG	1	1	28
(N20)NGG	1	33480181	-	TTTACATACGTCATCTTTCATGG	1	3	43
(N20)NGG	1	33486982	+	TTTACAGCTCGATGACCTCATGG	1	2	15
(N20)NGG	1	33486990	+	TCGATGACCTCATGGAGAAGAGG	3	4	27
(N20)NGG	1	33487058	+	CTGCTGATCCGAAGAATCACAGG	2	3	23
(N20)NGG	1	33487062	+	TGATCCGAAGAATCACAGGAAGG	2	2	27
(N20)NGG	1	33487079	+	GGAAGGTATTTGTCCCTTGAAGG	1	2	30
(N20)NGG	1	33486949	-	TCGAGCTGTAAAAGAATGTGTGG	1	1	22
(N20)NGG	1	33486975	-	TCTCTTTCCTCTTCTCCATGAGG	4	20	282
(N20)NGG	1	33487026	-	TTCGGATCAGCAGAGAGTCTGGG	2	4	14
(N20)NGG	1	33487027	-	CTTCGGATCAGCAGAGAGTCTGG	2	3	16
(N20)NGG	1	33487044	-	AATACCTTCCTGTGATTCTTCGG	1	5	70
(N20)NGG	1	33487193	+	CTATTTTGTTCCTAACTTCCAGG	1	2	84
(N20)NGG	1	33487208	+	CTTCCAGGTGAGTGATGAAATGG	1	6	75
(N20)NGG	1	33487214	+	GGTGAGTGATGAAATGGTAGTGG	3	5	43
(N20)NGG	1	33487235	+	GGAGCTCATTGAGAAGAATTTGG	3	4	77
(N20)NGG	1	33487257	+	GAGACCCCCTTGTGCAAAAATGG	2	4	39
(N20)NGG	1	33487268	+	GTGCAAAAATGGTTTTCTTCTGG	3	7	58
(N20)NGG	1	33487272	+	AAAAATGGTTTTCTTCTGGATGG	3	8	176
(N20)NGG	1	33487282	+	TTCTTCTGGATGGCTTCCCTCGG	3	18	115
(N20)NGG	1	33487291	+	ATGGCTTCCCTCGGACTGTGAGG	3	4	29
(N20)NGG	1	33487295	+	CTTCCCTCGGACTGTGAGGCAGG	3	5	27
(N20)NGG	1	33487304	+	GACTGTGAGGCAGGCAGAAATGG	3	13	146
(N20)NGG	1	33487307	+	TGTGAGGCAGGCAGAAATGGTGG	1	19	158
(N20)NGG	1	33487308	+	GTGAGGCAGGCAGAAATGGTGGG	1	6	94
(N20)NGG	1	33487181	-	TCATCACTCACCTGGAAGTTAGG	1	3	50
(N20)NGG	1	33487189	-	CTACCATTTCATCACTCACCTGG	4	5	32

FIG. 2

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	1	33487239	-	AAAACCATTTTTGCACAAGGGGG	3	5	70
(N20)NGG	1	33487240	-	GAAAACCATTTTTGCACAAGGGG	3	5	73
(N20)NGG	1	33487241	-	AGAAAACCATTTTTGCACAAGGG	3	12	122
(N20)NGG	1	33487242	-	AAGAAAACCATTTTTGCACAAGG	3	6	134
(N20)NGG	1	33487276	-	CTGCCTGCCTCACAGTCCGAGGG	3	14	388
(N20)NGG	1	33487277	-	TCTGCCTGCCTCACAGTCCGAGG	3	8	84
(N20)NGG	1	33490042	+	GTTTTTGTCTTCCTCTCTGTAGG	1	18	183
(N20)NGG	1	33490054	+	CTCTCTGTAGGCACCCAGATTGG	1	2	25
(N20)NGG	1	33490088	+	TGTGTCTGCCATTTAGCTACTGG	2	6	41
(N20)NGG	1	33490089	+	GTGTCTGCCATTTAGCTACTGGG	2	7	36
(N20)NGG	1	33490090	+	TGTCTGCCATTTAGCTACTGGGG	3	4	44
(N20)NGG	1	33490101	+	TAGCTACTGGGGACATGCTGAGG	2	3	37
(N20)NGG	1	33490102	+	AGCTACTGGGGACATGCTGAGGG	2	4	51
(N20)NGG	1	33490108	+	TGGGGACATGCTGAGGGCCATGG	3	8	96
(N20)NGG	1	33490111	+	GGACATGCTGAGGGCCATGGTGG	3	6	74
(N20)NGG	1	33490118	+	CTGAGGGCCATGGTGGCTTCTGG	4	12	93
(N20)NGG	1	33490130	+	GTGGCTTCTGGCTCAGAGCTAGG	4	8	79
(N20)NGG	1	33490144	+	AGAGCTAGGAAAAAAGCTGAAGG	2	6	111
(N20)NGG	1	33490153	+	AAAAAAGCTGAAGGCAACTATGG	5	16	175
(N20)NGG	1	33490160	+	CTGAAGGCAACTATGGATGCTGG	3	3	27
(N20)NGG	1	33490161	+	TGAAGGCAACTATGGATGCTGGG	3	6	32
(N20)NGG	1	33490168	+	AACTATGGATGCTGGGAAACTGG	3	5	44
(N20)NGG	1	33490172	+	ATGGATGCTGGGAAACTGGTAGG	4	6	72
(N20)NGG	1	33490177	+	TGCTGGGAAACTGGTAGGTTTGG	1	2	41
(N20)NGG	1	33490180	+	TGGGAAACTGGTAGGTTTGGTGG	1	3	43
(N20)NGG	1	33490031	-	CAATCTGGGTGCCTACAGAGAGG	1	1	22
(N20)NGG	1	33490045	-	CAGAAGTTTTCAGCCAATCTGGG	3	4	65

FIG. 2

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	1	33490046	-	ACAGAAGTTTTCAGCCAATCTGG	3	8	40
(N20)NGG	1	33490074	-	GCATGTCCCCAGTAGCTAAATGG	2	4	24
(N20)NGG	1	33490103	-	CTCTGAGCCAGAAGCCACCATGG	5	13	113
(N20)NGG	1	33502333	+	GTGGCAGTGAGAGACTTCGGCGG	2	4	28
(N20)NGG	1	33502339	+	GTGAGAGACTTCGGCGGACATGG	2	3	8
(N20)NGG	1	33502357	+	CATGGCTCCCAGCGTGCCAGCGG	3	6	37
(N20)NGG	1	33502379	+	GCAGAACCCGAGTATCCTAAAGG	3	3	19
(N20)NGG	1	33502386	+	CCGAGTATCCTAAAGGCATCCGG	2	4	9
(N20)NGG	1	33502387	+	CGAGTATCCTAAAGGCATCCGGG	2	2	10
(N20)NGG	1	33502399	+	AGGCATCCGGGCCGTGCTGCTGG	2	2	13
(N20)NGG	1	33502400	+	GGCATCCGGGCCGTGCTGCTGGG	2	2	12
(N20)NGG	1	33502401	+	GCATCCGGGCCGTGCTGCTGGGG	2	3	22
(N20)NGG	1	33502409	+	GCCGTGCTGCTGGGGCCTCCCGG	3	5	80
(N20)NGG	1	33502410	+	CCGTGCTGCTGGGGCCTCCCGGG	3	14	165
(N20)NGG	1	33502411	+	CGTGCTGCTGGGGCCTCCCGGGG	2	3	50
(N20)NGG	1	33502415	+	CTGCTGGGGCCTCCCGGGGCCGG	3	27	142
(N20)NGG	1	33502421	+	GGGCCTCCCGGGGCCGGTAAAGG	3	5	22
(N20)NGG	1	33502422	+	GGCCTCCCGGGGCCGGTAAAGGG	1	3	15
(N20)NGG	1	33502429	+	CGGGGCCGGTAAAGGGACCCAGG	1	3	11
(N20)NGG	1	33502436	+	GGTAAAGGGACCCAGGTGAGCGG	1	3	55
(N20)NGG	1	33502440	+	AAGGGACCCAGGTGAGCGGCAGG	1	1	29
(N20)NGG	1	33502445	+	ACCCAGGTGAGCGGCAGGACTGG	1	3	43
(N20)NGG	1	33502446	+	CCCAGGTGAGCGGCAGGACTGGG	1	7	55
(N20)NGG	1	33502451	+	GTGAGCGGCAGGACTGGGCTTGG	1	5	101
(N20)NGG	1	33502342	-	GGTTCTGCCGCTGGCACGCTGGG	3	3	16
(N20)NGG	1	33502343	-	GGGTTCTGCCGCTGGCACGCTGG	3	3	14
(N20)NGG	1	33502351	-	GGATACTCGGGTTCTGCCGCTGG	3	3	9

FIG. 2

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	1	33502363	-	CGGATGCCTTTAGGATACTCGGG	2	2	11
(N20)NGG	1	33502364	-	CCGGATGCCTTTAGGATACTCGG	2	3	12
(N20)NGG	1	33502372	-	AGCACGGCCCGGATGCCTTTAGG	2	2	17
(N20)NGG	1	33502383	-	GAGGCCCCAGCAGCACGGCCCGG	3	7	90
(N20)NGG	1	33502388	-	CCCGGGAGGCCCCAGCAGCACGG	3	9	114
(N20)NGG	1	33502402	-	GTCCCTTTACCGGCCCCGGGAGG	1	3	13
(N20)NGG	1	33502405	-	TGGGTCCCTTTACCGGCCCCGGG	1	6	19
(N20)NGG	1	33502406	-	CTGGGTCCCTTTACCGGCCCCGG	2	4	16
(N20)NGG	1	33502412	-	GCTCACCTGGGTCCCTTTACCGG	1	2	24
(N20)NGG	1	33502424	-	CCCAGTCCTGCCGCTCACCTGGG	2	7	62
(N20)NGG	1	33502425	-	GCCCAGTCCTGCCGCTCACCTGG	1	1	46

FIG. 2

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	118209916	+	GATGCTCAGTACAGCCACCTTGG	1	1	32
(N20)NGG	11	118209919	+	GCTCAGTACAGCCACCTTGGAGG	1	4	47
(N20)NGG	11	118209926	+	ACAGCCACCTTGGAGGAAACTGG	1	3	56
(N20)NGG	11	118209927	+	CAGCCACCTTGGAGGAAACTGGG	1	6	70
(N20)NGG	11	118209932	+	ACCTTGGAGGAAACTGGGCTCGG	1	7	61
(N20)NGG	11	118209953	+	GGAACAAGTGAACCTGAGACTGG	1	1	31
(N20)NGG	11	118209956	+	ACAAGTGAACCTGAGACTGGTGG	1	1	29
(N20)NGG	11	118209852	-	TAAGAGAGGAGAAGAGAAAACGG	6	116	1279
(N20)NGG	11	118209866	-	GATCTCGGAGGGGCTAAGAGAGG	1	2	45
(N20)NGG	11	118209876	-	GCATCATCTCGATCTCGGAGGGG	1	1	9
(N20)NGG	11	118209877	-	AGCATCATCTCGATCTCGGAGGG	1	1	5
(N20)NGG	11	118209878	-	GAGCATCATCTCGATCTCGGAGG	1	1	4
(N20)NGG	11	118209881	-	ACTGAGCATCATCTCGATCTCGG	1	2	10
(N20)NGG	11	118209908	-	GAGCCCAGTTTCCTCCAAGGTGG	1	4	48
(N20)NGG	11	118209911	-	TCCGAGCCCAGTTTCCTCCAAGG	1	3	44
(N20)NGG	11	118209943	-	TTCTAGAAGCCACCAGTCTCAGG	1	6	53
(N20)NGG	11	118210190	+	CCGACACACAAGCTCTGTTGAGG	1	1	13
(N20)NGG	11	118210200	+	AGCTCTGTTGAGGAATGACCAGG	1	3	27
(N20)NGG	11	118210209	+	GAGGAATGACCAGGTCTATCAGG	1	1	23
(N20)NGG	11	118210221	+	GGTCTATCAGGTGAGCGTTGAGG	1	1	10
(N20)NGG	11	118210222	+	GTCTATCAGGTGAGCGTTGAGGG	1	1	15
(N20)NGG	11	118210223	+	TCTATCAGGTGAGCGTTGAGGGG	1	2	18
(N20)NGG	11	118210227	+	TCAGGTGAGCGTTGAGGGGAAGG	1	8	42
(N20)NGG	11	118210230	+	GGTGAGCGTTGAGGGGAAGGAGG	1	4	95
(N20)NGG	11	118210168	-	CCTCAACAGAGCTTGTGTGTCGG	1	4	26

FIG. 3

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	118210196	-	CAACGCTCACCTGATAGACCTGG	1	3	11
(N20)NGG	11	118210506	+	CACAGTGTGCCAGAGCTGTGTGG	1	12	110
(N20)NGG	11	118210512	+	GTGCCAGAGCTGTGTGGAGCTGG	1	6	58
(N20)NGG	11	118210527	+	GGAGCTGGATCCAGCCACCGTGG	1	3	32
(N20)NGG	11	118210531	+	CTGGATCCAGCCACCGTGGCTGG	1	2	43
(N20)NGG	11	118210575	+	TGCCACTCTGCTCCTTGCTTTGG	2	5	71
(N20)NGG	11	118210576	+	GCCACTCTGCTCCTTGCTTTGGG	1	3	60
(N20)NGG	11	118210594	+	TTGGGAGTCTTCTGCTTTGCTGG	1	2	44
(N20)NGG	11	118210606	+	TGCTTTGCTGGACATGAGACTGG	1	2	47
(N20)NGG	11	118210610	+	TTGCTGGACATGAGACTGGAAGG	1	5	66
(N20)NGG	11	118210618	+	CATGAGACTGGAAGGCTGTCTGG	1	2	38
(N20)NGG	11	118210619	+	ATGAGACTGGAAGGCTGTCTGGG	1	4	51
(N20)NGG	11	118210620	+	TGAGACTGGAAGGCTGTCTGGGG	1	4	76
(N20)NGG	11	118210621	+	GAGACTGGAAGGCTGTCTGGGGG	1	7	78
(N20)NGG	11	118210628	+	GAAGGCTGTCTGGGGGTTAGTGG	1	4	51
(N20)NGG	11	118210465	-	TGTGGGGGAAGGGAGGAGAGAGG	9	73	815
(N20)NGG	11	118210472	-	GGCACACTGTGGGGGAAGGGAGG	1	7	129
(N20)NGG	11	118210475	-	TCTGGCACACTGTGGGGGAAGGG	1	4	46
(N20)NGG	11	118210476	-	CTCTGGCACACTGTGGGGGAAGG	1	1	51
(N20)NGG	11	118210480	-	ACAGCTCTGGCACACTGTGGGGG	1	7	59
(N20)NGG	11	118210481	-	CACAGCTCTGGCACACTGTGGGG	1	4	70
(N20)NGG	11	118210482	-	ACACAGCTCTGGCACACTGTGGG	2	6	59
(N20)NGG	11	118210483	-	CACACAGCTCTGGCACACTGTGG	2	9	112
(N20)NGG	11	118210493	-	GATCCAGCTCCACACAGCTCTGG	1	4	45
(N20)NGG	11	118210515	-	ATGATGCCAGCCACGGTGGCTGG	1	2	54

FIG. 3

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	118210519	-	GACAATGATGCCAGCCACGGTGG	1	5	65
(N20)NGG	11	118210522	-	AGTGACAATGATGCCAGCCACGG	1	3	47
(N20)NGG	11	118210555	-	TCCCAAAGCAAGGAGCAGAGTGG	1	8	105
(N20)NGG	11	118210565	-	AGCAGAAGACTCCCAAAGCAAGG	1	7	54
(N20)NGG	11	118211115	+	CCCCTTCAAGATACCTATAGAGG	1	2	22
(N20)NGG	11	118211124	+	GATACCTATAGAGGAACTTGAGG	1	1	15
(N20)NGG	11	118211162	+	ATTGCAATACCAGCATCACATGG	1	4	44
(N20)NGG	11	118211163	+	TTGCAATACCAGCATCACATGGG	1	1	32
(N20)NGG	11	118211169	+	TACCAGCATCACATGGGTAGAGG	1	4	70
(N20)NGG	11	118211170	+	ACCAGCATCACATGGGTAGAGGG	1	2	37
(N20)NGG	11	118211175	+	CATCACATGGGTAGAGGGAACGG	1	4	69
(N20)NGG	11	118211178	+	CACATGGGTAGAGGGAACGGTGG	1	2	38
(N20)NGG	11	118211179	+	ACATGGGTAGAGGGAACGGTGGG	1	3	29
(N20)NGG	11	118211208	+	GCTCTCAGACATTACAAGGACTGG	1	4	31
(N20)NGG	11	118211214	+	AGACATTACAAGACTGGACCTGG	1	1	27
(N20)NGG	11	118211215	+	GACATTACAAGACTGGACCTGGG	1	1	18
(N20)NGG	11	118211229	+	GGACCTGGGAAAACGCATCCTGG	1	1	17
(N20)NGG	11	118211239	+	AAACGCATCCTGGACCCACGAGG	1	1	5
(N20)NGG	11	118211249	+	TGGACCCACGAGGAATATATAGG	1	2	13
(N20)NGG	11	118211257	+	CGAGGAATATATAGGTGTAATGG	1	1	22
(N20)NGG	11	118211258	+	GAGGAATATATAGGTGTAATGGG	1	1	51
(N20)NGG	11	118211274	+	TAATGGGACAGATATATACAAGG	1	9	142
(N20)NGG	11	118211331	+	TACGTGCTTCCTGAACCCTTTGG	1	2	14
(N20)NGG	11	118211332	+	ACGTGCTTCCTGAACCCTTTGGG	1	1	17
(N20)NGG	11	118211080	-	CTTGAAGGGGCTCACTAAAGGGG	1	1	20

FIG. 3

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	118211081	-	TCTTGAAGGGGCTCACTAAAGGG	1	2	23
(N20)NGG	11	118211082	-	ATCTTGAAGGGGCTCACTAAAGG	1	2	15
(N20)NGG	11	118211093	-	CCTCTATAGGTATCTTGAAGGGG	1	1	18
(N20)NGG	11	118211094	-	TCCTCTATAGGTATCTTGAAGGG	1	3	21
(N20)NGG	11	118211095	-	TTCCTCTATAGGTATCTTGAAGG	1	1	33
(N20)NGG	11	118211106	-	CTGTCCTCAAGTTCCTCTATAGG	1	3	35
(N20)NGG	11	118211149	-	TCCCTCTACCCATGTGATGCTGG	1	1	54
(N20)NGG	11	118211210	-	GGTCCAGGATGCGTTTTCCCAGG	1	3	19
(N20)NGG	11	118211225	-	TATATATTCCTCGTGGGTCCAGG	1	1	11
(N20)NGG	11	118211231	-	TACACCTATATATTCCTCGTGGG	1	1	9
(N20)NGG	11	118211232	-	TTACACCTATATATTCCTCGTGG	1	2	34
(N20)NGG	11	118211287	-	ACTTCGATAATGAACTTGCACGG	1	1	14
(N20)NGG	11	118213264	+	TCTACTGGATGAGTTCCGCTGGG	1	1	9
(N20)NGG	11	118213270	+	GGATGAGTTCCGCTGGGAGATGG	1	3	31
(N20)NGG	11	118213292	+	GAACATAGCACGTTTCTCTCTGG	1	1	17
(N20)NGG	11	118213297	+	TAGCACGTTTCTCTCTGGCCTGG	1	4	39
(N20)NGG	11	118213303	+	GTTTCTCTCTGGCCTGGTACTGG	1	2	19
(N20)NGG	11	118213322	+	CTGGCTACCCTTCTCTCGCAAGG	2	5	27
(N20)NGG	11	118213327	+	TACCCTTCTCTCGCAAGGTAAGG	1	2	12
(N20)NGG	11	118213337	+	TCGCAAGGTAAGGCTACTCCAGG	1	1	4
(N20)NGG	11	118213340	+	CAAGGTAAGGCTACTCCAGGTGG	1	2	30
(N20)NGG	11	118213341	+	AAGGTAAGGCTACTCCAGGTGGG	1	2	29
(N20)NGG	11	118213344	+	GTAAGGCTACTCCAGGTGGGTGG	1	3	26
(N20)NGG	11	118213345	+	TAAGGCTACTCCAGGTGGGTGGG	1	2	24
(N20)NGG	11	118213346	+	AAGGCTACTCCAGGTGGGTGGGG	1	2	27

FIG. 3

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	118213257	-	TGCTATGTTCCATCTCCCAGCGG	1	4	57
(N20)NGG	11	118213293	-	AGAGAAGGGTAGCCAGTACCAGG	1	4	38
(N20)NGG	11	118213307	-	AGCCTTACCTTGCGAGAGAAGGG	1	1	14
(N20)NGG	11	118213308	-	TAGCCTTACCTTGCGAGAGAAGG	1	1	9

FIG. 3

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	10	14950408	+	CTGTTTTGTTTGTCCCACAGAGG	3	7	100
(N20)NGG	10	14950411	+	TTTTGTTTGTCCCACAGAGGAGG	1	8	95
(N20)NGG	10	14950455	+	ATCCTCTGCCAATACCTTTAAGG	1	4	37
(N20)NGG	10	14950474	+	AAGGCACAAAGTTCCATACCCGG	1	1	31
(N20)NGG	10	14950492	+	CCCGGAAACTTTTCACCCTGAGG	1	2	12
(N20)NGG	10	14950550	+	GAAAAACTGAGACAAACCCCAGG	1	6	60
(N20)NGG	10	14950640	+	AGTGAAAGTGAAGAAGAAGTAGG	1	14	197
(N20)NGG	10	14950661	+	GGAATCCCAGCTTCACTGCAAGG	1	3	67
(N20)NGG	10	14950669	+	AGCTTCACTGCAAGGAGATCTGG	1	2	28
(N20)NGG	10	14950670	+	GCTTCACTGCAAGGAGATCTGGG	1	4	40
(N20)NGG	10	14950693	+	CTCTGTACTTCACCTGCAAAAGG	1	3	51
(N20)NGG	10	14950700	+	CTTCACCTGCAAAAGGCTGATGG	1	2	53
(N20)NGG	10	14950701	+	TTCACCTGCAAAAGGCTGATGGG	1	4	44
(N20)NGG	10	14950702	+	TCACCTGCAAAAGGCTGATGGGG	1	5	52
(N20)NGG	10	14950716	+	CTGATGGGGATGTACCCCAGTGG	1	2	23
(N20)NGG	10	14950717	+	TGATGGGGATGTACCCCAGTGGG	1	1	21
(N20)NGG	10	14950762	+	TGAAATCACAGATGAGAGTTTGG	2	4	66
(N20)NGG	10	14950786	+	AAACTTCCCTTCCTCCACAGTGG	1	4	85
(N20)NGG	10	14950790	+	TTCCCTTCCTCCACAGTGGCAGG	1	7	90
(N20)NGG	10	14950791	+	TCCCTTCCTCCACAGTGGCAGGG	1	6	83
(N20)NGG	10	14950792	+	CCCTTCCTCCACAGTGGCAGGGG	1	8	112
(N20)NGG	10	14950793	+	CCTTCCTCCACAGTGGCAGGGGG	3	8	98
(N20)NGG	10	14950829	+	AAGCTTTTCAGTGACTCTGATGG	1	3	63
(N20)NGG	10	14950889	+	TCAACACACATAACAGAACAAGG	1	4	82
(N20)NGG	10	14950898	+	ATAACAGAACAAGGAAGTCAAGG	1	10	104

FIG. 4

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	10	14950902	+	CAGAACAAGGAAGTCAAGGCTGG	1	6	74
(N20)NGG	10	14950903	+	AGAACAAGGAAGTCAAGGCTGGG	1	14	244
(N20)NGG	10	14950952	+	TCTTCCCAAGAGAGAAACAGTGG	1	7	125
(N20)NGG	10	14950953	+	CTTCCCAAGAGAGAAACAGTGGG	1	5	98
(N20)NGG	10	14950954	+	TTCCCAAGAGAGAAACAGTGGGG	1	6	70
(N20)NGG	10	14950969	+	CAGTGGGGATATTACTTCCTTGG	1	1	30
(N20)NGG	10	14951023	+	GAATATTCCTGCCTCTCTCATGG	1	4	39
(N20)NGG	10	14951047	+	ACAAAATGTAATTTGCCCAAAGG	2	12	88
(N20)NGG	10	14951105	+	GTGACAATAGTTCCTAGTACTGG	1	1	19
(N20)NGG	10	14951146	+	CAGTGAGACACATATACCCGAGG	1	2	8
(N20)NGG	10	14951272	+	ACAATATTTATATGAGAAGCTGG	1	5	70
(N20)NGG	10	14951279	+	TTATATGAGAAGCTGGCAACTGG	1	3	39
(N20)NGG	10	14950385	-	CTCTGTGGGACAAACAAAACAGG	1	5	76
(N20)NGG	10	14950399	-	TAGTCATCTTCCTCCTCTGTGGG	1	6	82
(N20)NGG	10	14950400	-	ATAGTCATCTTCCTCCTCTGTGG	1	5	77
(N20)NGG	10	14950435	-	TGCCTTAAAGGTATTGGCAGAGG	1	3	28
(N20)NGG	10	14950441	-	ACTTTGTGCCTTAAAGGTATTGG	1	2	37
(N20)NGG	10	14950447	-	TATGGAACTTTGTGCCTTAAAGG	1	3	49
(N20)NGG	10	14950465	-	GGGTGAAAAGTTTCCGGGTATGG	1	1	17
(N20)NGG	10	14950470	-	CCTCAGGGTGAAAAGTTTCCGGG	1	6	69
(N20)NGG	10	14950471	-	ACCTCAGGGTGAAAAGTTTCCGG	4	6	46
(N20)NGG	10	14950485	-	CAGTCATTGAAAATACCTCAGGG	1	2	52
(N20)NGG	10	14950486	-	GCAGTCATTGAAAATACCTCAGG	1	2	29
(N20)NGG	10	14950525	-	GGGGTTTGTCTCAGTTTTTCAGG	1	4	48
(N20)NGG	10	14950544	-	CTCTGCTCTGCAGCATCCTGGGG	2	17	132

FIG. 4

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	10	14950545	-	ACTCTGCTCTGCAGCATCCTGGG	3	10	93
(N20)NGG	10	14950546	-	CACTCTGCTCTGCAGCATCCTGG	1	9	79
(N20)NGG	10	14950613	-	TTCTTCTTCACTTTCACTGTTGG	1	10	150
(N20)NGG	10	14950644	-	GATCTCCTTGCAGTGAAGCTGGG	1	2	33
(N20)NGG	10	14950645	-	AGATCTCCTTGCAGTGAAGCTGG	1	4	45
(N20)NGG	10	14950683	-	CATCCCCATCAGCCTTTTGCAGG	1	6	57
(N20)NGG	10	14950708	-	TTAAAGAATACTCCCACTGGGG	1	6	67
(N20)NGG	10	14950709	-	TTTAAAGAATACTCCCACTGGG	1	4	89
(N20)NGG	10	14950710	-	TTTTAAAGAATACTTCCCACTGG	2	9	108
(N20)NGG	10	14950770	-	CCCCTGCCACTGTGGAGGAAGGG	1	5	68
(N20)NGG	10	14950771	-	CCCCCTGCCACTGTGGAGGAAGG	1	4	70
(N20)NGG	10	14950775	-	AGATCCCCCTGCCACTGTGGAGG	1	3	43
(N20)NGG	10	14950778	-	CTGAGATCCCCCTGCCACTGTGG	1	3	67
(N20)NGG	10	14950804	-	TCAGAGTCACTGAAAAGCTTTGG	1	6	66
(N20)NGG	10	14950847	-	TGACTGGGAAGAATTCTGGGAGG	1	4	86
(N20)NGG	10	14950850	-	TGTTGACTGGGAAGAATTCTGGG	1	6	74
(N20)NGG	10	14950851	-	GTGTTGACTGGGAAGAATTCTGG	1	4	57
(N20)NGG	10	14950862	-	TTCTGTTATGTGTGTTGACTGGG	1	7	48
(N20)NGG	10	14950863	-	GTTCTGTTATGTGTGTTGACTGG	1	2	37
(N20)NGG	10	14950908	-	ATAACAAAACAGTATCAGATTGG	1	7	120
(N20)NGG	10	14950934	-	ATCCCCACTGTTTCTCTCTTGGG	1	4	83
(N20)NGG	10	14950935	-	TATCCCCACTGTTTCTCTCTTGG	1	4	66
(N20)NGG	10	14950964	-	TCTGTAGTCAGCTTTGTCCAAGG	1	2	46
(N20)NGG	10	14950987	-	GGAATATTCTCTTTGATTGTTGG	1	1	64
(N20)NGG	10	14951008	-	TTTTGTTCCATGAGAGAGGCAGG	1	3	41

FIG. 4

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	10	14951012	-	TACATTTTGTTCCATGAGAGAGG	1	3	70
(N20)NGG	10	14951040	-	AATCAGAGTAAGTATCCTTTGGG	1	5	70
(N20)NGG	10	14951041	-	AAATCAGAGTAAGTATCCTTTGG	1	4	59
(N20)NGG	10	14951095	-	GTAGTTGGTTCTCCAGTACTAGG	1	2	33
(N20)NGG	10	14951110	-	GTCTCACTGCTTAGAGTAGTTGG	1	1	19
(N20)NGG	10	14951140	-	TTTAGCAAACTTTTTTCCTCGGG	1	10	106
(N20)NGG	10	14951141	-	ATTTAGCAAACTTTTTTCCTCGG	2	9	151
(N20)NGG	10	14951183	-	TTCAAAATCAGAAGAGCTCTGGG	1	4	77
(N20)NGG	10	14951184	-	CTTCAAAATCAGAAGAGCTCTGG	1	3	62
(N20)NGG	10	14951209	-	AACTCAGCTTCTGGAGTTGAGGG	1	9	165
(N20)NGG	10	14951210	-	TAACTCAGCTTCTGGAGTTGAGG	1	3	77
(N20)NGG	10	14951218	-	CGTTTAGGTAACTCAGCTTCTGG	1	2	12
(N20)NGG	10	14951233	-	TATTGTAAATGCTCTCGTTTAGG	1	3	37
(N20)NGG	10	14951324	-	TTGAAACGCTTTGAATTCTTAGG	2	6	54
(N20)NGG	10	14961754	+	TCAGCTTAAAGCCTTTATGCCGG	1	4	22
(N20)NGG	10	14961770	+	ATGCCGGTCTTCCCAAAGTACGG	1	2	11
(N20)NGG	10	14961791	+	GGAGCCAAAGTATAAACCACTGG	1	2	33
(N20)NGG	10	14961792	+	GAGCCAAAGTATAAACCACTGGG	1	3	43
(N20)NGG	10	14961831	+	AGAACAGTTCACCGAGACTCAGG	1	1	17
(N20)NGG	10	14961843	+	CGAGACTCAGGTAAGAAAAATGG	1	3	71
(N20)NGG	10	14961849	+	TCAGGTAAGAAAAATGGTCCTGG	1	3	48
(N20)NGG	10	14961850	+	CAGGTAAGAAAAATGGTCCTGGG	1	7	69
(N20)NGG	10	14961743	-	CTTTGGGAAGACCGGCATAAAGG	1	2	8
(N20)NGG	10	14961751	-	GCTCCGTACTTTGGGAAGACCGG	1	4	91
(N20)NGG	10	14961759	-	ATACTTTGGCTCCGTACTTTGGG	1	3	20

FIG. 4

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	10	14961760	-	TATACTTTGGCTCCGTACTTTGG	1	1	8
(N20)NGG	10	14961773	-	TTTCCCAGTGGTTTATACTTTGG	1	4	78
(N20)NGG	10	14961785	-	GCTCTCTTCAGTTTTCCCAGTGG	1	9	90
(N20)NGG	10	14961820	-	CATTTTTCTTACCTGAGTCTCGG	2	10	114
(N20)NGG	10	14965040	+	TATCCAAATGTCATTCCAGTTGG	1	3	53
(N20)NGG	10	14965051	+	CATTCCAGTTGGCACAACTATGG	1	2	25
(N20)NGG	10	14965082	+	GTCGAAATGTGAGTAGTCACTGG	1	1	9
(N20)NGG	10	14965088	+	ATGTGAGTAGTCACTGGTTGTGG	1	4	27
(N20)NGG	10	14965089	+	TGTGAGTAGTCACTGGTTGTGGG	2	2	28
(N20)NGG	10	14964956	-	CTAGAAAAAGGAAAATCACATGG	3	15	312
(N20)NGG	10	14964968	-	GAAATCTTTAATCTAGAAAAAGG	2	19	176
(N20)NGG	10	14964999	-	GATATGCGTTCACAGGACAGAGG	1	2	12
(N20)NGG	10	14965006	-	ACATTTGGATATGCGTTCACAGG	1	1	13
(N20)NGG	10	14965021	-	GTGCCAACTGGAATGACATTTGG	1	1	33
(N20)NGG	10	14965033	-	TTATCCATAGTTGTGCCAACTGG	1	2	22
(N20)NGG	10	14968841	+	TTGTGTTTTCACTTCCCTTTAGG	2	12	229
(N20)NGG	10	14968846	+	TTTTCACTTCCCTTTAGGACTGG	1	2	54
(N20)NGG	10	14968896	+	TTTTCACTCCTCCTACAGTGAGG	1	1	51
(N20)NGG	10	14968903	+	TCCTCCTACAGTGAGGTAAGAGG	1	2	27
(N20)NGG	10	14968833	-	GAACTCTCTCCAGTCCTAAAGGG	1	4	27
(N20)NGG	10	14968834	-	TGAACTCTCTCCAGTCCTAAAGG	1	1	28
(N20)NGG	10	14968882	-	TCCTCTTACCTCACTGTAGGAGG	2	2	44
(N20)NGG	10	14968885	-	GGATCCTCTTACCTCACTGTAGG	1	5	33
(N20)NGG	10	14970014	+	CTATGCTTTTTATCTTTTTTAGG	1	55	838
(N20)NGG	10	14970020	+	TTTTTATCTTTTTTAGGCAGAGG	2	43	1301

FIG. 4

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	10	14970034	+	AGGCAGAGGAATATTTTCAGTGG	2	9	115
(N20)NGG	10	14970051	+	CAGTGGAGCAAATTACCCTGTGG	1	3	35
(N20)NGG	10	14970112	+	GCATTAAGCCATCCACCATGTGG	1	2	21
(N20)NGG	10	14970117	+	AAGCCATCCACCATGTGGTTTGG	1	4	38
(N20)NGG	10	14970124	+	CCACCATGTGGTTTGGAGAAAGG	1	7	49
(N20)NGG	10	14970151	+	GAAAAACAAATGTAATTGTGAGG	2	11	216
(N20)NGG	10	14970171	+	AGGTAAGAGAGCAATATCATAGG	1	1	33
(N20)NGG	10	14970044	-	TTTCTGGAAGTAATTCCACAGGG	2	8	107
(N20)NGG	10	14970045	-	ATTTCTGGAAGTAATTCCACAGG	2	5	67
(N20)NGG	10	14970060	-	GTGGAGTGGAATTCTATTTCTGG	1	1	38
(N20)NGG	10	14970074	-	TTAATGCTGATTATGTGGAGTGG	1	1	60
(N20)NGG	10	14970079	-	ATGGCTTAATGCTGATTATGTGG	1	8	65
(N20)NGG	10	14970098	-	TCTCCAAACCACATGGTGGATGG	1	4	51
(N20)NGG	10	14970102	-	CCTTTCTCCAAACCACATGGTGG	1	9	53
(N20)NGG	10	14970105	-	GCTCCTTTCTCCAAACCACATGG	2	10	84
(N20)NGG	10	14974852	+	ATGTATGTATTATTTGCCTTAGG	1	7	147
(N20)NGG	10	14974881	+	TGAATAAGCTAGACATGTTTAGG	2	4	58
(N20)NGG	10	14974944	+	ACACTCAGATCCATGCATGCCGG	2	5	43
(N20)NGG	10	14974954	+	CCATGCATGCCGGCATCCCAAGG	1	2	34
(N20)NGG	10	14974846	-	AGCTTATTCACATGAACCTAAGG	1	5	45
(N20)NGG	10	14974888	-	GTGAGATGATGAAGGATCTCAGG	2	4	58
(N20)NGG	10	14974896	-	GGTCTGTTGTGAGATGATGAAGG	2	6	47
(N20)NGG	10	14974917	-	ATGCATGGATCTGAGTGTTGCGG	2	6	47
(N20)NGG	10	14974932	-	CCTTGGGATGCCGGCATGCATGG	1	1	23
(N20)NGG	10	14974941	-	GCACACGTACCTTGGGATGCCGG	1	1	7

FIG. 4

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	10	14974948	-	ATCACTTGCACACGTACCTTGGG	1	1	10
(N20)NGG	10	14974949	-	AATCACTTGCACACGTACCTTGG	1	1	22
(N20)NGG	10	14976378	+	GTCTCTTTAAAATCCTGTCTAGG	2	6	86
(N20)NGG	10	14976381	+	TCTTTAAAATCCTGTCTAGGAGG	2	6	64
(N20)NGG	10	14976394	+	GTCTAGGAGGAGTGTTTAAGTGG	2	2	30
(N20)NGG	10	14976408	+	TTTAAGTGGAGTCTTAGAGCTGG	2	2	35
(N20)NGG	10	14976419	+	TCTTAGAGCTGGTCCGAAGCTGG	1	3	9
(N20)NGG	10	14976428	+	TGGTCCGAAGCTGGATCACTCGG	1	2	8
(N20)NGG	10	14976449	+	GGAGCCCGTACCATGTTGTGTGG	1	2	13
(N20)NGG	10	14976465	+	TGTGTGGCTGAACTGCAAAGCGG	2	5	52
(N20)NGG	10	14976472	+	CTGAACTGCAAAGCGGCTTATGG	3	3	31
(N20)NGG	10	14976511	+	ACCAACCTTAGTGAAGAATTAGG	2	4	32
(N20)NGG	10	14976519	+	TAGTGAAGAATTAGGAGTCCAGG	2	5	35
(N20)NGG	10	14976524	+	AAGAATTAGGAGTCCAGGTATGG	2	6	86
(N20)NGG	10	14976369	-	CTTAAACACTCCTCCTAGACAGG	2	4	25
(N20)NGG	10	14976410	-	GGCTCCGAGTGATCCAGCTTCGG	1	3	22
(N20)NGG	10	14976431	-	TCAGCCACACAACATGGTACGGG	2	8	158
(N20)NGG	10	14976432	-	TTCAGCCACACAACATGGTACGG	2	4	30
(N20)NGG	10	14976437	-	TGCAGTTCAGCCACACAACATGG	2	3	60
(N20)NGG	10	14976490	-	TCCTAATTCTTCACTAAGGTTGG	2	6	37
(N20)NGG	10	14976494	-	GGACTCCTAATTCTTCACTAAGG	2	2	18
(N20)NGG	10	14976515	-	GAATGAACAGTCACCATACCTGG	2	6	26
(N20)NGG	10	14976729	+	AGACATCCAAAGTGTATATTTGG	2	6	50
(N20)NGG	10	14976773	+	GATTTTACCAAATTCCAAGTCGG	4	8	74
(N20)NGG	10	14976774	+	ATTTTACCAAATTCCAAGTCGGG	2	5	52

FIG. 4

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	10	14976787	+	CCAAGTCGGGTAAGTCTGCCTGG	2	2	14
(N20)NGG	10	14976790	+	AGTCGGGTAAGTCTGCCTGGAGG	2	4	29
(N20)NGG	10	14976796	+	GTAAGTCTGCCTGGAGGAACAGG	2	5	41
(N20)NGG	10	14976797	+	TAAGTCTGCCTGGAGGAACAGGG	2	3	53
(N20)NGG	10	14976713	-	TAGTATCCAAATATACACTTTGG	2	8	49
(N20)NGG	10	14976747	-	CTTGGAATTTGGTAAAATCTTGG	3	13	87
(N20)NGG	10	14976758	-	GACTTACCCGACTTGGAATTTGG	2	2	15
(N20)NGG	10	14976765	-	CCAGGCAGACTTACCCGACTTGG	2	2	16
(N20)NGG	10	14977461	+	CTGGGATATATTTCTTTTTCAGG	2	7	140
(N20)NGG	10	14977474	+	CTTTTTCAGGTTTTTATTTCAGG	3	21	378
(N20)NGG	10	14977475	+	TTTTTCAGGTTTTTATTTCAGGG	5	53	552
(N20)NGG	10	14977484	+	TTTTTATTTCAGGGCAATAATGG	2	11	217
(N20)NGG	10	14977502	+	AATGGAACTGTCCTGTACACAGG	1	6	36
(N20)NGG	10	14977516	+	GTACACAGGAGACTTCAGATTGG	2	3	44
(N20)NGG	10	14977523	+	GGAGACTTCAGATTGGCGCAAGG	1	3	15
(N20)NGG	10	14977540	+	GCAAGGAGAAGCTGCTAGAATGG	3	7	73
(N20)NGG	10	14977556	+	AGAATGGAGCTTCTGCACTCCGG	2	5	95
(N20)NGG	10	14977557	+	GAATGGAGCTTCTGCACTCCGGG	2	2	36
(N20)NGG	10	14977558	+	AATGGAGCTTCTGCACTCCGGGG	2	2	17
(N20)NGG	10	14977559	+	ATGGAGCTTCTGCACTCCGGGGG	2	3	20
(N20)NGG	10	14977563	+	AGCTTCTGCACTCCGGGGGCAGG	2	4	36
(N20)NGG	10	14977569	+	TGCACTCCGGGGGCAGGTACTGG	2	5	19
(N20)NGG	10	14977570	+	GCACTCCGGGGGCAGGTACTGGG	2	2	11
(N20)NGG	10	14977581	+	GCAGGTACTGGGCCTCGTATAGG	2	3	14
(N20)NGG	10	14977491	-	ATCTGAAGTCTCCTGTGTACAGG	2	4	39

FIG. 4

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	10	14977553	-	CGAGGCCCAGTACCTGCCCCCGG	2	4	57
(N20)NGG	10	14978539	+	TTCTTTATTTTCTTTTTAGAAGG	15	1012	20720
(N20)NGG	10	14978570	+	GTTGTGACTCTCTTACCAGCTGG	1	2	25
(N20)NGG	10	14978581	+	CTTACCAGCTGGTCACTGTCCGG	1	2	23
(N20)NGG	10	14978582	+	TTACCAGCTGGTCACTGTCCGGG	1	3	29
(N20)NGG	10	14978597	+	TGTCCGGGATCAGTTATGTAAGG	1	1	4
(N20)NGG	10	14978598	+	GTCCGGGATCAGTTATGTAAGGG	1	1	6
(N20)NGG	10	14978599	+	TCCGGGATCAGTTATGTAAGGGG	1	1	9
(N20)NGG	10	14978600	+	CCGGGATCAGTTATGTAAGGGGG	1	1	7
(N20)NGG	10	14978563	-	GATCCCGGACAGTGACCAGCTGG	1	1	11
(N20)NGG	10	14978578	-	CCCCCTTACATAACTGATCCCGG	1	1	5
(N20)NGG	10	14981850	+	TCCTACCCAGATATCTTTAGTGG	2	4	28
(N20)NGG	10	14981863	+	TCTTTAGTGGATGAAGCATCAGG	2	2	30
(N20)NGG	10	14981868	+	AGTGGATGAAGCATCAGGAGAGG	2	7	68
(N20)NGG	10	14981829	-	TCCACTAAAGATATCTGGGTAGG	2	4	31
(N20)NGG	10	14981833	-	TTCATCCACTAAAGATATCTGGG	2	4	48
(N20)NGG	10	14981834	-	CTTCATCCACTAAAGATATCTGG	2	2	29
(N20)NGG	10	14987110	+	CTTTTTTCCTTTCAGCTTGAAGG	1	8	175
(N20)NGG	10	14987140	+	ATACTGTTCACCTGTGACTAAGG	1	1	23
(N20)NGG	10	14987175	+	CGAGCCCGAAATACAGATTTTGG	1	1	14
(N20)NGG	10	14987095	-	AGATAAACCTTCAAGCTGAAAGG	1	5	44
(N20)NGG	10	14987128	-	AACAACAACTCCTTAGTCACAGG	1	1	17
(N20)NGG	10	14987157	-	TCTTCCAAAATCTGTATTTCGGG	1	16	173
(N20)NGG	10	14987158	-	TTCTTCCAAAATCTGTATTTCGG	4	19	226
(N20)NGG	10	14991046	+	TTGTTTTTAGATCACATGAAAGG	1	6	109

FIG. 4

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	10	14991074	+	GAGCCCCTACCTTGAAAAGAAGG	1	6	40
(N20)NGG	10	14991078	+	CCCTACCTTGAAAAGAAGGTTGG	1	2	29
(N20)NGG	10	14991086	+	TGAAAAGAAGGTTGGAGTGCAGG	1	3	60
(N20)NGG	10	14991055	-	CAACCTTCTTTTCAAGGTAGGGG	1	2	64
(N20)NGG	10	14991056	-	CCAACCTTCTTTTCAAGGTAGGG	1	3	43
(N20)NGG	10	14991057	-	TCCAACCTTCTTTTCAAGGTAGG	2	6	53
(N20)NGG	10	14991061	-	GCACTCCAACCTTCTTTTCAAGG	2	2	45
(N20)NGG	10	14995915	+	CGGCGCTATGAGTTCTTTCGAGG	1	1	2
(N20)NGG	10	14995916	+	GGCGCTATGAGTTCTTTCGAGGG	1	1	4
(N20)NGG	10	14995917	+	GCGCTATGAGTTCTTTCGAGGGG	1	1	8
(N20)NGG	10	14995924	+	GAGTTCTTTCGAGGGGCAGATGG	1	2	33
(N20)NGG	10	14995962	+	TCTCCATAGACCGCTTCGATAGG	1	1	5
(N20)NGG	10	14995963	+	CTCCATAGACCGCTTCGATAGGG	1	1	1
(N20)NGG	10	14995974	+	GCTTCGATAGGGAGAACCTGAGG	1	1	9
(N20)NGG	10	14995975	+	CTTCGATAGGGAGAACCTGAGGG	1	1	9
(N20)NGG	10	14996009	+	TTCCTGTCCCACTGCCACAAAGG	1	6	52
(N20)NGG	10	14996018	+	CACTGCCACAAAGGTGAGTGAGG	1	4	42
(N20)NGG	10	14996019	+	ACTGCCACAAAGGTGAGTGAGGG	1	5	56
(N20)NGG	10	14995875	-	CGCCGCCGATCCCAGAGTCCGGG	1	1	13
(N20)NGG	10	14995876	-	GCGCCGCCGATCCCAGAGTCCGG	1	1	10
(N20)NGG	10	14995925	-	TATGGAGATAGTTGGATACTCGG	1	1	25
(N20)NGG	10	14995933	-	AAGCGGTCTATGGAGATAGTTGG	1	1	10
(N20)NGG	10	14995943	-	CTCCCTATCGAAGCGGTCTATGG	1	1	2
(N20)NGG	10	14995950	-	TCAGGTTCTCCCTATCGAAGCGG	1	2	10
(N20)NGG	10	14995968	-	GGAAGTAGGCGCGGGCCCTCAGG	1	1	18

FIG. 4

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	10	14995976	-	GTGGGACAGGAAGTAGGCGCGGG	1	5	51
(N20)NGG	10	14995977	-	AGTGGGACAGGAAGTAGGCGCGG	1	4	48
(N20)NGG	10	14995982	-	GTGGCAGTGGGACAGGAAGTAGG	1	5	123
(N20)NGG	10	14995989	-	CACCTTTGTGGCAGTGGGACAGG	1	4	35
(N20)NGG	10	14995994	-	TCACTCACCTTTGTGGCAGTGGG	1	4	43
(N20)NGG	10	14995995	-	CTCACTCACCTTTGTGGCAGTGG	1	6	55
(N20)NGG	10	14996001	-	GCAGCCCTCACTCACCTTTGTGG	1	6	73

FIG. 4

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	5246833	+	TATCTTCCTCCCACAGCTCCTGG	1	6	114
(N20)NGG	11	5246834	+	ATCTTCCTCCCACAGCTCCTGGG	2	14	155
(N20)NGG	11	5246845	+	ACAGCTCCTGGGCAACGTGCTGG	1	6	44
(N20)NGG	11	5246857	+	CAACGTGCTGGTCTGTGTGCTGG	1	5	25
(N20)NGG	11	5246870	+	TGTGTGCTGGCCCATCACTTTGG	1	2	47
(N20)NGG	11	5246896	+	AGAATTCACCCCACCAGTGCAGG	1	3	31
(N20)NGG	11	5246914	+	GCAGGCTGCCTATCAGAAAGTGG	2	5	34
(N20)NGG	11	5246917	+	GGCTGCCTATCAGAAAGTGGTGG	2	5	50
(N20)NGG	11	5246921	+	GCCTATCAGAAAGTGGTGGCTGG	2	7	86
(N20)NGG	11	5246926	+	TCAGAAAGTGGTGGCTGGTGTGG	3	6	74
(N20)NGG	11	5246938	+	GGCTGGTGTGGCTAATGCCCTGG	2	5	34
(N20)NGG	11	5246806	-	AGCTGTGGGAGGAAGATAAGAGG	1	9	146
(N20)NGG	11	5246817	-	CGTTGCCCAGGAGCTGTGGGAGG	1	4	62
(N20)NGG	11	5246820	-	GCACGTTGCCCAGGAGCTGTGGG	1	3	39
(N20)NGG	11	5246821	-	AGCACGTTGCCCAGGAGCTGTGG	1	3	57
(N20)NGG	11	5246829	-	CACAGACCAGCACGTTGCCCAGG	1	3	26
(N20)NGG	11	5246858	-	GAATTCTTTGCCAAAGTGATGGG	1	6	77
(N20)NGG	11	5246859	-	TGAATTCTTTGCCAAAGTGATGG	1	6	102
(N20)NGG	11	5246882	-	ATAGGCAGCCTGCACTGGTGGGG	1	2	25
(N20)NGG	11	5246883	-	GATAGGCAGCCTGCACTGGTGGG	1	2	30
(N20)NGG	11	5246884	-	TGATAGGCAGCCTGCACTGGTGG	1	3	28
(N20)NGG	11	5246887	-	TTCTGATAGGCAGCCTGCACTGG	1	3	35
(N20)NGG	11	5246900	-	ACCAGCCACCACTTTCTGATAGG	2	4	59
(N20)NGG	11	5246933	-	TTAGTGATACTTGTGGGCCAGGG	1	3	27
(N20)NGG	11	5246934	-	CTTAGTGATACTTGTGGGCCAGG	1	1	22

FIG. 5

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	5246939	-	GCGAGCTTAGTGATACTTGTGGG	1	1	1
(N20)NGG	11	5246940	-	AGCGAGCTTAGTGATACTTGTGG	1	1	8
(N20)NGG	11	5247806	+	TGGTCTATTTTCCCACCCTTAGG	2	6	54
(N20)NGG	11	5247813	+	TTTCCCACCCTTAGGCTGCTGG	1	2	40
(N20)NGG	11	5247816	+	TCCCACCCTTAGGCTGCTGGTGG	1	7	50
(N20)NGG	11	5247827	+	GGCTGCTGGTGGTCTACCCTTGG	1	1	34
(N20)NGG	11	5247836	+	TGGTCTACCCTTGGACCCAGAGG	2	6	27
(N20)NGG	11	5247853	+	CAGAGGTTCTTTGAGTCCTTTGG	2	2	55
(N20)NGG	11	5247854	+	AGAGGTTCTTTGAGTCCTTTGGG	3	5	87
(N20)NGG	11	5247855	+	GAGGTTCTTTGAGTCCTTTGGGG	2	8	65
(N20)NGG	11	5247882	+	GTCCACTCCTGATGCTGTTATGG	2	6	50
(N20)NGG	11	5247883	+	TCCACTCCTGATGCTGTTATGGG	2	4	33
(N20)NGG	11	5247894	+	TGCTGTTATGGGCAACCCTAAGG	2	4	23
(N20)NGG	11	5247900	+	TATGGGCAACCCTAAGGTGAAGG	2	3	23
(N20)NGG	11	5247907	+	AACCCTAAGGTGAAGGCTCATGG	2	4	31
(N20)NGG	11	5247922	+	GCTCATGGCAAGAAAGTGCTCGG	2	6	45
(N20)NGG	11	5247937	+	GTGCTCGGTGCCTTTAGTGATGG	2	4	20
(N20)NGG	11	5247942	+	CGGTGCCTTTAGTGATGGCCTGG	2	3	23
(N20)NGG	11	5247951	+	TAGTGATGGCCTGGCTCACCTGG	2	5	29
(N20)NGG	11	5247963	+	GGCTCACCTGGACAACCTCAAGG	2	2	29
(N20)NGG	11	5247964	+	GCTCACCTGGACAACCTCAAGGG	2	3	40
(N20)NGG	11	5248011	+	GCACTGTGACAAGCTGCACGTGG	6	7	23
(N20)NGG	11	5248028	+	ACGTGGATCCTGAGAACTTCAGG	5	6	18
(N20)NGG	11	5248029	+	CGTGGATCCTGAGAACTTCAGGG	5	6	21
(N20)NGG	11	5248040	+	AGAACTTCAGGGTGAGTCTATGG	1	15	83

FIG. 5

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	5248041	+	GAACTTCAGGGTGAGTCTATGGG	1	5	32
(N20)NGG	11	5247795	-	ACCACCAGCAGCCTAAGGGTGGG	1	1	26
(N20)NGG	11	5247796	-	GACCACCAGCAGCCTAAGGGTGG	1	4	36
(N20)NGG	11	5247799	-	GTAGACCACCAGCAGCCTAAGGG	1	2	24
(N20)NGG	11	5247800	-	GGTAGACCACCAGCAGCCTAAGG	1	2	20
(N20)NGG	11	5247821	-	CAAAGAACCTCTGGGTCCAAGGG	4	8	41
(N20)NGG	11	5247822	-	TCAAAGAACCTCTGGGTCCAAGG	5	11	32
(N20)NGG	11	5247829	-	AAAGGACTCAAAGAACCTCTGGG	2	7	59
(N20)NGG	11	5247830	-	CAAAGGACTCAAAGAACCTCTGG	2	6	61
(N20)NGG	11	5247847	-	AGGAGTGGACAGATCCCCAAAGG	2	3	38
(N20)NGG	11	5247862	-	GCCCATAACAGCATCAGGAGTGG	2	2	42
(N20)NGG	11	5247867	-	GGGTTGCCCATAACAGCATCAGG	2	2	11
(N20)NGG	11	5247887	-	TGCCATGAGCCTTCACCTTAGGG	2	2	32
(N20)NGG	11	5247888	-	TTGCCATGAGCCTTCACCTTAGG	2	4	35
(N20)NGG	11	5247925	-	GTGAGCCAGGCCATCACTAAAGG	2	2	23
(N20)NGG	11	5247938	-	TGAGGTTGTCCAGGTGAGCCAGG	2	7	55
(N20)NGG	11	5247947	-	AGGTGCCCTTGAGGTTGTCCAGG	2	3	19
(N20)NGG	11	5247956	-	GTGTGGCAAAGGTGCCCTTGAGG	1	2	36
(N20)NGG	11	5247967	-	CAGCTCACTCAGTGTGGCAAAGG	1	4	40
(N20)NGG	11	5247973	-	ACAGTGCAGCTCACTCAGTGTGG	2	8	46
(N20)NGG	11	5248014	-	AGACTCACCCTGAAGTTCTCAGG	2	7	74
(N20)NGG	11	5248162	+	GCAACCTCAAACAGACACCATGG	2	3	35
(N20)NGG	11	5248180	+	CATGGTGCATCTGACTCCTGAGG	2	6	43
(N20)NGG	11	5248206	+	AGTCTGCCGTTACTGCCCTGTGG	1	3	20
(N20)NGG	11	5248207	+	GTCTGCCGTTACTGCCCTGTGGG	1	2	12

FIG. 5

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	5248208	+	TCTGCCCGTTACTGCCCTGTGGG	1	3	32
(N20)NGG	11	5248213	+	CGTTACTGCCCTGTGGGGCAAGG	1	2	18
(N20)NGG	11	5248222	+	CCTGTGGGGCAAGGTGAACGTGG	4	5	33
(N20)NGG	11	5248232	+	AAGGTGAACGTGGATGAAGTTGG	1	3	34
(N20)NGG	11	5248235	+	GTGAACGTGGATGAAGTTGGTGG	2	9	139
(N20)NGG	11	5248240	+	CGTGGATGAAGTTGGTGGTGAGG	2	4	30
(N20)NGG	11	5248246	+	TGAAGTTGGTGGTGAGGCCCTGG	2	5	49
(N20)NGG	11	5248247	+	GAAGTTGGTGGTGAGGCCCTGGG	2	5	46
(N20)NGG	11	5248251	+	TTGGTGGTGAGGCCCTGGGCAGG	2	13	109
(N20)NGG	11	5248255	+	TGGTGAGGCCCTGGGCAGGTTGG	3	14	130
(N20)NGG	11	5248263	+	CCCTGGGCAGGTTGGTATCAAGG	2	2	38
(N20)NGG	11	5248275	+	TGGTATCAAGGTTACAAGACAGG	1	5	45
(N20)NGG	11	5248144	-	TGCACCATGGTGTCTGTTTGAGG	2	5	45
(N20)NGG	11	5248157	-	CTCAGGAGTCAGATGCACCATGG	2	7	85
(N20)NGG	11	5248174	-	GTAACGGCAGACTTCTCCTCAGG	1	1	11
(N20)NGG	11	5248190	-	CTTGCCCCACAGGGCAGTAACGG	1	2	48
(N20)NGG	11	5248199	-	CACGTTCACCTTGCCCCACAGGG	2	4	22
(N20)NGG	11	5248200	-	CCACGTTCACCTTGCCCCACAGG	4	5	26
(N20)NGG	11	5248241	-	CCTTGATACCAACCTGCCCAGGG	2	2	16
(N20)NGG	11	5248242	-	ACCTTGATACCAACCTGCCCAGG	2	2	20

FIG. 5

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	X	70327585	+	ACCTGGACATATCTGTCTTTAGG	1	4	62
(N20)NGG	X	70327590	+	GACATATCTGTCTTTAGGCCTGG	1	2	39
(N20)NGG	X	70327595	+	ATCTGTCTTTAGGCCTGGAGTGG	1	2	52
(N20)NGG	X	70327606	+	GGCCTGGAGTGGTGTGTCTAAGG	1	4	54
(N20)NGG	X	70327607	+	GCCTGGAGTGGTGTGTCTAAGGG	1	2	45
(N20)NGG	X	70327612	+	GAGTGGTGTGTCTAAGGGACTGG	1	1	32
(N20)NGG	X	70327676	+	GTCAGTGAGATTCCCCCAAAAGG	1	2	30
(N20)NGG	X	70327679	+	AGTGAGATTCCCCCAAAAGGAGG	1	4	51
(N20)NGG	X	70327680	+	GTGAGATTCCCCCAAAAGGAGGG	1	2	59
(N20)NGG	X	70327681	+	TGAGATTCCCCCAAAAGGAGGGG	1	3	53
(N20)NGG	X	70327688	+	CCCCCAAAAGGAGGGGCCCTTGG	1	3	28
(N20)NGG	X	70327689	+	CCCCAAAAGGAGGGGCCCTTGGG	1	1	33
(N20)NGG	X	70327690	+	CCCAAAAGGAGGGGCCCTTGGGG	1	3	33
(N20)NGG	X	70327693	+	AAAAGGAGGGGCCCTTGGGGAGG	1	3	95
(N20)NGG	X	70327694	+	AAAGGAGGGGCCCTTGGGGAGGG	1	10	110
(N20)NGG	X	70327695	+	AAGGAGGGGCCCTTGGGGAGGGG	2	8	140
(N20)NGG	X	70327700	+	GGGGCCCTTGGGGAGGGGCCTGG	1	30	212
(N20)NGG	X	70327701	+	GGGCCCTTGGGGAGGGGCCTGGG	1	16	187
(N20)NGG	X	70327702	+	GGCCCTTGGGGAGGGGCCTGGGG	4	30	206
(N20)NGG	X	70327734	+	GCAACCAGCATAGCCCCTACTGG	1	3	14
(N20)NGG	X	70327735	+	CAACCAGCATAGCCCCTACTGGG	1	1	13
(N20)NGG	X	70327564	–	GCCTAAAGACAGATATGTCCAGG	1	1	24
(N20)NGG	X	70327586	–	TCCCTTAGACACACCACTCCAGG	1	3	26
(N20)NGG	X	70327627	–	CAGAGTCGTTCACTGTAGTCTGG	1	2	69
(N20)NGG	X	70327650	–	TTGGGGGAATCTCACTGACGAGG	1	2	16

FIG. 6

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	X	70327666	-	CCAAGGGCCCCTCCTTTTGGGGG	1	4	39
(N20)NGG	X	70327667	-	CCCAAGGGCCCCTCCTTTTGGGG	1	4	51
(N20)NGG	X	70327668	-	CCCCAAGGGCCCCTCCTTTTGGG	1	4	44
(N20)NGG	X	70327669	-	TCCCCAAGGGCCCCTCCTTTTGG	1	2	53
(N20)NGG	X	70327682	-	GGCCCCAGGCCCCTCCCCAAGGG	2	10	147
(N20)NGG	X	70327683	-	AGGCCCCAGGCCCCTCCCCAAGG	5	22	285
(N20)NGG	X	70327696	-	TGGTTGCATGGGGAGGCCCCAGG	1	1	74
(N20)NGG	X	70327703	-	GCTATGCTGGTTGCATGGGGAGG	1	3	22
(N20)NGG	X	70327706	-	GGGGCTATGCTGGTTGCATGGGG	1	1	26
(N20)NGG	X	70327707	-	AGGGGCTATGCTGGTTGCATGGG	1	3	29
(N20)NGG	X	70327708	-	TAGGGGCTATGCTGGTTGCATGG	1	3	28
(N20)NGG	X	70327716	-	GGGCCCAGTAGGGGCTATGCTGG	1	1	20
(N20)NGG	X	70327725	-	AACATGGGGGGGCCCAGTAGGGG	1	1	23
(N20)NGG	X	70327726	-	TAACATGGGGGGGCCCAGTAGGG	1	1	6
(N20)NGG	X	70327727	-	GTAACATGGGGGGGCCCAGTAGG	1	1	15
(N20)NGG	X	70327736	-	CTTTAGGGTGTAACATGGGGGGG	1	1	19
(N20)NGG	X	70327737	-	GCTTTAGGGTGTAACATGGGGGG	1	2	17
(N20)NGG	X	70327738	-	GGCTTTAGGGTGTAACATGGGGG	1	1	16
(N20)NGG	X	70327739	-	AGGCTTTAGGGTGTAACATGGGG	1	2	23
(N20)NGG	X	70327740	-	CAGGCTTTAGGGTGTAACATGGG	1	1	17
(N20)NGG	X	70327741	-	TCAGGCTTTAGGGTGTAACATGG	1	2	24
(N20)NGG	X	70327751	-	GGTTCAGGTTTCAGGCTTTAGGG	1	2	50
(N20)NGG	X	70327752	-	GGGTTCAGGTTTCAGGCTTTAGG	1	7	64
(N20)NGG	X	70327759	-	AGGATTGGGGTTCAGGTTTCAGG	1	3	35
(N20)NGG	X	70327766	-	CTGTCAGAGGATTGGGGTTCAGG	1	6	51

FIG. 6

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	X	70327772	-	GTTCTTCTGTCAGAGGATTGGGG	1	3	46
(N20)NGG	X	70327773	-	GGTTCTTCTGTCAGAGGATTGGG	1	4	33
(N20)NGG	X	70328126	+	CTCCCTCTTTCTCCCCTGTCAGG	1	15	220
(N20)NGG	X	70328163	+	TCCCACCCTGAAGAACCTAGAGG	1	2	23
(N20)NGG	X	70328185	+	GATCTTGTTACTGAATACCACGG	1	3	34
(N20)NGG	X	70328186	+	ATCTTGTTACTGAATACCACGGG	1	2	24
(N20)NGG	X	70328196	+	TGAATACCACGGGAACTTTTCGG	1	2	17
(N20)NGG	X	70328106	-	GTCCTGACAGGGGAGAAAGAGGG	1	6	137
(N20)NGG	X	70328107	-	CGTCCTGACAGGGGAGAAAGAGG	1	5	48
(N20)NGG	X	70328116	-	TCGGGGCATCGTCCTGACAGGGG	1	1	8
(N20)NGG	X	70328117	-	TTCGGGGCATCGTCCTGACAGGG	1	1	7
(N20)NGG	X	70328118	-	ATTCGGGGCATCGTCCTGACAGG	1	1	2
(N20)NGG	X	70328133	-	TTCTTCAGGGTGGGAATTCGGGG	1	1	33
(N20)NGG	X	70328134	-	GTTCTTCAGGGTGGGAATTCGGG	2	3	62
(N20)NGG	X	70328135	-	GGTTCTTCAGGGTGGGAATTCGG	1	6	42
(N20)NGG	X	70328142	-	TCCTCTAGGTTCTTCAGGGTGGG	1	2	39
(N20)NGG	X	70328143	-	ATCCTCTAGGTTCTTCAGGGTGG	1	2	36
(N20)NGG	X	70328146	-	AAGATCCTCTAGGTTCTTCAGGG	1	2	48
(N20)NGG	X	70328147	-	CAAGATCCTCTAGGTTCTTCAGG	1	2	54
(N20)NGG	X	70328156	-	ATTCAGTAACAAGATCCTCTAGG	1	4	33
(N20)NGG	X	70328180	-	TTCTCACCGAAAAGTTCCCGTGG	1	1	9
(N20)NGG	X	70328471	+	GAATCCTTTCCTGTTTGCATTGG	1	4	54
(N20)NGG	X	70328480	+	CCTGTTTGCATTGGAAGCCGTGG	2	3	18
(N20)NGG	X	70328493	+	GAAGCCGTGGTTATCTCTGTTGG	1	1	16
(N20)NGG	X	70328501	+	GGTTATCTCTGTTGGCTCCATGG	1	1	36

FIG. 6

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	X	70328502	+	GTTATCTCTGTTGGCTCCATGGG	1	5	55
(N20)NGG	X	70328536	+	GCCTTCTCTGTGTGTATTTCTGG	1	2	83
(N20)NGG	X	70328540	+	TCTCTGTGTGTATTTCTGGCTGG	2	9	112
(N20)NGG	X	70328545	+	GTGTGTATTTCTGGCTGGAACGG	1	5	78
(N20)NGG	X	70328555	+	CTGGCTGGAACGGTGAGATTTGG	1	3	14
(N20)NGG	X	70328453	–	GCTTCCAATGCAAACAGGAAAGG	1	1	54
(N20)NGG	X	70328458	–	CCACGGCTTCCAATGCAAACAGG	2	3	18
(N20)NGG	X	70328475	–	GGAGCCAACAGAGATAACCACGG	1	3	43
(N20)NGG	X	70328496	–	AAGGCTGATAATCAATCCCATGG	1	2	29
(N20)NGG	X	70328515	–	GCCAGAAATACACACAGAGAAGG	1	16	277
(N20)NGG	X	70329077	+	CCTCATCCTCTTTCTCCTCAAGG	2	27	343
(N20)NGG	X	70329089	+	TCTCCTCAAGGAACAATCAGTGG	1	1	33
(N20)NGG	X	70329122	+	TAAGTTCTCCTTGCCTAGTGTGG	1	2	29
(N20)NGG	X	70329126	+	TTCTCCTTGCCTAGTGTGGATGG	1	4	66
(N20)NGG	X	70329127	+	TCTCCTTGCCTAGTGTGGATGGG	1	4	32
(N20)NGG	X	70329154	+	AACGCTACACGTTTCGTGTTCGG	1	1	2
(N20)NGG	X	70329177	+	AGCCGCTTTAACCCACTCTGTGG	1	1	10
(N20)NGG	X	70329193	+	TCTGTGGAAGTGCTCAGCATTGG	2	5	51
(N20)NGG	X	70329202	+	GTGCTCAGCATTGGAGTGAATGG	1	2	36
(N20)NGG	X	70329220	+	AATGGAGCCACCCAATCCACTGG	1	2	23
(N20)NGG	X	70329221	+	ATGGAGCCACCCAATCCACTGGG	1	1	24
(N20)NGG	X	70329222	+	TGGAGCCACCCAATCCACTGGGG	1	1	46
(N20)NGG	X	70329223	+	GGAGCCACCCAATCCACTGGGGG	1	1	36
(N20)NGG	X	70329240	+	TGGGGGAGCAATACTTCAAAAGG	1	1	29
(N20)NGG	X	70329248	+	CAATACTTCAAAAGGTAAAATGG	2	7	167

FIG. 6

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	X	70329249	+	AATACTTCAAAAGGTAAAATGGG	2	11	213
(N20)NGG	X	70329054	-	CTTGAGGAGAAAGAGGATGAGGG	2	10	183
(N20)NGG	X	70329055	-	CCTTGAGGAGAAAGAGGATGAGG	1	16	187
(N20)NGG	X	70329061	-	ATTGTTCCTTGAGGAGAAAGAGG	1	5	77
(N20)NGG	X	70329070	-	AATCCACTGATTGTTCCTTGAGG	1	3	31
(N20)NGG	X	70329108	-	CTGCCCATCCACACTAGGCAAGG	1	6	51
(N20)NGG	X	70329113	-	CGTTTCTGCCCATCCACACTAGG	1	1	18
(N20)NGG	X	70329157	-	TTCCACAGAGTGGGTTAAAGCGG	1	1	39
(N20)NGG	X	70329166	-	GCTGAGCACTTCCACAGAGTGGG	1	3	36
(N20)NGG	X	70329167	-	TGCTGAGCACTTCCACAGAGTGG	2	8	90
(N20)NGG	X	70329205	-	TGCTCCCCCAGTGGATTGGGTGG	1	4	50
(N20)NGG	X	70329208	-	TATTGCTCCCCCAGTGGATTGGG	1	3	20
(N20)NGG	X	70329209	-	GTATTGCTCCCCCAGTGGATTGG	1	2	18
(N20)NGG	X	70329214	-	TTGAAGTATTGCTCCCCCAGTGG	1	1	18
(N20)NGG	X	70330015	+	ACATATCTCCAGTGATCCCCTGG	1	3	31
(N20)NGG	X	70330016	+	CATATCTCCAGTGATCCCCTGGG	1	1	31
(N20)NGG	X	70330072	+	AATCCCAGCTAGAACTGAACTGG	1	4	32
(N20)NGG	X	70330100	+	CAGATTCTTGAACCACTGTTTGG	1	4	44
(N20)NGG	X	70330109	+	GAACCACTGTTTGGAGCACTTGG	1	3	36
(N20)NGG	X	70330120	+	TGGAGCACTTGGTGCAGTACCGG	1	3	23
(N20)NGG	X	70330129	+	TGGTGCAGTACCGGACTGACTGG	1	2	8
(N20)NGG	X	70330130	+	GGTGCAGTACCGGACTGACTGGG	1	1	1
(N20)NGG	X	70330141	+	GGACTGACTGGGACCACAGCTGG	1	4	50
(N20)NGG	X	70330157	+	CAGCTGGACTGTGAGTGACTAGG	1	2	57
(N20)NGG	X	70330158	+	AGCTGGACTGTGAGTGACTAGGG	1	2	35

FIG. 6

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	X	70329981	-	TGGAGATATGTGTGCATATGTGG	1	11	182
(N20)NGG	X	70330001	-	TCTGGAGCCCAGGGGATCACTGG	1	2	61
(N20)NGG	X	70330009	-	TTAGGTTCTCTGGAGCCCAGGGG	1	8	215
(N20)NGG	X	70330010	-	GTTAGGTTCTCTGGAGCCCAGGG	1	4	40
(N20)NGG	X	70330011	-	TGTTAGGTTCTCTGGAGCCCAGG	1	4	112
(N20)NGG	X	70330019	-	TTGTGAAGTGTTAGGTTCTCTGG	1	1	31
(N20)NGG	X	70330027	-	CACTCAGTTTGTGAAGTGTTAGG	1	3	36
(N20)NGG	X	70330053	-	GTTCCAGTTCAGTTCTAGCTGGG	1	2	29
(N20)NGG	X	70330054	-	TGTTCCAGTTCAGTTCTAGCTGG	1	2	21
(N20)NGG	X	70330090	-	GCACCAAGTGCTCCAAACAGTGG	1	2	25
(N20)NGG	X	70330117	-	AGCTGTGGTCCCAGTCAGTCCGG	1	16	472
(N20)NGG	X	70330132	-	AGTCACTCACAGTCCAGCTGTGG	1	5	52
(N20)NGG	X	70330353	+	CCTTCCAACCTTTCTCCTCTAGG	1	8	135
(N20)NGG	X	70330366	+	CTCCTCTAGGTACAAGAACTCGG	1	1	26
(N20)NGG	X	70330424	+	TTCTCTGAAGAAATCACTTCTGG	2	8	90
(N20)NGG	X	70330444	+	TGGCTGTCAGTTGCAAAAAAAGG	1	2	57
(N20)NGG	X	70330483	+	AACATTTGTTGTTCAGCTCCAGG	1	4	43
(N20)NGG	X	70330491	+	TTGTTCAGCTCCAGGACCCACGG	1	4	38
(N20)NGG	X	70330492	+	TGTTCAGCTCCAGGACCCACGGG	1	2	39
(N20)NGG	X	70330500	+	TCCAGGACCCACGGGAACCCAGG	1	6	53
(N20)NGG	X	70330507	+	CCCACGGGAACCCAGGAGACAGG	1	1	42
(N20)NGG	X	70330537	+	GATGCTAAAACTGCAGAATCTGG	2	7	55
(N20)NGG	X	70330538	+	ATGCTAAAACTGCAGAATCTGGG	3	20	217
(N20)NGG	X	70330546	+	ACTGCAGAATCTGGGTAATTTGG	1	2	48
(N20)NGG	X	70330555	+	TCTGGGTAATTTGGAAAGAAAGG	9	482	8109

FIG. 6

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	X	70330556	+	CTGGGTAATTTGGAAAGAAAGGG	126	2902	13176
(N20)NGG	X	70330331	–	CCTAGAGGAGAAAGGTTGGAAGG	1	5	75
(N20)NGG	X	70330335	–	TGTACCTAGAGGAGAAAGGTTGG	1	4	52
(N20)NGG	X	70330339	–	TTCTTGTACCTAGAGGAGAAAGG	1	2	43
(N20)NGG	X	70330346	–	ATCCGAGTTCTTGTACCTAGAGG	1	1	7
(N20)NGG	X	70330380	–	ATAGATAGTGGCTGCACTTCTGG	1	2	21
(N20)NGG	X	70330392	–	TTTCTTCAGAGAATAGATAGTGG	1	6	86
(N20)NGG	X	70330449	–	CAACAAATGTTTGGTAGAGGTGG	1	4	64
(N20)NGG	X	70330452	–	GAACAACAAATGTTTGGTAGAGG	1	5	45
(N20)NGG	X	70330458	–	GGAGCTGAACAACAAATGTTTGG	1	1	48
(N20)NGG	X	70330479	–	TCCTGGGTTCCCGTGGGTCCTGG	1	2	68
(N20)NGG	X	70330485	–	CCTGTCTCCTGGGTTCCCGTGGG	1	2	111
(N20)NGG	X	70330486	–	GCCTGTCTCCTGGGTTCCCGTGG	1	6	77
(N20)NGG	X	70330495	–	ATCTGTGTGGCCTGTCTCCTGGG	1	7	72
(N20)NGG	X	70330496	–	CATCTGTGTGGCCTGTCTCCTGG	1	5	62
(N20)NGG	X	70330508	–	CTGCAGTTTTAGCATCTGTGTGG	1	10	89
(N20)NGG	X	70330808	+	TTCCACTCTGCCCCTCCCAGAGG	3	7	115
(N20)NGG	X	70330852	+	TCGAGTACATGAATTGCACTTGG	1	1	9
(N20)NGG	X	70330900	+	CCAACCTCACTCTGCATTATTGG	1	6	42
(N20)NGG	X	70330910	+	TCTGCATTATTGGTATGAGAAGG	1	4	36
(N20)NGG	X	70330911	+	CTGCATTATTGGTATGAGAAGGG	1	2	42
(N20)NGG	X	70330917	+	TATTGGTATGAGAAGGGACGAGG	1	2	23
(N20)NGG	X	70330918	+	ATTGGTATGAGAAGGGACGAGGG	1	1	23
(N20)NGG	X	70330919	+	TTGGTATGAGAAGGGACGAGGGG	1	3	25
(N20)NGG	X	70330920	+	TGGTATGAGAAGGGACGAGGGGG	2	6	57

FIG. 6

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	X	70330923	+	TATGAGAAGGGACGAGGGGGAGG	1	6	62
(N20)NGG	X	70330924	+	ATGAGAAGGGACGAGGGGGAGGG	1	5	168
(N20)NGG	X	70330723	–	CTAGATTGGGAGAAAATGAAGG	1	8	128
(N20)NGG	X	70330735	–	TCAGGAAGAAATCTAGATTGGGG	1	8	83
(N20)NGG	X	70330736	–	GTCAGGAAGAAATCTAGATTGGG	1	3	68
(N20)NGG	X	70330737	–	GGTCAGGAAGAAATCTAGATTGG	1	3	50
(N20)NGG	X	70330753	–	AGTCAGTGGGCATAGTGGTCAGG	1	2	42
(N20)NGG	X	70330758	–	GAGGGAGTCAGTGGGCATAGTGG	1	4	82
(N20)NGG	X	70330766	–	GAAACACTGAGGGAGTCAGTGGG	1	2	68
(N20)NGG	X	70330767	–	GGAAACACTGAGGGAGTCAGTGG	1	6	81
(N20)NGG	X	70330776	–	GGGCAGAGTGGAAACACTGAGGG	2	6	93
(N20)NGG	X	70330777	–	GGGGCAGAGTGGAAACACTGAGG	2	8	95
(N20)NGG	X	70330788	–	AACCTCTGGGAGGGGCAGAGTGG	1	6	132
(N20)NGG	X	70330796	–	AAACACTGAACCTCTGGGAGGGG	1	3	46
(N20)NGG	X	70330797	–	AAAACACTGAACCTCTGGGAGGG	1	4	63
(N20)NGG	X	70330798	–	CAAAACACTGAACCTCTGGGAGG	1	8	69
(N20)NGG	X	70330801	–	ACACAAAACACTGAACCTCTGGG	1	11	102
(N20)NGG	X	70330802	–	AACACAAAACACTGAACCTCTGG	1	4	92
(N20)NGG	X	70330868	–	AGAGTGAGGTTGGTAGGCTGGGG	1	6	61
(N20)NGG	X	70330869	–	CAGAGTGAGGTTGGTAGGCTGGG	1	2	33
(N20)NGG	X	70330870	–	GCAGAGTGAGGTTGGTAGGCTGG	1	5	37
(N20)NGG	X	70330874	–	TAATGCAGAGTGAGGTTGGTAGG	1	1	32
(N20)NGG	X	70330878	–	CCAATAATGCAGAGTGAGGTTGG	1	5	31
(N20)NGG	X	70330882	–	CATACCAATAATGCAGAGTGAGG	1	3	28
(N20)NGG	X	70331331	+	ATTCCTGCAGCTGCCCCTGCTGG	1	8	110

FIG. 6

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	X	70331332	+	TTCCTGCAGCTGCCCCCTGCTGGG	2	21	144
(N20)NGG	X	70331337	+	GCAGCTGCCCCTGCTGGGAGTGG	1	15	206
(N20)NGG	X	70331338	+	CAGCTGCCCCTGCTGGGAGTGGG	2	13	196
(N20)NGG	X	70331339	+	AGCTGCCCCTGCTGGGAGTGGGG	1	8	162
(N20)NGG	X	70331368	+	ACGACAATTCTGACGCCCAATGG	1	1	3
(N20)NGG	X	70331369	+	CGACAATTCTGACGCCCAATGGG	1	1	5
(N20)NGG	X	70331389	+	GGGAATGAAGACACCACAGCTGG	1	5	59
(N20)NGG	X	70331392	+	AATGAAGACACCACAGCTGGTGG	3	9	74
(N20)NGG	X	70331393	+	ATGAAGACACCACAGCTGGTGGG	1	7	54
(N20)NGG	X	70331401	+	ACCACAGCTGGTGGGAAATCTGG	1	2	34
(N20)NGG	X	70331402	+	CCACAGCTGGTGGGAAATCTGGG	1	6	105
(N20)NGG	X	70331407	+	GCTGGTGGGAAATCTGGGACTGG	2	8	64
(N20)NGG	X	70331410	+	GGTGGGAAATCTGGGACTGGAGG	1	4	96
(N20)NGG	X	70331411	+	GTGGGAAATCTGGGACTGGAGGG	2	7	66
(N20)NGG	X	70331412	+	TGGGAAATCTGGGACTGGAGGGG	1	8	95
(N20)NGG	X	70331413	+	GGGAAATCTGGGACTGGAGGGGG	1	4	101
(N20)NGG	X	70331250	-	GCGCTTGCTCTTCATTCCCTGGG	1	2	21
(N20)NGG	X	70331251	-	GGCGCTTGCTCTTCATTCCCTGG	1	1	23
(N20)NGG	X	70331272	-	TGGTAATGATGGCTTCAACATGG	2	4	44
(N20)NGG	X	70331283	-	AGGGATGTGAATGGTAATGATGG	1	5	65
(N20)NGG	X	70331292	-	AGGAATAAGAGGGATGTGAATGG	1	11	130
(N20)NGG	X	70331302	-	GGGCAGCTGCAGGAATAAGAGGG	1	4	71
(N20)NGG	X	70331303	-	GGGGCAGCTGCAGGAATAAGAGG	1	4	82
(N20)NGG	X	70331312	-	CTCCCAGCAGGGGCAGCTGCAGG	3	44	380
(N20)NGG	X	70331322	-	TTCAGCCCCCACTCCCAGCAGGGG	1	12	114

FIG. 6

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	X	70331323	-	GTTCAGCCCCACTCCCAGCAGGG	2	8	74
(N20)NGG	X	70331324	-	TGTTCAGCCCCACTCCCAGCAGG	1	4	89
(N20)NGG	X	70331361	-	GTGGTGTCTTCATTCCCATTGGG	1	8	113
(N20)NGG	X	70331362	-	TGTGGTGTCTTCATTCCCATTGG	4	45	242
(N20)NGG	X	70331380	-	CCCAGATTTCCCACCAGCTGTGG	1	7	101

FIG. 6

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	5	35857092	+	TCTCTCAGAATGACAATTCTAGG	1	5	65
(N20)NGG	5	35857104	+	ACAATTCTAGGTACAACTTTTGG	1	1	53
(N20)NGG	5	35857109	+	TCTAGGTACAACTTTTGGCATGG	1	2	25
(N20)NGG	5	35857137	+	TCTTTACTTCAAGTCGTTTCTGG	1	3	24
(N20)NGG	5	35857146	+	CAAGTCGTTTCTGGAGAAAGTGG	1	3	41
(N20)NGG	5	35857161	+	GAAAGTGGCTATGCTCAAAATGG	1	5	49
(N20)NGG	5	35860953	+	CTGCATGTTTGTTCCTCCCCAGG	1	7	138
(N20)NGG	5	35860961	+	TTGTTCCTCCCCAGGAGACTTGG	1	4	43
(N20)NGG	5	35860976	+	AGACTTGGAAGATGCAGAACTGG	1	3	89
(N20)NGG	5	35861009	+	ATTCTCATGCTATAGCCAGTTGG	1	1	24
(N20)NGG	5	35861019	+	TATAGCCAGTTGGAAGTGAATGG	1	4	44
(N20)NGG	5	35861051	+	CTCACTGACCTGTGCTTTTGAGG	1	3	45
(N20)NGG	5	35861078	+	AGATGTCAACATCACCAATCTGG	1	2	27
(N20)NGG	5	35861092	+	CCAATCTGGAATTTGAAATATGG	1	6	84
(N20)NGG	5	35861097	+	CTGGAATTTGAAATATGGTGAGG	1	3	67
(N20)NGG	5	35861098	+	TGGAATTTGAAATATGGTGAGGG	1	4	109
(N20)NGG	5	35861102	+	ATTTGAAATATGGTGAGGGATGG	1	6	107
(N20)NGG	5	35861105	+	TGAAATATGGTGAGGGATGGTGG	1	2	79
(N20)NGG	5	35861114	+	GTGAGGGATGGTGGTTTTTAATGG	1	3	47
(N20)NGG	5	35860944	-	ATCTTCCAAGTCTCCTGGGGAGG	2	7	42
(N20)NGG	5	35860947	-	TGCATCTTCCAAGTCTCCTGGGG	1	6	71
(N20)NGG	5	35860948	-	CTGCATCTTCCAAGTCTCCTGGG	1	5	70
(N20)NGG	5	35860949	-	TCTGCATCTTCCAAGTCTCCTGG	1	8	86
(N20)NGG	5	35861002	-	GCGATCCATTCACTTCCAACTGG	1	4	82
(N20)NGG	5	35861037	-	ATCTGGGTCCTCAAAAGCACAGG	1	2	34

FIG. 7

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	5	35861053	-	GATTGGTGATGTTGACATCTGGG	1	3	36
(N20)NGG	5	35861054	-	AGATTGGTGATGTTGACATCTGG	1	4	28
(N20)NGG	5	35861070	-	CCATATTTCAAATTCCAGATTGG	1	5	91
(N20)NGG	5	35867409	+	TCCCCTTTTTATTCCTACAGTGG	1	3	68
(N20)NGG	5	35867410	+	CCCCTTTTTATTCCTACAGTGGG	1	5	52
(N20)NGG	5	35867411	+	CCCTTTTTATTCCTACAGTGGGG	1	9	56
(N20)NGG	5	35867420	+	TTCCTACAGTGGGGCCCTCGTGG	1	1	11
(N20)NGG	5	35867423	+	CTACAGTGGGGCCCTCGTGGAGG	1	3	22
(N20)NGG	5	35867443	+	AGGTAAAGTGCCTGAATTTCAGG	1	3	47
(N20)NGG	5	35867493	+	ACAAAGAAATTCTTACTGATTGG	1	4	81
(N20)NGG	5	35867516	+	AAAGAGCAATATATGTGTGAAGG	2	9	100
(N20)NGG	5	35867520	+	AGCAATATATGTGTGAAGGTTGG	2	2	37
(N20)NGG	5	35867565	+	AAAATAGACCTAACCACTATAGG	1	3	38
(N20)NGG	5	35867388	-	CCCACTGTAGGAATAAAAAGGGG	1	2	57
(N20)NGG	5	35867389	-	CCCCACTGTAGGAATAAAAAGGG	1	5	66
(N20)NGG	5	35867390	-	GCCCCACTGTAGGAATAAAAAGG	1	5	43
(N20)NGG	5	35867400	-	CTCCACGAGGGCCCCACTGTAGG	1	1	30
(N20)NGG	5	35867412	-	CAGGCACTTTACCTCCACGAGGG	1	1	17
(N20)NGG	5	35867413	-	TCAGGCACTTTACCTCCACGAGG	1	2	20
(N20)NGG	5	35867431	-	CTTGTAGTTTCCTGAAATTCAGG	1	1	70
(N20)NGG	5	35867535	-	GGTTAGGTCTATTTTTTTTGCAGG	1	1	35
(N20)NGG	5	35867551	-	ACTTCTTACCTATAGTGGTTAGG	1	1	33
(N20)NGG	5	35867556	-	ATACAACTTCTTACCTATAGTGG	2	3	57
(N20)NGG	5	35871168	+	TTCTTTTCCAGTTAAACCTGAGG	1	6	90
(N20)NGG	5	35871197	+	TTGACCTGAGTGTCGTCTATCGG	1	3	13

FIG. 7

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	5	35871198	+	TGACCTGAGTGTCGTCTATCGGG	1	4	13
(N20)NGG	5	35871202	+	CTGAGTGTCGTCTATCGGGAAGG	1	1	3
(N20)NGG	5	35871219	+	GGAAGGAGCCAATGACTTTGTGG	1	3	70
(N20)NGG	5	35871291	+	GCACGATGTAGCTTACCGCCAGG	1	1	1
(N20)NGG	5	35871297	+	TGTAGCTTACCGCCAGGAAAAGG	1	2	11
(N20)NGG	5	35871311	+	AGGAAAAGGATGAAAACAAATGG	2	48	722
(N20)NGG	5	35871315	+	AAAGGATGAAAACAAATGGACGG	3	70	1031
(N20)NGG	5	35871153	-	AAAGGAGCCTCAGGTTTAACTGG	1	3	24
(N20)NGG	5	35871162	-	CTCAGGTCAAAAGGAGCCTCAGG	1	2	45
(N20)NGG	5	35871171	-	TAGACGACACTCAGGTCAAAAGG	1	3	13
(N20)NGG	5	35871179	-	CTTCCCGATAGACGACACTCAGG	1	1	2
(N20)NGG	5	35871205	-	AAATGTCACCACAAAGTCATTGG	1	3	80
(N20)NGG	5	35871284	-	TGTTTTCATCCTTTCCTGGCGG	1	10	151
(N20)NGG	5	35871287	-	ATTTGTTTTCATCCTTTTCCTGG	2	10	217
(N20)NGG	5	35873635	+	CCTGCAGAGAAAGCTCCAACCGG	1	5	50
(N20)NGG	5	35873687	+	ATCCCTGATCACTATTTTAAAGG	1	3	48
(N20)NGG	5	35873694	+	ATCACTATTTTAAAGGCTTCTGG	2	3	68
(N20)NGG	5	35873703	+	TTAAAGGCTTCTGGAGTGAATGG	1	6	109
(N20)NGG	5	35873750	+	CCAGAGATCAATAATAGCTCAGG	1	3	26
(N20)NGG	5	35873755	+	GATCAATAATAGCTCAGGTAAGG	1	2	20
(N20)NGG	5	35873760	+	ATAATAGCTCAGGTAAGGAATGG	1	9	58
(N20)NGG	5	35873763	+	ATAGCTCAGGTAAGGAATGGTGG	1	2	47
(N20)NGG	5	35873594	-	CAGGAGTGTCAGCTTTGTGCTGG	1	8	52
(N20)NGG	5	35873613	-	CCGGTTGGAGCTTTCTCTGCAGG	1	1	17
(N20)NGG	5	35873628	-	TCTCATACATTGCTGCCGGTTGG	1	5	57

FIG. 7

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	5	35873632	-	TTAATCTCATACATTGCTGCCGG	1	9	114
(N20)NGG	5	35873663	-	TTTAAAATAGTGATCAGGGATGG	2	9	131
(N20)NGG	5	35873667	-	AGCCTTTAAAATAGTGATCAGGG	1	11	135
(N20)NGG	5	35873668	-	AAGCCTTTAAAATAGTGATCAGG	1	6	66
(N20)NGG	5	35873707	-	GGAGTTCTGAAGTAATAACTTGG	1	4	31
(N20)NGG	5	35873728	-	CCTGAGCTATTATTGATCTCTGG	1	1	25
(N20)NGG	5	35874550	+	ACAATCTATTCTTGCTTTCCAGG	1	10	59
(N20)NGG	5	35874551	+	CAATCTATTCTTGCTTTCCAGGG	1	8	70
(N20)NGG	5	35874552	+	AATCTATTCTTGCTTTCCAGGGG	2	7	77
(N20)NGG	5	35874558	+	TTCTTGCTTTCCAGGGGAGATGG	1	11	89
(N20)NGG	5	35874612	+	TTTTTCTCTGTCGCTCTGTTGG	1	9	192
(N20)NGG	5	35874621	+	TGTCGCTCTGTTGGTCATCTTGG	1	1	26
(N20)NGG	5	35874635	+	TCATCTTGGCCTGTGTGTTATGG	1	4	46
(N20)NGG	5	35874644	+	CCTGTGTGTTATGGAAAAAAAGG	1	7	98
(N20)NGG	5	35874526	-	TGGAAAGCAAGAATAGATTGTGG	2	5	129
(N20)NGG	5	35874546	-	AAGATAGGATCCATCTCCCCTGG	1	3	27
(N20)NGG	5	35874561	-	ATGCTGATGGTTAGTAAGATAGG	1	2	30
(N20)NGG	5	35874574	-	GAAAAAACTCAAAATGCTGATGG	1	14	200
(N20)NGG	5	35874622	-	CCTTTTTTTCCATAACACACAGG	1	1	75
(N20)NGG	5	35875613	+	TATCAATGTTCTCTGATTTCAGG	1	12	84
(N20)NGG	5	35875631	+	TCAGGATTAAGCCTATCGTATGG	1	1	5
(N20)NGG	5	35875662	+	CCCCGATCATAAGAAGACTCTGG	1	1	6
(N20)NGG	5	35875702	+	CCAAGAAAAGTGAGTGTTTTTGG	1	17	122
(N20)NGG	5	35875620	-	GGGAGACTGGGCCATACGATAGG	1	1	6
(N20)NGG	5	35875632	-	TTCTTATGATCGGGGAGACTGGG	1	2	26

FIG. 7

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	5	35875633	-	CTTCTTATGATCGGGGAGACTGG	1	1	11
(N20)NGG	5	35875640	-	CCAGAGTCTTCTTATGATCGGGG	1	1	12
(N20)NGG	5	35875641	-	TCCAGAGTCTTCTTATGATCGGG	1	2	27
(N20)NGG	5	35875642	-	TTCCAGAGTCTTCTTATGATCGG	1	5	82
(N20)NGG	5	35875680	-	CCAAAAACACTCACTTTCTTGG	1	5	106
(N20)NGG	5	35876120	+	TTTCAATCCTGAAAGTTTCCTGG	1	7	96
(N20)NGG	5	35876137	+	TCCTGGACTGCCAGATTCATAGG	1	1	37
(N20)NGG	5	35876138	+	CCTGGACTGCCAGATTCATAGGG	1	2	39
(N20)NGG	5	35876141	+	GGACTGCCAGATTCATAGGGTGG	1	1	22
(N20)NGG	5	35876168	+	CATTCAAGCTAGAGATGAAGTGG	1	2	50
(N20)NGG	5	35876172	+	CAAGCTAGAGATGAAGTGGAAGG	2	4	66
(N20)NGG	5	35876224	+	TAGAAGAATCTGAGAAGCAGAGG	3	17	163
(N20)NGG	5	35876229	+	GAATCTGAGAAGCAGAGGCTTGG	1	12	241
(N20)NGG	5	35876232	+	TCTGAGAAGCAGAGGCTTGGAGG	2	9	113
(N20)NGG	5	35876233	+	CTGAGAAGCAGAGGCTTGGAGGG	1	17	193
(N20)NGG	5	35876234	+	TGAGAAGCAGAGGCTTGGAGGGG	5	27	261
(N20)NGG	5	35876264	+	GAGCCCCAACTGCCCATCTGAGG	1	6	53
(N20)NGG	5	35876292	+	GTCATCACTCCAGAAAGCTTTGG	1	2	35
(N20)NGG	5	35876318	+	AGATTCATCCCCTCACATGCCTGG	1	1	43
(N20)NGG	5	35876322	+	TCATCCCTCACATGCCTGGCTGG	1	4	69
(N20)NGG	5	35876323	+	CATCCCTCACATGCCTGGCTGGG	1	5	91
(N20)NGG	5	35876365	+	CCCCTATTCTCTCCTCTTCCAGG	3	15	178
(N20)NGG	5	35876380	+	CTTCCAGGTCCCTAGACTGCAGG	1	3	69
(N20)NGG	5	35876381	+	TTCCAGGTCCCTAGACTGCAGGG	1	8	143
(N20)NGG	5	35876388	+	TCCCTAGACTGCAGGGAGAGTGG	1	3	75

FIG. 7

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	5	35876397	+	TGCAGGGAGAGTGGCAAGAATGG	1	13	157
(N20)NGG	5	35876398	+	GCAGGGAGAGTGGCAAGAATGGG	1	7	94
(N20)NGG	5	35876414	+	GAATGGGCCTCATGTGTACCAGG	1	2	18
(N20)NGG	5	35876433	+	CAGGACCTCCTGCTTAGCCTTGG	2	37	129
(N20)NGG	5	35876434	+	AGGACCTCCTGCTTAGCCTTGGG	2	4	43
(N20)NGG	5	35876478	+	CCTCCATTTTCTCTCCAATCTGG	1	7	95
(N20)NGG	5	35876507	+	GACATTGAACCCAGTTGCTCAGG	1	6	37
(N20)NGG	5	35876508	+	ACATTGAACCCAGTTGCTCAGGG	1	4	49
(N20)NGG	5	35876531	+	TCAGCCCATTCTTACTTCCCTGG	1	5	54
(N20)NGG	5	35876532	+	CAGCCCATTCTTACTTCCCTGGG	1	2	59
(N20)NGG	5	35876061	-	CTGCACAGAAAAAGGAGAAAGGG	2	26	307
(N20)NGG	5	35876062	-	TCTGCACAGAAAAAGGAGAAAGG	2	15	207
(N20)NGG	5	35876069	-	TTTAAATTCTGCACAGAAAAAGG	2	22	385
(N20)NGG	5	35876105	-	TGGCAGTCCAGGAAACTTTCAGG	1	3	25
(N20)NGG	5	35876116	-	CCCTATGAATCTGGCAGTCCAGG	1	2	39
(N20)NGG	5	35876125	-	TGTCATCCACCCTATGAATCTGG	1	2	8
(N20)NGG	5	35876192	-	TCAGATTCTTCTAGTTGCTGAGG	1	4	66
(N20)NGG	5	35876245	-	CATCCTCAGATGGGCAGTTGGGG	1	2	52
(N20)NGG	5	35876246	-	ACATCCTCAGATGGGCAGTTGGG	1	2	33
(N20)NGG	5	35876247	-	TACATCCTCAGATGGGCAGTTGG	1	2	36
(N20)NGG	5	35876254	-	TGATGACTACATCCTCAGATGGG	1	3	25
(N20)NGG	5	35876255	-	GTGATGACTACATCCTCAGATGG	2	3	23
(N20)NGG	5	35876279	-	GAATCTCTTCCAAAGCTTTCTGG	2	9	69
(N20)NGG	5	35876304	-	ATTCCCAGCCAGGCATGTGAGGG	1	6	54
(N20)NGG	5	35876305	-	CATTCCCAGCCAGGCATGTGAGG	1	9	61

FIG. 7

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	5	35876314	-	ATGCACTGACATTCCCAGCCAGG	1	4	42
(N20)NGG	5	35876343	-	CCTGGAAGAGGAGAGAATAGGGG	2	10	144
(N20)NGG	5	35876344	-	ACCTGGAAGAGGAGAGAATAGGG	1	7	142
(N20)NGG	5	35876345	-	GACCTGGAAGAGGAGAGAATAGG	1	7	150
(N20)NGG	5	35876355	-	GCAGTCTAGGGACCTGGAAGAGG	1	5	109
(N20)NGG	5	35876361	-	CTCCCTGCAGTCTAGGGACCTGG	1	2	69
(N20)NGG	5	35876367	-	GCCACTCTCCCTGCAGTCTAGGG	1	2	38
(N20)NGG	5	35876368	-	TGCCACTCTCCCTGCAGTCTAGG	1	4	71
(N20)NGG	5	35876399	-	AGGAGGTCCTGGTACACATGAGG	1	2	43
(N20)NGG	5	35876410	-	CAAGGCTAAGCAGGAGGTCCTGG	1	2	28
(N20)NGG	5	35876416	-	TAGTCCCAAGGCTAAGCAGGAGG	1	3	35
(N20)NGG	5	35876419	-	TTGTAGTCCCAAGGCTAAGCAGG	1	1	21
(N20)NGG	5	35876428	-	GCGTGCTGTTTGTAGTCCCAAGG	1	1	9
(N20)NGG	5	35876453	-	GATTGGAGAGAAAATGGAGGGGG	1	19	192
(N20)NGG	5	35876454	-	AGATTGGAGAGAAAATGGAGGGG	2	24	394
(N20)NGG	5	35876455	-	CAGATTGGAGAGAAAATGGAGGG	4	13	191
(N20)NGG	5	35876456	-	CCAGATTGGAGAGAAAATGGAGG	1	6	115
(N20)NGG	5	35876459	-	ATTCCAGATTGGAGAGAAAATGG	2	11	145
(N20)NGG	5	35876470	-	TCAATGTCAGGATTCCAGATTGG	1	4	39
(N20)NGG	5	35876482	-	GAGCAACTGGGTTCAATGTCAGG	1	3	20
(N20)NGG	5	35876494	-	TGGGCTGACCCTGAGCAACTGGG	1	4	36
(N20)NGG	5	35876495	-	ATGGGCTGACCCTGAGCAACTGG	1	3	39
(N20)NGG	5	35876513	-	GATCCCAGGGAAGTAAGAATGGG	1	7	81
(N20)NGG	5	35876514	-	TGATCCCAGGGAAGTAAGAATGG	1	18	211
(N20)NGG	5	35876526	-	TTCTTCTTGATTTGATCCCAGGG	1	2	82

FIG. 7

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	5	35876527	-	CTTCTTCTTGATTTGATCCCAGG	1	7	173
(N20)NGG	5	35876559	-	GTTTTGGTAGAAGCTGGACATGG	1	5	131
(N20)NGG	5	35876565	-	TCACTGGTTTTGGTAGAAGCTGG	1	5	53
(N20)NGG	5	35876575	-	TTCTTACACTTCACTGGTTTTGG	1	7	62
(N20)NGG	5	35876581	-	CTGGGTTTCTTACACTTCACTGG	1	1	37

FIG. 7

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17937551	+	TTATCTGTCCCCCGCCCCTCAGG	1	2	35
(N20)NGG	19	17937577	+	ACGAGCTCATGAAGCTGTGCTGG	1	3	13
(N20)NGG	19	17937578	+	CGAGCTCATGAAGCTGTGCTGGG	1	3	18
(N20)NGG	19	17937593	+	GTGCTGGGCCCCTAGCCCACAGG	1	5	61
(N20)NGG	19	17937598	+	GGGCCCCTAGCCCACAGGACCGG	1	4	83
(N20)NGG	19	17937617	+	CCGGCCATCATTCAGCGCCCTGG	1	1	7
(N20)NGG	19	17937618	+	CGGCCATCATTCAGCGCCCTGGG	1	2	3
(N20)NGG	19	17937629	+	CAGCGCCCTGGGCCCCCAGCTGG	1	9	113
(N20)NGG	19	17937640	+	GCCCCCAGCTGGACATGCTGTGG	1	3	74
(N20)NGG	19	17937645	+	CAGCTGGACATGCTGTGGAGCGG	1	8	69
(N20)NGG	19	17937652	+	ACATGCTGTGGAGCGGAAGCCGG	1	1	25
(N20)NGG	19	17937653	+	CATGCTGTGGAGCGGAAGCCGGG	1	5	28
(N20)NGG	19	17937654	+	ATGCTGTGGAGCGGAAGCCGGGG	1	2	18
(N20)NGG	19	17937655	+	TGCTGTGGAGCGGAAGCCGGGGG	1	1	21
(N20)NGG	19	17937689	+	TGCCTTCACTGCTCACCCAGAGG	1	2	60
(N20)NGG	19	17937690	+	GCCTTCACTGCTCACCCAGAGGG	1	7	51
(N20)NGG	19	17937739	+	AGCTCCTGCCCGCAGACCTCTGG	1	6	64
(N20)NGG	19	17937526	-	GAGGGGCGGGGGACAGATAATGG	1	8	99
(N20)NGG	19	17937537	-	CTCGTGAACCTGAGGGGCGGGGG	1	63	1843
(N20)NGG	19	17937538	-	GCTCGTGAACCTGAGGGGCGGGG	1	5	100
(N20)NGG	19	17937539	-	AGCTCGTGAACCTGAGGGGCGGG	1	3	36
(N20)NGG	19	17937540	-	GAGCTCGTGAACCTGAGGGGCGG	1	1	22
(N20)NGG	19	17937543	-	CATGAGCTCGTGAACCTGAGGGG	1	1	9
(N20)NGG	19	17937544	-	TCATGAGCTCGTGAACCTGAGGG	1	1	13
(N20)NGG	19	17937545	-	TTCATGAGCTCGTGAACCTGAGG	1	3	19

FIG. 8

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17937579	-	TGGCCGGTCCTGTGGGCTAGGGG	1	5	18
(N20)NGG	19	17937580	-	ATGGCCGGTCCTGTGGGCTAGGG	1	1	14
(N20)NGG	19	17937581	-	GATGGCCGGTCCTGTGGGCTAGG	1	1	22
(N20)NGG	19	17937586	-	TGAATGATGGCCGGTCCTGTGGG	1	7	93
(N20)NGG	19	17937587	-	CTGAATGATGGCCGGTCCTGTGG	1	2	16
(N20)NGG	19	17937595	-	CCAGGGCGCTGAATGATGGCCGG	1	1	12
(N20)NGG	19	17937599	-	GGGCCCAGGGCGCTGAATGATGG	1	3	33
(N20)NGG	19	17937612	-	CATGTCCAGCTGGGGGCCCAGGG	1	7	59
(N20)NGG	19	17937613	-	GCATGTCCAGCTGGGGGCCCAGG	1	6	70
(N20)NGG	19	17937619	-	TCCACAGCATGTCCAGCTGGGGG	1	5	67
(N20)NGG	19	17937620	-	CTCCACAGCATGTCCAGCTGGGG	1	2	71
(N20)NGG	19	17937621	-	GCTCCACAGCATGTCCAGCTGGG	1	3	37
(N20)NGG	19	17937622	-	CGCTCCACAGCATGTCCAGCTGG	1	2	28
(N20)NGG	19	17937649	-	AGGCATGAGTCTCACACCCCCGG	1	5	38
(N20)NGG	19	17937669	-	GCCCTCTGGGTGAGCAGTGAAGG	1	4	62
(N20)NGG	19	17937682	-	GGGAGTGGTGTTTGCCCTCTGGG	1	2	42
(N20)NGG	19	17937683	-	AGGGAGTGGTGTTTGCCCTCTGG	1	4	49
(N20)NGG	19	17937697	-	GCTATGAAAAGGACAGGGAGTGG	1	6	89
(N20)NGG	19	17937702	-	CAGGAGCTATGAAAAGGACAGGG	2	6	79
(N20)NGG	19	17937703	-	GCAGGAGCTATGAAAAGGACAGG	1	4	47
(N20)NGG	19	17937708	-	TGCGGGCAGGAGCTATGAAAAGG	1	4	28
(N20)NGG	19	17937721	-	TAATCCAGAGGTCTGCGGGCAGG	1	1	21
(N20)NGG	19	17940916	+	ATGCGCTCCTCCTTGGCTCCAGG	1	6	33
(N20)NGG	19	17940927	+	CTTGGCTCCAGGAGTTCCTGCGG	1	9	84
(N20)NGG	19	17940934	+	CCAGGAGTTCCTGCGGATGATGG	1	3	27

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17940935	+	CAGGAGTTCCTGCGGATGATGGG	1	1	17
(N20)NGG	19	17940945	+	TGCGGATGATGGGATGTGAGCGG	1	2	38
(N20)NGG	19	17940946	+	GCGGATGATGGGATGTGAGCGGG	1	1	19
(N20)NGG	19	17940973	+	CCCCGCCCTCTGCCGCCTCTTGG	1	8	80
(N20)NGG	19	17940982	+	CTGCCGCCTCTTGGAACTGCTGG	1	3	29
(N20)NGG	19	17940985	+	CCGCCTCTTGGAACTGCTGGAGG	2	5	31
(N20)NGG	19	17940988	+	CCTCTTGGAACTGCTGGAGGAGG	1	6	63
(N20)NGG	19	17940989	+	CTCTTGGAACTGCTGGAGGAGGG	1	3	67
(N20)NGG	19	17940996	+	AACTGCTGGAGGAGGGCCAGAGG	2	8	91
(N20)NGG	19	17941003	+	GGAGGAGGGCCAGAGGCTGCCGG	2	24	274
(N20)NGG	19	17941027	+	GCCTCCTGCCTGCCCTGCTGAGG	5	32	242
(N20)NGG	19	17941040	+	CCTGCTGAGGTGAGCGCCGCAGG	1	1	26
(N20)NGG	19	17941041	+	CTGCTGAGGTGAGCGCCGCAGGG	1	2	17
(N20)NGG	19	17940901	-	AGGAACTCCTGGAGCCAAGGAGG	1	4	96
(N20)NGG	19	17940904	-	CGCAGGAACTCCTGGAGCCAAGG	1	5	67
(N20)NGG	19	17940912	-	CCATCATCCGCAGGAACTCCTGG	1	1	21
(N20)NGG	19	17940921	-	GCTCACATCCCATCATCCGCAGG	1	1	10
(N20)NGG	19	17940951	-	CCAAGAGGCGGCAGAGGGCGGGG	1	4	58
(N20)NGG	19	17940952	-	TCCAAGAGGCGGCAGAGGGCGGG	1	2	46
(N20)NGG	19	17940953	-	TTCCAAGAGGCGGCAGAGGGCGG	2	3	53
(N20)NGG	19	17940956	-	CAGTTCCAAGAGGCGGCAGAGGG	1	3	33
(N20)NGG	19	17940957	-	GCAGTTCCAAGAGGCGGCAGAGG	1	2	34
(N20)NGG	19	17940963	-	CCTCCAGCAGTTCCAAGAGGCGG	1	6	49
(N20)NGG	19	17940966	-	CCTCCTCCAGCAGTTCCAAGAGG	1	6	64
(N20)NGG	19	17940990	-	CAGGAGGCGCCGGCAGCCTCTGG	1	4	60

FIG. 8

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17941000	-	GCAGGGCAGGCAGGAGGCGCCGG	2	28	284
(N20)NGG	19	17941006	-	ACCTCAGCAGGGCAGGCAGGAGG	2	9	170
(N20)NGG	19	17941009	-	CTCACCTCAGCAGGGCAGGCAGG	1	7	82
(N20)NGG	19	17941013	-	GGCGCTCACCTCAGCAGGGCAGG	1	2	30
(N20)NGG	19	17941017	-	CTGCGGCGCTCACCTCAGCAGGG	1	3	15
(N20)NGG	19	17941018	-	CCTGCGGCGCTCACCTCAGCAGG	1	1	25
(N20)NGG	19	17941311	+	CAAGACCTTGTCCCCTCTCCAGG	2	4	63
(N20)NGG	19	17941333	+	GTATGCCCCCGAATCCCTCTCGG	1	1	11
(N20)NGG	19	17941365	+	TCTCTCGCCAGTCAGACGTCTGG	1	2	9
(N20)NGG	19	17941373	+	CAGTCAGACGTCTGGAGCTTCGG	1	5	39
(N20)NGG	19	17941374	+	AGTCAGACGTCTGGAGCTTCGGG	1	1	15
(N20)NGG	19	17941375	+	GTCAGACGTCTGGAGCTTCGGGG	1	1	7
(N20)NGG	19	17941426	+	CGACAAAAGCTGCAGCCCCTCGG	1	2	34
(N20)NGG	19	17941437	+	GCAGCCCCTCGGCCGTGAGTCGG	1	2	31
(N20)NGG	19	17941294	-	GCATACCTGGAGAGGGGACAAGG	1	3	70
(N20)NGG	19	17941300	-	TCGGGGGCATACCTGGAGAGGGG	1	2	25
(N20)NGG	19	17941301	-	TTCGGGGGCATACCTGGAGAGGG	1	1	24
(N20)NGG	19	17941302	-	ATTCGGGGGCATACCTGGAGAGG	1	1	11
(N20)NGG	19	17941307	-	GAGGGATTCGGGGGCATACCTGG	1	2	14
(N20)NGG	19	17941316	-	GTTGTCCGAGAGGGATTCGGGGG	1	1	3
(N20)NGG	19	17941317	-	TGTTGTCCGAGAGGGATTCGGGG	1	1	4
(N20)NGG	19	17941318	-	ATGTTGTCCGAGAGGGATTCGGG	1	1	7
(N20)NGG	19	17941319	-	GATGTTGTCCGAGAGGGATTCGG	1	1	13
(N20)NGG	19	17941325	-	AGAGAAGATGTTGTCCGAGAGGG	1	2	32
(N20)NGG	19	17941326	-	GAGAGAAGATGTTGTCCGAGAGG	1	4	26

FIG. 8

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17941350	-	CGAAGCTCCAGACGTCTGACTGG	1	1	4
(N20)NGG	19	17941380	-	AGTAGGTGAAGAGCTCGTACAGG	1	2	6
(N20)NGG	19	17941397	-	GCTGCAGCTTTTGTCGCAGTAGG	1	1	17
(N20)NGG	19	17941419	-	GAAGCCGACTCACGGCCGAGGGG	1	1	3
(N20)NGG	19	17941420	-	GGAAGCCGACTCACGGCCGAGGG	1	1	3
(N20)NGG	19	17941421	-	GGGAAGCCGACTCACGGCCGAGG	1	1	4
(N20)NGG	19	17941427	-	GGCTCTGGGAAGCCGACTCACGG	1	4	34
(N20)NGG	19	17942036	+	CGCTCACACCGCCCGCCCGCAGG	2	5	26
(N20)NGG	19	17942037	+	GCTCACACCGCCCGCCCGCAGGG	1	5	22
(N20)NGG	19	17942042	+	CACCGCCCGCCCGCAGGGCATGG	1	2	35
(N20)NGG	19	17942051	+	CCCGCAGGGCATGGAGTACCTGG	1	3	21
(N20)NGG	19	17942052	+	CCGCAGGGCATGGAGTACCTGGG	1	4	24
(N20)NGG	19	17942081	+	CCGCTGCGTGCACCGCGACCTGG	1	1	11
(N20)NGG	19	17942102	+	GGCCGCCCGAAACATCCTCGTGG	1	1	6
(N20)NGG	19	17942111	+	AAACATCCTCGTGGAGAGCGAGG	1	1	5
(N20)NGG	19	17942136	+	CACGTCAAGATCGCTGACTTCGG	2	6	15
(N20)NGG	19	17942177	+	GCTTGACAAAGACTACTACGTGG	1	1	9
(N20)NGG	19	17942190	+	TACTACGTGGTCCGCGAGCCAGG	1	1	3
(N20)NGG	19	17942209	+	CAGGCCAGAGCCCCATTTTCTGG	1	7	63
(N20)NGG	19	17942212	+	GCCAGAGCCCCATTTTCTGGTGG	1	4	52
(N20)NGG	19	17942213	+	CCAGAGCCCCATTTTCTGGTGGG	1	5	52
(N20)NGG	19	17942214	+	CAGAGCCCCATTTTCTGGTGGGG	1	3	56
(N20)NGG	19	17942228	+	CTGGTGGGGAACCCGCGCCTAGG	1	1	19
(N20)NGG	19	17942022	-	CTCCATGCCCTGCGGGCGGGCGG	1	2	37
(N20)NGG	19	17942025	-	GTACTCCATGCCCTGCGGGCGGG	1	1	17

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17942026	-	GGTACTCCATGCCCTGCGGGCGG	1	2	17
(N20)NGG	19	17942029	-	CCAGGTACTCCATGCCCTGCGGG	1	3	54
(N20)NGG	19	17942030	-	CCCAGGTACTCCATGCCCTGCGG	1	3	70
(N20)NGG	19	17942047	-	GCACGCAGCGGCGGGAGCCCAGG	1	3	42
(N20)NGG	19	17942055	-	GTCGCGGTGCACGCAGCGGCGGG	1	1	6
(N20)NGG	19	17942056	-	GGTCGCGGTGCACGCAGCGGCGG	1	1	8
(N20)NGG	19	17942059	-	CCAGGTCGCGGTGCACGCAGCGG	1	1	15
(N20)NGG	19	17942071	-	TGTTTCGGGCGGCCAGGTCGCGG	2	2	10
(N20)NGG	19	17942077	-	CGAGGATGTTTCGGGCGGCCAGG	1	6	13
(N20)NGG	19	17942082	-	CTCCACGAGGATGTTTCGGGCGG	1	2	14
(N20)NGG	19	17942085	-	GCTCTCCACGAGGATGTTTCGGG	1	1	17
(N20)NGG	19	17942086	-	CGCTCTCCACGAGGATGTTTCGG	1	1	7
(N20)NGG	19	17942095	-	CGTGTGCCTCGCTCTCCACGAGG	1	1	13
(N20)NGG	19	17942137	-	CAAGCGGCAGCAGCTTAGCTAGG	1	1	32
(N20)NGG	19	17942153	-	ACGTAGTAGTCTTTGTCAAGCGG	1	1	12
(N20)NGG	19	17942179	-	TGGGGCTCTGGCCTGGCTCGCGG	2	5	79
(N20)NGG	19	17942186	-	CAGAAAATGGGGCTCTGGCCTGG	1	7	80
(N20)NGG	19	17942191	-	CCCACCAGAAAATGGGGCTCTGG	1	5	46
(N20)NGG	19	17942197	-	GGGTTCCCCACCAGAAAATGGGG	1	2	32
(N20)NGG	19	17942198	-	CGGGTTCCCCACCAGAAAATGGG	1	3	19
(N20)NGG	19	17942199	-	GCGGGTTCCCCACCAGAAAATGG	1	1	17
(N20)NGG	19	17942482	+	TGACAGATCCTGCCTTCTCCAGG	1	4	66
(N20)NGG	19	17942498	+	CTCCAGGCCGCCAGAGCCTGCGG	1	12	92
(N20)NGG	19	17942502	+	AGGCCGCCAGAGCCTGCGGCTGG	2	3	29
(N20)NGG	19	17942508	+	CCAGAGCCTGCGGCTGGTCATGG	1	4	75

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17942524	+	GTCATGGAGTACCTGCCCAGCGG	1	4	41
(N20)NGG	19	17942549	+	GCTTGCGCGACTTCCTGCAGCGG	1	1	12
(N20)NGG	19	17942607	+	CTATTCCTCGCAGATCTGCAAGG	1	2	14
(N20)NGG	19	17942614	+	TCGCAGATCTGCAAGGTGCGAGG	1	3	14
(N20)NGG	19	17942615	+	CGCAGATCTGCAAGGTGCGAGGG	1	1	9
(N20)NGG	19	17942616	+	GCAGATCTGCAAGGTGCGAGGGG	1	3	25
(N20)NGG	19	17942617	+	CAGATCTGCAAGGTGCGAGGGGG	1	2	28
(N20)NGG	19	17942625	+	CAAGGTGCGAGGGGGCGCCCCGG	1	1	25
(N20)NGG	19	17942626	+	AAGGTGCGAGGGGGCGCCCCGGG	1	2	16
(N20)NGG	19	17942468	-	TCTGGCGGCCTGGAGAAGGCAGG	1	20	75
(N20)NGG	19	17942472	-	AGGCTCTGGCGGCCTGGAGAAGG	1	10	74
(N20)NGG	19	17942478	-	AGCCGCAGGCTCTGGCGGCCTGG	1	3	36
(N20)NGG	19	17942483	-	TGACCAGCCGCAGGCTCTGGCGG	1	5	49
(N20)NGG	19	17942486	-	CCATGACCAGCCGCAGGCTCTGG	1	1	29
(N20)NGG	19	17942492	-	GGTACTCCATGACCAGCCGCAGG	1	1	10
(N20)NGG	19	17942513	-	CGCGCAAGCAGCCGCTGGGCAGG	1	1	8
(N20)NGG	19	17942517	-	AAGTCGCGCAAGCAGCCGCTGGG	1	1	3
(N20)NGG	19	17942518	-	GAAGTCGCGCAAGCAGCCGCTGG	1	1	1
(N20)NGG	19	17942540	-	GGCGCGCGCGGTGCCGCTGCAGG	1	2	38
(N20)NGG	19	17942552	-	GGCTGGCATCGAGGCGCGCGCGG	1	4	15
(N20)NGG	19	17942561	-	GAAGGAGGCGGCTGGCATCGAGG	1	2	28
(N20)NGG	19	17942569	-	GGAATAGAGAAGGAGGCGGCTGG	1	5	66
(N20)NGG	19	17942573	-	GCGAGGAATAGAGAAGGAGGCGG	1	9	243
(N20)NGG	19	17942576	-	TCTGCGAGGAATAGAGAAGGAGG	1	4	45
(N20)NGG	19	17942579	-	AGATCTGCGAGGAATAGAGAAGG	1	6	38

FIG. 8

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17942590	-	TCGCACCTTGCAGATCTGCGAGG	1	1	11
(N20)NGG	19	17943327	+	CATCAGTCCCGCTATCCCCCAGG	1	1	10
(N20)NGG	19	17943328	+	ATCAGTCCCGCTATCCCCCAGGG	1	1	14
(N20)NGG	19	17943337	+	GCTATCCCCCAGGGCAACTTTGG	1	1	20
(N20)NGG	19	17943345	+	CCAGGGCAACTTTGGCAGCGTGG	1	2	17
(N20)NGG	19	17943370	+	CTGTGCCGCTATGACCCGCTAGG	1	1	6
(N20)NGG	19	17943382	+	GACCCGCTAGGCGACAATACAGG	1	1	3
(N20)NGG	19	17943390	+	AGGCGACAATACAGGTGCCCTGG	1	2	10
(N20)NGG	19	17943393	+	CGACAATACAGGTGCCCTGGTGG	1	2	12
(N20)NGG	19	17943418	+	GTGAAACAGCTGCAGCACAGCGG	1	3	70
(N20)NGG	19	17943419	+	TGAAACAGCTGCAGCACAGCGGG	2	4	97
(N20)NGG	19	17943434	+	ACAGCGGGCCAGACCAGCAGAGG	1	1	33
(N20)NGG	19	17943435	+	CAGCGGGCCAGACCAGCAGAGGG	1	3	30
(N20)NGG	19	17943446	+	ACCAGCAGAGGGACTTTCAGCGG	1	5	71
(N20)NGG	19	17943447	+	CCAGCAGAGGGACTTTCAGCGGG	1	5	65
(N20)NGG	19	17943499	+	GATTTCATTGTCAAGTATCGTGG	1	2	15
(N20)NGG	19	17943511	+	AAGTATCGTGGTGTCAGCTATGG	1	1	20
(N20)NGG	19	17943516	+	TCGTGGTGTCAGCTATGGCCCGG	1	3	19
(N20)NGG	19	17943517	+	CGTGGTGTCAGCTATGGCCCGGG	2	11	26
(N20)NGG	19	17943532	+	GGCCCGGGTGAGCCAGCTCCCGG	1	2	50
(N20)NGG	19	17943312	-	AAGTTGCCCTGGGGGATAGCGGG	1	1	16
(N20)NGG	19	17943313	-	AAAGTTGCCCTGGGGGATAGCGG	1	3	37
(N20)NGG	19	17943320	-	CGCTGCCAAAGTTGCCCTGGGGG	1	1	18
(N20)NGG	19	17943321	-	ACGCTGCCAAAGTTGCCCTGGGG	1	2	22
(N20)NGG	19	17943322	-	CACGCTGCCAAAGTTGCCCTGGG	1	1	13

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17943323	-	CCACGCTGCCAAAGTTGCCCTGG	1	2	18
(N20)NGG	19	17943353	-	TGTCGCCTAGCGGGTCATAGCGG	1	1	4
(N20)NGG	19	17943362	-	CACCTGTATTGTCGCCTAGCGGG	1	1	5
(N20)NGG	19	17943363	-	GCACCTGTATTGTCGCCTAGCGG	1	1	5
(N20)NGG	19	17943385	-	CAGCTGTTTCACGGCCACCAGGG	1	3	21
(N20)NGG	19	17943386	-	GCAGCTGTTTCACGGCCACCAGG	1	3	17
(N20)NGG	19	17943394	-	GCTGTGCTGCAGCTGTTTCACGG	2	3	57
(N20)NGG	19	17943420	-	TGAAAGTCCCTCTGCTGGTCTGG	1	4	42
(N20)NGG	19	17943425	-	CCCGCTGAAAGTCCCTCTGCTGG	1	2	15
(N20)NGG	19	17943458	-	AATCACTGTGCAGTGCTTTGAGG	1	1	73
(N20)NGG	19	17943512	-	ATCCGGGAGCTGGCTCACCCGGG	1	2	19
(N20)NGG	19	17943513	-	CATCCGGGAGCTGGCTCACCCGG	1	3	24
(N20)NGG	19	17943628	+	CTCCTCTCAGACCCCACACCTGG	3	14	136
(N20)NGG	19	17943636	+	AGACCCCACACCTGGTGCCCTGG	2	7	51
(N20)NGG	19	17943649	+	GGTGCCCTGGCACCTCGTGATGG	1	1	17
(N20)NGG	19	17943650	+	GTGCCCTGGCACCTCGTGATGGG	1	2	9
(N20)NGG	19	17943656	+	TGGCACCTCGTGATGGGCTGTGG	1	1	27
(N20)NGG	19	17943661	+	CCTCGTGATGGGCTGTGGAATGG	2	4	24
(N20)NGG	19	17943702	+	CCAAGACCCCACGATCTTCGAGG	1	1	5
(N20)NGG	19	17943732	+	CCTCAAGTACATCTCACAGCTGG	1	3	38
(N20)NGG	19	17943733	+	CTCAAGTACATCTCACAGCTGGG	1	3	43
(N20)NGG	19	17943738	+	GTACATCTCACAGCTGGGCAAGG	1	2	51
(N20)NGG	19	17943743	+	TCTCACAGCTGGGCAAGGTAAGG	1	5	66
(N20)NGG	19	17943746	+	CACAGCTGGGCAAGGTAAGGTGG	2	7	85
(N20)NGG	19	17943747	+	ACAGCTGGGCAAGGTAAGGTGGG	1	2	45

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17943751	+	CTGGGCAAGGTAAGGTGGGCAGG	1	4	67
(N20)NGG	19	17943752	+	TGGGCAAGGTAAGGTGGGCAGGG	1	5	107
(N20)NGG	19	17943757	+	AAGGTAAGGTGGGCAGGGCCAGG	2	9	141
(N20)NGG	19	17943758	+	AGGTAAGGTGGGCAGGGCCAGGG	3	15	128
(N20)NGG	19	17943761	+	TAAGGTGGGCAGGGCCAGGGTGG	1	11	220
(N20)NGG	19	17943762	+	AAGGTGGGCAGGGCCAGGGTGGG	2	25	282
(N20)NGG	19	17943574	-	TGGGGTGGGGGCATGGGCAGTGG	6	54	656
(N20)NGG	19	17943580	-	ATAGTCTGGGGTGGGGGCATGGG	1	5	88
(N20)NGG	19	17943581	-	CATAGTCTGGGGTGGGGGCATGG	1	10	133
(N20)NGG	19	17943586	-	GAGCTCATAGTCTGGGGTGGGGG	3	10	112
(N20)NGG	19	17943587	-	GGAGCTCATAGTCTGGGGTGGGG	2	12	80
(N20)NGG	19	17943588	-	AGGAGCTCATAGTCTGGGGTGGG	1	13	121
(N20)NGG	19	17943589	-	GAGGAGCTCATAGTCTGGGGTGG	1	14	149
(N20)NGG	19	17943592	-	TGAGAGGAGCTCATAGTCTGGGG	1	3	54
(N20)NGG	19	17943593	-	CTGAGAGGAGCTCATAGTCTGGG	1	4	51
(N20)NGG	19	17943594	-	TCTGAGAGGAGCTCATAGTCTGG	1	5	48
(N20)NGG	19	17943608	-	CACCAGGTGTGGGGTCTGAGAGG	1	6	70
(N20)NGG	19	17943617	-	GTGCCAGGGCACCAGGTGTGGGG	4	14	64
(N20)NGG	19	17943618	-	GGTGCCAGGGCACCAGGTGTGGG	3	11	64
(N20)NGG	19	17943619	-	AGGTGCCAGGGCACCAGGTGTGG	2	6	82
(N20)NGG	19	17943624	-	TCACGAGGTGCCAGGGCACCAGG	1	1	23
(N20)NGG	19	17943631	-	CAGCCCATCACGAGGTGCCAGGG	1	2	21
(N20)NGG	19	17943632	-	ACAGCCCATCACGAGGTGCCAGG	1	3	11
(N20)NGG	19	17943639	-	CCATTCCACAGCCCATCACGAGG	2	3	24
(N20)NGG	19	17943664	-	GTCTTGGCAGGCATAGAGCTGGG	1	3	36

FIG. 8

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17943665	-	GGTCTTGGCAGGCATAGAGCTGG	2	5	53
(N20)NGG	19	17943676	-	GAAGATCGTGGGGTCTTGGCAGG	1	2	24
(N20)NGG	19	17943680	-	CCTCGAAGATCGTGGGGTCTTGG	1	1	7
(N20)NGG	19	17943686	-	GTCTCTCCTCGAAGATCGTGGGG	1	2	5
(N20)NGG	19	17943687	-	TGTCTCTCCTCGAAGATCGTGGG	1	1	6
(N20)NGG	19	17943688	-	GTGTCTCTCCTCGAAGATCGTGG	1	2	7
(N20)NGG	19	17943710	-	CCAGCTGTGAGATGTACTTGAGG	1	2	37
(N20)NGG	19	17945397	+	TCAGAAACTCCAATTTTATGAGG	1	7	86
(N20)NGG	19	17945402	+	AACTCCAATTTTATGAGGACCGG	1	3	40
(N20)NGG	19	17945415	+	TGAGGACCGGCAGCAGCTGCCGG	1	6	66
(N20)NGG	19	17945426	+	AGCAGCTGCCGGCCCCCAAGTGG	1	1	43
(N20)NGG	19	17945436	+	GGCCCCCAAGTGGACAGAGCTGG	1	4	67
(N20)NGG	19	17945460	+	CCTGCTGATTCAACAGTGCATGG	1	3	37
(N20)NGG	19	17945472	+	ACAGTGCATGGCCTATGAGCCGG	1	2	32
(N20)NGG	19	17945480	+	TGGCCTATGAGCCGGTCCAGAGG	1	2	15
(N20)NGG	19	17945530	+	CTCAATAGCCTCATCTCTTCAGG	1	2	45
(N20)NGG	19	17945540	+	TCATCTCTTCAGGTGCCCGCTGG	1	2	16
(N20)NGG	19	17945541	+	CATCTCTTCAGGTGCCCGCTGGG	2	2	25
(N20)NGG	19	17945545	+	TCTTCAGGTGCCCGCTGGGACGG	2	2	27
(N20)NGG	19	17945546	+	CTTCAGGTGCCCGCTGGGACGGG	1	3	24
(N20)NGG	19	17945550	+	AGGTGCCCGCTGGGACGGGTTGG	1	2	12
(N20)NGG	19	17945551	+	GGTGCCCGCTGGGACGGGTTGGG	1	2	18
(N20)NGG	19	17945554	+	GCCCGCTGGGACGGGTTGGGTGG	1	1	22
(N20)NGG	19	17945356	-	CTGAGGGTGAGAGGAGCAGTCGG	1	6	131
(N20)NGG	19	17945365	-	TTGGAGTTTCTGAGGGTGAGAGG	1	10	100

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17945372	-	CATAAAATTGGAGTTTCTGAGGG	1	8	117
(N20)NGG	19	17945373	-	TCATAAAATTGGAGTTTCTGAGG	1	10	88
(N20)NGG	19	17945384	-	GCTGCCGGTCCTCATAAAATTGG	1	2	12
(N20)NGG	19	17945399	-	TGGGGGCCGGCAGCTGCTGCCGG	1	8	83
(N20)NGG	19	17945412	-	AGCTCTGTCCACTTGGGGCCGG	1	4	66
(N20)NGG	19	17945416	-	GGCCAGCTCTGTCCACTTGGGGG	1	11	71
(N20)NGG	19	17945417	-	GGGCCAGCTCTGTCCACTTGGGG	1	5	58
(N20)NGG	19	17945418	-	AGGGCCAGCTCTGTCCACTTGGG	1	7	74
(N20)NGG	19	17945419	-	CAGGGCCAGCTCTGTCCACTTGG	2	7	118
(N20)NGG	19	17945437	-	CATGCACTGTTGAATCAGCAGGG	1	3	32
(N20)NGG	19	17945438	-	CCATGCACTGTTGAATCAGCAGG	2	2	27
(N20)NGG	19	17945461	-	GGGCCTCTGGACCGGCTCATAGG	1	2	19
(N20)NGG	19	17945469	-	CGGAAGGAGGGCCTCTGGACCGG	1	2	23
(N20)NGG	19	17945474	-	CGGCTCGGAAGGAGGGCCTCTGG	1	2	12
(N20)NGG	19	17945481	-	CGAATGACGGCTCGGAAGGAGGG	1	1	4
(N20)NGG	19	17945482	-	ACGAATGACGGCTCGGAAGGAGG	1	1	4
(N20)NGG	19	17945485	-	GTCACGAATGACGGCTCGGAAGG	1	1	1
(N20)NGG	19	17945489	-	TGAGGTCACGAATGACGGCTCGG	1	1	9
(N20)NGG	19	17945494	-	GCTATTGAGGTCACGAATGACGG	1	1	15
(N20)NGG	19	17945507	-	CTGAAGAGATGAGGCTATTGAGG	1	3	54
(N20)NGG	19	17945516	-	AGCGGGCACCTGAAGAGATGAGG	1	3	26
(N20)NGG	19	17945673	+	TTCCCTCAGTGCTCACCGACAGG	1	1	25
(N20)NGG	19	17945682	+	TGCTCACCGACAGGATCCCCTGG	1	2	14
(N20)NGG	19	17945683	+	GCTCACCGACAGGATCCCCTGGG	1	2	12
(N20)NGG	19	17945686	+	CACCGACAGGATCCCCTGGGTGG	1	2	16

FIG. 8

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17945703	+	GGGTGGCCCCCGAGTGTCTCCGG	1	1	13
(N20)NGG	19	17945704	+	GGTGGCCCCCGAGTGTCTCCGGG	1	2	27
(N20)NGG	19	17945707	+	GGCCCCCGAGTGTCTCCGGGAGG	1	2	24
(N20)NGG	19	17945725	+	GGAGGCGCAGACACTTAGCTTGG	1	1	9
(N20)NGG	19	17945739	+	TTAGCTTGGAAGCTGACAAGTGG	1	2	29
(N20)NGG	19	17945740	+	TAGCTTGGAAGCTGACAAGTGGG	1	5	33
(N20)NGG	19	17945741	+	AGCTTGGAAGCTGACAAGTGGGG	1	3	47
(N20)NGG	19	17945747	+	GAAGCTGACAAGTGGGGCTTCGG	1	2	38
(N20)NGG	19	17945755	+	CAAGTGGGGCTTCGGCGCCACGG	1	1	8
(N20)NGG	19	17945760	+	GGGGCTTCGGCGCCACGGTCTGG	1	1	9
(N20)NGG	19	17945761	+	GGGCTTCGGCGCCACGGTCTGGG	1	1	8
(N20)NGG	19	17945774	+	ACGGTCTGGGAAGTGTTTAGTGG	1	1	16
(N20)NGG	19	17945800	+	CACCATGCCCATCAGTGCCCTGG	1	8	63
(N20)NGG	19	17945812	+	CAGTGCCCTGGATCCTGCTAAGG	1	4	51
(N20)NGG	19	17945830	+	TAAGGTCAGAGCCCCTCACCCGG	1	2	38
(N20)NGG	19	17945836	+	CAGAGCCCCTCACCCGGCATCGG	1	3	43
(N20)NGG	19	17945635	-	GAGGGAATGAAAGTGGGATCAGG	1	7	74
(N20)NGG	19	17945641	-	AGCACTGAGGGAATGAAAGTGGG	1	8	86
(N20)NGG	19	17945642	-	GAGCACTGAGGGAATGAAAGTGG	1	8	106
(N20)NGG	19	17945653	-	ATCCTGTCGGTGAGCACTGAGGG	1	1	16
(N20)NGG	19	17945654	-	GATCCTGTCGGTGAGCACTGAGG	1	2	15
(N20)NGG	19	17945666	-	GGCCACCCAGGGGATCCTGTCGG	1	2	36
(N20)NGG	19	17945676	-	GACACTCGGGGGCCACCCAGGGG	1	2	18
(N20)NGG	19	17945677	-	AGACACTCGGGGGCCACCCAGGG	1	1	25
(N20)NGG	19	17945678	-	GAGACACTCGGGGGCCACCCAGG	1	1	16

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17945687	-	CGCCTCCCGGAGACACTCGGGGG	1	2	11
(N20)NGG	19	17945688	-	GCGCCTCCCGGAGACACTCGGGG	1	2	13
(N20)NGG	19	17945689	-	TGCGCCTCCCGGAGACACTCGGG	1	1	14
(N20)NGG	19	17945690	-	CTGCGCCTCCCGGAGACACTCGG	1	2	32
(N20)NGG	19	17945700	-	AGCTAAGTGTCTGCGCCTCCCGG	1	1	11
(N20)NGG	19	17945750	-	ACTAAACACTTCCCAGACCGTGG	1	2	14
(N20)NGG	19	17945780	-	ATCCAGGGCACTGATGGGCATGG	1	5	64
(N20)NGG	19	17945785	-	GCAGGATCCAGGGCACTGATGGG	2	7	75
(N20)NGG	19	17945786	-	AGCAGGATCCAGGGCACTGATGG	1	10	73
(N20)NGG	19	17945795	-	TCTGACCTTAGCAGGATCCAGGG	1	1	26
(N20)NGG	19	17945796	-	CTCTGACCTTAGCAGGATCCAGG	1	2	25
(N20)NGG	19	17945803	-	TGAGGGGCTCTGACCTTAGCAGG	1	3	36
(N20)NGG	19	17945891	+	TTCCTGTGTCTGGCCCCCTTAGG	1	6	38
(N20)NGG	19	17945894	+	CTGTGTCTGGCCCCCTTAGGAGG	1	2	37
(N20)NGG	19	17945901	+	TGGCCCCCTTAGGAGGACAAAGG	1	1	26
(N20)NGG	19	17945913	+	GAGGACAAAGGCCTGCCCCCATGG	1	1	82
(N20)NGG	19	17945929	+	CCCATGGCAATGTCTCTGCCCGG	1	4	46
(N20)NGG	19	17945933	+	TGGCAATGTCTCTGCCCGGAAGG	1	3	31
(N20)NGG	19	17945942	+	CTCTGCCCGGAAGGTGCTCCTGG	3	3	60
(N20)NGG	19	17945947	+	CCCGGAAGGTGCTCCTGGCTCGG	1	4	52
(N20)NGG	19	17945948	+	CCGGAAGGTGCTCCTGGCTCGGG	1	3	33
(N20)NGG	19	17945951	+	GAAGGTGCTCCTGGCTCGGGAGG	1	2	38
(N20)NGG	19	17945952	+	AAGGTGCTCCTGGCTCGGGAGGG	1	2	32
(N20)NGG	19	17945953	+	AGGTGCTCCTGGCTCGGGAGGGG	1	2	58
(N20)NGG	19	17945954	+	GGTGCTCCTGGCTCGGGAGGGGG	1	4	61

FIG. 8

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17945961	+	CTGGCTCGGGAGGGGGCTGATGG	1	6	71
(N20)NGG	19	17945962	+	TGGCTCGGGAGGGGGCTGATGGG	1	2	41
(N20)NGG	19	17945994	+	TTCATCAAGCTGAGTGACCCTGG	3	5	37
(N20)NGG	19	17945995	+	TCATCAAGCTGAGTGACCCTGGG	1	4	59
(N20)NGG	19	17945996	+	CATCAAGCTGAGTGACCCTGGGG	1	8	61
(N20)NGG	19	17946020	+	CAGCCCCGCTGTGTTAAGCCTGG	1	1	11
(N20)NGG	19	17946035	+	AAGCCTGGAGAGTAAGTTCCTGG	1	2	32
(N20)NGG	19	17946038	+	CCTGGAGAGTAAGTTCCTGGAGG	2	9	56
(N20)NGG	19	17946041	+	GGAGAGTAAGTTCCTGGAGGTGG	1	7	79
(N20)NGG	19	17946044	+	GAGTAAGTTCCTGGAGGTGGAGG	3	4	90
(N20)NGG	19	17946047	+	TAAGTTCCTGGAGGTGGAGGAGG	1	9	103
(N20)NGG	19	17946048	+	AAGTTCCTGGAGGTGGAGGAGGG	2	10	150
(N20)NGG	19	17945871	-	CTCCTAAGGGGGCCAGACACAGG	1	1	23
(N20)NGG	19	17945882	-	AGGCCTTTGTCCTCCTAAGGGGG	1	5	27
(N20)NGG	19	17945883	-	CAGGCCTTTGTCCTCCTAAGGGG	1	4	42
(N20)NGG	19	17945884	-	GCAGGCCTTTGTCCTCCTAAGGG	1	3	34
(N20)NGG	19	17945885	-	GGCAGGCCTTTGTCCTCCTAAGG	1	1	35
(N20)NGG	19	17945902	-	CAGAGACATTGCCATGGGGCAGG	1	2	74
(N20)NGG	19	17945906	-	CGGGCAGAGACATTGCCATGGGG	1	1	22
(N20)NGG	19	17945907	-	CCGGGCAGAGACATTGCCATGGG	1	1	13
(N20)NGG	19	17945908	-	TCCGGGCAGAGACATTGCCATGG	2	3	22
(N20)NGG	19	17945925	-	CCGAGCCAGGAGCACCTTCCGGG	2	3	29
(N20)NGG	19	17945926	-	CCCGAGCCAGGAGCACCTTCCGG	1	3	26
(N20)NGG	19	17945938	-	CATCAGCCCCCTCCCGAGCCAGG	1	5	56
(N20)NGG	19	17945965	-	CACTCAGCTTGATGAAGGGCGGG	1	4	36

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17945966	-	TCACTCAGCTTGATGAAGGGCGG	1	3	36
(N20)NGG	19	17945969	-	GGGTCACTCAGCTTGATGAAGGG	3	3	19
(N20)NGG	19	17945970	-	AGGGTCACTCAGCTTGATGAAGG	2	4	44
(N20)NGG	19	17945989	-	ACACAGCGGGGCTGACCCCAGGG	1	2	31
(N20)NGG	19	17945990	-	AACACAGCGGGGCTGACCCCAGG	1	2	18
(N20)NGG	19	17946001	-	TCTCCAGGCTTAACACAGCGGGG	1	1	24
(N20)NGG	19	17946002	-	CTCTCCAGGCTTAACACAGCGGG	1	3	26
(N20)NGG	19	17946003	-	ACTCTCCAGGCTTAACACAGCGG	1	3	46
(N20)NGG	19	17946016	-	CCTCCAGGAACTTACTCTCCAGG	2	7	64
(N20)NGG	19	17946732	+	GCCTCTCCCTGCTGCCAACCAGG	1	8	88
(N20)NGG	19	17946740	+	CTGCTGCCAACCAGGCACCATGG	1	8	71
(N20)NGG	19	17946746	+	CCAACCAGGCACCATGGTGCAGG	1	5	43
(N20)NGG	19	17946761	+	GGTGCAGGAATTTGTACACCTGG	1	2	22
(N20)NGG	19	17946762	+	GTGCAGGAATTTGTACACCTGGG	1	1	28
(N20)NGG	19	17946763	+	TGCAGGAATTTGTACACCTGGGG	1	2	33
(N20)NGG	19	17946764	+	GCAGGAATTTGTACACCTGGGGG	1	2	26
(N20)NGG	19	17946792	+	GACATGTATCTGCGAAAACGTGG	1	1	8
(N20)NGG	19	17946800	+	TCTGCGAAAACGTGGCCACCTGG	1	1	9
(N20)NGG	19	17946814	+	GCCACCTGGTGCCAGCCAGCTGG	1	7	83
(N20)NGG	19	17946824	+	GCCAGCCAGCTGGAAGCTGCAGG	2	7	88
(N20)NGG	19	17946827	+	AGCCAGCTGGAAGCTGCAGGTGG	1	9	117
(N20)NGG	19	17946839	+	GCTGCAGGTGGTCAAACAGCTGG	1	6	63
(N20)NGG	19	17946860	+	GGCCTACGCCCTCAACTATCTGG	1	1	4
(N20)NGG	19	17946707	-	GGTTGGCAGCAGGGAGAGGCGGG	1	17	229
(N20)NGG	19	17946708	-	TGGTTGGCAGCAGGGAGAGGCGG	1	27	393

FIG. 8

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17946711	-	GCCTGGTTGGCAGCAGGGAGAGG	1	14	135
(N20)NGG	19	17946716	-	ATGGTGCCTGGTTGGCAGCAGGG	1	2	48
(N20)NGG	19	17946717	-	CATGGTGCCTGGTTGGCAGCAGG	1	5	66
(N20)NGG	19	17946724	-	CCTGCACCATGGTGCCTGGTTGG	1	5	83
(N20)NGG	19	17946728	-	AATTCCTGCACCATGGTGCCTGG	1	2	26
(N20)NGG	19	17946735	-	GTGTACAAATTCCTGCACCATGG	1	1	32
(N20)NGG	19	17946757	-	GATACATGTCTATGGCCCCCAGG	1	3	18
(N20)NGG	19	17946765	-	TTTTCGCAGATACATGTCTATGG	1	2	18
(N20)NGG	19	17946793	-	TCCAGCTGGCTGGCACCAGGTGG	1	5	80
(N20)NGG	19	17946796	-	GCTTCCAGCTGGCTGGCACCAGG	1	5	88
(N20)NGG	19	17946803	-	ACCTGCAGCTTCCAGCTGGCTGG	1	3	63
(N20)NGG	19	17946807	-	GACCACCTGCAGCTTCCAGCTGG	1	4	56
(N20)NGG	19	17946840	-	CACCAGATAGTTGAGGGCGTAGG	1	1	12
(N20)NGG	19	17946846	-	AGCACTCACCAGATAGTTGAGGG	1	3	35
(N20)NGG	19	17946847	-	GAGCACTCACCAGATAGTTGAGG	1	1	26
(N20)NGG	19	17947946	+	CCACCTTCCCCAGTCATTCCTGG	1	9	117
(N20)NGG	19	17947981	+	TGATGAGCCAAGTGTCGTACCGG	1	1	12
(N20)NGG	19	17948001	+	CGGCATCTCGTGCTGCTCCACGG	1	2	13
(N20)NGG	19	17948012	+	GCTGCTCCACGGCGTGTGCATGG	1	1	20
(N20)NGG	19	17948016	+	CTCCACGGCGTGTGCATGGCTGG	1	2	12
(N20)NGG	19	17947918	-	ATGACTGGGGAAGGTGGGAAGGG	2	9	149
(N20)NGG	19	17947919	-	AATGACTGGGGAAGGTGGGAAGG	1	9	154
(N20)NGG	19	17947923	-	CAGGAATGACTGGGGAAGGTGGG	1	11	118
(N20)NGG	19	17947924	-	CCAGGAATGACTGGGGAAGGTGG	2	12	157
(N20)NGG	19	17947927	-	CTTCCAGGAATGACTGGGGAAGG	2	7	86

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17947931	-	GCTGCTTCCAGGAATGACTGGGG	1	10	75
(N20)NGG	19	17947932	-	CGCTGCTTCCAGGAATGACTGGG	1	2	27
(N20)NGG	19	17947933	-	TCGCTGCTTCCAGGAATGACTGG	1	3	24
(N20)NGG	19	17947942	-	TCATCAAGCTCGCTGCTTCCAGG	1	4	23
(N20)NGG	19	17947966	-	CGAGATGCCGGTACGACACTTGG	1	1	3
(N20)NGG	19	17947978	-	CGTGGAGCAGCACGAGATGCCGG	1	2	16
(N20)NGG	19	17947996	-	CTCCAGCCATGCACACGCCGTGG	1	3	26
(N20)NGG	19	17948752	+	CACCATTCAGCATGAGAACCTGG	1	2	23
(N20)NGG	19	17948753	+	ACCATTCAGCATGAGAACCTGGG	1	2	30
(N20)NGG	19	17948759	+	CAGCATGAGAACCTGGGCCATGG	1	4	58
(N20)NGG	19	17948760	+	AGCATGAGAACCTGGGCCATGGG	1	3	36
(N20)NGG	19	17948781	+	GGTCCTTCACCAAGATTTACCGG	1	2	23
(N20)NGG	19	17948782	+	GTCCTTCACCAAGATTTACCGGG	1	2	32
(N20)NGG	19	17948783	+	TCCTTCACCAAGATTTACCGGGG	1	1	16
(N20)NGG	19	17948797	+	TTACCGGGGCTGTCGCCATGAGG	1	1	5
(N20)NGG	19	17948800	+	CCGGGGCTGTCGCCATGAGGTGG	1	3	21
(N20)NGG	19	17948803	+	GGGCTGTCGCCATGAGGTGGTGG	1	3	38
(N20)NGG	19	17948807	+	TGTCGCCATGAGGTGGTGGATGG	1	1	19
(N20)NGG	19	17948808	+	GTCGCCATGAGGTGGTGGATGGG	1	1	13
(N20)NGG	19	17948809	+	TCGCCATGAGGTGGTGGATGGGG	1	2	25
(N20)NGG	19	17948812	+	CCATGAGGTGGTGGATGGGGAGG	2	14	159
(N20)NGG	19	17948827	+	TGGGGAGGCCCGAAAGACAGAGG	1	3	36
(N20)NGG	19	17948839	+	AAAGACAGAGGTGCTGCTGAAGG	1	5	101
(N20)NGG	19	17948845	+	AGAGGTGCTGCTGAAGGTCATGG	1	7	105
(N20)NGG	19	17948869	+	TGCCAAGCACAAGAACTGCATGG	1	3	52

FIG. 8

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17948872	+	CAAGCACAAGAACTGCATGGAGG	1	26	858
(N20)NGG	19	17948886	+	GCATGGAGGTGAGAGCAATGTGG	1	3	66
(N20)NGG	19	17948725	-	TTCTCATGCTGAATGGTGAGGGG	2	4	48
(N20)NGG	19	17948726	-	GTTCTCATGCTGAATGGTGAGGG	1	8	52
(N20)NGG	19	17948727	-	GGTTCTCATGCTGAATGGTGAGG	1	5	36
(N20)NGG	19	17948732	-	GCCCAGGTTCTCATGCTGAATGG	1	1	35
(N20)NGG	19	17948748	-	TGGTGAAGGACCCATGGCCCAGG	1	1	41
(N20)NGG	19	17948754	-	AAATCTTGGTGAAGGACCCATGG	1	5	45
(N20)NGG	19	17948762	-	GCCCCGGTAAATCTTGGTGAAGG	1	1	8
(N20)NGG	19	17948768	-	GCGACAGCCCCGGTAAATCTTGG	1	1	6
(N20)NGG	19	17948778	-	CCACCTCATGGCGACAGCCCCGG	1	2	31
(N20)NGG	19	17948790	-	CCTCCCCATCCACCACCTCATGG	5	17	178
(N20)NGG	19	17948813	-	CAGCAGCACCTCTGTCTTTCGGG	1	6	85
(N20)NGG	19	17948814	-	TCAGCAGCACCTCTGTCTTTCGG	1	5	70
(N20)NGG	19	17948849	-	CTCCATGCAGTTCTTGTGCTTGG	1	12	406
(N20)NGG	19	17949091	+	AGAAAAGTCCAACCTGATCGTGG	1	1	20
(N20)NGG	19	17949101	+	AACCTGATCGTGGTCCAGAGAGG	1	1	6
(N20)NGG	19	17949127	+	CAGCCCACCCACATCATCCTTGG	1	8	83
(N20)NGG	19	17949193	+	CAAGATCCCTGCTGACAGCCTGG	1	2	54
(N20)NGG	19	17949198	+	TCCCTGCTGACAGCCTGGAGTGG	1	8	92
(N20)NGG	19	17949199	+	CCCTGCTGACAGCCTGGAGTGGG	1	8	92
(N20)NGG	19	17949206	+	GACAGCCTGGAGTGGGTAAGAGG	1	4	56
(N20)NGG	19	17949212	+	CTGGAGTGGGTAAGAGGCCCTGG	1	3	58
(N20)NGG	19	17949213	+	TGGAGTGGGTAAGAGGCCCTGGG	2	4	45
(N20)NGG	19	17949221	+	GTAAGAGGCCCTGGGAAATGAGG	1	8	122

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17949051	-	TTTCTATGGGGAGAGGATGAGGG	1	12	105
(N20)NGG	19	17949052	-	TTTTCTATGGGGAGAGGATGAGG	2	9	112
(N20)NGG	19	17949058	-	TTGGACTTTTCTATGGGGAGAGG	1	4	44
(N20)NGG	19	17949063	-	TCAGGTTGGACTTTTCTATGGGG	1	3	31
(N20)NGG	19	17949064	-	ATCAGGTTGGACTTTTCTATGGG	2	2	30
(N20)NGG	19	17949065	-	GATCAGGTTGGACTTTTCTATGG	1	5	40
(N20)NGG	19	17949077	-	TCTCTGGACCACGATCAGGTTGG	1	1	8
(N20)NGG	19	17949081	-	GACCTCTCTGGACCACGATCAGG	1	1	5
(N20)NGG	19	17949093	-	TGGGTGGGCTGTGACCTCTCTGG	1	5	54
(N20)NGG	19	17949108	-	GAACCAAGGATGATGTGGGTGGG	1	3	40
(N20)NGG	19	17949109	-	TGAACCAAGGATGATGTGGGTGG	1	2	45
(N20)NGG	19	17949112	-	GGCTGAACCAAGGATGATGTGGG	1	2	27
(N20)NGG	19	17949113	-	GGGCTGAACCAAGGATGATGTGG	1	2	43
(N20)NGG	19	17949122	-	TTGGGATTGGGGCTGAACCAAGG	1	1	34
(N20)NGG	19	17949133	-	CTCAGCTGGTATTGGGATTGGGG	1	2	33
(N20)NGG	19	17949134	-	ACTCAGCTGGTATTGGGATTGGG	1	2	30
(N20)NGG	19	17949135	-	GACTCAGCTGGTATTGGGATTGG	1	3	19
(N20)NGG	19	17949140	-	CATCTGACTCAGCTGGTATTGGG	1	2	29
(N20)NGG	19	17949141	-	TCATCTGACTCAGCTGGTATTGG	1	1	25
(N20)NGG	19	17949147	-	GAAATGTCATCTGACTCAGCTGG	1	4	172
(N20)NGG	19	17949177	-	CCCACTCCAGGCTGTCAGCAGGG	1	9	108
(N20)NGG	19	17949178	-	ACCCACTCCAGGCTGTCAGCAGG	1	9	61
(N20)NGG	19	17949189	-	CAGGGCCTCTTACCCACTCCAGG	1	4	54
(N20)NGG	19	17950295	+	TCTTCTTTGCAGAACCCCCCTTGG	1	4	45
(N20)NGG	19	17950309	+	CCCCCTTGGTCCTGATTATAAGG	1	2	19

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17950310	+	CCCCTTGGTCCTGATTATAAGGG	1	3	38
(N20)NGG	19	17950323	+	ATTATAAGGGCTGCCTCATCCGG	1	4	23
(N20)NGG	19	17950337	+	CTCATCCGGCGCAGCCCCACAGG	1	1	15
(N20)NGG	19	17950351	+	CCCCACAGGAACCTTCCTTCTGG	1	8	59
(N20)NGG	19	17950355	+	ACAGGAACCTTCCTTCTGGTTGG	1	3	37
(N20)NGG	19	17950393	+	CAGCAGTCTTCGAGAGCTCCTGG	1	5	27
(N20)NGG	19	17950404	+	GAGAGCTCCTGGCAACCTGCTGG	2	7	66
(N20)NGG	19	17950405	+	AGAGCTCCTGGCAACCTGCTGGG	1	2	41
(N20)NGG	19	17950409	+	CTCCTGGCAACCTGCTGGGATGG	1	4	58
(N20)NGG	19	17950410	+	TCCTGGCAACCTGCTGGGATGGG	1	1	49
(N20)NGG	19	17950411	+	CCTGGCAACCTGCTGGGATGGGG	1	3	57
(N20)NGG	19	17950412	+	CTGGCAACCTGCTGGGATGGGGG	1	4	56
(N20)NGG	19	17950413	+	TGGCAACCTGCTGGGATGGGGGG	1	3	58
(N20)NGG	19	17950427	+	GATGGGGGGGCTGCACGTAGATGG	1	5	18
(N20)NGG	19	17950428	+	ATGGGGGGCTGCACGTAGATGGG	1	1	6
(N20)NGG	19	17950429	+	TGGGGGGCTGCACGTAGATGGGG	1	1	24
(N20)NGG	19	17950432	+	GGGGCTGCACGTAGATGGGGTGG	1	6	41
(N20)NGG	19	17950472	+	TGCTGTATCCCCCAGACCCAAAGG	1	9	97
(N20)NGG	19	17950492	+	AGGTGAGCCCCCTTCCTCCCCTGG	2	6	93
(N20)NGG	19	17950269	-	GGGGGTTCTGCAAAGAAGAGTGG	1	4	75
(N20)NGG	19	17950287	-	CCTTATAATCAGGACCAAGGGGG	1	3	56
(N20)NGG	19	17950288	-	CCCTTATAATCAGGACCAAGGGG	1	3	28
(N20)NGG	19	17950289	-	GCCCTTATAATCAGGACCAAGGG	1	1	34
(N20)NGG	19	17950290	-	AGCCCTTATAATCAGGACCAAGG	1	2	18
(N20)NGG	19	17950297	-	ATGAGGCAGCCCTTATAATCAGG	1	2	19

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17950314	-	CTGTGGGGCTGCGCCGGATGAGG	1	4	27
(N20)NGG	19	17950320	-	AGGTTCCTGTGGGGCTGCGCCGG	1	5	44
(N20)NGG	19	17950329	-	CCAGAAGGAAGGTTCCTGTGGGG	1	3	70
(N20)NGG	19	17950330	-	ACCAGAAGGAAGGTTCCTGTGGG	1	3	50
(N20)NGG	19	17950331	-	AACCAGAAGGAAGGTTCCTGTGG	1	5	83
(N20)NGG	19	17950340	-	GCTGAGGCCAACCAGAAGGAAGG	1	2	60
(N20)NGG	19	17950344	-	GTCGGCTGAGGCCAACCAGAAGG	1	1	16
(N20)NGG	19	17950356	-	GACTGCTGTGGGGTCGGCTGAGG	1	11	462
(N20)NGG	19	17950362	-	CTCGAAGACTGCTGTGGGGTCGG	1	2	25
(N20)NGG	19	17950366	-	AGCTCTCGAAGACTGCTGTGGGG	1	3	21
(N20)NGG	19	17950367	-	GAGCTCTCGAAGACTGCTGTGGG	1	2	26
(N20)NGG	19	17950368	-	GGAGCTCTCGAAGACTGCTGTGG	1	3	31
(N20)NGG	19	17950389	-	CCCCATCCCAGCAGGTTGCCAGG	1	2	68
(N20)NGG	19	17950397	-	GTGCAGCCCCCCATCCCAGCAGG	2	6	62
(N20)NGG	19	17950439	-	GGGGATACAGCAGGAAGTGAGGG	3	16	147
(N20)NGG	19	17950440	-	TGGGGATACAGCAGGAAGTGAGG	2	22	135
(N20)NGG	19	17950448	-	TTTGGGTCTGGGGATACAGCAGG	1	1	76
(N20)NGG	19	17950458	-	GGGGCTCACCTTTGGGTCTGGGG	1	3	51
(N20)NGG	19	17950459	-	AGGGGCTCACCTTTGGGTCTGGG	1	3	37
(N20)NGG	19	17950460	-	AAGGGGCTCACCTTTGGGTCTGG	1	3	14
(N20)NGG	19	17950465	-	GGAGGAAGGGGCTCACCTTTGGG	1	8	53
(N20)NGG	19	17950466	-	GGGAGGAAGGGGCTCACCTTTGG	1	5	64
(N20)NGG	19	17951042	+	TCTCACCTTCCCCCACAGTCTGG	1	5	72
(N20)NGG	19	17951070	+	GCCATCAACAAGCTCAAGACTGG	1	3	33
(N20)NGG	19	17951071	+	CCATCAACAAGCTCAAGACTGGG	1	5	52

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17951072	+	CATCAACAAGCTCAAGACTGGGG	1	4	42
(N20)NGG	19	17951073	+	ATCAACAAGCTCAAGACTGGGGG	1	3	35
(N20)NGG	19	17951085	+	AAGACTGGGGGCTCACGTCCTGG	1	1	19
(N20)NGG	19	17951114	+	TGTTCTCCGCCGCAGCCCCCAGG	1	4	26
(N20)NGG	19	17951150	+	CCTCCTCACTGTCTGTGTCCAGG	1	8	102
(N20)NGG	19	17951154	+	CTCACTGTCTGTGTCCAGGTCGG	3	8	76
(N20)NGG	19	17951166	+	GTCCAGGTCGGTCTACTGCTAGG	1	2	10
(N20)NGG	19	17951167	+	TCCAGGTCGGTCTACTGCTAGGG	1	2	13
(N20)NGG	19	17951170	+	AGGTCGGTCTACTGCTAGGGTGG	1	1	6
(N20)NGG	19	17951171	+	GGTCGGTCTACTGCTAGGGTGGG	1	1	3
(N20)NGG	19	17951017	-	GACTGTGGGGGAAGGTGAGAGGG	1	8	176
(N20)NGG	19	17951018	-	AGACTGTGGGGGAAGGTGAGAGG	1	12	195
(N20)NGG	19	17951025	-	AAAGTCCAGACTGTGGGGGAAGG	2	5	65
(N20)NGG	19	17951029	-	TGGCAAAGTCCAGACTGTGGGGG	1	7	80
(N20)NGG	19	17951030	-	ATGGCAAAGTCCAGACTGTGGGG	1	3	54
(N20)NGG	19	17951031	-	GATGGCAAAGTCCAGACTGTGGG	1	6	52
(N20)NGG	19	17951032	-	TGATGGCAAAGTCCAGACTGTGG	1	11	64
(N20)NGG	19	17951049	-	CCCAGTCTTGAGCTTGTTGATGG	1	2	30
(N20)NGG	19	17951081	-	CGGCGGAGAACATAGGAGCCAGG	1	1	6
(N20)NGG	19	17951088	-	GGGGCTGCGGCGGAGAACATAGG	1	1	15
(N20)NGG	19	17951098	-	CAAAGTCCTGGGGGCTGCGGCGG	1	8	72
(N20)NGG	19	17951101	-	TGTCAAAGTCCTGGGGGCTGCGG	1	10	141
(N20)NGG	19	17951107	-	GGAAGCTGTCAAAGTCCTGGGGG	1	9	85
(N20)NGG	19	17951108	-	AGGAAGCTGTCAAAGTCCTGGGG	1	5	81
(N20)NGG	19	17951109	-	GAGGAAGCTGTCAAAGTCCTGGG	1	2	57

FIG. 8

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17951110	-	GGAGGAAGCTGTCAAAGTCCTGG	1	1	49
(N20)NGG	19	17951128	-	CCTGGACACAGACAGTGAGGAGG	1	6	106
(N20)NGG	19	17951131	-	CGACCTGGACACAGACAGTGAGG	1	3	26
(N20)NGG	19	17951146	-	ACCCTAGCAGTAGACCGACCTGG	1	1	6
(N20)NGG	19	17952197	+	CTCTGACGCTTGTCCCTCGCAGG	1	1	10
(N20)NGG	19	17952200	+	TGACGCTTGTCCCTCGCAGGAGG	1	1	6
(N20)NGG	19	17952213	+	TCGCAGGAGGCCGAGTTCCCAGG	1	1	16
(N20)NGG	19	17952214	+	CGCAGGAGGCCGAGTTCCCAGGG	1	4	28
(N20)NGG	19	17952224	+	CGAGTTCCCAGGGCTGCCCGAGG	1	2	39
(N20)NGG	19	17952239	+	GCCCGAGGCTCTGTCGTTCGTGG	1	1	6
(N20)NGG	19	17952248	+	TCTGTCGTTCGTGGCGCTCGTGG	1	1	4
(N20)NGG	19	17952252	+	TCGTTCGTGGCGCTCGTGGACGG	1	1	6
(N20)NGG	19	17952262	+	CGCTCGTGGACGGCTACTTCCGG	1	1	2
(N20)NGG	19	17952272	+	CGGCTACTTCCGGCTGACCACGG	1	1	14
(N20)NGG	19	17952296	+	CTCCCAGCACTTCTTCTGCAAGG	1	6	100
(N20)NGG	19	17952299	+	CCAGCACTTCTTCTGCAAGGAGG	1	4	54
(N20)NGG	19	17952302	+	GCACTTCTTCTGCAAGGAGGTGG	1	4	43
(N20)NGG	19	17952313	+	GCAAGGAGGTGGCACCGCCGAGG	1	1	19
(N20)NGG	19	17952320	+	GGTGGCACCGCCGAGGCTGCTGG	1	4	29
(N20)NGG	19	17952323	+	GGCACCGCCGAGGCTGCTGGAGG	1	2	49
(N20)NGG	19	17952329	+	GCCGAGGCTGCTGGAGGAAGTGG	3	15	162
(N20)NGG	19	17952345	+	GAAGTGGCCGAGCAGTGCCACGG	1	1	29
(N20)NGG	19	17952360	+	TGCCACGGCCCCATCACGTAAGG	1	2	10
(N20)NGG	19	17952379	+	AAGGACCTGTCCCCCATTCCCGG	1	1	32
(N20)NGG	19	17952188	-	GGGAACTCGGCCTCCTGCGAGGG	1	1	8

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17952189	-	TGGGAACTCGGCCTCCTGCGAGG	1	2	22
(N20)NGG	19	17952201	-	CTCGGGCAGCCCTGGGAACTCGG	1	3	54
(N20)NGG	19	17952208	-	ACAGAGCCTCGGGCAGCCCTGGG	1	8	75
(N20)NGG	19	17952209	-	GACAGAGCCTCGGGCAGCCCTGG	2	7	70
(N20)NGG	19	17952218	-	GCCACGAACGACAGAGCCTCGGG	1	1	21
(N20)NGG	19	17952219	-	CGCCACGAACGACAGAGCCTCGG	1	1	9
(N20)NGG	19	17952259	-	GCTGGGAGTCCGTGGTCAGCCGG	1	2	33
(N20)NGG	19	17952267	-	GAAGAAGTGCTGGGAGTCCGTGG	1	1	41
(N20)NGG	19	17952276	-	CTCCTTGCAGAAGAAGTGCTGGG	1	5	51
(N20)NGG	19	17952277	-	CCTCCTTGCAGAAGAAGTGCTGG	1	3	46
(N20)NGG	19	17952305	-	ACTTCCTCCAGCAGCCTCGGCGG	1	4	58
(N20)NGG	19	17952308	-	GCCACTTCCTCCAGCAGCCTCGG	1	12	123
(N20)NGG	19	17952330	-	GATGGGGCCGTGGCACTGCTCGG	1	2	21
(N20)NGG	19	17952340	-	GTCCTTACGTGATGGGGCCGTGG	1	1	7
(N20)NGG	19	17952346	-	GGACAGGTCCTTACGTGATGGGG	1	1	9
(N20)NGG	19	17952347	-	GGGACAGGTCCTTACGTGATGGG	1	1	13
(N20)NGG	19	17952348	-	GGGGACAGGTCCTTACGTGATGG	1	2	13
(N20)NGG	19	17952448	+	CGGTACTCCCCCTCCTTCCCAGG	1	3	41
(N20)NGG	19	17952502	+	CGTAGACATTAGCATCAAGCAGG	1	1	9
(N20)NGG	19	17952515	+	ATCAAGCAGGCCCCGCGCGTTGG	1	2	4
(N20)NGG	19	17952520	+	GCAGGCCCCGCGCGTTGGCCCGG	1	2	16
(N20)NGG	19	17952524	+	GCCCCGCGCGTTGGCCCGGCCGG	1	2	15
(N20)NGG	19	17952538	+	CCCGGCCGGAGAGCACCGCCTGG	1	2	30
(N20)NGG	19	17952552	+	ACCGCCTGGTCACTGTTACCAGG	1	1	4
(N20)NGG	19	17952574	+	GACAGACAACCAGATTTAGTGG	1	3	47

FIG. 8

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17952575	+	ACAGACAACCAGATTTTAGTGGG	1	3	37
(N20)NGG	19	17952581	+	AACCAGATTTTAGTGGGTGCAGG	2	3	31
(N20)NGG	19	17952433	-	TGGAGGACCTGGGAAGGAGGGGG	1	22	279
(N20)NGG	19	17952434	-	CTGGAGGACCTGGGAAGGAGGGG	2	15	206
(N20)NGG	19	17952435	-	GCTGGAGGACCTGGGAAGGAGGG	1	7	167
(N20)NGG	19	17952436	-	GGCTGGAGGACCTGGGAAGGAGG	1	14	219
(N20)NGG	19	17952439	-	AAGGGCTGGAGGACCTGGGAAGG	2	11	124
(N20)NGG	19	17952443	-	GCAGAAGGGCTGGAGGACCTGGG	1	6	100
(N20)NGG	19	17952444	-	CGCAGAAGGGCTGGAGGACCTGG	1	7	57
(N20)NGG	19	17952450	-	GAAAGTCGCAGAAGGGCTGGAGG	1	2	35
(N20)NGG	19	17952453	-	CTGGAAAGTCGCAGAAGGGCTGG	1	1	26
(N20)NGG	19	17952457	-	ATTTCTGGAAAGTCGCAGAAGGG	1	3	44
(N20)NGG	19	17952458	-	GATTTCTGGAAAGTCGCAGAAGG	1	2	37
(N20)NGG	19	17952472	-	ATGCTAATGTCTACGATTTCTGG	1	1	16
(N20)NGG	19	17952503	-	TCCGGCCGGGCCAACGCGCGGGG	1	1	9
(N20)NGG	19	17952504	-	CTCCGGCCGGGCCAACGCGCGGG	1	1	13
(N20)NGG	19	17952505	-	TCTCCGGCCGGGCCAACGCGCGG	1	1	11
(N20)NGG	19	17952516	-	CCAGGCGGTGCTCTCCGGCCGGG	1	2	34
(N20)NGG	19	17952517	-	ACCAGGCGGTGCTCTCCGGCCGG	1	1	16
(N20)NGG	19	17952521	-	AGTGACCAGGCGGTGCTCTCCGG	1	2	20
(N20)NGG	19	17952531	-	TCCTGGTAACAGTGACCAGGCGG	1	3	35
(N20)NGG	19	17952534	-	CTGTCCTGGTAACAGTGACCAGG	1	1	37
(N20)NGG	19	17952548	-	TAAAATCTGGTTGTCTGTCCTGG	1	3	37
(N20)NGG	19	17952561	-	ATCCTGCACCCACTAAAATCTGG	1	1	30
(N20)NGG	19	17953131	+	CTCCAACCCCTGCAGCTACAAGG	1	5	78

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17953167	+	AAGCCTGCGCGACCTGATCCAGG	1	1	7
(N20)NGG	19	17953168	+	AGCCTGCGCGACCTGATCCAGGG	1	3	22
(N20)NGG	19	17953187	+	AGGGCCTGAGCTTCGTGACGCGG	1	1	11
(N20)NGG	19	17953190	+	GCCTGAGCTTCGTGACGCGGAGG	1	1	3
(N20)NGG	19	17953199	+	TCGTGACGCGGAGGCGTATTCGG	1	1	1
(N20)NGG	19	17953202	+	TGACGCGGAGGCGTATTCGGAGG	1	1	3
(N20)NGG	19	17953206	+	GCGGAGGCGTATTCGGAGGACGG	1	1	7
(N20)NGG	19	17953230	+	GCGCAGAGCCCTGCGCCGCGTGG	1	2	32
(N20)NGG	19	17953242	+	GCGCCGCGTGGCCGCCTGCCAGG	1	3	27
(N20)NGG	19	17953250	+	TGGCCGCCTGCCAGGCAGACCGG	3	3	29
(N20)NGG	19	17953263	+	GGCAGACCGGCACTCGCTCATGG	1	1	9
(N20)NGG	19	17953278	+	GCTCATGGCCAAGTACATCATGG	2	4	39
(N20)NGG	19	17953284	+	GGCCAAGTACATCATGGACCTGG	1	1	13
(N20)NGG	19	17953289	+	AGTACATCATGGACCTGGAGCGG	1	1	34
(N20)NGG	19	17953293	+	CATCATGGACCTGGAGCGGCTGG	1	5	22
(N20)NGG	19	17953303	+	CTGGAGCGGCTGGATCCAGCCGG	1	3	46
(N20)NGG	19	17953304	+	TGGAGCGGCTGGATCCAGCCGGG	2	4	44
(N20)NGG	19	17953305	+	GGAGCGGCTGGATCCAGCCGGGG	1	6	33
(N20)NGG	19	17953326	+	GGCCGCCGAGACCTTCCACGTGG	1	1	8
(N20)NGG	19	17953327	+	GCCGCCGAGACCTTCCACGTGGG	1	1	5
(N20)NGG	19	17953336	+	ACCTTCCACGTGGGCCTCCCTGG	2	11	234
(N20)NGG	19	17953337	+	CCTTCCACGTGGGCCTCCCTGGG	2	30	1326
(N20)NGG	19	17953338	+	CTTCCACGTGGGCCTCCCTGGGG	1	2	74
(N20)NGG	19	17953345	+	GTGGGCCTCCCTGGGGCCCTTGG	1	6	132
(N20)NGG	19	17953348	+	GGCCTCCCTGGGGCCCTTGGTGG	1	7	129

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17953357	+	GGGGCCCTTGGTGGCCACGACGG	1	2	33
(N20)NGG	19	17953358	+	GGGCCCTTGGTGGCCACGACGGG	1	5	23
(N20)NGG	19	17953362	+	CCTTGGTGGCCACGACGGGCTGG	1	3	26
(N20)NGG	19	17953363	+	CTTGGTGGCCACGACGGGCTGGG	1	1	11
(N20)NGG	19	17953364	+	TTGGTGGCCACGACGGGCTGGGG	1	3	26
(N20)NGG	19	17953377	+	CGGGCTGGGGCTGCTCCGCGTGG	1	5	51
(N20)NGG	19	17953381	+	CTGGGGCTGCTCCGCGTGGCTGG	1	3	49
(N20)NGG	19	17953387	+	CTGCTCCGCGTGGCTGGTGACGG	1	1	35
(N20)NGG	19	17953390	+	CTCCGCGTGGCTGGTGACGGCGG	1	1	15
(N20)NGG	19	17953400	+	CTGGTGACGGCGGCATCGCCTGG	1	2	5
(N20)NGG	19	17953407	+	CGGCGGCATCGCCTGGACCCAGG	1	1	13
(N20)NGG	19	17953408	+	GGCGGCATCGCCTGGACCCAGGG	1	1	17
(N20)NGG	19	17953416	+	CGCCTGGACCCAGGGAGAACAGG	1	3	29
(N20)NGG	19	17953419	+	CTGGACCCAGGGAGAACAGGAGG	2	13	137
(N20)NGG	19	17953424	+	CCCAGGGAGAACAGGAGGTGAGG	1	7	157
(N20)NGG	19	17953425	+	CCAGGGAGAACAGGAGGTGAGGG	2	9	149
(N20)NGG	19	17953428	+	GGGAGAACAGGAGGTGAGGGCGG	3	33	396
(N20)NGG	19	17953441	+	GTGAGGGCGGACTCCCCCGCTGG	1	2	12
(N20)NGG	19	17953442	+	TGAGGGCGGACTCCCCCGCTGGG	1	1	9
(N20)NGG	19	17953102	-	GCTGCAGGGGTTGGAGGGGAGGG	2	23	266
(N20)NGG	19	17953103	-	AGCTGCAGGGGTTGGAGGGGAGG	1	19	260
(N20)NGG	19	17953106	-	TGTAGCTGCAGGGGTTGGAGGGG	1	7	99
(N20)NGG	19	17953107	-	TTGTAGCTGCAGGGGTTGGAGGG	1	2	61
(N20)NGG	19	17953108	-	CTTGTAGCTGCAGGGGTTGGAGG	1	6	56
(N20)NGG	19	17953111	-	GGCCTTGTAGCTGCAGGGGTTGG	1	4	54

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17953115	-	GGCAGGCCTTGTAGCTGCAGGGG	1	5	51
(N20)NGG	19	17953116	-	AGGCAGGCCTTGTAGCTGCAGGG	1	3	43
(N20)NGG	19	17953117	-	TAGGCAGGCCTTGTAGCTGCAGG	1	2	32
(N20)NGG	19	17953132	-	GCGCAGGCTTGGGGGTAGGCAGG	1	4	37
(N20)NGG	19	17953136	-	GGTCGCGCAGGCTTGGGGGTAGG	1	2	28
(N20)NGG	19	17953140	-	ATCAGGTCGCGCAGGCTTGGGGG	1	1	5
(N20)NGG	19	17953141	-	GATCAGGTCGCGCAGGCTTGGGG	1	1	10
(N20)NGG	19	17953142	-	GGATCAGGTCGCGCAGGCTTGGG	1	1	11
(N20)NGG	19	17953143	-	TGGATCAGGTCGCGCAGGCTTGG	1	1	4
(N20)NGG	19	17953148	-	GGCCCTGGATCAGGTCGCGCAGG	1	3	8
(N20)NGG	19	17953157	-	CGAAGCTCAGGCCCTGGATCAGG	1	3	34
(N20)NGG	19	17953163	-	GCGTCACGAAGCTCAGGCCCTGG	1	1	13
(N20)NGG	19	17953169	-	GCCTCCGCGTCACGAAGCTCAGG	1	1	25
(N20)NGG	19	17953216	-	GCAGGCGGCCACGCGGCGCAGGG	1	3	21
(N20)NGG	19	17953217	-	GGCAGGCGGCCACGCGGCGCAGG	1	3	35
(N20)NGG	19	17953223	-	CTGCCTGGCAGGCGGCCACGCGG	2	8	56
(N20)NGG	19	17953231	-	GTGCCGGTCTGCCTGGCAGGCGG	1	2	37
(N20)NGG	19	17953234	-	CGAGTGCCGGTCTGCCTGGCAGG	1	2	14
(N20)NGG	19	17953238	-	TGAGCGAGTGCCGGTCTGCCTGG	1	1	9
(N20)NGG	19	17953247	-	ACTTGGCCATGAGCGAGTGCCGG	1	2	8
(N20)NGG	19	17953264	-	CTCCAGGTCCATGATGTACTTGG	1	4	29
(N20)NGG	19	17953280	-	CGGCTGGATCCAGCCGCTCCAGG	2	5	33
(N20)NGG	19	17953296	-	AAGGTCTCGGCGGCCCCCGGCTGG	1	2	12
(N20)NGG	19	17953300	-	GTGGAAGGTCTCGGCGGCCCCGG	1	2	11
(N20)NGG	19	17953306	-	GCCCACGTGGAAGGTCTCGGCGG	1	2	12

FIG. 8

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17953309	-	GAGGCCCACGTGGAAGGTCTCGG	1	2	30
(N20)NGG	19	17953315	-	CCCAGGGAGGCCCACGTGGAAGG	1	4	102
(N20)NGG	19	17953319	-	GGGCCCCAGGGAGGCCCACGTGG	2	8	88
(N20)NGG	19	17953328	-	GGCCACCAAGGGCCCCAGGGAGG	1	8	112
(N20)NGG	19	17953331	-	CGTGGCCACCAAGGGCCCCAGGG	1	6	45
(N20)NGG	19	17953332	-	TCGTGGCCACCAAGGGCCCCAGG	1	3	42
(N20)NGG	19	17953339	-	CAGCCCGTCGTGGCCACCAAGGG	1	1	46
(N20)NGG	19	17953340	-	CCAGCCCGTCGTGGCCACCAAGG	1	4	59
(N20)NGG	19	17953349	-	GGAGCAGCCCCAGCCCGTCGTGG	1	6	49
(N20)NGG	19	17953370	-	TGCCGCCGTCACCAGCCACGCGG	1	1	14
(N20)NGG	19	17953396	-	CTCCTGTTCTCCCTGGGTCCAGG	2	9	115
(N20)NGG	19	17953402	-	CCTCACCTCCTGTTCTCCCTGGG	1	7	141
(N20)NGG	19	17953403	-	CCCTCACCTCCTGTTCTCCCTGG	1	9	145
(N20)NGG	19	17953850	+	CCCCCAGCACCGCAGTGACCTGG	1	5	53
(N20)NGG	19	17953857	+	CACCGCAGTGACCTGGTGAGTGG	1	2	32
(N20)NGG	19	17953858	+	ACCGCAGTGACCTGGTGAGTGGG	1	2	15
(N20)NGG	19	17953871	+	GGTGAGTGGGCGCCTCCCCGTGG	1	4	34
(N20)NGG	19	17953872	+	GTGAGTGGGCGCCTCCCCGTGGG	1	1	10
(N20)NGG	19	17953886	+	CCCCGTGGGCCTCAGTCTCAAGG	1	6	39
(N20)NGG	19	17953892	+	GGGCCTCAGTCTCAAGGAGCAGG	1	2	44
(N20)NGG	19	17953893	+	GGCCTCAGTCTCAAGGAGCAGGG	1	2	36
(N20)NGG	19	17953910	+	GCAGGGTGAGTGTCTCAGCCTGG	1	6	70
(N20)NGG	19	17953919	+	GTGTCTCAGCCTGGCCGTGTTGG	1	4	32
(N20)NGG	19	17953925	+	CAGCCTGGCCGTGTTGGACCTGG	1	10	30
(N20)NGG	19	17953930	+	TGGCCGTGTTGGACCTGGCCCGG	1	1	15

FIG. 8

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17953934	+	CGTGTTGGACCTGGCCCGGATGG	1	2	8
(N20)NGG	19	17953946	+	GGCCCGGATGGCGCGAGAGCAGG	1	1	10
(N20)NGG	19	17953954	+	TGGCGCGAGAGCAGGCCCAGCGG	1	4	34
(N20)NGG	19	17953958	+	GCGAGAGCAGGCCCAGCGGCCGG	1	3	47
(N20)NGG	19	17953959	+	CGAGAGCAGGCCCAGCGGCCGGG	1	9	45
(N20)NGG	19	17953981	+	GAGAGCTGCTGAAGACTGTCAGG	1	3	36
(N20)NGG	19	17953995	+	ACTGTCAGGTGAGAGCCACCAGG	2	5	65
(N20)NGG	19	17954001	+	AGGTGAGAGCCACCAGGCTGTGG	3	27	432
(N20)NGG	19	17954002	+	GGTGAGAGCCACCAGGCTGTGGG	1	5	69
(N20)NGG	19	17954003	+	GTGAGAGCCACCAGGCTGTGGGG	1	8	71
(N20)NGG	19	17953816	-	GGTGCTGGGGGGCCGCCACAGGG	1	2	29
(N20)NGG	19	17953817	-	CGGTGCTGGGGGGCCGCCACAGG	1	1	23
(N20)NGG	19	17953827	-	CAGGTCACTGCGGTGCTGGGGGG	1	4	41
(N20)NGG	19	17953828	-	CCAGGTCACTGCGGTGCTGGGGG	1	4	52
(N20)NGG	19	17953829	-	ACCAGGTCACTGCGGTGCTGGGG	1	4	24
(N20)NGG	19	17953830	-	CACCAGGTCACTGCGGTGCTGGG	1	1	29
(N20)NGG	19	17953831	-	TCACCAGGTCACTGCGGTGCTGG	1	1	17
(N20)NGG	19	17953837	-	GCCCACTCACCAGGTCACTGCGG	1	5	45
(N20)NGG	19	17953846	-	CGGGGAGGCGCCCACTCACCAGG	1	3	35
(N20)NGG	19	17953861	-	TGAGACTGAGGCCCACGGGGAGG	1	5	104
(N20)NGG	19	17953864	-	CCTTGAGACTGAGGCCCACGGGG	1	4	29
(N20)NGG	19	17953865	-	TCCTTGAGACTGAGGCCCACGGG	2	2	41
(N20)NGG	19	17953866	-	CTCCTTGAGACTGAGGCCCACGG	2	8	69
(N20)NGG	19	17953873	-	CACCCTGCTCCTTGAGACTGAGG	1	2	40
(N20)NGG	19	17953906	-	GGGCCAGGTCCAACACGGCCAGG	1	2	24

FIG. 8

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17953911	-	CATCCGGGCCAGGTCCAACACGG	1	2	19
(N20)NGG	19	17953921	-	GCTCTCGCGCCATCCGGGCCAGG	1	1	6
(N20)NGG	19	17953926	-	GGCCTGCTCTCGCGCCATCCGGG	1	1	16
(N20)NGG	19	17953927	-	GGGCCTGCTCTCGCGCCATCCGG	1	2	12
(N20)NGG	19	17953947	-	CAGCAGCTCTCCCGGCCGCTGGG	1	1	38
(N20)NGG	19	17953948	-	TCAGCAGCTCTCCCGGCCGCTGG	1	1	25
(N20)NGG	19	17953955	-	ACAGTCTTCAGCAGCTCTCCCGG	1	4	45
(N20)NGG	19	17954206	+	ACAGCTTTTACTTCCCCAATTGG	1	5	52
(N20)NGG	19	17954211	+	TTTTACTTCCCCAATTGGTTTGG	1	3	55
(N20)NGG	19	17954212	+	TTTACTTCCCCAATTGGTTTGGG	1	2	32
(N20)NGG	19	17954216	+	CTTCCCCAATTGGTTTGGGCTGG	1	1	14
(N20)NGG	19	17954235	+	CTGGAGAAGTGCCACCGCTTCGG	1	2	13
(N20)NGG	19	17954236	+	TGGAGAAGTGCCACCGCTTCGGG	1	2	14
(N20)NGG	19	17954246	+	CCACCGCTTCGGGCTACGCAAGG	1	1	2
(N20)NGG	19	17954252	+	CTTCGGGCTACGCAAGGATTTGG	1	2	4
(N20)NGG	19	17954282	+	TATCCTTGACCTGCCAGTCCTGG	1	2	28
(N20)NGG	19	17954300	+	CCTGGAGCACCTCTTTGCCCAGG	1	7	57
(N20)NGG	19	17954303	+	GGAGCACCTCTTTGCCCAGGTGG	1	4	46
(N20)NGG	19	17954304	+	GAGCACCTCTTTGCCCAGGTGGG	1	6	43
(N20)NGG	19	17954305	+	AGCACCTCTTTGCCCAGGTGGGG	1	7	64
(N20)NGG	19	17954315	+	TGCCCAGGTGGGGTTCTGCCTGG	3	4	64
(N20)NGG	19	17954316	+	GCCCAGGTGGGGTTCTGCCTGGG	2	4	58
(N20)NGG	19	17954317	+	CCCAGGTGGGGTTCTGCCTGGGG	2	7	75
(N20)NGG	19	17954163	-	GTGAGGAGAGGAGAGAACCCTGG	1	6	147
(N20)NGG	19	17954175	-	GAAGTAAAAGCTGTGAGGAGAGG	1	7	74

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17954180	-	TTGGGGAAGTAAAAGCTGTGAGG	1	6	70
(N20)NGG	19	17954197	-	TCTCCAGCCCAAACCAATTGGGG	1	1	40
(N20)NGG	19	17954198	-	TTCTCCAGCCCAAACCAATTGGG	1	3	53
(N20)NGG	19	17954199	-	CTTCTCCAGCCCAAACCAATTGG	1	3	46
(N20)NGG	19	17954224	-	CCTTGCGTAGCCCGAAGCGGTGG	1	1	5
(N20)NGG	19	17954227	-	AATCCTTGCGTAGCCCGAAGCGG	1	1	3
(N20)NGG	19	17954253	-	TGGCAGGTCAAGGATAGCACTGG	1	1	40
(N20)NGG	19	17954263	-	GCTCCAGGACTGGCAGGTCAAGG	1	3	62
(N20)NGG	19	17954269	-	AGAGGTGCTCCAGGACTGGCAGG	1	4	60
(N20)NGG	19	17954273	-	GCAAAGAGGTGCTCCAGGACTGG	1	2	34
(N20)NGG	19	17954278	-	CCTGGGCAAAGAGGTGCTCCAGG	1	3	54
(N20)NGG	19	17954287	-	AGAACCCCACCTGGGCAAAGAGG	2	2	46
(N20)NGG	19	17954295	-	CCCCAGGCAGAACCCCACCTGGG	2	6	89
(N20)NGG	19	17954296	-	ACCCCAGGCAGAACCCCACCTGG	1	4	61
(N20)NGG	19	17954585	+	CTGATGGGACCATCCCCTGTAGG	1	2	22
(N20)NGG	19	17954620	+	GTACCACTCCCTCTTTGCTCTGG	1	2	24
(N20)NGG	19	17954626	+	CTCCCTCTTTGCTCTGGCCACGG	1	2	126
(N20)NGG	19	17954629	+	CCTCTTTGCTCTGGCCACGGAGG	1	1	45
(N20)NGG	19	17954643	+	CCACGGAGGACCTGTCCTGCTGG	1	1	24
(N20)NGG	19	17954671	+	CCCGAGCCACATCTTCTCCGTGG	1	3	17
(N20)NGG	19	17954674	+	GAGCCACATCTTCTCCGTGGAGG	1	2	23
(N20)NGG	19	17954703	+	GCACCCAAGTCCTGCTGTACAGG	1	4	22
(N20)NGG	19	17954709	+	AAGTCCTGCTGTACAGGATTCGG	1	1	32
(N20)NGG	19	17954713	+	CCTGCTGTACAGGATTCGGTAGG	1	1	8
(N20)NGG	19	17954572	-	GGCAGGATGCCTACAGGGGATGG	1	3	71

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17954576	-	CACAGGCAGGATGCCTACAGGGG	1	8	69
(N20)NGG	19	17954577	-	ACACAGGCAGGATGCCTACAGGG	1	5	54
(N20)NGG	19	17954578	-	TACACAGGCAGGATGCCTACAGG	1	2	20
(N20)NGG	19	17954589	-	AGAGGGAGTGGTACACAGGCAGG	1	5	64
(N20)NGG	19	17954593	-	GCAAAGAGGGAGTGGTACACAGG	1	3	32
(N20)NGG	19	17954601	-	TGGCCAGAGCAAAGAGGGAGTGG	2	15	482
(N20)NGG	19	17954606	-	CTCCGTGGCCAGAGCAAAGAGGG	1	2	39
(N20)NGG	19	17954607	-	CCTCCGTGGCCAGAGCAAAGAGG	1	7	41
(N20)NGG	19	17954621	-	CCAGCAGGACAGGTCCTCCGTGG	1	1	32
(N20)NGG	19	17954631	-	TCGGGGGGAACCAGCAGGACAGG	1	1	20
(N20)NGG	19	17954636	-	GTGGCTCGGGGGGAACCAGCAGG	1	2	25
(N20)NGG	19	17954646	-	CGGAGAAGATGTGGCTCGGGGGG	1	1	21
(N20)NGG	19	17954647	-	ACGGAGAAGATGTGGCTCGGGGG	1	2	17
(N20)NGG	19	17954648	-	CACGGAGAAGATGTGGCTCGGGG	1	2	12
(N20)NGG	19	17954649	-	CCACGGAGAAGATGTGGCTCGGG	1	4	25
(N20)NGG	19	17954650	-	TCCACGGAGAAGATGTGGCTCGG	1	3	31
(N20)NGG	19	17954655	-	CATCCTCCACGGAGAAGATGTGG	1	2	32
(N20)NGG	19	17954666	-	TTGGGTGCTGGCATCCTCCACGG	1	3	53
(N20)NGG	19	17954678	-	GTACAGCAGGACTTGGGTGCTGG	1	3	38
(N20)NGG	19	17954684	-	AATCCTGTACAGCAGGACTTGGG	1	2	38
(N20)NGG	19	17954685	-	GAATCCTGTACAGCAGGACTTGG	1	2	25
(N20)NGG	19	17954691	-	CCTACCGAATCCTGTACAGCAGG	1	1	2
(N20)NGG	19	17955045	+	CCCCAGGCAAGTTGCACTCATGG	1	4	47
(N20)NGG	19	17955105	+	TTCATGCAGCCTCTTGTCCACGG	1	2	48
(N20)NGG	19	17955108	+	ATGCAGCCTCTTGTCCACGGAGG	1	2	13

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17955112	+	AGCCTCTTGTCCACGGAGGCTGG	1	1	19
(N20)NGG	19	17955140	+	TGCATGTGCTGCTGCCCGCTCGG	1	2	22
(N20)NGG	19	17955141	+	GCATGTGCTGCTGCCCGCTCGGG	1	3	27
(N20)NGG	19	17955142	+	CATGTGCTGCTGCCCGCTCGGGG	1	2	7
(N20)NGG	19	17955148	+	CTGCTGCCCGCTCGGGGCCCCGG	1	4	52
(N20)NGG	19	17955149	+	TGCTGCCCGCTCGGGGCCCCGGG	1	1	51
(N20)NGG	19	17955178	+	CAGCGCCTATCTTTCTCCTTTGG	1	2	27
(N20)NGG	19	17955179	+	AGCGCCTATCTTTCTCCTTTGGG	1	2	23
(N20)NGG	19	17955180	+	GCGCCTATCTTTCTCCTTTGGGG	1	1	20
(N20)NGG	19	17955189	+	TTTCTCCTTTGGGGACCACTTGG	1	3	51
(N20)NGG	19	17955195	+	CTTTGGGGACCACTTGGCTGAGG	1	4	72
(N20)NGG	19	17955210	+	GGCTGAGGACCTGTGCGTGCAGG	1	4	33
(N20)NGG	19	17955219	+	CCTGTGCGTGCAGGCTGCCAAGG	1	4	40
(N20)NGG	19	17955226	+	GTGCAGGCTGCCAAGGCCAGCGG	1	10	130
(N20)NGG	19	17955244	+	AGCGGTGAGTGCATCCCTAGTGG	2	2	6
(N20)NGG	19	17955249	+	TGAGTGCATCCCTAGTGGATCGG	1	2	31
(N20)NGG	19	17955250	+	GAGTGCATCCCTAGTGGATCGGG	1	1	10
(N20)NGG	19	17955023	-	CCATGAGTGCAACTTGCCTGGGG	1	12	546
(N20)NGG	19	17955024	-	GCCATGAGTGCAACTTGCCTGGG	1	9	338
(N20)NGG	19	17955025	-	TGCCATGAGTGCAACTTGCCTGG	1	3	34
(N20)NGG	19	17955048	-	AGGGGCGTCTCTTCACTTGGAGG	1	1	17
(N20)NGG	19	17955051	-	ATCAGGGGCGTCTCTTCACTTGG	1	1	12
(N20)NGG	19	17955066	-	CATGAACGCTGAGGGATCAGGGG	1	2	19
(N20)NGG	19	17955067	-	GCATGAACGCTGAGGGATCAGGG	1	1	23
(N20)NGG	19	17955068	-	TGCATGAACGCTGAGGGATCAGG	1	1	21

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	19	17955074	-	AGAGGCTGCATGAACGCTGAGGG	1	2	24
(N20)NGG	19	17955075	-	AAGAGGCTGCATGAACGCTGAGG	1	2	34
(N20)NGG	19	17955092	-	CACCAGCCTCCGTGGACAAGAGG	1	3	27
(N20)NGG	19	17955100	-	ATGCAGGGCACCAGCCTCCGTGG	1	3	36
(N20)NGG	19	17955115	-	AGCGGGCAGCAGCACATGCAGGG	2	4	58
(N20)NGG	19	17955116	-	GAGCGGGCAGCAGCACATGCAGG	1	3	47
(N20)NGG	19	17955132	-	GGGGGCCCGGGGCCCCGAGCGGG	1	13	120
(N20)NGG	19	17955133	-	GGGGGGCCCGGGGCCCCGAGCGG	1	8	125
(N20)NGG	19	17955143	-	ATAGGCGCTGGGGGGGCCCGGGG	1	2	13
(N20)NGG	19	17955144	-	GATAGGCGCTGGGGGGGCCCGGG	1	2	33
(N20)NGG	19	17955145	-	AGATAGGCGCTGGGGGGGCCCGG	1	1	26
(N20)NGG	19	17955150	-	GAGAAAGATAGGCGCTGGGGGGG	1	1	45
(N20)NGG	19	17955151	-	GGAGAAAGATAGGCGCTGGGGGG	1	9	159
(N20)NGG	19	17955152	-	AGGAGAAAGATAGGCGCTGGGGG	1	3	129
(N20)NGG	19	17955153	-	AAGGAGAAAGATAGGCGCTGGGG	1	5	50
(N20)NGG	19	17955154	-	AAAGGAGAAAGATAGGCGCTGGG	1	5	45
(N20)NGG	19	17955155	-	CAAAGGAGAAAGATAGGCGCTGG	1	2	48
(N20)NGG	19	17955161	-	GGTCCCCAAAGGAGAAAGATAGG	1	7	46
(N20)NGG	19	17955172	-	CTCAGCCAAGTGGTCCCCAAAGG	1	5	40
(N20)NGG	19	17955182	-	CGCACAGGTCCTCAGCCAAGTGG	1	3	20
(N20)NGG	19	17955197	-	CCTTGGCAGCCTGCACGCACAGG	1	5	30
(N20)NGG	19	17955214	-	GATGCACTCACCGCTGGCCTTGG	1	1	22
(N20)NGG	19	17955220	-	ACTAGGGATGCACTCACCGCTGG	1	2	4

FIG. 8

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	13	108860971	+	GAACGAATACAGAAAAGTAAAGG	1	4	132
(N20)NGG	13	108860999	+	CAGAAAAAATCAGACACTTCAGG	2	4	102
(N20)NGG	13	108861000	+	AGAAAAAATCAGACACTTCAGGG	1	7	193
(N20)NGG	13	108861017	+	TCAGGGAATTTTTAGATTCTTGG	1	4	97
(N20)NGG	13	108861120	+	TCAGCTAGAAAGAGAGAGAATGG	1	24	320
(N20)NGG	13	108861127	+	GAAAGAGAGAGAATGGCCTATGG	1	9	187
(N20)NGG	13	108861187	+	TTGCTTAATTTACCTAGAGATGG	1	3	71
(N20)NGG	13	108861229	+	TTAAACTACAGAACACCCACTGG	1	2	40
(N20)NGG	13	108861238	+	AGAACACCCACTGGAACTCATGG	1	5	43
(N20)NGG	13	108861247	+	ACTGGAACTCATGGAGATGCTGG	1	3	54
(N20)NGG	13	108861301	+	AAGCCAAGATGTTTACAGAAAGG	1	8	83
(N20)NGG	13	108861434	+	GTTCAGCACTTGAGCAAAAGTGG	2	4	30
(N20)NGG	13	108861443	+	TTGAGCAAAAGTGGCTTATACGG	1	1	42
(N20)NGG	13	108861456	+	GCTTATACGGATGATCATAAAGG	1	2	11
(N20)NGG	13	108861469	+	ATCATAAAGGATTTAAAGCTTGG	1	7	76
(N20)NGG	13	108861543	+	GCATAATGTCACTACAGATCTGG	1	2	17
(N20)NGG	13	108861557	+	CAGATCTGGAAAAAGTCTGTAGG	1	5	67
(N20)NGG	13	108861580	+	CAACTGCATGATCCTTCTGTAGG	1	3	22
(N20)NGG	13	108861663	+	AGATATTGAGCACATTGAGAAGG	1	3	47
(N20)NGG	13	108861706	+	TACATAGAAACCAAGCTAGATGG	1	3	65
(N20)NGG	13	108861733	+	CGTATGCAAATGCACACAAGATGG	1	6	63
(N20)NGG	13	108861763	+	TATAAATACTTCTCTCGAAATGG	1	3	55
(N20)NGG	13	108861787	+	TATAACTACACTGATCAGTTTGG	1	3	28
(N20)NGG	13	108861805	+	TTTGGTGCTTCTCCTACTGAAGG	1	3	41
(N20)NGG	13	108861868	+	ATACAAATCTGTATTCTTGATGG	1	4	80

FIG. 9

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	13	108861879	+	TATTCTTGATGGTGAGATGATGG	1	5	52
(N20)NGG	13	108861915	+	TACACAAACTTTCATGCAAAAGG	1	6	92
(N20)NGG	13	108861916	+	ACACAAACTTTCATGCAAAAGGG	1	9	109
(N20)NGG	13	108861942	+	TAAGTTTGATATTAAAAGAATGG	1	13	223
(N20)NGG	13	108861948	+	TGATATTAAAAGAATGGTAGAGG	1	7	109
(N20)NGG	13	108861993	+	TTGTGTTTTTGATGTATTGATGG	1	8	188
(N20)NGG	13	108862012	+	ATGGTTAATAATAAAAAGCTAGG	1	10	140
(N20)NGG	13	108862013	+	TGGTTAATAATAAAAAGCTAGGG	1	5	129
(N20)NGG	13	108862034	+	GGCATGAGACTCTGAGAAAGAGG	2	6	82
(N20)NGG	13	108862072	+	AGTATTTTTACACCAATTCCAGG	2	2	72
(N20)NGG	13	108862161	+	AGCAATAGATAAAAGAGAAGAGG	1	13	203
(N20)NGG	13	108862162	+	GCAATAGATAAAAGAGAAGAGGG	2	13	232
(N20)NGG	13	108862170	+	TAAAAGAGAAGAGGGAATTATGG	1	13	241
(N20)NGG	13	108862210	+	ATCTACAAGCCAGACAAAAGAGG	2	10	219
(N20)NGG	13	108862216	+	AAGCCAGACAAAAGAGGTGAAGG	2	13	147
(N20)NGG	13	108862217	+	AGCCAGACAAAAGAGGTGAAGGG	1	7	94
(N20)NGG	13	108862220	+	CAGACAAAAGAGGTGAAGGGTGG	1	5	107
(N20)NGG	13	108862249	+	ATTAAACCAGAGTATGTCAGTGG	1	4	25
(N20)NGG	13	108862257	+	AGAGTATGTCAGTGGACTAATGG	1	3	40
(N20)NGG	13	108862266	+	CAGTGGACTAATGGATGAATTGG	2	6	92
(N20)NGG	13	108862282	+	GAATTGGACATTTTAATTGTTGG	1	8	108
(N20)NGG	13	108862285	+	TTGGACATTTTAATTGTTGGAGG	1	5	89
(N20)NGG	13	108862292	+	TTTTAATTGTTGGAGGATATTGG	1	3	107
(N20)NGG	13	108862293	+	TTTAATTGTTGGAGGATATTGGG	1	7	118
(N20)NGG	13	108862294	+	TTAATTGTTGGAGGATATTGGGG	1	4	60

FIG. 9

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	13	108862300	+	GTTGGAGGATATTGGGGTAAAGG	1	4	35
(N20)NGG	13	108862307	+	GATATTGGGGTAAAGGATCACGG	1	2	25
(N20)NGG	13	108862308	+	ATATTGGGGTAAAGGATCACGGG	1	3	23
(N20)NGG	13	108862309	+	TATTGGGGTAAAGGATCACGGGG	1	2	16
(N20)NGG	13	108862312	+	TGGGGTAAAGGATCACGGGGTGG	1	2	18
(N20)NGG	13	108862360	+	GTAGCAGAGAAGCCCCCTCCTGG	1	2	35
(N20)NGG	13	108862399	+	TTTCATACTCTCTCTCGTGTTGG	1	2	23
(N20)NGG	13	108862400	+	TTCATACTCTCTCTCGTGTTGGG	1	1	30
(N20)NGG	13	108862405	+	ACTCTCTCTCGTGTTGGGTCTGG	1	1	13
(N20)NGG	13	108862434	+	CATGAAAGAACTGTATGATCTGG	1	2	41
(N20)NGG	13	108862435	+	ATGAAAGAACTGTATGATCTGGG	1	4	76
(N20)NGG	13	108862446	+	GTATGATCTGGGTTTGAAATTGG	1	2	51
(N20)NGG	13	108862457	+	GTTTGAAATTGGCCAAGTATTGG	1	5	44
(N20)NGG	13	108862501	+	CCACCAAGCAGCATTTTATGTGG	1	3	44
(N20)NGG	13	108862597	+	CCCAGTGATATGTATAAAACTGG	1	4	34
(N20)NGG	13	108862644	+	TGAAAAGATAAGAGATGACAAGG	1	10	202
(N20)NGG	13	108862649	+	AGATAAGAGATGACAAGGAGTGG	2	11	152
(N20)NGG	13	108862668	+	GTGGCATGAGTGCATGACCCTGG	1	1	50
(N20)NGG	13	108862688	+	TGGACGACCTAGAACAACTTAGG	1	2	8
(N20)NGG	13	108862689	+	GGACGACCTAGAACAACTTAGGG	1	2	6
(N20)NGG	13	108862690	+	GACGACCTAGAACAACTTAGGGG	1	1	12
(N20)NGG	13	108862691	+	ACGACCTAGAACAACTTAGGGGG	1	1	14
(N20)NGG	13	108862695	+	CCTAGAACAACTTAGGGGGAAGG	1	1	21
(N20)NGG	13	108862702	+	CAACTTAGGGGGAAGGCATCTGG	1	4	59
(N20)NGG	13	108862732	+	GCATCTAAACACCTTTATATAGG	1	4	38

FIG. 9

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	13	108862735	+	TCTAAACACCTTTATATAGGTGG	1	2	40
(N20)NGG	13	108862763	+	ATGAACCACAAGAAAAAAAGCGG	1	8	286
(N20)NGG	13	108862795	+	CCAAAGATGAAGAAAGTTATTGG	1	10	120
(N20)NGG	13	108862885	+	GTAGAGTTTTGTGTTATGAGTGG	1	2	38
(N20)NGG	13	108862914	+	TAGCCAGCCAAAGCCTGACCTGG	1	2	19
(N20)NGG	13	108862936	+	GAGAACAGAATTGCAGAATTTGG	1	8	110
(N20)NGG	13	108862939	+	AACAGAATTGCAGAATTTGGTGG	1	6	106
(N20)NGG	13	108862960	+	GGTTATATAGTACAAAATCCAGG	1	2	21
(N20)NGG	13	108862987	+	GACACGTACTGTGTAATTGCAGG	1	1	13
(N20)NGG	13	108862988	+	ACACGTACTGTGTAATTGCAGGG	1	2	19
(N20)NGG	13	108863054	+	ATGATGTTGTCAAGCCTGCATGG	1	5	38
(N20)NGG	13	108863093	+	AGACCAAAAGCTTTGTACCATGG	1	3	40
(N20)NGG	13	108863164	+	GCCCGTGAATATGATTGCTATGG	1	2	7
(N20)NGG	13	108863205	+	TACAGACTTGAACCAACTGAAGG	1	1	38
(N20)NGG	13	108863218	+	CAACTGAAGGAAGTATTCTCAGG	1	1	41
(N20)NGG	13	108863256	+	CGAGCAGACTCCTGAAGAAATGG	1	2	37
(N20)NGG	13	108863285	+	TGATTGCTGATTTAGAATATCGG	1	4	88
(N20)NGG	13	108863294	+	ATTTAGAATATCGGTATTCCTGG	1	1	18
(N20)NGG	13	108863295	+	TTTAGAATATCGGTATTCCTGGG	1	2	27
(N20)NGG	13	108863340	+	TCGACGCCACACCGTTTATTTGG	1	1	2
(N20)NGG	13	108863382	+	TGACCTGAGTACCAAAAATGAGG	1	3	33
(N20)NGG	13	108863383	+	GACCTGAGTACCAAAAATGAGGG	1	2	32
(N20)NGG	13	108863384	+	ACCTGAGTACCAAAAATGAGGGG	1	5	34
(N20)NGG	13	108863390	+	GTACCAAAAATGAGGGGACAAGG	2	2	41
(N20)NGG	13	108863409	+	AAGGTTAGCTATTAAAGCCTTGG	1	4	27

FIG. 9

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	13	108863417	+	CTATTAAAGCCTTGGAGCTTCGG	1	2	31
(N20)NGG	13	108863425	+	GCCTTGGAGCTTCGGTTTCATGG	1	3	18
(N20)NGG	13	108863454	+	AGTAGTTTCTTGTTTAGCTGAGG	1	5	47
(N20)NGG	13	108863455	+	GTAGTTTCTTGTTTAGCTGAGGG	1	4	51
(N20)NGG	13	108863476	+	GGAGTGTCTCATGTAATAATTGG	1	2	29
(N20)NGG	13	108863477	+	GAGTGTCTCATGTAATAATTGGG	1	7	48
(N20)NGG	13	108863478	+	AGTGTCTCATGTAATAATTGGGG	1	6	62
(N20)NGG	13	108863558	+	TTAAAATCCTAAAGAAAGTTGG	2	22	272
(N20)NGG	13	108863559	+	TAAAATCCTAAAGAAAGTTGGG	2	14	269
(N20)NGG	13	108860887	-	AACAGTTTGTGAAGTTTGTGAGG	1	6	80
(N20)NGG	13	108860922	-	GTTGAACACAAATCTGCAAAAGG	1	6	72
(N20)NGG	13	108861047	-	AAGAGTCTGTGACATCTTTGTGG	1	5	70
(N20)NGG	13	108861075	-	GGAAGAATTAGTCTCATTGCTGG	1	2	28
(N20)NGG	13	108861096	-	ATTCTCTCTCTTTCTAGCTGAGG	1	10	144
(N20)NGG	13	108861121	-	CATAGTTTCTTTAATTCCATAGG	1	15	131
(N20)NGG	13	108861177	-	AGGGCATCTTTTCCATCTCTAGG	1	4	72
(N20)NGG	13	108861196	-	TCTGTAGTTTAAAAGTTTGAGGG	1	14	139
(N20)NGG	13	108861197	-	TTCTGTAGTTTAAAAGTTTGAGG	1	12	235
(N20)NGG	13	108861222	-	GCATCTCCATGAGTTCCAGTGGG	1	1	33
(N20)NGG	13	108861223	-	AGCATCTCCATGAGTTCCAGTGG	1	4	57
(N20)NGG	13	108861282	-	CTTCCTTTCTGTAAACATCTTGG	2	9	100
(N20)NGG	13	108861310	-	AAGGTCGTTTACTTGCTGTATGG	1	1	14
(N20)NGG	13	108861329	-	TGCTGGCAATTGAGTCTAAAAGG	1	2	27
(N20)NGG	13	108861346	-	TCTTTTAGCAGAATTATTGCTGG	1	5	61
(N20)NGG	13	108861374	-	GAAGAAGGCTCTTTTTTATTAGG	1	4	98

FIG. 9

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	13	108861389	-	TCTGAGTTATAAGTTGAAGAAGG	1	2	58
(N20)NGG	13	108861570	-	ATATCACTGAGTCCTACAGAAGG	1	4	39
(N20)NGG	13	108861621	-	TCTGCAATAGCAGCTAGCATTGG	1	1	31
(N20)NGG	13	108861694	-	CATACGTTCACCATCTAGCTTGG	1	1	15
(N20)NGG	13	108861795	-	GGGGTAAGAGAACCTTCAGTAGG	1	1	18
(N20)NGG	13	108861814	-	GAATGCATTATGAATGAATGGGG	2	21	230
(N20)NGG	13	108861815	-	TGAATGCATTATGAATGAATGGG	2	32	329
(N20)NGG	13	108861816	-	TTGAATGCATTATGAATGAATGG	1	10	174
(N20)NGG	13	108861880	-	AGTTTGTGTATTAGGATTATAGG	1	3	41
(N20)NGG	13	108861888	-	TGCATGAAAGTTTGTGTATTAGG	1	5	76
(N20)NGG	13	108862062	-	ATTTCTATTCTACCTGGAATTGG	1	5	154
(N20)NGG	13	108862068	-	TGCACTATTTCTATTCTACCTGG	1	4	37
(N20)NGG	13	108862179	-	TCTGGCTTGTAGATGGATAGAGG	1	5	35
(N20)NGG	13	108862186	-	TCTTTTGTCTGGCTTGTAGATGG	1	4	81
(N20)NGG	13	108862197	-	CACCCTTCACCTCTTTTGTCTGG	1	8	33
(N20)NGG	13	108862233	-	ATTAGTCCACTGACATACTCTGG	1	2	24
(N20)NGG	13	108862350	-	GATGGCTTCTCACCAGGAGGGGG	1	9	121
(N20)NGG	13	108862351	-	AGATGGCTTCTCACCAGGAGGGG	1	4	53
(N20)NGG	13	108862352	-	CAGATGGCTTCTCACCAGGAGGG	2	8	60
(N20)NGG	13	108862353	-	ACAGATGGCTTCTCACCAGGAGG	2	5	74
(N20)NGG	13	108862356	-	AACACAGATGGCTTCTCACCAGG	1	5	49
(N20)NGG	13	108862368	-	GAGAGAGTATGAAACACAGATGG	1	15	279
(N20)NGG	13	108862411	-	CAGATCATACAGTTCTTTCATGG	1	5	51
(N20)NGG	13	108862447	-	ATGAAAAGGCTTCCAATACTTGG	1	1	36
(N20)NGG	13	108862461	-	GGTGGAGCTTTTCTATGAAAAGG	1	4	45

FIG. 9

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	13	108862479	-	CCACATAAAATGCTGCTTGGTGG	1	2	44
(N20)NGG	13	108862482	-	GTTCCACATAAAATGCTGCTTGG	1	2	44
(N20)NGG	13	108862512	-	CAAGGTTCAATGTATACTTCTGG	1	2	24
(N20)NGG	13	108862530	-	TGAACAATGACAGAATTACAAGG	1	8	103
(N20)NGG	13	108862575	-	CCAGTTTTATACATATCACTGGG	1	3	54
(N20)NGG	13	108862576	-	GCCAGTTTTATACATATCACTGG	1	2	26
(N20)NGG	13	108862603	-	TTCAATTCGTGGAAAACGCAAGG	1	2	13
(N20)NGG	13	108862614	-	TCTCTTATCTTTTCAATTCGTGG	1	3	54
(N20)NGG	13	108862663	-	AAGTTGTTCTAGGTCGTCCAGGG	1	2	9
(N20)NGG	13	108862664	-	TAAGTTGTTCTAGGTCGTCCAGG	1	1	8
(N20)NGG	13	108862673	-	CCTTCCCCCTAAGTTGTTCTAGG	1	4	40
(N20)NGG	13	108862721	-	CATCATCACCACCTATATAAAGG	1	6	43
(N20)NGG	13	108862746	-	GCTTTCCGCTTTTTTTCTTGTGG	1	4	72
(N20)NGG	13	108862771	-	AATAACTTTCTTCATCTTTGGGG	3	14	170
(N20)NGG	13	108862772	-	CAATAACTTTCTTCATCTTTGGG	1	13	151
(N20)NGG	13	108862773	-	CCAATAACTTTCTTCATCTTTGG	1	5	82
(N20)NGG	13	108862818	-	TTGTTAACGTTAGTAAGGTTAGG	1	2	14
(N20)NGG	13	108862823	-	AAATTTTGTTAACGTTAGTAAGG	1	3	83
(N20)NGG	13	108862895	-	TCTCCAGGTCAGGCTTTGGCTGG	1	2	36
(N20)NGG	13	108862899	-	CTGTTCTCCAGGTCAGGCTTTGG	1	4	47
(N20)NGG	13	108862905	-	GCAATTCTGTTCTCCAGGTCAGG	1	4	30
(N20)NGG	13	108862910	-	ATTCTGCAATTCTGTTCTCCAGG	1	4	92
(N20)NGG	13	108862956	-	ACACAGTACGTGTCTGGGCCTGG	1	3	21
(N20)NGG	13	108862961	-	CAATTACACAGTACGTGTCTGGG	1	2	21
(N20)NGG	13	108862962	-	GCAATTACACAGTACGTGTCTGG	1	3	12

FIG. 9

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	13	108863046	-	AAACATTCTAAAAGCCATGCAGG	2	5	51
(N20)NGG	13	108863074	-	CTGCCATGGTACAAAGCTTTGG	1	2	31
(N20)NGG	13	108863088	-	ATCATAAAGCGAGGCTGCCATGG	1	1	14
(N20)NGG	13	108863097	-	CACATATGAATCATAAAGCGAGG	1	2	22
(N20)NGG	13	108863120	-	CAAAATGTTCTTTGGTTGATGGG	1	8	84
(N20)NGG	13	108863121	-	GCAAAATGTTCTTTGGTTGATGG	1	5	77
(N20)NGG	13	108863128	-	TTCACGGGCAAAATGTTCTTTGG	1	2	19
(N20)NGG	13	108863143	-	ACCATAGCAATCATATTCACGGG	1	1	26
(N20)NGG	13	108863144	-	CACCATAGCAATCATATTCACGG	1	4	44
(N20)NGG	13	108863195	-	CTGAGAATACTTCCTTCAGTTGG	1	2	48
(N20)NGG	13	108863244	-	ATCAGAGAAGCCATTTCTTCAGG	1	3	79
(N20)NGG	13	108863290	-	ACTGAGAGGAGAGCAATCCCAGG	1	2	43
(N20)NGG	13	108863304	-	TGGCGTCGAAACATACTGAGAGG	1	1	3
(N20)NGG	13	108863324	-	ACGAGTCCAAATAAACGGTGTGG	1	1	4
(N20)NGG	13	108863329	-	AGCATACGAGTCCAAATAAACGG	1	1	16
(N20)NGG	13	108863363	-	TCCCCTCATTTTTGGTACTCAGG	1	3	46
(N20)NGG	13	108863371	-	TAACCTTGTCCCCTCATTTTTGG	1	2	42
(N20)NGG	13	108863404	-	TCCATGAAACCGAAGCTCCAAGG	1	3	21
(N20)NGG	13	108863543	-	CAGTTACCCAACTTTCTTTTTAGG	1	3	56

FIG. 9

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	219941102	+	ACTTGGGTTCCCTTTTTTCTAGG	1	3	85
(N20)NGG	2	219941103	+	CTTGGGTTCCCTTTTTTCTAGGG	1	4	98
(N20)NGG	2	219941112	+	CCTTTTTTCTAGGGTACTTCAGG	1	5	42
(N20)NGG	2	219941141	+	GCAGAGACCTCAGCTGTCAAAGG	2	7	49
(N20)NGG	2	219941149	+	CTCAGCTGTCAAAGGTCAAGAGG	1	5	67
(N20)NGG	2	219941161	+	AGGTCAAGAGGAAGAAGCCAAGG	1	12	171
(N20)NGG	2	219941162	+	GGTCAAGAGGAAGAAGCCAAGGG	1	9	103
(N20)NGG	2	219941163	+	GTCAAGAGGAAGAAGCCAAGGGG	1	6	120
(N20)NGG	2	219941186	+	TCTCTTCAGTTAATCTGTTGTGG	1	2	51
(N20)NGG	2	219941201	+	TGTTGTGGCCTCAGCTGCTGAGG	2	5	75
(N20)NGG	2	219941089	-	CTGAAGTACCCTAGAAAAAAGGG	2	2	53
(N20)NGG	2	219941090	-	CCTGAAGTACCCTAGAAAAAAGG	1	5	44
(N20)NGG	2	219941113	-	ACAGCTGAGGTCTCTGCAGAGGG	1	13	200
(N20)NGG	2	219941114	-	GACAGCTGAGGTCTCTGCAGAGG	3	7	90
(N20)NGG	2	219941126	-	CTCTTGACCTTTGACAGCTGAGG	2	5	47
(N20)NGG	2	219941156	-	GATTAACTGAAGAGACCCCTTGG	1	1	16
(N20)NGG	2	219941967	+	CTCTTGATCTTTCTGATTTCAGG	1	5	119
(N20)NGG	2	219942003	+	TCAAACAGTGCTTCCCTGCAAGG	1	3	57
(N20)NGG	2	219942041	+	TGTAAACCAGCCAGAACAACTGG	1	4	61
(N20)NGG	2	219942086	+	AGCACCTGAGAAAGAGTCCACGG	1	2	66
(N20)NGG	2	219942108	+	GTGAGTCATGAGCAGCTTCCTGG	1	1	30
(N20)NGG	2	219941972	-	GAAGCACTGTTTGAGGTATGAGG	1	3	40
(N20)NGG	2	219941979	-	TTGCAGGGAAGCACTGTTTGAGG	1	2	54
(N20)NGG	2	219941994	-	TTGGCTATCGATTCCTTGCAGGG	1	2	7
(N20)NGG	2	219941995	-	ATTGGCTATCGATTCCTTGCAGG	1	1	30

FIG. 10

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	219942013	-	GTTCTGGCTGGTTTACACATTGG	1	3	38
(N20)NGG	2	219942025	-	AGGAGACCAGTTGTTCTGGCTGG	1	1	31
(N20)NGG	2	219942029	-	GCTGAGGAGACCAGTTGTTCTGG	1	1	23
(N20)NGG	2	219942045	-	TGCTGAGAGGGTTGGGGCTGAGG	1	12	181
(N20)NGG	2	219942051	-	CTCAGGTGCTGAGAGGGTTGGGG	1	7	79
(N20)NGG	2	219942052	-	TCTCAGGTGCTGAGAGGGTTGGG	1	2	73
(N20)NGG	2	219942053	-	TTCTCAGGTGCTGAGAGGGTTGG	1	6	74
(N20)NGG	2	219942057	-	CTCTTTCTCAGGTGCTGAGAGGG	1	3	80
(N20)NGG	2	219942058	-	ACTCTTTCTCAGGTGCTGAGAGG	1	2	58
(N20)NGG	2	219942068	-	CTCACCGTGGACTCTTTCTCAGG	1	2	39
(N20)NGG	2	219942081	-	AAGCTGCTCATGACTCACCGTGG	1	1	9
(N20)NGG	2	219942822	+	TCTCTTACAGAAACTGCCAGAGG	1	5	60
(N20)NGG	2	219942835	+	CTGCCAGAGGCATGCAGCATTGG	1	2	42
(N20)NGG	2	219942841	+	GAGGCATGCAGCATTGGTGATGG	1	6	90
(N20)NGG	2	219942867	+	GCCCTTTGTCATGAATCTGCAGG	1	2	33
(N20)NGG	2	219942879	+	GAATCTGCAGGATCTGTATATGG	1	5	31
(N20)NGG	2	219942897	+	TATGGCAGTCACCACACAAGAGG	1	3	28
(N20)NGG	2	219942906	+	CACCACACAAGAGGTCCAAGTGG	1	2	32
(N20)NGG	2	219942907	+	ACCACACAAGAGGTCCAAGTGGG	1	2	30
(N20)NGG	2	219942922	+	CAAGTGGGACAGAAGCATCAAGG	1	3	52
(N20)NGG	2	219942928	+	GGACAGAAGCATCAAGGCGCTGG	1	2	24
(N20)NGG	2	219942943	+	GGCGCTGGTGAGCCCTCCAGAGG	1	1	30
(N20)NGG	2	219942950	+	GTGAGCCCTCCAGAGGTACCCGG	1	1	23
(N20)NGG	2	219942796	-	TGGCAGTTTCTGTAAGAGAGAGG	1	3	78
(N20)NGG	2	219942816	-	TCACCAATGCTGCATGCCTCTGG	1	2	32

FIG. 10

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	219942846	-	TCCTGCAGATTCATGACAAAGGG	1	2	47
(N20)NGG	2	219942847	-	ATCCTGCAGATTCATGACAAAGG	1	2	32
(N20)NGG	2	219942886	-	TCCCACTTGGACCTCTTGTGTGG	1	2	60
(N20)NGG	2	219942899	-	CTTGATGCTTCTGTCCCACTTGG	1	3	31
(N20)NGG	2	220011442	+	ATTTGAAGAAAATTCCTTCTTGG	1	15	228
(N20)NGG	2	220011460	+	CTTGGAACAATTTATGATAGAGG	1	5	45
(N20)NGG	2	220011465	+	AACAATTTATGATAGAGGTAAGG	1	2	83
(N20)NGG	2	220011387	-	TCAATCGATCTGTAATAAGAAGG	1	1	25
(N20)NGG	2	220011418	-	AAGAAGGAATTTTCTTCAAATGG	1	16	274
(N20)NGG	2	220011434	-	TATCATAAATTGTTCCAAGAAGG	1	5	55
(N20)NGG	2	220012378	+	ATTGATATCTCTTCCCTCAAAGG	1	1	67
(N20)NGG	2	220012408	+	ACATTTGATTCGTCCTCTGATGG	1	2	14
(N20)NGG	2	220012409	+	CATTTGATTCGTCCTCTGATGGG	1	3	17
(N20)NGG	2	220012420	+	TCCTCTGATGGGCATGAGTCTGG	1	1	44
(N20)NGG	2	220012440	+	TGGCATTACAGTGCCAAGTGAGG	1	4	37
(N20)NGG	2	220012441	+	GGCATTACAGTGCCAAGTGAGGG	1	1	26
(N20)NGG	2	220012492	+	CCTAGAGATCCAAGACTACCAGG	1	1	12
(N20)NGG	2	220012499	+	ATCCAAGACTACCAGGAGAGTGG	1	4	42
(N20)NGG	2	220012500	+	TCCAAGACTACCAGGAGAGTGGG	1	6	44
(N20)NGG	2	220012501	+	CCAAGACTACCAGGAGAGTGGGG	2	4	44
(N20)NGG	2	220012517	+	AGTGGGGCTACGCTGATTCGAGG	1	1	5
(N20)NGG	2	220012524	+	CTACGCTGATTCGAGGTAAGAGG	1	1	5
(N20)NGG	2	220012534	+	TCGAGGTAAGAGGACATTCTTGG	1	2	55
(N20)NGG	2	220012537	+	AGGTAAGAGGACATTCTTGGAGG	1	3	66
(N20)NGG	2	220012369	-	AAATGTTGGGAGACCTTTGAGGG	1	5	66

FIG. 10

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	220012370	-	CAAATGTTGGGGAGACCTTTGAGG	1	2	43
(N20)NGG	2	220012382	-	CAGAGGACGAATCAAATGTTGGG	1	3	22
(N20)NGG	2	220012383	-	TCAGAGGACGAATCAAATGTTGG	1	2	23
(N20)NGG	2	220012399	-	GCCAGACTCATGCCCATCAGAGG	1	3	33
(N20)NGG	2	220012431	-	ACGTTGCTAGCTCCCTCACTTGG	1	2	16
(N20)NGG	2	220012470	-	CCTGGTAGTCTTGGATCTCTAGG	1	1	25
(N20)NGG	2	220012479	-	CCCCACTCTCCTGGTAGTCTTGG	1	5	37
(N20)NGG	2	220012488	-	TCAGCGTAGCCCCACTCTCCTGG	1	3	63
(N20)NGG	2	220022193	+	TGTACCACTGCTCTCTCTTTAGG	1	6	57
(N20)NGG	2	220022207	+	CTCTTTAGGAGCTGAACAAGCGG	1	4	43
(N20)NGG	2	220022244	+	TGCAGCTTTCCTCTGTCATTTGG	1	5	67
(N20)NGG	2	220022271	+	TCTCCTTCGCCCATTGTTGAAGG	3	13	95
(N20)NGG	2	220022316	+	TACCTTCTCCTGTGATTGTGTGG	4	70	594
(N20)NGG	2	220022336	+	TGGCAGATGCACTGATTCTACGG	1	3	32
(N20)NGG	2	220022337	+	GGCAGATGCACTGATTCTACGGG	1	2	19
(N20)NGG	2	220022356	+	CGGGTGCGAAGTGAGCTCTCTGG	1	2	6
(N20)NGG	2	220022372	+	TCTCTGGCCTCCCCTTCTATTGG	1	6	82
(N20)NGG	2	220022406	+	CATGCTAGCTAGTCCTTCCCTGG	1	2	15
(N20)NGG	2	220022426	+	TGGTAAGTGTAATTCGAATGTGG	1	2	12
(N20)NGG	2	220022427	+	GGTAAGTGTAATTCGAATGTGGG	1	3	19
(N20)NGG	2	220022428	+	GTAAGTGTAATTCGAATGTGGGG	1	2	19
(N20)NGG	2	220022175	-	AGCTCCTAAAGAGAGAGCAGTGG	2	4	69
(N20)NGG	2	220022217	-	TGACAGAGGAAAGCTGCAGGAGG	2	11	120
(N20)NGG	2	220022220	-	AAATGACAGAGGAAAGCTGCAGG	4	9	110
(N20)NGG	2	220022231	-	GGAGATTATCCAAATGACAGAGG	1	4	45

FIG. 10

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	220022252	-	CGTCCTTCAACAATGGGCGAAGG	1	1	4
(N20)NGG	2	220022258	-	GAGCAGCGTCCTTCAACAATGGG	1	1	13
(N20)NGG	2	220022259	-	TGAGCAGCGTCCTTCAACAATGG	1	2	9
(N20)NGG	2	220022282	-	AGGAGAAGGTAGCTTCGCTAGGG	1	1	10
(N20)NGG	2	220022283	-	CAGGAGAAGGTAGCTTCGCTAGG	1	2	18
(N20)NGG	2	220022296	-	TGCCACACAATCACAGGAGAAGG	1	6	119
(N20)NGG	2	220022302	-	TGCATCTGCCACACAATCACAGG	1	3	26
(N20)NGG	2	220022357	-	GGAAATTCCAATAGAAGGGGAGG	1	3	48
(N20)NGG	2	220022360	-	AGTGGAAATTCCAATAGAAGGGG	2	4	68
(N20)NGG	2	220022361	-	CAGTGGAAATTCCAATAGAAGGG	1	4	79
(N20)NGG	2	220022362	-	GCAGTGGAAATTCCAATAGAAGG	1	3	33
(N20)NGG	2	220022378	-	AAGGACTAGCTAGCATGCAGTGG	1	1	20
(N20)NGG	2	220022397	-	CGAATTACACTTACCAGGGAAGG	1	1	14
(N20)NGG	2	220022401	-	CATTCGAATTACACTTACCAGGG	1	2	21
(N20)NGG	2	220022402	-	ACATTCGAATTACACTTACCAGG	1	3	14
(N20)NGG	2	220022910	+	AATGAGGACTTTTTTGCAGATGG	1	5	99
(N20)NGG	2	220022919	+	TTTTTTGCAGATGGAAGAACTGG	1	7	146
(N20)NGG	2	220022926	+	CAGATGGAAGAACTGGAGCAAGG	2	19	216
(N20)NGG	2	220022945	+	AAGGCCTGTTGATGCAGCCATGG	1	5	40
(N20)NGG	2	220022946	+	AGGCCTGTTGATGCAGCCATGGG	1	1	29
(N20)NGG	2	220022951	+	TGTTGATGCAGCCATGGGCGTGG	1	2	17
(N20)NGG	2	220022979	+	GCTTGCAGAGAACTCCCTCTTGG	1	3	30
(N20)NGG	2	220022985	+	AGAGAACTCCCTCTTGGCCAAGG	1	10	95
(N20)NGG	2	220023003	+	CAAGGTTTTTATCACCAAGCAGG	1	1	20
(N20)NGG	2	220023004	+	AAGGTTTTTATCACCAAGCAGGG	1	3	55

FIG. 10

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	220023018	+	CAAGCAGGGCTATGCCTTGTTGG	1	1	25
(N20)NGG	2	220023036	+	GTTGGTTTCAGATCTTCAACAGG	1	1	28
(N20)NGG	2	220023041	+	TTTCAGATCTTCAACAGGTGTGG	1	2	31
(N20)NGG	2	220023051	+	TCAACAGGTGTGGCATGAACAGG	1	2	38
(N20)NGG	2	220023054	+	ACAGGTGTGGCATGAACAGGTGG	1	3	58
(N20)NGG	2	220023066	+	TGAACAGGTGGACACTAGTGTGG	1	1	19
(N20)NGG	2	220023084	+	TGTGGTCAGCCAGCGAGCCAAGG	1	4	39
(N20)NGG	2	220023095	+	AGCGAGCCAAGGTAAGTATGAGG	1	1	14
(N20)NGG	2	220022927	–	ACGCCCATGGCTGCATCAACAGG	1	1	14
(N20)NGG	2	220022940	–	GCAAGCTGTAGCCACGCCCATGG	1	1	17
(N20)NGG	2	220022971	–	GATAAAAACCTTGGCCAAGAGGG	1	2	40
(N20)NGG	2	220022972	–	TGATAAAAACCTTGGCCAAGAGG	1	2	40
(N20)NGG	2	220022980	–	CTGCTTGGTGATAAAAACCTTGG	1	1	33
(N20)NGG	2	220022995	–	CAACAAGGCATAGCCCTGCTTGG	1	2	27
(N20)NGG	2	220023010	–	TTGAAGATCTGAAACCAACAAGG	1	3	66
(N20)NGG	2	220023071	–	TCATACTTACCTTGGCTCGCTGG	1	1	6
(N20)NGG	2	220023079	–	ACTTCTCCTCATACTTACCTTGG	1	2	35

FIG. 10

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	14	20937686	+	AGAAGGCGTCTGCGAGACCATGG	1	1	13
(N20)NGG	14	20937693	+	GTCTGCGAGACCATGGAGAACGG	1	2	21
(N20)NGG	14	20937694	+	TCTGCGAGACCATGGAGAACGGG	1	2	25
(N20)NGG	14	20937699	+	GAGACCATGGAGAACGGGTGAGG	1	3	40
(N20)NGG	14	20937702	+	ACCATGGAGAACGGGTGAGGAGG	1	3	41
(N20)NGG	14	20937703	+	CCATGGAGAACGGGTGAGGAGGG	1	2	47
(N20)NGG	14	20937710	+	GAACGGGTGAGGAGGGCACCAGG	1	4	36
(N20)NGG	14	20937718	+	GAGGAGGGCACCAGGCCCGCAGG	1	5	57
(N20)NGG	14	20937681	-	CCCTCCTCACCCGTTCTCCATGG	1	4	50
(N20)NGG	14	20940502	+	ATTATAAGAACACTGCAGAATGG	2	12	138
(N20)NGG	14	20940549	+	CCTCAAGTTGCAATAATCTGTGG	1	1	37
(N20)NGG	14	20940555	+	GTTGCAATAATCTGTGGTTCTGG	1	5	26
(N20)NGG	14	20940561	+	ATAATCTGTGGTTCTGGATTAGG	1	2	54
(N20)NGG	14	20940564	+	ATCTGTGGTTCTGGATTAGGAGG	1	5	39
(N20)NGG	14	20940587	+	TCTGACTGATAAATTAACTCAGG	2	3	41
(N20)NGG	14	20940606	+	CAGGCCCAGATCTTTGACTACGG	1	2	42
(N20)NGG	14	20940636	+	CCCAACTTTCCCCGAAGTACAGG	1	1	17
(N20)NGG	14	20940642	+	TTTCCCCGAAGTACAGGTACTGG	1	2	31
(N20)NGG	14	20940647	+	CCGAAGTACAGGTACTGGCAAGG	1	2	14
(N20)NGG	14	20940648	+	CGAAGTACAGGTACTGGCAAGGG	1	1	15
(N20)NGG	14	20940655	+	CAGGTACTGGCAAGGGAAAGTGG	1	2	87
(N20)NGG	14	20940656	+	AGGTACTGGCAAGGGAAAGTGGG	1	4	61
(N20)NGG	14	20940657	+	GGTACTGGCAAGGGAAAGTGGGG	1	5	69
(N20)NGG	14	20940443	-	CTGGGGGAGAAAAAATATCAAGG	1	10	154
(N20)NGG	14	20940459	-	ATCTTCATAGGTGTATCTGGGGG	1	1	33

FIG. 11

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	14	20940460	-	AATCTTCATAGGTGTATCTGGGG	1	2	39
(N20)NGG	14	20940461	-	TAATCTTCATAGGTGTATCTGGG	1	6	47
(N20)NGG	14	20940462	-	ATAATCTTCATAGGTGTATCTGG	1	3	36
(N20)NGG	14	20940471	-	AGTGTTCTTATAATCTTCATAGG	1	1	75
(N20)NGG	14	20940523	-	AGATTATTGCAACTTGAGGTCGG	1	7	57
(N20)NGG	14	20940527	-	CCACAGATTATTGCAACTTGAGG	1	7	61
(N20)NGG	14	20940588	-	TTCACCGTAGTCAAAGATCTGGG	1	1	11
(N20)NGG	14	20940589	-	TTTCACCGTAGTCAAAGATCTGG	1	1	20
(N20)NGG	14	20940613	-	CTGTACTTCGGGGAAAGTTGGGG	1	1	14
(N20)NGG	14	20940614	-	CCTGTACTTCGGGGAAAGTTGGG	1	1	12
(N20)NGG	14	20940615	-	ACCTGTACTTCGGGGAAAGTTGG	1	1	10
(N20)NGG	14	20940623	-	TTGCCAGTACCTGTACTTCGGGG	1	2	13
(N20)NGG	14	20940624	-	CTTGCCAGTACCTGTACTTCGGG	1	2	22
(N20)NGG	14	20940625	-	CCTTGCCAGTACCTGTACTTCGG	1	4	33
(N20)NGG	14	20942636	+	TCTGTTTTGTATACAGTGCCAGG	1	3	59
(N20)NGG	14	20942645	+	TATACAGTGCCAGGTCATGCTGG	1	1	17
(N20)NGG	14	20942653	+	GCCAGGTCATGCTGGCCGACTGG	1	1	7
(N20)NGG	14	20942660	+	CATGCTGGCCGACTGGTGTTTGG	1	2	16
(N20)NGG	14	20942661	+	ATGCTGGCCGACTGGTGTTTGGG	1	3	16
(N20)NGG	14	20942672	+	CTGGTGTTTGGGTTCCTGAATGG	2	4	41
(N20)NGG	14	20942676	+	TGTTTGGGTTCCTGAATGGCAGG	1	9	44
(N20)NGG	14	20942677	+	GTTTGGGTTCCTGAATGGCAGGG	2	2	43
(N20)NGG	14	20942695	+	CAGGGCCTGTGTGATGATGCAGG	1	2	66
(N20)NGG	14	20942696	+	AGGGCCTGTGTGATGATGCAGGG	1	3	46
(N20)NGG	14	20942700	+	CCTGTGTGATGATGCAGGGCAGG	1	3	43

FIG. 11

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	14	20942717	+	GGCAGGTTCCACATGTATGAAGG	1	1	23
(N20)NGG	14	20942718	+	GCAGGTTCCACATGTATGAAGGG	1	2	38
(N20)NGG	14	20942730	+	TGTATGAAGGGTACCCACTCTGG	1	1	14
(N20)NGG	14	20942734	+	TGAAGGGTACCCACTCTGGAAGG	1	2	24
(N20)NGG	14	20942745	+	CACTCTGGAAGGTAAGTCAGAGG	2	7	158
(N20)NGG	14	20942746	+	ACTCTGGAAGGTAAGTCAGAGGG	1	8	112
(N20)NGG	14	20942751	+	GGAAGGTAAGTCAGAGGGATAGG	1	4	63
(N20)NGG	14	20942756	+	GTAAGTCAGAGGGATAGGTCCGG	2	2	29
(N20)NGG	14	20942632	-	ACCAGTCGGCCAGCATGACCTGG	1	1	8
(N20)NGG	14	20942646	-	TCAGGAACCCAAACACCAGTCGG	2	2	31
(N20)NGG	14	20942664	-	TCACACAGGCCCTGCCATTCAGG	1	4	46
(N20)NGG	14	20942678	-	CCTGCCCTGCATCATCACACAGG	1	5	47
(N20)NGG	14	20942703	-	GTGGGTACCCTTCATACATGTGG	1	1	12
(N20)NGG	14	20942721	-	TCTGACTTACCTTCCAGAGTGGG	1	5	48
(N20)NGG	14	20942722	-	CTCTGACTTACCTTCCAGAGTGG	1	6	92
(N20)NGG	14	20942931	+	TTTCGGATTGTTTGCTTCGAAGG	1	2	17
(N20)NGG	14	20942948	+	CGAAGGTGACATTCCCAGTGAGG	1	1	23
(N20)NGG	14	20942949	+	GAAGGTGACATTCCCAGTGAGGG	1	6	55
(N20)NGG	14	20942964	+	AGTGAGGGTTTTCCACCTTCTGG	3	7	40
(N20)NGG	14	20942965	+	GTGAGGGTTTTCCACCTTCTGGG	1	3	32
(N20)NGG	14	20942970	+	GGTTTTCCACCTTCTGGGTGTGG	2	3	33
(N20)NGG	14	20942979	+	CCTTCTGGGTGTGGACACCCTGG	1	8	59
(N20)NGG	14	20942998	+	CTGGTAGTCACCAATGCAGCAGG	1	1	21
(N20)NGG	14	20943001	+	GTAGTCACCAATGCAGCAGGAGG	1	1	22
(N20)NGG	14	20943002	+	TAGTCACCAATGCAGCAGGAGGG	1	1	35

FIG. 11

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	14	20943021	+	AGGGCTGAACCCCAAGTTTGAGG	1	6	51
(N20)NGG	14	20943025	+	CTGAACCCCAAGTTTGAGGTTGG	1	7	48
(N20)NGG	14	20943064	+	CGTGACCATATCAACCTACCTGG	1	1	11
(N20)NGG	14	20943073	+	ATCAACCTACCTGGTTTCAGTGG	1	4	25
(N20)NGG	14	20943091	+	AGTGGTCAGAACCCTCTCAGAGG	1	2	29
(N20)NGG	14	20943092	+	GTGGTCAGAACCCTCTCAGAGGG	1	2	48
(N20)NGG	14	20943107	+	TCAGAGGGCCCAATGATGAAAGG	1	3	26
(N20)NGG	14	20942939	-	GAAGGTGGAAAACCCTCACTGGG	3	6	47
(N20)NGG	14	20942940	-	AGAAGGTGGAAAACCCTCACTGG	1	3	41
(N20)NGG	14	20942954	-	GGGTGTCCACACCCAGAAGGTGG	1	3	75
(N20)NGG	14	20942957	-	CCAGGGTGTCCACACCCAGAAGG	2	4	66
(N20)NGG	14	20942974	-	TGCTGCATTGGTGACTACCAGGG	1	4	24
(N20)NGG	14	20942975	-	CTGCTGCATTGGTGACTACCAGG	1	3	23
(N20)NGG	14	20942986	-	GTTCAGCCCTCCTGCTGCATTGG	1	6	37
(N20)NGG	14	20943008	-	TATCTCCAACCTCAAACTTGGGG	1	2	45
(N20)NGG	14	20943009	-	ATATCTCCAACCTCAAACTTGGG	1	2	35
(N20)NGG	14	20943010	-	GATATCTCCAACCTCAAACTTGG	1	1	33
(N20)NGG	14	20943041	-	CAGGTAGGTTGATATGGTCACGG	1	3	24
(N20)NGG	14	20943047	-	TGAAACCAGGTAGGTTGATATGG	1	3	25
(N20)NGG	14	20943056	-	TCTGACCACTGAAACCAGGTAGG	1	6	45
(N20)NGG	14	20943060	-	GGGTTCTGACCACTGAAACCAGG	1	2	20
(N20)NGG	14	20943080	-	CATCATTGGGCCCTCTGAGAGGG	1	2	20
(N20)NGG	14	20943081	-	TCATCATTGGGCCCTCTGAGAGG	1	1	27
(N20)NGG	14	20943093	-	CATACATACCTTTCATCATTGGG	1	3	50
(N20)NGG	14	20943094	-	ACATACATACCTTTCATCATTGG	1	4	52

FIG. 11

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	14	20943220	+	GATAATTCAACCTGTGTCCTAGG	1	2	32
(N20)NGG	14	20943225	+	TTCAACCTGTGTCCTAGGTTTGG	1	3	40
(N20)NGG	14	20943262	+	CCATGTCTGATGCCTACGACCGG	1	2	10
(N20)NGG	14	20943271	+	ATGCCTACGACCGGACTATGAGG	1	1	3
(N20)NGG	14	20943277	+	ACGACCGGACTATGAGGCAGAGG	1	1	9
(N20)NGG	14	20943278	+	CGACCGGACTATGAGGCAGAGGG	1	1	9
(N20)NGG	14	20943292	+	GGCAGAGGGCTCTCAGTACCTGG	1	4	36
(N20)NGG	14	20943302	+	TCTCAGTACCTGGAAACAAATGG	1	5	70
(N20)NGG	14	20943303	+	CTCAGTACCTGGAAACAAATGGG	1	2	54
(N20)NGG	14	20943304	+	TCAGTACCTGGAAACAAATGGGG	1	5	60
(N20)NGG	14	20943305	+	CAGTACCTGGAAACAAATGGGGG	1	8	49
(N20)NGG	14	20943323	+	GGGGGAGCAACGTGAGCTACAGG	1	1	5
(N20)NGG	14	20943327	+	GAGCAACGTGAGCTACAGGAAGG	1	3	20
(N20)NGG	14	20943341	+	ACAGGAAGGCACCTATGTGATGG	2	5	29
(N20)NGG	14	20943344	+	GGAAGGCACCTATGTGATGGTGG	1	4	41
(N20)NGG	14	20943348	+	GGCACCTATGTGATGGTGGCAGG	1	1	26
(N20)NGG	14	20943368	+	AGGCCCCAGCTTTGAGACTGTGG	1	7	96
(N20)NGG	14	20943395	+	ATGTCGTGTGCTGCAGAAGCTGG	1	2	37
(N20)NGG	14	20943396	+	TGTCGTGTGCTGCAGAAGCTGGG	1	4	25
(N20)NGG	14	20943411	+	AAGCTGGGAGCAGACGCTGTTGG	1	2	38
(N20)NGG	14	20943419	+	AGCAGACGCTGTTGGTGAGAAGG	1	3	35
(N20)NGG	14	20943420	+	GCAGACGCTGTTGGTGAGAAGGG	1	2	37
(N20)NGG	14	20943421	+	CAGACGCTGTTGGTGAGAAGGGG	1	2	39
(N20)NGG	14	20943428	+	TGTTGGTGAGAAGGGGAATTTGG	1	9	109
(N20)NGG	14	20943432	+	GGTGAGAAGGGGAATTTGGCTGG	1	5	57

FIG. 11

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	14	20943208	-	GATCTCCAAACCTAGGACACAGG	1	1	22
(N20)NGG	14	20943215	-	GGGAAACGATCTCCAAACCTAGG	1	1	10
(N20)NGG	14	20943235	-	CGTAGGCATCAGACATGGCAGGG	1	1	17
(N20)NGG	14	20943236	-	TCGTAGGCATCAGACATGGCAGG	1	2	17
(N20)NGG	14	20943240	-	CCGGTCGTAGGCATCAGACATGG	1	1	4
(N20)NGG	14	20943252	-	CTGCCTCATAGTCCGGTCGTAGG	1	1	6
(N20)NGG	14	20943259	-	GAGCCCTCTGCCTCATAGTCCGG	1	3	26
(N20)NGG	14	20943288	-	TTGCTCCCCCATTTGTTTCCAGG	1	5	49
(N20)NGG	14	20943330	-	GGGGCCTGCCACCATCACATAGG	1	2	43
(N20)NGG	14	20943349	-	CTGCCACAGTCTCAAAGCTGGGG	1	3	74
(N20)NGG	14	20943350	-	TCTGCCACAGTCTCAAAGCTGGG	1	4	55
(N20)NGG	14	20943351	-	TTCTGCCACAGTCTCAAAGCTGG	1	7	50
(N20)NGG	14	20944542	+	TTTCCATCTTTCTCACTATCAGG	1	13	112
(N20)NGG	14	20944576	+	TACCAGAAGTTATCGTTGCACGG	1	3	9
(N20)NGG	14	20944584	+	GTTATCGTTGCACGGCACTGTGG	1	1	10
(N20)NGG	14	20944599	+	CACTGTGGACTTCGAGTCTTTGG	1	2	23
(N20)NGG	14	20944622	+	CTTCTCACTCATCACTAACAAGG	2	3	48
(N20)NGG	14	20944631	+	CATCACTAACAAGGTCATCATGG	2	6	50
(N20)NGG	14	20944646	+	CATCATGGATTATGAAAGCCTGG	3	10	43
(N20)NGG	14	20944652	+	GGATTATGAAAGCCTGGAGAAGG	2	4	62
(N20)NGG	14	20944680	+	CATGAAGAAGTCTTAGCAGCTGG	2	5	31
(N20)NGG	14	20944703	+	CAAACAAGCTGCACAGAAATTGG	2	5	57
(N20)NGG	14	20944727	+	ACAGTTTGTCTCCATTCTTATGG	2	5	60
(N20)NGG	14	20944769	+	CAAAGCCAGTTGACCTGCCTTGG	1	3	39
(N20)NGG	14	20944779	+	TGACCTGCCTTGGAGTCGTCTGG	1	1	14

FIG. 11

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	14	20944523	-	ATGCCTGATAGTGAGAAAGATGG	1	5	60
(N20)NGG	14	20944556	-	TGCCGTGCAACGATAACTTCTGG	1	1	6
(N20)NGG	14	20944642	-	CTTCATGGTTGGCCTTCTCCAGG	1	1	32
(N20)NGG	14	20944653	-	TGCTAAGACTTCTTCATGGTTGG	2	4	30
(N20)NGG	14	20944657	-	CAGCTGCTAAGACTTCTTCATGG	1	5	56
(N20)NGG	14	20944716	-	TGGAATGCTGGCCATAAGAATGG	1	4	47
(N20)NGG	14	20944728	-	TTTGTCAGGGAGTGGAATGCTGG	1	4	51
(N20)NGG	14	20944736	-	CAACTGGCTTTGTCAGGGAGTGG	1	2	44
(N20)NGG	14	20944741	-	CAGGTCAACTGGCTTTGTCAGGG	1	4	36
(N20)NGG	14	20944742	-	GCAGGTCAACTGGCTTTGTCAGG	1	1	22
(N20)NGG	14	20944752	-	CGACTCCAAGGCAGGTCAACTGG	1	1	13
(N20)NGG	14	20944760	-	ATGCCAGACGACTCCAAGGCAGG	1	1	10

FIG. 11

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48686749	+	TTCCAGTGATGAGCTACTCCTGG	1	3	23
(N20)NGG	8	48686750	+	TCCAGTGATGAGCTACTCCTGGG	1	2	19
(N20)NGG	8	48686761	+	GCTACTCCTGGGTCATGAGAAGG	1	1	24
(N20)NGG	8	48686785	+	CCCTGCCTTCAGAGACTATGTGG	1	6	64
(N20)NGG	8	48686791	+	CTTCAGAGACTATGTGGCTGTGG	1	3	39
(N20)NGG	8	48686798	+	GACTATGTGGCTGTGGCACGAGG	1	2	27
(N20)NGG	8	48686840	+	CGTGCCCAAGAACCAGAGAGTGG	2	5	35
(N20)NGG	8	48686841	+	GTGCCCAAGAACCAGAGAGTGGG	2	4	44
(N20)NGG	8	48686875	+	GACTCAAGTGAAGTGCCTGATGG	1	2	29
(N20)NGG	8	48686881	+	AGTGAAGTGCCTGATGGACCAGG	1	3	51
(N20)NGG	8	48686903	+	GCAACAGACCCCAACATCCTTGG	1	7	44
(N20)NGG	8	48686913	+	CCAACATCCTTGGCAGAACCTGG	1	2	46
(N20)NGG	8	48686914	+	CAACATCCTTGGCAGAACCTGGG	1	4	41
(N20)NGG	8	48686918	+	ATCCTTGGCAGAACCTGGGAAGG	1	3	53
(N20)NGG	8	48686922	+	TTGGCAGAACCTGGGAAGGATGG	1	12	201
(N20)NGG	8	48686923	+	TGGCAGAACCTGGGAAGGATGGG	1	4	78
(N20)NGG	8	48686931	+	CCTGGGAAGGATGGGAGCCCTGG	2	13	133
(N20)NGG	8	48686939	+	GGATGGGAGCCCTGGATGTGAGG	1	9	87
(N20)NGG	8	48686946	+	AGCCCTGGATGTGAGGTCTGTGG	2	12	178
(N20)NGG	8	48686947	+	GCCCTGGATGTGAGGTCTGTGGG	1	5	45
(N20)NGG	8	48686729	-	ACCCAGGAGTAGCTCATCACTGG	1	1	23
(N20)NGG	8	48686745	-	CAGGGGCCTTCTCATGACCCAGG	1	5	41
(N20)NGG	8	48686762	-	CACATAGTCTCTGAAGGCAGGGG	1	1	97
(N20)NGG	8	48686763	-	CCACATAGTCTCTGAAGGCAGGG	2	5	40
(N20)NGG	8	48686764	-	GCCACATAGTCTCTGAAGGCAGG	1	2	28

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48686768	-	CACAGCCACATAGTCTCTGAAGG	1	4	39
(N20)NGG	8	48686822	-	AAGCCCACTCTCTGGTTCTTGGG	1	6	53
(N20)NGG	8	48686823	-	AAAGCCCACTCTCTGGTTCTTGG	2	6	91
(N20)NGG	8	48686830	-	TCTTCTGAAAGCCCACTCTCTGG	1	3	57
(N20)NGG	8	48686868	-	GGTCTGTTGCCTGGTCCATCAGG	1	1	14
(N20)NGG	8	48686877	-	GGATGTTGGGGTCTGTTGCCTGG	1	1	28
(N20)NGG	8	48686889	-	AGGTTCTGCCAAGGATGTTGGGG	1	2	42
(N20)NGG	8	48686890	-	CAGGTTCTGCCAAGGATGTTGGG	1	2	79
(N20)NGG	8	48686891	-	CCAGGTTCTGCCAAGGATGTTGG	2	8	62
(N20)NGG	8	48686898	-	ATCCTTCCCAGGTTCTGCCAAGG	1	4	65
(N20)NGG	8	48686909	-	CCAGGGCTCCCATCCTTCCCAGG	2	11	112
(N20)NGG	8	48686926	-	TCCCACAGACCTCACATCCAGGG	2	4	162
(N20)NGG	8	48686927	-	CTCCCACAGACCTCACATCCAGG	1	11	200
(N20)NGG	8	48689432	+	GAACAGAAAATGCTGAAAAAAGG	1	14	354
(N20)NGG	8	48689435	+	CAGAAAATGCTGAAAAAAGGAGG	1	15	204
(N20)NGG	8	48689436	+	AGAAAATGCTGAAAAAAGGAGGG	3	26	403
(N20)NGG	8	48689442	+	TGCTGAAAAAAGGAGGGTCATGG	1	4	67
(N20)NGG	8	48689475	+	TAAATGTTGCTGAAAAAAATTGG	3	49	626
(N20)NGG	8	48689519	+	TACGCTAAGAGAAAGTTAGCAGG	1	2	14
(N20)NGG	8	48689544	+	CCAATCCAGCAGTCATTACTTGG	1	4	28
(N20)NGG	8	48689562	+	CTTGGTAAGATTTTTATATGTGG	1	5	95
(N20)NGG	8	48689478	-	CGTAACATATTTTCTGTCGGGGG	1	1	7
(N20)NGG	8	48689479	-	GCGTAACATATTTTCTGTCGGGG	1	3	16
(N20)NGG	8	48689480	-	AGCGTAACATATTTTCTGTCGGG	2	12	185
(N20)NGG	8	48689481	-	TAGCGTAACATATTTTCTGTCGG	1	2	40

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48689522	-	CCAAGTAATGACTGCTGGATTGG	1	3	25
(N20)NGG	8	48689527	-	TCTTACCAAGTAATGACTGCTGG	1	3	21
(N20)NGG	8	48690278	+	TCCCTGAGTTGATGCCTTTTCGG	2	5	57
(N20)NGG	8	48690324	+	GATGTTACCAATGAAAGAAACGG	2	10	154
(N20)NGG	8	48690325	+	ATGTTACCAATGAAAGAAACGGG	3	19	266
(N20)NGG	8	48690345	+	GGGCCTTATGTACAGCATCATGG	1	4	31
(N20)NGG	8	48690359	+	GCATCATGGTACACGCACTCCGG	1	1	8
(N20)NGG	8	48690360	+	CATCATGGTACACGCACTCCGGG	1	1	8
(N20)NGG	8	48690379	+	CGGGCCTTCCGCTCAGACCCTGG	1	1	22
(N20)NGG	8	48690399	+	TGGCCTGCTCACCAACACCATGG	1	2	38
(N20)NGG	8	48690414	+	CACCATGGATGTGTTTGTCAAGG	1	3	47
(N20)NGG	8	48690431	+	TCAAGGAGCCCTCCTTTGATTGG	1	3	47
(N20)NGG	8	48690439	+	CCCTCCTTTGATTGGAAAGTAGG	1	6	31
(N20)NGG	8	48690224	-	ACTAAACAAGAAAAAAGGCAAGG	1	20	401
(N20)NGG	8	48690229	-	CAGAAACTAAACAAGAAAAAAGG	2	47	851
(N20)NGG	8	48690252	-	AAAGGCATCAACTCAGGGACTGG	1	3	36
(N20)NGG	8	48690257	-	GCCGAAAAGGCATCAACTCAGGG	1	1	12
(N20)NGG	8	48690258	-	AGCCGAAAAGGCATCAACTCAGG	1	2	15
(N20)NGG	8	48690270	-	AACTGGCGAGTTAGCCGAAAAGG	1	1	3
(N20)NGG	8	48690287	-	GTAACATCAGATTGATAAACTGG	1	7	35
(N20)NGG	8	48690309	-	ATAAGGCCCGTTTCTTTCATTGG	1	2	23
(N20)NGG	8	48690326	-	GTACCATGATGCTGTACATAAGG	1	2	25
(N20)NGG	8	48690356	-	CAGGGTCTGAGCGGAAGGCCCGG	1	3	35
(N20)NGG	8	48690361	-	CAGGCCAGGGTCTGAGCGGAAGG	1	4	60
(N20)NGG	8	48690365	-	TGAGCAGGCCAGGGTCTGAGCGG	1	14	94

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48690374	-	TGGTGTTGGTGAGCAGGCCAGGG	1	4	52
(N20)NGG	8	48690375	-	ATGGTGTTGGTGAGCAGGCCAGG	1	3	64
(N20)NGG	8	48690380	-	CATCCATGGTGTTGGTGAGCAGG	1	1	22
(N20)NGG	8	48690388	-	GACAAACACATCCATGGTGTTGG	1	2	42
(N20)NGG	8	48690394	-	CTCCTTGACAAACACATCCATGG	2	3	53
(N20)NGG	8	48690417	-	CCTACTTTCCAATCAAAGGAGGG	1	1	35
(N20)NGG	8	48690418	-	ACCTACTTTCCAATCAAAGGAGG	2	2	33
(N20)NGG	8	48690421	-	AAAACCTACTTTCCAATCAAAGG	2	4	68
(N20)NGG	8	48691019	+	CACAGCTGTGTCTCTTTTGTAGG	1	5	67
(N20)NGG	8	48691022	+	AGCTGTGTCTCTTTTGTAGGCGG	1	5	50
(N20)NGG	8	48691023	+	GCTGTGTCTCTTTTGTAGGCGGG	1	3	42
(N20)NGG	8	48691034	+	TTTGTAGGCGGGCCTTCGTGAGG	1	1	9
(N20)NGG	8	48691053	+	GAGGATGAGTACAAGCCCTGAGG	1	2	34
(N20)NGG	8	48691062	+	TACAAGCCCTGAGGCTTTCCTGG	2	5	39
(N20)NGG	8	48691115	+	CTCTGATATGCATCAGCCACTGG	1	1	28
(N20)NGG	8	48691123	+	TGCATCAGCCACTGGATCCTCGG	1	2	37
(N20)NGG	8	48691124	+	GCATCAGCCACTGGATCCTCGGG	1	2	36
(N20)NGG	8	48691129	+	AGCCACTGGATCCTCGGGATTGG	1	1	11
(N20)NGG	8	48691155	+	CAGACATCTGAACAACTTTATGG	2	3	37
(N20)NGG	8	48691158	+	ACATCTGAACAACTTTATGGTGG	1	3	54
(N20)NGG	8	48691164	+	GAACAACTTTATGGTGGCCATGG	1	4	30
(N20)NGG	8	48691171	+	TTTATGGTGGCCATGGAGACTGG	1	5	49
(N20)NGG	8	48691174	+	ATGGTGGCCATGGAGACTGGCGG	1	10	88
(N20)NGG	8	48691183	+	ATGGAGACTGGCGGCGTGATCGG	1	2	7
(N20)NGG	8	48691184	+	TGGAGACTGGCGGCGTGATCGGG	1	1	16

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48691195	+	GGCGTGATCGGGATCGACTTTGG	1	1	3
(N20)NGG	8	48691196	+	GCGTGATCGGGATCGACTTTGGG	1	1	1
(N20)NGG	8	48691207	+	ATCGACTTTGGGCATGCGTTTGG	1	1	5
(N20)NGG	8	48691221	+	TGCGTTTGGATCCGCTACACAGG	1	1	3
(N20)NGG	8	48690994	-	ACAAAAGAGACACAGCTGTGCGG	1	7	106
(N20)NGG	8	48691024	-	GCTTGTACTCATCCTCACGAAGG	1	2	8
(N20)NGG	8	48691046	-	GGAGCGCCAGGAAAGCCTCAGGG	1	3	39
(N20)NGG	8	48691047	-	CGGAGCGCCAGGAAAGCCTCAGG	1	1	24
(N20)NGG	8	48691058	-	CGAAGTGGGAGCGGAGCGCCAGG	1	2	15
(N20)NGG	8	48691067	-	GAGAGCTGGCGAAGTGGGAGCGG	1	6	91
(N20)NGG	8	48691072	-	AGCGTGAGAGCTGGCGAAGTGGG	1	1	12
(N20)NGG	8	48691073	-	GAGCGTGAGAGCTGGCGAAGTGG	1	1	26
(N20)NGG	8	48691081	-	GCATATCAGAGCGTGAGAGCTGG	1	2	27
(N20)NGG	8	48691109	-	CTCCAATCCCGAGGATCCAGTGG	1	2	23
(N20)NGG	8	48691118	-	GATGTCTGTCTCCAATCCCGAGG	1	2	21
(N20)NGG	8	48691159	-	GATCACGCCGCCAGTCTCCATGG	1	1	5
(N20)NGG	8	48691210	-	CAGCAAGTGCACCTGTGTAGCGG	1	1	24
(N20)NGG	8	48691288	+	TGTTTCTATTATTAAATCATAGG	1	13	240
(N20)NGG	8	48691289	+	GTTTCTATTATTAAATCATAGGG	2	4	146
(N20)NGG	8	48691290	+	TTTCTATTATTAAATCATAGGGG	1	10	202
(N20)NGG	8	48691343	-	ACTTACTTTAAGAGATCAGCAGG	1	11	45
(N20)NGG	8	48691573	+	TCTCACTCATTAGTGATCCCAGG	1	2	28
(N20)NGG	8	48691574	+	CTCACTCATTAGTGATCCCAGGG	1	3	36
(N20)NGG	8	48691600	+	CGCCGTGTGAATATAAAGATTGG	1	2	5
(N20)NGG	8	48691617	+	GATTGGCTGACAAAAATGTCAGG	3	9	59

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48691632	+	ATGTCAGGAAAACATGATGTTGG	2	6	92
(N20)NGG	8	48691663	+	TGCTAATGTATAAGTAAGTTTGG	1	1	39
(N20)NGG	8	48691544	-	TCACTAATGAGTGAGAAAAGGGG	1	10	154
(N20)NGG	8	48691545	-	ATCACTAATGAGTGAGAAAAGGG	1	5	139
(N20)NGG	8	48691546	-	GATCACTAATGAGTGAGAAAAGG	1	5	66
(N20)NGG	8	48691568	-	TATTCACACGGCGGTGCCCTGGG	1	1	7
(N20)NGG	8	48691569	-	ATATTCACACGGCGGTGCCCTGG	1	1	4
(N20)NGG	8	48691577	-	CAATCTTTATATTCACACGGCGG	1	2	18
(N20)NGG	8	48691580	-	AGCCAATCTTTATATTCACACGG	1	2	65
(N20)NGG	8	48694722	+	AACCTTTTATTCTCCCTTTCAGG	1	4	95
(N20)NGG	8	48694727	+	TTTATTCTCCCTTTCAGGTTAGG	1	4	118
(N20)NGG	8	48694740	+	TCAGGTTAGGATTAATTGAGTGG	1	4	46
(N20)NGG	8	48694765	+	TGAAAATACTGTTACCTTGAAGG	1	10	83
(N20)NGG	8	48694795	+	TTTGAACACCATGTCCCAAGAGG	2	3	38
(N20)NGG	8	48694801	+	CACCATGTCCCAAGAGGAGAAGG	1	7	62
(N20)NGG	8	48694804	+	CATGTCCCAAGAGGAGAAGGCGG	1	7	94
(N20)NGG	8	48694815	+	AGGAGAAGGCGGCTTACCTGAGG	1	2	39
(N20)NGG	8	48694820	+	AAGGCGGCTTACCTGAGGTAAGG	1	10	658
(N20)NGG	8	48694821	+	AGGCGGCTTACCTGAGGTAAGGG	1	10	637
(N20)NGG	8	48694824	+	CGGCTTACCTGAGGTAAGGGCGG	1	2	21
(N20)NGG	8	48694702	-	AACCTGAAAGGGAGAATAAAAGG	1	4	134
(N20)NGG	8	48694713	-	CAATTAATCCTAACCTGAAAGGG	1	3	48
(N20)NGG	8	48694714	-	TCAATTAATCCTAACCTGAAAGG	1	2	41
(N20)NGG	8	48694757	-	GTTCAAAAGAAGGTCCTTCAAGG	1	3	31
(N20)NGG	8	48694767	-	GGGACATGGTGTTCAAAAGAAGG	1	3	53

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48694781	-	CGCCTTCTCCTCTTGGGACATGG	1	4	36
(N20)NGG	8	48694787	-	GTAAGCCGCCTTCTCCTCTTGGG	1	1	16
(N20)NGG	8	48694788	-	GGTAAGCCGCCTTCTCCTCTTGG	1	2	18
(N20)NGG	8	48694809	-	CGTGTGGCCGCCCTTACCTCAGG	1	3	10
(N20)NGG	8	48694938	+	GATGACATTCTGATTTTTGAAGG	1	5	91
(N20)NGG	8	48694950	+	ATTTTTGAAGGTGACAGTCATGG	1	3	71
(N20)NGG	8	48694964	+	CAGTCATGGCGTCTCTGCGAAGG	1	1	7
(N20)NGG	8	48694987	+	CCCAAGCGCATCATCATCCGTGG	1	1	2
(N20)NGG	8	48695000	+	TCATCCGTGGCCATGACGAGAGG	1	2	9
(N20)NGG	8	48695001	+	CATCCGTGGCCATGACGAGAGGG	1	1	12
(N20)NGG	8	48695016	+	CGAGAGGGAACACCCTTTCCTGG	1	3	16
(N20)NGG	8	48695022	+	GGAACACCCTTTCCTGGTGAAGG	1	7	82
(N20)NGG	8	48695023	+	GAACACCCTTTCCTGGTGAAGGG	1	5	53
(N20)NGG	8	48695026	+	CACCCTTTCCTGGTGAAGGGTGG	1	5	84
(N20)NGG	8	48695031	+	TTTCCTGGTGAAGGGTGGCGAGG	1	1	38
(N20)NGG	8	48695039	+	TGAAGGGTGGCGAGGACCTGCGG	1	3	40
(N20)NGG	8	48695043	+	GGGTGGCGAGGACCTGCGGCAGG	1	1	38
(N20)NGG	8	48695055	+	CCTGCGGCAGGACCAGCGCGTGG	1	6	32
(N20)NGG	8	48695070	+	GCGCGTGGAGCAGCTCTTCCAGG	1	3	24
(N20)NGG	8	48695080	+	CAGCTCTTCCAGGTCATGAATGG	1	6	56
(N20)NGG	8	48695081	+	AGCTCTTCCAGGTCATGAATGGG	1	2	50
(N20)NGG	8	48695088	+	CCAGGTCATGAATGGGATCCTGG	1	3	32
(N20)NGG	8	48695114	+	AAGACTCCGCCTGCAGCCAGAGG	1	3	37
(N20)NGG	8	48695115	+	AGACTCCGCCTGCAGCCAGAGGG	1	2	26
(N20)NGG	8	48695129	+	GCCAGAGGGCCCTGCAGCTGAGG	1	16	148

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48695159	+	GCGTTGTGCCCATGACCTCCAGG	1	1	10
(N20)NGG	8	48695170	+	ATGACCTCCAGGTAACTGCCAGG	2	5	28
(N20)NGG	8	48694965	-	CCACGGATGATGATGCGCTTGGG	1	1	4
(N20)NGG	8	48694966	-	GCCACGGATGATGATGCGCTTGG	1	1	10
(N20)NGG	8	48694982	-	GTTCCCTCTCGTCATGGCCACGG	1	1	9
(N20)NGG	8	48694988	-	AAGGGTGTTCCCTCTCGTCATGG	1	1	15
(N20)NGG	8	48695006	-	CGCCACCCTTCACCAGGAAAGGG	1	2	36
(N20)NGG	8	48695007	-	TCGCCACCCTTCACCAGGAAAGG	1	2	25
(N20)NGG	8	48695012	-	GGTCCTCGCCACCCTTCACCAGG	1	1	37
(N20)NGG	8	48695033	-	CCACGCGCTGGTCCTGCCGCAGG	1	4	24
(N20)NGG	8	48695045	-	GGAAGAGCTGCTCCACGCGCTGG	1	2	23
(N20)NGG	8	48695066	-	CCAGGATCCCATTCATGACCTGG	1	4	44
(N20)NGG	8	48695084	-	TGCAGGCGGAGTCTTGGGCCAGG	1	2	36
(N20)NGG	8	48695089	-	CTGGCTGCAGGCGGAGTCTTGGG	1	4	34
(N20)NGG	8	48695090	-	TCTGGCTGCAGGCGGAGTCTTGG	2	2	41
(N20)NGG	8	48695098	-	CAGGGCCCTCTGGCTGCAGGCGG	1	11	187
(N20)NGG	8	48695101	-	CTGCAGGGCCCTCTGGCTGCAGG	2	18	161
(N20)NGG	8	48695108	-	TCCTCAGCTGCAGGGCCCTCTGG	1	12	121
(N20)NGG	8	48695116	-	GCTATAGGTCCTCAGCTGCAGGG	1	2	18
(N20)NGG	8	48695117	-	CGCTATAGGTCCTCAGCTGCAGG	1	1	14
(N20)NGG	8	48695131	-	GGTCATGGGCACAACGCTATAGG	1	1	9
(N20)NGG	8	48695145	-	GGCAGTTACCTGGAGGTCATGGG	1	5	55
(N20)NGG	8	48695146	-	TGGCAGTTACCTGGAGGTCATGG	1	6	46
(N20)NGG	8	48695152	-	GCAGCCTGGCAGTTACCTGGAGG	1	7	62
(N20)NGG	8	48695155	-	GGAGCAGCCTGGCAGTTACCTGG	1	4	45

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48696302	+	GCAAGGTTCTGGTTTGTTTTAGG	1	2	59
(N20)NGG	8	48696314	+	TTTGTTTTAGGTCAGTATGACGG	1	7	84
(N20)NGG	8	48696318	+	TTTTAGGTCAGTATGACGGTAGG	1	1	8
(N20)NGG	8	48696319	+	TTTAGGTCAGTATGACGGTAGGG	1	3	11
(N20)NGG	8	48696320	+	TTAGGTCAGTATGACGGTAGGGG	1	1	8
(N20)NGG	8	48696356	+	GAGTACCACGTGCGAATCGCCGG	1	1	2
(N20)NGG	8	48696357	+	AGTACCACGTGCGAATCGCCGGG	1	1	3
(N20)NGG	8	48696369	+	GAATCGCCGGGTTTGATGAGCGG	1	1	4
(N20)NGG	8	48696370	+	AATCGCCGGGTTTGATGAGCGGG	1	1	3
(N20)NGG	8	48696374	+	GCCGGGTTTGATGAGCGGGTAGG	1	1	8
(N20)NGG	8	48696381	+	TTGATGAGCGGGTAGGTGTGAGG	1	3	46
(N20)NGG	8	48696382	+	TGATGAGCGGGTAGGTGTGAGGG	1	1	20
(N20)NGG	8	48696325	-	CGCACGTGGTACTCTGGCAATGG	1	1	10
(N20)NGG	8	48696331	-	GCGATTCGCACGTGGTACTCTGG	1	1	5
(N20)NGG	8	48696339	-	CAAACCCGGCGATTCGCACGTGG	1	1	1
(N20)NGG	8	48696353	-	ACCTACCCGCTCATCAAACCCGG	1	1	6
(N20)NGG	8	48697680	+	TCTTACTAATTTCAGACTTTTGG	1	7	117
(N20)NGG	8	48697704	+	AAAGAATTTGATAAACATTTTGG	2	20	413
(N20)NGG	8	48697705	+	AAGAATTTGATAAACATTTTGGG	1	26	397
(N20)NGG	8	48697710	+	TTTGATAAACATTTTGGGAAAGG	1	14	188
(N20)NGG	8	48697713	+	GATAAACATTTTGGGAAAGGAGG	1	11	192
(N20)NGG	8	48697803	+	AACAAAGACTCAAAGCCCCCTGG	1	5	32
(N20)NGG	8	48697804	+	ACAAAGACTCAAAGCCCCCTGGG	1	3	28
(N20)NGG	8	48697828	+	ATCTGAAAGAATGTTCACCCTGG	1	2	43
(N20)NGG	8	48697847	+	CTGGATGAGCGACTTCAAAGTGG	1	2	18

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48697868	+	GGAGTTCCTGAGAAATGAGCTGG	1	5	56
(N20)NGG	8	48697878	+	AGAAATGAGCTGGAGATTCCCGG	1	3	62
(N20)NGG	8	48697894	+	TTCCCGGTGAGTTAACCTCCAGG	1	2	12
(N20)NGG	8	48697895	+	TCCCGGTGAGTTAACCTCCAGGG	1	1	6
(N20)NGG	8	48697896	+	CCCGGTGAGTTAACCTCCAGGGG	1	1	7
(N20)NGG	8	48697758	-	CATTTTTAAAAGTAGCATGTTGG	2	14	210
(N20)NGG	8	48697796	-	CATTCTTTCAGATTCCCAGGGGG	3	10	80
(N20)NGG	8	48697797	-	ACATTCTTTCAGATTCCCAGGGG	1	8	82
(N20)NGG	8	48697798	-	AACATTCTTTCAGATTCCCAGGG	1	6	85
(N20)NGG	8	48697799	-	GAACATTCTTTCAGATTCCCAGG	1	4	65
(N20)NGG	8	48697823	-	ACTTTGAAGTCGCTCATCCAGGG	1	3	17
(N20)NGG	8	48697824	-	CACTTTGAAGTCGCTCATCCAGG	1	1	9
(N20)NGG	8	48697852	-	GAATCTCCAGCTCATTTCTCAGG	1	6	53
(N20)NGG	8	48697874	-	CCCCTGGAGGTTAACTCACCGGG	1	1	19
(N20)NGG	8	48697875	-	ACCCCTGGAGGTTAACTCACCGG	1	1	12
(N20)NGG	8	48701466	+	TACTTTTTTTTTCCCCTGACAGG	2	15	278
(N20)NGG	8	48701471	+	TTTTTTTCCCCTGACAGGATTGG	2	10	115
(N20)NGG	8	48701559	+	TGAAAGAATGTATGCAGCCTTGG	1	5	69
(N20)NGG	8	48701560	+	GAAAGAATGTATGCAGCCTTGGG	2	6	73
(N20)NGG	8	48701571	+	TGCAGCCTTGGGTGACCCAAAGG	1	1	34
(N20)NGG	8	48701578	+	TTGGGTGACCCAAAGGCTCCAGG	1	1	22
(N20)NGG	8	48701583	+	TGACCCAAAGGCTCCAGGCCTGG	1	6	51
(N20)NGG	8	48701584	+	GACCCAAAGGCTCCAGGCCTGGG	1	7	60
(N20)NGG	8	48701585	+	ACCCAAAGGCTCCAGGCCTGGGG	1	7	91
(N20)NGG	8	48701586	+	CCCAAAGGCTCCAGGCCTGGGGG	2	9	103

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48701597	+	CAGGCCTGGGGGCCTTTAGAAGG	3	7	59
(N20)NGG	8	48701610	+	CTTTAGAAGGAAGTTTATTCAGG	1	3	78
(N20)NGG	8	48701615	+	GAAGGAAGTTTATTCAGGTATGG	1	4	69
(N20)NGG	8	48701620	+	AAGTTTATTCAGGTATGGACTGG	1	2	19
(N20)NGG	8	48701456	-	CATTGCTCCAATCCTGTCAGGGG	1	3	38
(N20)NGG	8	48701457	-	TCATTGCTCCAATCCTGTCAGGG	1	3	21
(N20)NGG	8	48701458	-	ATCATTGCTCCAATCCTGTCAGG	1	2	36
(N20)NGG	8	48701503	-	AATGTTTTTTTTATTTACAGGGG	1	47	1234
(N20)NGG	8	48701504	-	CAATGTTTTTTTTATTTACAGGG	1	22	559
(N20)NGG	8	48701505	-	TCAATGTTTTTTTTATTTACAGG	1	14	413
(N20)NGG	8	48701554	-	TGGAGCCTTTGGGTCACCCAAGG	1	4	40
(N20)NGG	8	48701564	-	CCCCCAGGCCTGGAGCCTTTGGG	2	8	86
(N20)NGG	8	48701565	-	GCCCCCAGGCCTGGAGCCTTTGG	1	10	133
(N20)NGG	8	48701574	-	CTTCTAAAGGCCCCCAGGCCTGG	1	3	36
(N20)NGG	8	48701579	-	ACTTCCTTCTAAAGGCCCCCAGG	1	2	39
(N20)NGG	8	48701587	-	CTGAATAAACTTCCTTCTAAAGG	1	4	60
(N20)NGG	8	48701711	+	CTTTGTAAATTTTTTTAAATAGG	3	81	973
(N20)NGG	8	48701727	+	AAATAGGATTAAAAGTAAGTTGG	1	6	140
(N20)NGG	8	48701734	+	ATTAAAAGTAAGTTGGATCAAGG	1	8	84
(N20)NGG	8	48701737	+	AAAAGTAAGTTGGATCAAGGAGG	1	4	54
(N20)NGG	8	48701799	+	TAATCCTGAACTGCTCTTTAAGG	1	3	37
(N20)NGG	8	48701813	+	TCTTTAAGGTAATGATAGAACGG	1	4	110
(N20)NGG	8	48701820	+	GGTAATGATAGAACGGCTTCTGG	1	1	3
(N20)NGG	8	48701761	-	AGGATTAGAGAGCTGATCTAAGG	1	2	27
(N20)NGG	8	48701781	-	ATTACCTTAAAGAGCAGTTCAGG	1	1	37

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48706870	+	AGATCTCTTCCGTTCCCTGCTGG	1	1	22
(N20)NGG	8	48706885	+	CCTGCTGGCAGTTCATCAGCTGG	1	2	28
(N20)NGG	8	48706898	+	CATCAGCTGGATCAGCCACATGG	1	6	39
(N20)NGG	8	48706901	+	CAGCTGGATCAGCCACATGGTGG	1	3	53
(N20)NGG	8	48706910	+	CAGCCACATGGTGGCCTTACTGG	1	5	51
(N20)NGG	8	48706946	+	CGTTGCTGTTCAGCACTCTGTGG	1	3	17
(N20)NGG	8	48706973	+	AATCACTGATAACTACCCGCAGG	1	1	6
(N20)NGG	8	48707021	+	CAGCGAAAGCTATTCCTTCAAGG	1	2	21
(N20)NGG	8	48707034	+	TCCTTCAAGGATACTTCTACTGG	1	2	23
(N20)NGG	8	48707048	+	TTCTACTGGTCATAAGAATAAGG	1	1	31
(N20)NGG	8	48707057	+	TCATAAGAATAAGGAGTTTGTGG	1	3	66
(N20)NGG	8	48707062	+	AGAATAAGGAGTTTGTGGCAAGG	1	7	95
(N20)NGG	8	48707066	+	TAAGGAGTTTGTGGCAAGGTAGG	1	3	51
(N20)NGG	8	48707081	+	AAGGTAGGTAATATTACAGAAGG	2	5	71
(N20)NGG	8	48706857	-	GATGAACTGCCAGCAGGGAACGG	2	4	64
(N20)NGG	8	48706862	-	CAGCTGATGAACTGCCAGCAGGG	1	2	78
(N20)NGG	8	48706863	-	CCAGCTGATGAACTGCCAGCAGG	1	2	35
(N20)NGG	8	48706891	-	TGTCCAGTAAGGCCACCATGTGG	1	3	31
(N20)NGG	8	48706902	-	GGCTTGGTCTTTGTCCAGTAAGG	1	3	28
(N20)NGG	8	48706918	-	AGTGCTGAACAGCAACGGCTTGG	1	2	14
(N20)NGG	8	48706923	-	CACAGAGTGCTGAACAGCAACGG	1	6	66
(N20)NGG	8	48706966	-	AGGGATAAACAATAGCCTGCGGG	1	1	24
(N20)NGG	8	48706967	-	AAGGGATAAACAATAGCCTGCGG	1	5	37
(N20)NGG	8	48706985	-	CTTTCGCTGCTTATGATGAAGGG	1	1	11
(N20)NGG	8	48706986	-	GCTTTCGCTGCTTATGATGAAGG	1	1	15

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48707013	-	ACCAGTAGAAGTATCCTTGAAGG	1	1	18
(N20)NGG	8	48710820	+	TATTGATTCTGCAGAACTGCAGG	1	2	62
(N20)NGG	8	48710838	+	GCAGGCGTATCCAGCACTTGTGG	1	2	12
(N20)NGG	8	48710841	+	GGCGTATCCAGCACTTGTGGTGG	1	1	3
(N20)NGG	8	48710921	+	GATTACTTCAGATTATAGAACGG	1	5	80
(N20)NGG	8	48710931	+	GATTATAGAACGGTATCCAGAGG	1	1	10
(N20)NGG	8	48710958	+	TTTGAGCCTCATGACAAAAGAGG	1	4	43
(N20)NGG	8	48710962	+	AGCCTCATGACAAAAGAGGTTGG	1	3	30
(N20)NGG	8	48710980	+	GTTGGTGTCTTTATTCTACTTGG	1	2	45
(N20)NGG	8	48710788	-	TGCAGAATCAATAACTATCAAGG	2	3	45
(N20)NGG	8	48710826	-	ATTTTCTCCACCACAAGTGCTGG	1	1	39
(N20)NGG	8	48710872	-	AAACTTCAATCTGGCTTCATTGG	1	3	56
(N20)NGG	8	48710881	-	TAATCTAGGAAACTTCAATCTGG	1	3	49
(N20)NGG	8	48710895	-	TCTATAATCTGAAGTAATCTAGG	2	6	57
(N20)NGG	8	48710925	-	ATGAGGCTCAAAGTCTCCTCTGG	1	2	36
(N20)NGG	8	48710942	-	CACCAACCTCTTTTGTCATGAGG	1	3	37
(N20)NGG	8	48711770	+	TTTAGGTCTCTGTGAATTCCAGG	1	2	50
(N20)NGG	8	48711779	+	CTGTGAATTCCAGGTGATCGCGG	1	3	22
(N20)NGG	8	48711780	+	TGTGAATTCCAGGTGATCGCGGG	1	2	16
(N20)NGG	8	48711815	+	AGCATTCCAGCACCTCTCTGAGG	1	4	50
(N20)NGG	8	48711824	+	GCACCTCTCTGAGGCTGTGCAGG	1	1	68
(N20)NGG	8	48711827	+	CCTCTCTGAGGCTGTGCAGGCGG	1	12	134
(N20)NGG	8	48711833	+	TGAGGCTGTGCAGGCGGCTGAGG	1	6	97
(N20)NGG	8	48711836	+	GGCTGTGCAGGCGGCTGAGGAGG	1	37	893
(N20)NGG	8	48711839	+	TGTGCAGGCGGCTGAGGAGGAGG	1	18	407

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48711856	+	AGGAGGCCCAGCCTCCCTCCTGG	6	14	129
(N20)NGG	8	48711864	+	CAGCCTCCCTCCTGGAGCTGTGG	3	18	180
(N20)NGG	8	48711865	+	AGCCTCCCTCCTGGAGCTGTGGG	2	14	98
(N20)NGG	8	48711876	+	TGGAGCTGTGGGCCTGCAGCTGG	2	14	122
(N20)NGG	8	48711877	+	GGAGCTGTGGGCCTGCAGCTGGG	1	19	138
(N20)NGG	8	48711878	+	GAGCTGTGGGCCTGCAGCTGGGG	1	10	148
(N20)NGG	8	48711902	+	GATTGATGCTTACATGACGCTGG	1	1	7
(N20)NGG	8	48711932	+	CTGTGACCAACAGCTGCGCAAGG	1	2	29
(N20)NGG	8	48711935	+	TGACCAACAGCTGCGCAAGGAGG	1	2	23
(N20)NGG	8	48711951	+	AAGGAGGAAGAGAATGCATCAGG	1	6	147
(N20)NGG	8	48711766	–	GGTACAGACCCGCGATCACCTGG	1	1	3
(N20)NGG	8	48711787	–	AGAGGTGCTGGAATGCTCTCTGG	1	4	32
(N20)NGG	8	48711799	–	GCACAGCCTCAGAGAGGTGCTGG	1	4	84
(N20)NGG	8	48711805	–	CCGCCTGCACAGCCTCAGAGAGG	1	3	61
(N20)NGG	8	48711840	–	ACAGCTCCAGGAGGGAGGCTGGG	2	13	114
(N20)NGG	8	48711841	–	CACAGCTCCAGGAGGGAGGCTGG	2	14	149
(N20)NGG	8	48711845	–	GGCCCACAGCTCCAGGAGGGAGG	1	18	172
(N20)NGG	8	48711848	–	GCAGGCCCACAGCTCCAGGAGGG	1	8	101
(N20)NGG	8	48711849	–	TGCAGGCCCACAGCTCCAGGAGG	2	11	104
(N20)NGG	8	48711852	–	AGCTGCAGGCCCACAGCTCCAGG	2	17	119
(N20)NGG	8	48711866	–	GCATCAATCACCCCAGCTGCAGG	1	1	32
(N20)NGG	8	48711916	–	CTTCCTCCTTGCGCAGCTGTTGG	1	2	55
(N20)NGG	8	48713394	+	CTACTTAAGCAAAAATATTCTGG	1	7	87
(N20)NGG	8	48713421	+	CCGTGACCAGAACATTCTCTTGG	2	6	31
(N20)NGG	8	48713422	+	CGTGACCAGAACATTCTCTTGGG	1	5	33

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48713435	+	TTCTCTTGGGTACAACTTACAGG	1	3	35
(N20)NGG	8	48713487	+	AGCCTGCCTTGCTGAAATCGAGG	1	2	21
(N20)NGG	8	48713490	+	CTGCCTTGCTGAAATCGAGGAGG	1	1	24
(N20)NGG	8	48713496	+	TGCTGAAATCGAGGAGGACAAGG	1	3	23
(N20)NGG	8	48713521	+	AGAAGAATCTTAGAGCTTTCTGG	1	6	67
(N20)NGG	8	48713535	+	GCTTTCTGGATCCAGTTCAGAGG	1	2	39
(N20)NGG	8	48713547	+	CAGTTCAGAGGATTCAGAGAAGG	1	5	92
(N20)NGG	8	48713556	+	GGATTCAGAGAAGGTAATACTGG	1	3	47
(N20)NGG	8	48713559	+	TTCAGAGAAGGTAATACTGGAGG	1	4	64
(N20)NGG	8	48713346	-	GACACGTTGTTCTCATCTGTTGG	1	2	26
(N20)NGG	8	48713399	-	CCAAGAGAATGTTCTGGTCACGG	1	7	53
(N20)NGG	8	48713405	-	TTGTACCCAAGAGAATGTTCTGG	1	3	36
(N20)NGG	8	48713463	-	TCGATTTCAGCAAGGCAGGCTGG	1	2	17
(N20)NGG	8	48713467	-	CTCCTCGATTTCAGCAAGGCAGG	1	1	19
(N20)NGG	8	48713471	-	TGTCCTCCTCGATTTCAGCAAGG	1	2	17
(N20)NGG	8	48713524	-	CTTCTCTGAATCCTCTGAACTGG	2	5	57
(N20)NGG	8	48715899	+	ACTTGCTATGAAACTACTGAAGG	1	4	45
(N20)NGG	8	48715934	+	AGTCAAAAACCAGAGACGATTGG	1	2	43
(N20)NGG	8	48715938	+	AAAAACCAGAGACGATTGGCTGG	1	3	30
(N20)NGG	8	48715946	+	GAGACGATTGGCTGGTGAGCTGG	1	1	30
(N20)NGG	8	48715947	+	AGACGATTGGCTGGTGAGCTGGG	1	2	21
(N20)NGG	8	48715979	+	ACTGCCGCCTGAGCCACTGCCGG	1	3	39
(N20)NGG	8	48715985	+	GCCTGAGCCACTGCCGGAGCCGG	1	20	98
(N20)NGG	8	48715992	+	CCACTGCCGGAGCCGGTCCCAGG	1	2	14
(N20)NGG	8	48715993	+	CACTGCCGGAGCCGGTCCCAGGG	1	3	24

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48716007	+	GTCCCAGGGCTGCTCTGAGCAGG	2	15	239
(N20)NGG	8	48716040	+	GCTGAAAACAGTCTCTTTGTTGG	1	7	89
(N20)NGG	8	48716041	+	CTGAAAACAGTCTCTTTGTTGGG	1	8	89
(N20)NGG	8	48715921	–	GCTCACCAGCCAATCGTCTCTGG	1	1	14
(N20)NGG	8	48715961	–	GGCTCCGGCAGTGGCTCAGGCGG	1	20	66
(N20)NGG	8	48715964	–	ACCGGCTCCGGCAGTGGCTCAGG	1	4	40
(N20)NGG	8	48715970	–	CCTGGGACCGGCTCCGGCAGTGG	1	5	33
(N20)NGG	8	48715976	–	AGCAGCCCTGGGACCGGCTCCGG	1	3	56
(N20)NGG	8	48715982	–	GCTCAGAGCAGCCCTGGGACCGG	1	7	141
(N20)NGG	8	48715987	–	CACCTGCTCAGAGCAGCCCTGGG	2	11	145
(N20)NGG	8	48715988	–	GCACCTGCTCAGAGCAGCCCTGG	1	5	98
(N20)NGG	8	48719722	+	TTTCTTTCTCAGCAAAATAGAGG	2	19	253
(N20)NGG	8	48719764	+	AGAAGATAATAGTATGAATGTGG	1	6	95
(N20)NGG	8	48719774	+	AGTATGAATGTGGATCAAGATGG	2	3	58
(N20)NGG	8	48719790	+	AAGATGGAGACCCCAGTGACAGG	1	3	40
(N20)NGG	8	48719794	+	TGGAGACCCCAGTGACAGGATGG	2	9	81
(N20)NGG	8	48719809	+	CAGGATGGAAGTGCAAGAGCAGG	2	8	126
(N20)NGG	8	48719835	+	AAGATATCAGCTCCCTGATCAGG	1	1	23
(N20)NGG	8	48719880	+	TGAAGATGATAGACAGTGCCCGG	1	3	40
(N20)NGG	8	48719887	+	GATAGACAGTGCCCGGAAGCAGG	1	1	11
(N20)NGG	8	48719890	+	AGACAGTGCCCGGAAGCAGGTGG	1	4	45
(N20)NGG	8	48719891	+	GACAGTGCCCGGAAGCAGGTGGG	1	2	29
(N20)NGG	8	48719732	–	ACTATTATCTCTTCTGGAAGAGGGG	1	10	71
(N20)NGG	8	48719733	–	TACTATTATCTCTTCTGGAAGAGGG	1	4	79
(N20)NGG	8	48719734	–	ATACTATTATCTCTTCTGGAAGAGG	1	3	56

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48719740	-	ACATTCATACTATTATCTTCTGG	1	6	173
(N20)NGG	8	48719778	-	GCACTTCCATCCTGTCACTGGGG	1	3	33
(N20)NGG	8	48719779	-	TGCACTTCCATCCTGTCACTGGG	1	2	25
(N20)NGG	8	48719780	-	TTGCACTTCCATCCTGTCACTGG	2	4	26
(N20)NGG	8	48719825	-	AAACTTGCAACTCCTGATCAGGG	1	1	30
(N20)NGG	8	48719826	-	AAAACTTGCAACTCCTGATCAGG	1	3	23
(N20)NGG	8	48719849	-	GTCTATCATCTTCATTTTCATGG	1	10	115
(N20)NGG	8	48719876	-	ACGAGTACCCACCTGCTTCCGGG	1	1	11
(N20)NGG	8	48719877	-	CACGAGTACCCACCTGCTTCCGG	1	1	12
(N20)NGG	8	48730010	+	CACCCTCTAATACTATTTTTAGG	1	4	61
(N20)NGG	8	48730056	+	TTAAGAGACTTCTGAACACCTGG	1	5	47
(N20)NGG	8	48730084	+	CAGATATCCAGATGCTAAAATGG	1	2	78
(N20)NGG	8	48730101	+	AAATGGACCCAATGAACATCTGG	1	3	67
(N20)NGG	8	48730102	+	AATGGACCCAATGAACATCTGGG	1	3	39
(N20)NGG	8	48730122	+	GGGATGACATCATCACAAATCGG	1	2	37
(N20)NGG	8	48730132	+	CATCACAAATCGGTAAGACGTGG	1	1	9
(N20)NGG	8	48729990	-	TGCCTAAAAATAGTATTAGAGGG	1	4	74
(N20)NGG	8	48729991	-	TTGCCTAAAAATAGTATTAGAGG	1	2	75
(N20)NGG	8	48730030	-	GTGTTCAGAAGTCTCTTAAGGGG	1	3	45
(N20)NGG	8	48730031	-	GGTGTTCAGAAGTCTCTTAAGGG	1	3	34
(N20)NGG	8	48730032	-	AGGTGTTCAGAAGTCTCTTAAGG	1	8	49
(N20)NGG	8	48730052	-	ATCTGGATATCTGTTTGTCCAGG	1	6	143
(N20)NGG	8	48730069	-	ATTGGGTCCATTTTAGCATCTGG	1	1	19
(N20)NGG	8	48730086	-	TGTCATCCCAGATGTTCATTGGG	1	3	30
(N20)NGG	8	48730087	-	ATGTCATCCCAGATGTTCATTGG	1	1	34

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48732025	+	CACCAAATTGCAGTCTGTACAGG	1	1	26
(N20)NGG	8	48732043	+	ACAGGCTTTAACAGAAATTCAGG	1	2	51
(N20)NGG	8	48732071	+	ATCAGCTTTATAAGCAAACAAGG	1	4	65
(N20)NGG	8	48732087	+	AACAAGGTAATTTTTTTCATCGG	1	17	171
(N20)NGG	8	48731982	-	TGAGTCTACTTTGGTGTAAGAGG	1	3	26
(N20)NGG	8	48731991	-	GCAATTTGGTGAGTCTACTTTGG	1	4	21
(N20)NGG	8	48732005	-	AGCCTGTACAGACTGCAATTTGG	1	3	21
(N20)NGG	8	48733279	+	AGTATATTTTTATGTTCCTTAGG	3	21	253
(N20)NGG	8	48733330	+	CAAGCTGAAGCTGCTGCTCCAGG	2	13	138
(N20)NGG	8	48733331	+	AAGCTGAAGCTGCTGCTCCAGGG	4	30	315
(N20)NGG	8	48733336	+	GAAGCTGCTGCTCCAGGGAGAGG	2	9	186
(N20)NGG	8	48733379	+	TTTATTGACAAAGCTATGCACGG	1	6	76
(N20)NGG	8	48733380	+	TTATTGACAAAGCTATGCACGGG	1	1	29
(N20)NGG	8	48733381	+	TATTGACAAAGCTATGCACGGGG	1	1	18
(N20)NGG	8	48733393	+	TATGCACGGGGAGCTCCAGAAGG	1	5	26
(N20)NGG	8	48733484	+	GCCAAATATTACATTCAAAATGG	1	7	127
(N20)NGG	8	48733504	+	TGGCATTCAGAGTTTTATGCAGG	1	4	34
(N20)NGG	8	48733273	-	TAAGGTAGATATGTTTCCTAAGG	1	3	54
(N20)NGG	8	48733291	-	AGCTTGCTGCGGATCATGTAAGG	1	1	7
(N20)NGG	8	48733302	-	GCAGCAGCTTCAGCTTGCTGCGG	1	8	96
(N20)NGG	8	48733326	-	GGGACTGGTCAGCCTCTCCCTGG	1	4	41
(N20)NGG	8	48733341	-	CAATAAATGTCAGCAGGGACTGG	1	5	56
(N20)NGG	8	48733346	-	TTTGTCAATAAATGTCAGCAGGG	1	7	80
(N20)NGG	8	48733347	-	CTTTGTCAATAAATGTCAGCAGG	1	6	51
(N20)NGG	8	48733386	-	GAAGCTCTAGAATCGCCTTCTGG	1	1	14

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48733437	-	TGTCAACATCATCTTGCAGGAGG	1	1	37
(N20)NGG	8	48733440	-	CTCTGTCAACATCATCTTGCAGG	1	3	41
(N20)NGG	8	48733463	-	GCCATTTTGAATGTAATATTTGG	1	4	97
(N20)NGG	8	48734164	+	TTTATTAACTTTTCTCCACTAGG	1	9	169
(N20)NGG	8	48734184	+	AGGCTCTCAATAAACAAGACTGG	1	3	34
(N20)NGG	8	48734185	+	GGCTCTCAATAAACAAGACTGGG	1	5	31
(N20)NGG	8	48734192	+	AATAAACAAGACTGGGTAGATGG	1	5	73
(N20)NGG	8	48734215	+	TGAGCCCACAGAAGCCGAGAAGG	1	5	67
(N20)NGG	8	48734223	+	CAGAAGCCGAGAAGGATTTTTGG	1	3	40
(N20)NGG	8	48734224	+	AGAAGCCGAGAAGGATTTTTGGG	1	2	44
(N20)NGG	8	48734265	+	GTTACAACCACCTTGCTGAGTGG	2	3	22
(N20)NGG	8	48734334	+	CCCCAGACCTAAATAAAATCTGG	1	2	38
(N20)NGG	8	48734353	+	CTGGAGTGAACCATTTTATCAGG	1	5	41
(N20)NGG	8	48734356	+	GAGTGAACCATTTTATCAGGTGG	1	2	42
(N20)NGG	8	48734357	+	AGTGAACCATTTTATCAGGTGGG	1	3	42
(N20)NGG	8	48734157	-	CTTGTTTATTGAGAGCCTAGTGG	1	2	39
(N20)NGG	8	48734197	-	AAATCCTTCTCGGCTTCTGTGGG	1	2	29
(N20)NGG	8	48734198	-	AAAATCCTTCTCGGCTTCTGTGG	1	1	39
(N20)NGG	8	48734207	-	AAGTTCCCAAAAATCCTTCTCGG	1	4	67
(N20)NGG	8	48734234	-	AAGGTGGTTGTAACAGTCAAGGG	1	3	29
(N20)NGG	8	48734235	-	CAAGGTGGTTGTAACAGTCAAGG	1	2	39
(N20)NGG	8	48734250	-	GTGATTTCCACTCAGCAAGGTGG	1	2	36
(N20)NGG	8	48734253	-	CAAGTGATTTCCACTCAGCAAGG	1	2	36
(N20)NGG	8	48734291	-	GGGGTTCTCACTGTCTATACTGG	1	1	24
(N20)NGG	8	48734310	-	AGATTTTATTTAGGTCTGGGGGG	1	2	44

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48734311	-	CAGATTTTATTTAGGTCTGGGGG	2	3	58
(N20)NGG	8	48734312	-	CCAGATTTTATTTAGGTCTGGGG	1	1	49
(N20)NGG	8	48734313	-	TCCAGATTTTATTTAGGTCTGGG	1	3	83
(N20)NGG	8	48734314	-	CTCCAGATTTTATTTAGGTCTGG	1	5	43
(N20)NGG	8	48734319	-	GTTCACTCCAGATTTTATTTAGG	2	6	102
(N20)NGG	8	48734341	-	ATTTTACCCACCTGATAAAATGG	1	5	95
(N20)NGG	8	48736418	+	GCCTTTTTGATTTGTTTTGTAGG	1	19	440
(N20)NGG	8	48736435	+	TGTAGGCTGTATAGATCAATTGG	1	2	24
(N20)NGG	8	48736456	+	GGAGAATACGACGTCCTCCGTGG	1	1	3
(N20)NGG	8	48736457	+	GAGAATACGACGTCCTCCGTGGG	1	1	2
(N20)NGG	8	48736477	+	GGGATTTTTACCAGTGAGATAGG	1	5	46
(N20)NGG	8	48736557	+	AGCTGCTAAGCAGTATGATGAGG	1	3	41
(N20)NGG	8	48736573	+	GATGAGGTAAAATTGATCTCTGG	1	2	48
(N20)NGG	8	48736397	-	GCCTACAAAACAAATCAAAAAGG	1	12	260
(N20)NGG	8	48736448	-	CACTGGTAAAAATCCCACGGAGG	1	2	19
(N20)NGG	8	48736451	-	TCTCACTGGTAAAAATCCCACGG	1	7	62
(N20)NGG	8	48736465	-	TTGCTTTGTTCCTATCTCACTGG	2	3	79
(N20)NGG	8	48736516	-	AGCTTCAGAATAATCACTTCTGG	1	3	60
(N20)NGG	8	48739216	+	GGTTGTATGTGTGGTTTCACAGG	1	2	41
(N20)NGG	8	48739261	+	CCTGCTGAGCCTCGACCCAGCGG	1	2	42
(N20)NGG	8	48739274	+	GACCCAGCGGCTGTTAGCGCTGG	1	1	3
(N20)NGG	8	48739282	+	GGCTGTTAGCGCTGGTTGCCTGG	1	1	6
(N20)NGG	8	48739303	+	GGCCAGCCTACAGCAGCCCGTGG	1	2	30
(N20)NGG	8	48739304	+	GCCAGCCTACAGCAGCCCGTGGG	1	2	17
(N20)NGG	8	48739321	+	CGTGGGCATCCGCCTGCTAGAGG	1	6	20

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48739324	+	GGGCATCCGCCTGCTAGAGGAGG	1	8	30
(N20)NGG	8	48739373	+	CTGCCTGCCAAGCGAGTCCGTGG	1	1	8
(N20)NGG	8	48739374	+	TGCCTGCCAAGCGAGTCCGTGGG	1	1	5
(N20)NGG	8	48739378	+	TGCCAAGCGAGTCCGTGGGAAGG	1	1	9
(N20)NGG	8	48739407	+	TCCCTCCTGATGTCCTCAGATGG	1	2	55
(N20)NGG	8	48739408	+	CCCTCCTGATGTCCTCAGATGGG	1	3	39
(N20)NGG	8	48739411	+	TCCTGATGTCCTCAGATGGGTGG	1	5	46
(N20)NGG	8	48739433	+	GAGCTTGCTAAGTAAGTGTGAGG	1	6	26
(N20)NGG	8	48739438	+	TGCTAAGTAAGTGTGAGGTCAGG	1	1	35
(N20)NGG	8	48739238	-	CGCTGGGTCGAGGCTCAGCAGGG	1	1	26
(N20)NGG	8	48739239	-	CCGCTGGGTCGAGGCTCAGCAGG	1	1	17
(N20)NGG	8	48739248	-	CGCTAACAGCCGCTGGGTCGAGG	1	1	2
(N20)NGG	8	48739254	-	AACCAGCGCTAACAGCCGCTGGG	1	1	4
(N20)NGG	8	48739255	-	CAACCAGCGCTAACAGCCGCTGG	1	2	4
(N20)NGG	8	48739278	-	CGGGCTGCTGTAGGCTGGCCAGG	1	2	26
(N20)NGG	8	48739283	-	GCCCACGGGCTGCTGTAGGCTGG	1	1	25
(N20)NGG	8	48739287	-	GGATGCCCACGGGCTGCTGTAGG	1	2	38
(N20)NGG	8	48739297	-	TCTAGCAGGCGGATGCCCACGGG	1	3	28
(N20)NGG	8	48739298	-	CTCTAGCAGGCGGATGCCCACGG	1	7	13
(N20)NGG	8	48739308	-	GCAGAGCCTCCCTCTAGCAGGCGG	1	5	72
(N20)NGG	8	48739311	-	GGAGCAGAGCCTCCCTCTAGCAGG	1	4	43
(N20)NGG	8	48739332	-	GCAGCTCAGCAGGCAGCAGGCGG	2	14	212
(N20)NGG	8	48739335	-	CAGGCAGCTCAGCAGGCAGCAGG	2	28	218
(N20)NGG	8	48739342	-	CGCTTGGCAGGCAGCTCAGCAGG	2	5	47
(N20)NGG	8	48739354	-	TTCCCCACGGACTCGCTTGGCAGG	1	1	7

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48739358	-	GGCCTTCCCACGGACTCGCTTGG	1	2	6
(N20)NGG	8	48739368	-	GAGGGAGGCGGGCCTTCCCACGG	2	5	57
(N20)NGG	8	48739379	-	GAGGACATCAGGAGGGAGGCGGG	1	7	124
(N20)NGG	8	48739380	-	TGAGGACATCAGGAGGGAGGCGG	2	17	168
(N20)NGG	8	48739383	-	ATCTGAGGACATCAGGAGGGAGG	1	3	71
(N20)NGG	8	48739386	-	CCCATCTGAGGACATCAGGAGGG	1	2	52
(N20)NGG	8	48739387	-	ACCCATCTGAGGACATCAGGAGG	1	1	33
(N20)NGG	8	48739390	-	TCCACCCATCTGAGGACATCAGG	1	1	35
(N20)NGG	8	48739398	-	TAGCAAGCTCCACCCATCTGAGG	1	2	24
(N20)NGG	8	48740730	+	TTGTTTTGAATTTTTTACAGAGG	1	38	467
(N20)NGG	8	48740731	+	TGTTTTGAATTTTTTACAGAGGG	3	24	669
(N20)NGG	8	48740774	+	CTCTTTAGCAGCTTGTTTTCTGG	1	6	55
(N20)NGG	8	48740791	+	TTCTGGAATTTTGAAAGAGATGG	3	15	244
(N20)NGG	8	48740908	+	ACCCTTTGTCTCTTGTATTCAGG	1	3	89
(N20)NGG	8	48740733	-	AGAGCTGTTTTGCAATTATTGGG	2	4	87
(N20)NGG	8	48740734	-	AAGAGCTGTTTTGCAATTATTGG	1	5	73
(N20)NGG	8	48740867	-	GGGTGGAAAGAAAGAGAAGGTGG	6	51	772
(N20)NGG	8	48740870	-	AAAGGGTGGAAAGAAAGAGAAGG	4	94	1695
(N20)NGG	8	48740884	-	TGAATACAAGAGACAAAGGGTGG	1	5	118
(N20)NGG	8	48740887	-	ACCTGAATACAAGAGACAAAGGG	1	2	67
(N20)NGG	8	48740888	-	TACCTGAATACAAGAGACAAAGG	1	6	51
(N20)NGG	8	48743165	+	TCTTTGGTTCTGGTGCTTATAGG	1	2	51
(N20)NGG	8	48743195	+	GAGTGAGTTAAAAATGAAGCAGG	1	4	76
(N20)NGG	8	48743204	+	AAAAATGAAGCAGGATGCCCAGG	1	3	93
(N20)NGG	8	48743227	+	TCGTTCTGTACAGAAGCTACCGG	1	1	13

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48743232	+	CTGTACAGAAGCTACCGGCACGG	1	3	14
(N20)NGG	8	48743285	+	CAGCCTCATCACCCCGTTACAGG	1	2	18
(N20)NGG	8	48743291	+	CATCACCCCGTTACAGGCCGTGG	1	1	28
(N20)NGG	8	48743297	+	CCCGTTACAGGCCGTGGCCCAGG	1	1	5
(N20)NGG	8	48743199	-	GCTTCTGTACAGAACGACCTGGG	1	1	19
(N20)NGG	8	48743200	-	AGCTTCTGTACAGAACGACCTGG	1	1	7
(N20)NGG	8	48743224	-	TGTCAGGAAGGTCTCCGTGCCGG	1	3	23
(N20)NGG	8	48743236	-	GCTTGATCTGAATGTCAGGAAGG	1	5	42
(N20)NGG	8	48743240	-	CTGTGCTTGATCTGAATGTCAGG	1	2	28
(N20)NGG	8	48743266	-	CGGCCTGTAACGGGGTGATGAGG	1	1	7
(N20)NGG	8	48743274	-	CTGGGCCACGGCCTGTAACGGGG	1	1	8
(N20)NGG	8	48743275	-	CCTGGGCCACGGCCTGTAACGGG	1	1	31
(N20)NGG	8	48743276	-	ACCTGGGCCACGGCCTGTAACGG	1	2	11
(N20)NGG	8	48743286	-	GCAAAAACTGACCTGGGCCACGG	1	3	40
(N20)NGG	8	48743292	-	GCAGCGGCAAAAACTGACCTGGG	1	2	19
(N20)NGG	8	48743293	-	CGCAGCGGCAAAAACTGACCTGG	1	1	12
(N20)NGG	8	48744374	+	TGGGCCTGCTTTCCCTCTCCAGG	1	8	68
(N20)NGG	8	48744379	+	CTGCTTTCCCTCTCCAGGTGCGG	2	12	111
(N20)NGG	8	48744383	+	TTTCCCTCTCCAGGTGCGGCCGG	1	2	30
(N20)NGG	8	48744387	+	CCTCTCCAGGTGCGGCCGGCCGG	1	3	25
(N20)NGG	8	48744391	+	TCCAGGTGCGGCCGGCCGGACGG	1	2	23
(N20)NGG	8	48744414	+	ACCTACTACGACTGCGCAGACGG	1	1	5
(N20)NGG	8	48744423	+	GACTGCGCAGACGGTTTATGAGG	1	1	3
(N20)NGG	8	48744424	+	ACTGCGCAGACGGTTTATGAGGG	1	1	2
(N20)NGG	8	48744430	+	CAGACGGTTTATGAGGGACCAGG	1	1	10

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48744461	+	AGTTTGATGTATGCCAGAAAAGG	1	1	77
(N20)NGG	8	48744487	+	TGCTGAGCAAAAACGAGAGAAGG	1	4	56
(N20)NGG	8	48744356	-	CGCACCTGGAGAGGGAAAGCAGG	1	3	41
(N20)NGG	8	48744364	-	CGGCCGGCCGCACCTGGAGAGGG	1	4	22
(N20)NGG	8	48744365	-	CCGGCCGGCCGCACCTGGAGAGG	1	3	35
(N20)NGG	8	48744370	-	TCCGTCCGGCCGGCCGCACCTGG	1	2	25
(N20)NGG	8	48744380	-	TCGTAGTAGGTCCGTCCGGCCGG	1	1	1
(N20)NGG	8	48744384	-	GCAGTCGTAGTAGGTCCGTCCGG	1	1	1
(N20)NGG	8	48744393	-	ACCGTCTGCGCAGTCGTAGTAGG	1	1	3
(N20)NGG	8	48744426	-	ACATCAAACTGAGCTTCTCCTGG	1	3	41
(N20)NGG	8	48744452	-	TTGCTCAGCAACGCCTTTTCTGG	1	2	26
(N20)NGG	8	48746759	+	CTCTGATTGCATGTCACAGATGG	1	2	46
(N20)NGG	8	48746778	+	ATGGAAGAAGCTCATTTGATTGG	1	2	51
(N20)NGG	8	48746786	+	AGCTCATTTGATTGGCTGACCGG	1	1	28
(N20)NGG	8	48746787	+	GCTCATTTGATTGGCTGACCGGG	1	1	13
(N20)NGG	8	48746806	+	CGGGAGCAGCACTGACCCGCTGG	2	2	18
(N20)NGG	8	48746856	+	CCTTGCTGTTTGCCCACAAGAGG	1	4	45
(N20)NGG	8	48746865	+	TTGCCCACAAGAGGAGTGAAAGG	1	3	47
(N20)NGG	8	48746893	+	GAGAGCACCCTTGAAGTCAGTGG	1	2	38
(N20)NGG	8	48746894	+	AGAGCACCCTTGAAGTCAGTGGG	1	1	29
(N20)NGG	8	48746895	+	GAGCACCCTTGAAGTCAGTGGGG	1	1	36
(N20)NGG	8	48746906	+	AAGTCAGTGGGGCCTGATTTTGG	1	1	40
(N20)NGG	8	48746907	+	AGTCAGTGGGGCCTGATTTTGGG	1	1	42
(N20)NGG	8	48746916	+	GGCCTGATTTTGGGAAAAAAAGG	1	4	82
(N20)NGG	8	48746920	+	TGATTTTGGGAAAAAAGGCTGG	2	11	128

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48746921	+	GATTTTGGGAAAAAAAGGCTGGG	1	9	103
(N20)NGG	8	48746930	+	AAAAAAAGGCTGGGCCTTCCAGG	1	6	87
(N20)NGG	8	48746931	+	AAAAAAGGCTGGGCCTTCCAGGG	1	3	46
(N20)NGG	8	48746932	+	AAAAAGGCTGGGCCTTCCAGGGG	2	3	54
(N20)NGG	8	48746938	+	GCTGGGCCTTCCAGGGGACGAGG	1	6	58
(N20)NGG	8	48746941	+	GGGCCTTCCAGGGGACGAGGTGG	1	5	63
(N20)NGG	8	48746957	+	GAGGTGGATAACAAAGTGAAAGG	1	3	104
(N20)NGG	8	48746965	+	TAACAAAGTGAAAGGTAAGCTGG	1	7	64
(N20)NGG	8	48746966	+	AACAAAGTGAAAGGTAAGCTGGG	1	8	103
(N20)NGG	8	48746734	-	TCTGTGACATGCAATCAGAGAGG	1	2	56
(N20)NGG	8	48746783	-	CAGCGGGTCAGTGCTGCTCCCGG	1	3	31
(N20)NGG	8	48746799	-	GACTGGTGTGGTCGACCAGCGGG	1	1	5
(N20)NGG	8	48746800	-	GGACTGGTGTGGTCGACCAGCGG	1	2	11
(N20)NGG	8	48746811	-	AGTCAGATGAGGGACTGGTGTGG	1	4	64
(N20)NGG	8	48746816	-	CAAGGAGTCAGATGAGGGACTGG	2	2	50
(N20)NGG	8	48746821	-	AACAGCAAGGAGTCAGATGAGGG	1	5	57
(N20)NGG	8	48746822	-	AAACAGCAAGGAGTCAGATGAGG	2	5	103
(N20)NGG	8	48746834	-	CCTCTTGTGGGCAAACAGCAAGG	1	1	45
(N20)NGG	8	48746846	-	TAACCTTTCACTCCTCTTGTGGG	1	4	51
(N20)NGG	8	48746847	-	GTAACCTTTCACTCCTCTTGTGG	1	1	20
(N20)NGG	8	48746878	-	TCAGGCCCCACTGACTTCAAGGG	1	5	50
(N20)NGG	8	48746879	-	ATCAGGCCCCACTGACTTCAAGG	1	3	47
(N20)NGG	8	48746896	-	AGCCTTTTTTTCCCAAAATCAGG	1	6	84
(N20)NGG	8	48746922	-	TATCCACCTCGTCCCCTGGAAGG	1	2	13
(N20)NGG	8	48746926	-	TTGTTATCCACCTCGTCCCCCTGG	1	1	18

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48748898	+	TTTGAAACTTTCTTATGTACAGG	1	5	95
(N20)NGG	8	48748921	+	AATATACCATTGATTCTGATTGG	2	2	58
(N20)NGG	8	48748958	+	TGTTCTCACTCCGATGTTTGTGG	1	2	18
(N20)NGG	8	48748967	+	TCCGATGTTTGTGGAGACCCAGG	1	3	17
(N20)NGG	8	48748976	+	TGTGGAGACCCAGGCCTCCCAGG	1	11	71
(N20)NGG	8	48748977	+	GTGGAGACCCAGGCCTCCCAGGG	2	8	79
(N20)NGG	8	48749000	+	CACTCTCCAGACCCGTACCCAGG	1	3	19
(N20)NGG	8	48749004	+	CTCCAGACCCGTACCCAGGAAGG	1	2	27
(N20)NGG	8	48749005	+	TCCAGACCCGTACCCAGGAAGGG	1	2	41
(N20)NGG	8	48749023	+	AAGGGTCCCTCTCAGCTCGCTGG	1	3	26
(N20)NGG	8	48749030	+	CCTCTCAGCTCGCTGGCCAGTGG	1	3	38
(N20)NGG	8	48749034	+	TCAGCTCGCTGGCCAGTGGCAGG	1	3	26
(N20)NGG	8	48749035	+	CAGCTCGCTGGCCAGTGGCAGGG	2	10	62
(N20)NGG	8	48749044	+	GGCCAGTGGCAGGGCAGATAAGG	1	6	71
(N20)NGG	8	48749045	+	GCCAGTGGCAGGGCAGATAAGGG	1	7	75
(N20)NGG	8	48749088	+	TTCACACTGACACAGACTGCAGG	2	2	53
(N20)NGG	8	48749110	+	GTAACAGTGACCCTGCCCGCTGG	1	1	13
(N20)NGG	8	48748905	-	GAAACGCCAATCAGAATCAATGG	1	2	35
(N20)NGG	8	48748927	-	TCGGAGTGAGAACAGTACTTCGG	1	3	19
(N20)NGG	8	48748946	-	GCCTGGGTCTCCACAAACATCGG	2	4	55
(N20)NGG	8	48748962	-	GAGAGTGCCCTGGGAGGCCTGGG	1	6	76
(N20)NGG	8	48748963	-	GGAGAGTGCCCTGGGAGGCCTGG	1	13	140
(N20)NGG	8	48748968	-	GGTCTGGAGAGTGCCCTGGGAGG	1	5	107
(N20)NGG	8	48748971	-	ACGGGTCTGGAGAGTGCCCTGGG	1	1	22
(N20)NGG	8	48748972	-	TACGGGTCTGGAGAGTGCCCTGG	1	1	12

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48748984	-	ACCCTTCCTGGGTACGGGTCTGG	1	1	17
(N20)NGG	8	48748989	-	GAGGGACCCTTCCTGGGTACGGG	1	3	35
(N20)NGG	8	48748990	-	AGAGGGACCCTTCCTGGGTACGG	1	3	41
(N20)NGG	8	48748995	-	AGCTGAGAGGGACCCTTCCTGGG	1	4	47
(N20)NGG	8	48748996	-	GAGCTGAGAGGGACCCTTCCTGG	1	6	49
(N20)NGG	8	48749007	-	CACTGGCCAGCGAGCTGAGAGGG	1	5	25
(N20)NGG	8	48749008	-	CCACTGGCCAGCGAGCTGAGAGG	1	2	38
(N20)NGG	8	48749024	-	GCCCTTATCTGCCCTGCCACTGG	1	3	44
(N20)NGG	8	48749046	-	GAAGTCATGCTGCTGCTGGGTGG	1	9	71
(N20)NGG	8	48749049	-	TGTGAAGTCATGCTGCTGCTGGG	1	2	53
(N20)NGG	8	48749050	-	GTGTGAAGTCATGCTGCTGCTGG	1	3	34
(N20)NGG	8	48749793	+	GATTAATTATTCGAAATTTCTGG	1	2	34
(N20)NGG	8	48749808	+	ATTTCTGGAGCCATGAAACTAGG	1	5	94
(N20)NGG	8	48749827	+	TAGGTTACCTTCAAATACCTTGG	1	1	22
(N20)NGG	8	48749832	+	TACCTTCAAATACCTTGGACCGG	1	1	27
(N20)NGG	8	48749839	+	AAATACCTTGGACCGGTTGCTGG	1	1	6
(N20)NGG	8	48749980	+	TCTGTCAGAATGCGAATTTCAGG	1	1	22
(N20)NGG	8	48749988	+	AATGCGAATTTCAGGTAATGTGG	1	5	40
(N20)NGG	8	48749796	-	TTGAAGGTAACCTAGTTTCATGG	1	3	31
(N20)NGG	8	48749812	-	AACCGGTCCAAGGTATTTGAAGG	1	1	6
(N20)NGG	8	48749822	-	TAGTGCCAGCAACCGGTCCAAGG	1	1	10
(N20)NGG	8	48749829	-	AGGAATTTAGTGCCAGCAACCGG	1	5	51
(N20)NGG	8	48749849	-	TTCTATCTTAGGAGAATATAAGG	1	5	95
(N20)NGG	8	48749860	-	AAAAAGTGCACTTCTATCTTAGG	1	4	72
(N20)NGG	8	48749915	-	TGGATAATCTGGGCTCATGCTGG	1	2	12

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48749925	-	ACATGGGGTTTGGATAATCTGGG	2	2	30
(N20)NGG	8	48749926	-	AACATGGGGTTTGGATAATCTGG	1	4	28
(N20)NGG	8	48749935	-	GGATGCTCGAACATGGGGTTTGG	1	3	14
(N20)NGG	8	48749940	-	ACAGAGGATGCTCGAACATGGGG	1	1	18
(N20)NGG	8	48749941	-	GACAGAGGATGCTCGAACATGGG	1	1	6
(N20)NGG	8	48749942	-	TGACAGAGGATGCTCGAACATGG	1	2	14
(N20)NGG	8	48749956	-	TGAAATTCGCATTCTGACAGAGG	1	2	25
(N20)NGG	8	48751742	+	TGAGACAGATAATGACTCCCAGG	1	4	36
(N20)NGG	8	48751757	+	CTCCCAGGAAATATTTAAGTTGG	1	4	69
(N20)NGG	8	48751779	+	GCAAAAGATGTGCTGATTCAAGG	1	1	50
(N20)NGG	8	48751800	+	GGATTGATCGATGAGAACCCTGG	1	1	5
(N20)NGG	8	48751822	+	GACTTCAGTACGTGAATAACTGG	1	4	17
(N20)NGG	8	48751823	+	ACTTCAGTACGTGAATAACTGGG	1	2	16
(N20)NGG	8	48751827	+	CAGTACGTGAATAACTGGGCTGG	1	1	6
(N20)NGG	8	48751828	+	AGTACGTGAATAACTGGGCTGGG	1	1	14
(N20)NGG	8	48751712	-	TCATTATCTGTCTCACTTTCTGG	1	29	133
(N20)NGG	8	48751737	-	TGCCAACTTAAATATTTCCTGGG	1	2	82
(N20)NGG	8	48751738	-	TTGCCAACTTAAATATTTCCTGG	1	6	76
(N20)NGG	8	48751795	-	TATTCACGTACTGAAGTCCAGGG	1	1	16
(N20)NGG	8	48751796	-	TTATTCACGTACTGAAGTCCAGG	1	1	14
(N20)NGG	8	48752604	+	TGAAAGACAAAAAGTATGTTTGG	2	14	184
(N20)NGG	8	48752673	+	AGAACTTCTGAACCCCGTTGTGG	1	2	15
(N20)NGG	8	48752705	+	CCCATCCTTCTACAACATGTAGG	1	3	24
(N20)NGG	8	48752706	+	CCATCCTTCTACAACATGTAGGG	2	4	28
(N20)NGG	8	48752732	+	AAATGTATAATATTCTCATGTGG	2	11	185

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48752750	+	TGTGGATTCATGATAATTACAGG	1	3	31
(N20)NGG	8	48752569	-	TTGTCTTTCATCATCTCTATGGG	2	7	124
(N20)NGG	8	48752570	-	TTTGTCTTTCATCATCTCTATGG	3	12	151
(N20)NGG	8	48752625	-	AGTTCTACTGGTTTTAACTTTGG	1	4	62
(N20)NGG	8	48752637	-	AGAAGTTCTCGGAGTTCTACTGG	1	3	26
(N20)NGG	8	48752648	-	CAACGGGGTTCAGAAGTTCTCGG	1	1	11
(N20)NGG	8	48752663	-	GGGAAACGAATTCCACAACGGGG	1	1	7
(N20)NGG	8	48752664	-	TGGGAAACGAATTCCACAACGGG	1	1	20
(N20)NGG	8	48752665	-	ATGGGAAACGAATTCCACAACGG	1	1	25
(N20)NGG	8	48752683	-	CCTACATGTTGTAGAAGGATGGG	1	1	28
(N20)NGG	8	48752684	-	CCCTACATGTTGTAGAAGGATGG	1	3	39
(N20)NGG	8	48752688	-	TGTTCCCTACATGTTGTAGAAGG	1	4	34
(N20)NGG	8	48761714	+	CACCAGTTCCCTTCCCCGCCAGG	1	3	48
(N20)NGG	8	48761755	+	TTTCTGCTGCCAAAATTTCATGG	1	5	114
(N20)NGG	8	48761778	+	AGTGTTGAAAACACTCTGTCTGG	1	2	35
(N20)NGG	8	48761781	+	GTTGAAAACACTCTGTCTGGAGG	1	8	93
(N20)NGG	8	48761784	+	GAAAACACTCTGTCTGGAGGTGG	1	4	68
(N20)NGG	8	48761799	+	GGAGGTGGTACTTTGTCGTGTGG	1	2	25
(N20)NGG	8	48761802	+	GGTGGTACTTTGTCGTGTGGAGG	1	1	8
(N20)NGG	8	48761803	+	GTGGTACTTTGTCGTGTGGAGGG	1	1	16
(N20)NGG	8	48761838	+	GTACTTCCAGTTAAAGAGCAAGG	1	4	77
(N20)NGG	8	48761864	+	TCGTTCAAGTCATGAGACATAGG	1	3	20
(N20)NGG	8	48761694	-	AACCTGGCGGGGAAGGGAACTGG	1	4	36
(N20)NGG	8	48761700	-	TTCATGAACCTGGCGGGGAAGGG	1	2	28
(N20)NGG	8	48761701	-	ATTCATGAACCTGGCGGGGAAGG	1	2	16

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48761705	-	CAGCATTCATGAACCTGGCGGGG	1	2	36
(N20)NGG	8	48761706	-	ACAGCATTCATGAACCTGGCGGG	1	2	50
(N20)NGG	8	48761707	-	CACAGCATTCATGAACCTGGCGG	2	15	179
(N20)NGG	8	48761710	-	GAACACAGCATTCATGAACCTGG	1	7	49
(N20)NGG	8	48761742	-	TTCAACACTCCATGAAATTTTGG	1	2	60
(N20)NGG	8	48761822	-	CGAAGTCCTTGCTCTTTAACTGG	2	3	19
(N20)NGG	8	48761945	+	AAACTTAATTTTTCAGATACTGG	1	12	154
(N20)NGG	8	48761948	+	CTTAATTTTTCAGATACTGGAGG	1	2	75
(N20)NGG	8	48761966	+	GGAGGAGTCTCTGTGTGAACTGG	1	3	99
(N20)NGG	8	48762002	+	GAAGCAACATCAGAATACTATGG	1	1	45
(N20)NGG	8	48762005	+	GCAACATCAGAATACTATGGAGG	1	3	34
(N20)NGG	8	48762064	+	GCTTCCCTCCTCTTGCAGACAGG	1	4	48
(N20)NGG	8	48762069	+	CCTCCTCTTGCAGACAGGTATGG	1	2	33
(N20)NGG	8	48762070	+	CTCCTCTTGCAGACAGGTATGGG	1	2	21
(N20)NGG	8	48762079	+	CAGACAGGTATGGGCTGTCCAGG	1	2	36
(N20)NGG	8	48762080	+	AGACAGGTATGGGCTGTCCAGGG	1	2	32
(N20)NGG	8	48762036	-	TGCAAGAGGAGGGAAGCTCTTGG	1	6	49
(N20)NGG	8	48762046	-	CATACCTGTCTGCAAGAGGAGGG	1	3	29
(N20)NGG	8	48762047	-	CCATACCTGTCTGCAAGAGGAGG	1	2	40
(N20)NGG	8	48762050	-	AGCCCATACCTGTCTGCAAGAGG	1	2	25
(N20)NGG	8	48765243	+	TGTTTATTGTAGATACTTCCAGG	1	14	73
(N20)NGG	8	48765249	+	TTGTAGATACTTCCAGGCTTTGG	1	2	27
(N20)NGG	8	48765310	+	GCCGCTGCAGCAGAAGTTCTAGG	1	2	25
(N20)NGG	8	48765333	+	ACTTATACTTCGATATGTTATGG	1	2	23
(N20)NGG	8	48765239	-	ACATATTATTCACCAAAGCCTGG	1	3	54

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48765262	-	CACTTCTTTATATCTTACAAAGG	1	3	83
(N20)NGG	8	48765289	-	TCCTAGAACTTCTGCTGCAGCGG	1	4	71
(N20)NGG	8	48766643	+	CTCCTTTGTGCTTATGTTTCAGG	3	8	74
(N20)NGG	8	48766666	+	TTAATATTTGAAAAGTTTTCCGG	3	30	414
(N20)NGG	8	48766699	+	AATTCTAAAGACAACTCAGTAGG	1	7	92
(N20)NGG	8	48766700	+	ATTCTAAAGACAACTCAGTAGGG	1	6	74
(N20)NGG	8	48766714	+	TCAGTAGGGATTCAATTGCTAGG	1	2	25
(N20)NGG	8	48766725	+	TCAATTGCTAGGCATCGTGATGG	1	2	12
(N20)NGG	8	48766759	+	CCTCCCTATGACCCACAGTGTGG	1	5	40
(N20)NGG	8	48766623	-	AACCTGAAACATAAGCACAAAGG	1	4	105
(N20)NGG	8	48766663	-	TTTAGAATTAGGATCTTTACCGG	1	11	138
(N20)NGG	8	48766674	-	ACTGAGTTGTCTTTAGAATTAGG	1	4	65
(N20)NGG	8	48766726	-	GTCATAGGGAGGCAGGTCATTGG	1	1	30
(N20)NGG	8	48766733	-	ACTGTGGGTCATAGGGAGGCAGG	1	1	47
(N20)NGG	8	48766737	-	CCACACTGTGGGTCATAGGGAGG	1	5	35
(N20)NGG	8	48766740	-	ATGCCACACTGTGGGTCATAGGG	1	7	33
(N20)NGG	8	48766741	-	GATGCCACACTGTGGGTCATAGG	1	2	36
(N20)NGG	8	48766748	-	TACTCTGGATGCCACACTGTGGG	1	1	35
(N20)NGG	8	48766749	-	CTACTCTGGATGCCACACTGTGG	1	2	41
(N20)NGG	8	48766763	-	CAAACACGTACTCGCTACTCTGG	1	1	2
(N20)NGG	8	48767782	+	CAGAATTTCTGTACCTTTTCAGG	1	9	243
(N20)NGG	8	48767783	+	AGAATTTCTGTACCTTTTCAGGG	1	8	278
(N20)NGG	8	48767784	+	GAATTTCTGTACCTTTTCAGGGG	1	11	112
(N20)NGG	8	48767785	+	AATTTCTGTACCTTTTCAGGGGG	1	9	110
(N20)NGG	8	48767907	+	TAAAGACCCTTGTCGAGTGCTGG	1	1	10

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48767911	+	GACCCTTGTCGAGTGCTGGAAGG	1	1	10
(N20)NGG	8	48767934	+	ATTGTTTATCCATCCCTTATAGG	1	5	57
(N20)NGG	8	48767946	+	TCCCTTATAGGTATGTTTACTGG	1	3	22
(N20)NGG	8	48767773	-	TCTTTAGGGACCCCCTGAAAAGG	1	1	26
(N20)NGG	8	48767787	-	TTGCTAACACTTCATCTTTAGGG	1	5	57
(N20)NGG	8	48767788	-	TTTGCTAACACTTCATCTTTAGG	1	3	81
(N20)NGG	8	48767826	-	GATGAAAGACATGTTTCATTAGG	1	6	92
(N20)NGG	8	48767848	-	TGTCTAAACACAGCTCTTTTTGG	1	1	59
(N20)NGG	8	48767874	-	CAAGGGTCTTTATAATTTCAAGG	1	7	88
(N20)NGG	8	48767891	-	ATCCTTCCAGCACTCGACAAGGG	1	2	12
(N20)NGG	8	48767892	-	AATCCTTCCAGCACTCGACAAGG	1	1	19
(N20)NGG	8	48767921	-	GTAAACATACCTATAAGGGATGG	1	2	25
(N20)NGG	8	48767925	-	ACCAGTAAACATACCTATAAGGG	1	1	33
(N20)NGG	8	48767926	-	AACCAGTAAACATACCTATAAGG	1	5	51
(N20)NGG	8	48769716	+	TGACTTTTACATCCTCTTGTAGG	1	7	62
(N20)NGG	8	48769742	+	TTCGCCCTTACGCGAAGCACTGG	1	1	1
(N20)NGG	8	48769764	+	GCTTAGCCCCTTGCTGCAGCTGG	1	2	28
(N20)NGG	8	48769783	+	CTGGCTGCTTCTGAAAACAATGG	2	12	98
(N20)NGG	8	48769786	+	GCTGCTTCTGAAAACAATGGAGG	1	6	80
(N20)NGG	8	48769792	+	TCTGAAAACAATGGAGGAGAAGG	1	13	150
(N20)NGG	8	48769806	+	AGGAGAAGGAATTCACTACATGG	1	5	110
(N20)NGG	8	48769809	+	AGAAGGAATTCACTACATGGTGG	1	2	66
(N20)NGG	8	48769821	+	CTACATGGTGGTTGAGATAGTGG	1	3	47
(N20)NGG	8	48769838	+	TAGTGGCCACTATTCTTTCATGG	1	4	31
(N20)NGG	8	48769843	+	GCCACTATTCTTTCATGGACAGG	1	1	13

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48769848	+	TATTCTTTCATGGACAGGCTTGG	1	4	42
(N20)NGG	8	48769865	+	GCTTGGCCACTCCAACAGTAAGG	1	2	18
(N20)NGG	8	48769706	-	AAGGGCGAAAGACCTACAAGAGG	1	1	19
(N20)NGG	8	48769724	-	TAAGCCAGTGCTTCGCGTAAGGG	1	1	3
(N20)NGG	8	48769725	-	CTAAGCCAGTGCTTCGCGTAAGG	1	1	7
(N20)NGG	8	48769748	-	AAGCAGCCAGCTGCAGCAAGGGG	1	3	83
(N20)NGG	8	48769749	-	GAAGCAGCCAGCTGCAGCAAGGG	3	11	92
(N20)NGG	8	48769750	-	AGAAGCAGCCAGCTGCAGCAAGG	1	6	114
(N20)NGG	8	48769822	-	GCCTGTCCATGAAAGAATAGTGG	1	1	25
(N20)NGG	8	48769849	-	ATCAATCCTTACTGTTGGAGTGG	1	1	22
(N20)NGG	8	48769854	-	GATGCATCAATCCTTACTGTTGG	1	1	23
(N20)NGG	8	48771076	+	AATTTTGAATGTTTTATTTTAGG	2	82	1250
(N20)NGG	8	48771105	+	TGCCAAGAGATCTTCCTTCTTGG	1	4	62
(N20)NGG	8	48771122	+	TCTTGGATGAAATTCCTCCATGG	1	5	66
(N20)NGG	8	48771130	+	GAAATTCCTCCATGGCAAACTGG	1	2	34
(N20)NGG	8	48771131	+	AAATTCCTCCATGGCAAACTGGG	1	1	40
(N20)NGG	8	48771196	+	GCTTGTTATTAATACAGAAGAGG	1	3	56
(N20)NGG	8	48771085	-	ATCCAAGAAGGAAGATCTCTTGG	1	1	70
(N20)NGG	8	48771097	-	TGGAGGAATTTCATCCAAGAAGG	2	7	77
(N20)NGG	8	48771114	-	GATTTCCCAGTTTGCCATGGAGG	1	4	27
(N20)NGG	8	48771117	-	TTGGATTTCCCAGTTTGCCATGG	1	4	70
(N20)NGG	8	48771136	-	CGGATATTTAATGGTACTATTGG	1	1	17
(N20)NGG	8	48771145	-	AAGAAGAGACGGATATTTAATGG	1	2	74
(N20)NGG	8	48771156	-	CAAGCTTGGCTAAGAAGAGACGG	1	9	65
(N20)NGG	8	48771170	-	TTCTGTATTAATAACAAGCTTGG	2	4	79

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48771409	+	TCCTGGGCCCTCCCTTTCGCAGG	1	12	59
(N20)NGG	8	48771417	+	CCTCCCTTTCGCAGGAGCAGCGG	1	4	40
(N20)NGG	8	48771418	+	CTCCCTTTCGCAGGAGCAGCGGG	1	4	41
(N20)NGG	8	48771427	+	GCAGGAGCAGCGGGACCCCACGG	1	5	67
(N20)NGG	8	48771445	+	CACGGTGCATGATGATGTGCTGG	1	2	10
(N20)NGG	8	48771451	+	GCATGATGATGTGCTGGAGCTGG	2	2	33
(N20)NGG	8	48771457	+	TGATGTGCTGGAGCTGGAGATGG	1	8	102
(N20)NGG	8	48771471	+	TGGAGATGGACGAGCTCAATCGG	1	2	30
(N20)NGG	8	48771484	+	GCTCAATCGGCATGAGTGCATGG	1	1	7
(N20)NGG	8	48771496	+	TGAGTGCATGGCGCCCCTGACGG	1	1	14
(N20)NGG	8	48771502	+	CATGGCGCCCCTGACGGCCCTGG	1	1	14
(N20)NGG	8	48771526	+	CAAGCACATGCACACAGAAGCCTGG	1	3	95
(N20)NGG	8	48771527	+	AAGCACATGCACACAGAAGCCTGGG	1	2	71
(N20)NGG	8	48771539	+	AGAAGCCTGGGCCCGCCTCAAGG	1	1	36
(N20)NGG	8	48771547	+	GGGCCCGCCTCAAGGAGAAGAGG	1	2	33
(N20)NGG	8	48771388	-	TCCTGCGAAAGGGAGGGCCCAGG	1	2	39
(N20)NGG	8	48771394	-	CGCTGCTCCTGCGAAAGGGAGGG	1	3	21
(N20)NGG	8	48771395	-	CCGCTGCTCCTGCGAAAGGGAGG	1	2	19
(N20)NGG	8	48771398	-	GTCCCGCTGCTCCTGCGAAAGGG	1	2	16
(N20)NGG	8	48771399	-	GGTCCCGCTGCTCCTGCGAAAGG	1	3	19
(N20)NGG	8	48771420	-	GCACATCATCATGCACCGTGGGG	1	2	9
(N20)NGG	8	48771421	-	AGCACATCATCATGCACCGTGGG	1	2	12
(N20)NGG	8	48771422	-	CAGCACATCATCATGCACCGTGG	1	2	11
(N20)NGG	8	48771487	-	TGCTTGACCAGGGCCGTCAGGGG	1	1	19
(N20)NGG	8	48771488	-	GTGCTTGACCAGGGCCGTCAGGG	1	2	13

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48771489	-	TGTGCTTGACCAGGGCCGTCAGG	1	1	7
(N20)NGG	8	48771497	-	TCTGTGCATGTGCTTGACCAGGG	1	3	59
(N20)NGG	8	48771498	-	TTCTGTGCATGTGCTTGACCAGG	1	3	47
(N20)NGG	8	48771522	-	CTTCTCCTTGAGGCGGGCCCAGG	1	4	34
(N20)NGG	8	48771528	-	GCACCTCTTCTCCTTGAGGCGGG	1	4	34
(N20)NGG	8	48771529	-	AGCACCTCTTCTCCTTGAGGCGG	1	3	58
(N20)NGG	8	48771532	-	AAAAGCACCTCTTCTCCTTGAGG	1	5	79
(N20)NGG	8	48772174	+	CTCCTTTTTTATATTTCAGATGG	2	15	386
(N20)NGG	8	48772206	+	TATGTCTTCCCTGTCATATTTGG	1	6	55
(N20)NGG	8	48772227	+	GGCAGACAGTACCCTGAGTGAGG	1	5	35
(N20)NGG	8	48772255	+	AGTCAATTTGATTTCTCAACCGG	1	5	62
(N20)NGG	8	48772303	+	CAAGACCCTAGACCTGCCACTGG	1	3	55
(N20)NGG	8	48772313	+	GACCTGCCACTGGTCGTTTTCGG	1	1	6
(N20)NGG	8	48772319	+	CCACTGGTCGTTTTCGGAGACGG	1	2	9
(N20)NGG	8	48772320	+	CACTGGTCGTTTTCGGAGACGGG	1	1	5
(N20)NGG	8	48772154	-	GACCATCTGAAATATAAAAAAGG	1	5	183
(N20)NGG	8	48772176	-	GACAGGGAAGACATATAGGAAGG	1	8	70
(N20)NGG	8	48772180	-	ATATGACAGGGAAGACATATAGG	1	2	55
(N20)NGG	8	48772192	-	ACTGTCTGCCAAATATGACAGGG	1	3	47
(N20)NGG	8	48772193	-	TACTGTCTGCCAAATATGACAGG	1	4	37
(N20)NGG	8	48772216	-	TTGACTCATTTCCTCACTCAGGG	1	8	81
(N20)NGG	8	48772217	-	ATTGACTCATTTCCTCACTCAGG	1	5	81
(N20)NGG	8	48772252	-	GTATGAATAGCTCTGAACTCCGG	1	1	28
(N20)NGG	8	48772279	-	AGTGGCAGGTCTAGGGTCTTGGG	1	1	26
(N20)NGG	8	48772280	-	CAGTGGCAGGTCTAGGGTCTTGG	1	2	41

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48772286	-	AACGACCAGTGGCAGGTCTAGGG	1	1	5
(N20)NGG	8	48772287	-	AAACGACCAGTGGCAGGTCTAGG	1	1	15
(N20)NGG	8	48772293	-	CTCCGAAAACGACCAGTGGCAGG	1	1	3
(N20)NGG	8	48772297	-	CCGTCTCCGAAAACGACCAGTGG	1	1	3
(N20)NGG	8	48773459	+	GTTTATTTGTTCTTCCCAATAGG	1	2	105
(N20)NGG	8	48773468	+	TTCTTCCCAATAGGTTCCTATGG	1	2	38
(N20)NGG	8	48773497	+	AGAAAAAGTACATTGAAATTAGG	1	19	349
(N20)NGG	8	48773523	+	GAAGCCAGAGAAGCAGCAAATGG	1	14	212
(N20)NGG	8	48773524	+	AAGCCAGAGAAGCAGCAAATGGG	2	7	141
(N20)NGG	8	48773525	+	AGCCAGAGAAGCAGCAAATGGGG	1	9	150
(N20)NGG	8	48773532	+	GAAGCAGCAAATGGGGATTCAGG	1	7	39
(N20)NGG	8	48773536	+	CAGCAAATGGGGATTCAGGTAGG	1	2	43
(N20)NGG	8	48773451	-	TCTTTCCATAGGAACCTATTGGG	1	3	50
(N20)NGG	8	48773452	-	TTCTTTCCATAGGAACCTATTGG	1	3	42
(N20)NGG	8	48773462	-	TACTTTTTCTTTCTTTCCATAGG	5	51	869
(N20)NGG	8	48773505	-	ATCCCCATTTGCTGCTTCTCTGG	1	3	52
(N20)NGG	8	48774688	+	TAATTTTCCTGTAGAAGTTGAGG	1	8	83
(N20)NGG	8	48774651	-	GAAAATTATAGCGGCGCTTCAGG	1	1	2
(N20)NGG	8	48774660	-	CTTCTACAGGAAAATTATAGCGG	1	3	50
(N20)NGG	8	48774673	-	TCACTCACCTCAACTTCTACAGG	1	2	33
(N20)NGG	8	48774964	+	CGATGCATTTACAGAGAACATGG	1	2	25
(N20)NGG	8	48774968	+	GCATTTACAGAGAACATGGCAGG	1	6	58
(N20)NGG	8	48774985	+	GGCAGGAGAGAATCAGCTGCTGG	1	5	74
(N20)NGG	8	48774990	+	GAGAGAATCAGCTGCTGGAGAGG	1	7	88
(N20)NGG	8	48775073	+	AATGAGTTAAAATTTTACCAAGG	1	14	204

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48775102	+	GTTTAGTGAAAAACCAGAAAAGG	2	12	108
(N20)NGG	8	48775106	+	AGTGAAAAACCAGAAAAGGTAGG	1	10	137
(N20)NGG	8	48775118	+	GAAAAGGTAGGCCACTCCTACGG	1	1	31
(N20)NGG	8	48775002	-	CGCAGTTGTATGCTGCACAATGG	1	5	16
(N20)NGG	8	48775025	-	GACACAGCAGATGACAGATATGG	1	6	62
(N20)NGG	8	48775068	-	TTTCACTAAACAGAAAAACCTTGG	3	6	131
(N20)NGG	8	48775093	-	TAGGAGTGGCCTACCTTTTCTGG	1	2	14
(N20)NGG	8	48776001	+	TACTCAAATCACCAAGAAGATGG	1	5	106
(N20)NGG	8	48776002	+	ACTCAAATCACCAAGAAGATGGG	1	5	87
(N20)NGG	8	48776064	+	CAAAGATGATGTTCATGCTAAGG	1	2	46
(N20)NGG	8	48776092	+	AAAATTAATCAAGTTTTCCATGG	1	16	209
(N20)NGG	8	48776110	+	CATGGCTCGTGTATTACAGAAGG	1	1	14
(N20)NGG	8	48776159	+	AGTAAGATTTTACTTAATTTTGG	1	19	212
(N20)NGG	8	48775948	-	AGATTCATTTAGCTTCAAAAAGG	1	7	113
(N20)NGG	8	48775972	-	CTTGGTGATTTGAGTATCAAAGG	1	4	37
(N20)NGG	8	48775990	-	CTTATAGTAGCCCATCTTCTTGG	1	2	16
(N20)NGG	8	48776036	-	CATGAACATCATCTTTGGGAAGG	1	2	53
(N20)NGG	8	48776040	-	TTAGCATGAACATCATCTTTGGG	1	7	75
(N20)NGG	8	48776041	-	CTTAGCATGAACATCATCTTTGG	1	4	43
(N20)NGG	8	48776087	-	CTTCTGTAATACACGAGCCATGG	1	2	12
(N20)NGG	8	48777116	+	TAATTTATCTTGTTTTCTTAGG	2	39	787
(N20)NGG	8	48777117	+	AATTTTATCTTGTTTTCTTAGGG	3	43	561
(N20)NGG	8	48777118	+	ATTTTATCTTGTTTTCTTAGGGG	2	25	472
(N20)NGG	8	48777139	+	GGTTCATGTGTCACACAAGTAGG	1	1	27
(N20)NGG	8	48777147	+	TGTCACACAAGTAGGCCTTCTGG	1	3	26

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48777170	+	AAAGCGTGTATGAAATGTTCAGG	1	1	15
(N20)NGG	8	48777174	+	CGTGTATGAAATGTTCAGGAAGG	2	9	99
(N20)NGG	8	48777213	+	TTTCACACGCCAGTCCTTTGTGG	1	1	18
(N20)NGG	8	48777239	+	GCTCCCTCCTCACTCTGCTGTGG	2	13	147
(N20)NGG	8	48777252	+	TCTGCTGTGGCACTGTAGCCTGG	1	4	58
(N20)NGG	8	48777285	+	AGAATTCTTCAGCACAATTGTGG	1	2	52
(N20)NGG	8	48777288	+	ATTCTTCAGCACAATTGTGGTGG	2	3	39
(N20)NGG	8	48777314	+	CCATTGATGTGTTGAAGTCCAGG	1	3	62
(N20)NGG	8	48777324	+	GTTGAAGTCCAGGTTTACAAAGG	1	2	29
(N20)NGG	8	48777140	-	TTTCATACACGCTTTCCAGAAGG	1	4	28
(N20)NGG	8	48777179	-	GGCGTGTGAAACTTAGGCGGGGG	1	3	6
(N20)NGG	8	48777180	-	TGGCGTGTGAAACTTAGGCGGGG	1	1	4
(N20)NGG	8	48777181	-	CTGGCGTGTGAAACTTAGGCGGG	1	1	16
(N20)NGG	8	48777182	-	ACTGGCGTGTGAAACTTAGGCGG	2	3	14
(N20)NGG	8	48777185	-	AGGACTGGCGTGTGAAACTTAGG	1	2	8
(N20)NGG	8	48777200	-	GGGAGCGGTCCACAAAGGACTGG	1	2	10
(N20)NGG	8	48777205	-	GAGGAGGGAGCGGTCCACAAAGG	1	2	48
(N20)NGG	8	48777215	-	ACAGCAGAGTGAGGAGGGAGCGG	1	30	331
(N20)NGG	8	48777220	-	GTGCCACAGCAGAGTGAGGAGGG	1	9	88
(N20)NGG	8	48777221	-	AGTGCCACAGCAGAGTGAGGAGG	1	6	74
(N20)NGG	8	48777224	-	TACAGTGCCACAGCAGAGTGAGG	1	3	41
(N20)NGG	8	48777248	-	AGAATTCTCTCAAAGCATCCAGG	1	3	51
(N20)NGG	8	48777292	-	CCTGGACTTCAACACATCAATGG	1	2	33
(N20)NGG	8	48777310	-	GTATGATACCTTTGTAAACCTGG	1	2	23
(N20)NGG	8	48790299	+	TTTCTAGTTTCTAGATGCATTGG	1	5	96

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48790326	+	ATCTCAAAGCCCTATGTTGTTGG	1	1	25
(N20)NGG	8	48790352	+	TGATGACAGAAGTTCTTTGTCGG	2	4	59
(N20)NGG	8	48790353	+	GATGACAGAAGTTCTTTGTCGGG	1	3	36
(N20)NGG	8	48790371	+	TCGGGAACAGCAGCATGTCATGG	1	1	17
(N20)NGG	8	48790397	+	AATTATTTCAATCCAGTTTCAGG	2	6	114
(N20)NGG	8	48790400	+	TATTTCAATCCAGTTTCAGGAGG	1	1	55
(N20)NGG	8	48790412	+	GTTTCAGGAGGATTGCCAGAAGG	1	2	26
(N20)NGG	8	48790425	+	TGCCAGAAGGTAAGTCATTCTGG	1	2	39
(N20)NGG	8	48790430	+	GAAGGTAAGTCATTCTGGCCTGG	1	5	28
(N20)NGG	8	48790431	+	AAGGTAAGTCATTCTGGCCTGGG	1	2	44
(N20)NGG	8	48790313	-	TCATCAATTCCAACACAACATAGGG	1	1	58
(N20)NGG	8	48790314	-	GTCATCAATTCCAACACAACATAGG	1	2	32
(N20)NGG	8	48790387	-	TCTGGCAATCCTCCTGAAACTGG	1	2	19
(N20)NGG	8	48790405	-	GGCCAGAATGACTTACCTTCTGG	1	3	28
(N20)NGG	8	48792051	+	TTATGTCTGTCTTGCTCCACAGG	1	5	79
(N20)NGG	8	48792052	+	TATGTCTGTCTTGCTCCACAGGG	1	6	71
(N20)NGG	8	48792094	+	CCATTCTTCACCAGCCTCACTGG	1	7	88
(N20)NGG	8	48792097	+	TTCTTCACCAGCCTCACTGGAGG	1	6	80
(N20)NGG	8	48792105	+	CAGCCTCACTGGAGGCAGTCTGG	1	2	56
(N20)NGG	8	48792108	+	CCTCACTGGAGGCAGTCTGGAGG	1	8	65
(N20)NGG	8	48792126	+	GGAGGAACTTAGACGTGTTCTGG	1	2	11
(N20)NGG	8	48792164	+	CTCACTTCCCCATGCAGTCCAGG	2	6	45
(N20)NGG	8	48792165	+	TCACTTCCCCATGCAGTCCAGGG	2	2	48
(N20)NGG	8	48792178	+	CAGTCCAGGGAATTTCCTCCAGG	1	3	60
(N20)NGG	8	48792188	+	AATTTCCTCCAGGAACTCCGCGG	1	2	25

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48792204	+	TCCGCGGTTCAATAATTATGTGG	1	1	5
(N20)NGG	8	48792219	+	TTATGTGGACTGCATGAAAAAGG	1	4	44
(N20)NGG	8	48792045	-	AGAGTGACAGCTTGGCCCTGTGG	1	6	58
(N20)NGG	8	48792053	-	ATGGAAGAAGAGTGACAGCTTGG	1	5	75
(N20)NGG	8	48792072	-	CCAGTGAGGCTGGTGAAGAATGG	1	11	115
(N20)NGG	8	48792082	-	CAGACTGCCTCCAGTGAGGCTGG	1	2	39
(N20)NGG	8	48792086	-	CCTCCAGACTGCCTCCAGTGAGG	2	7	58
(N20)NGG	8	48792149	-	GAAATTCCCTGGACTGCATGGGG	1	3	33
(N20)NGG	8	48792150	-	GGAAATTCCCTGGACTGCATGGG	1	3	24
(N20)NGG	8	48792151	-	AGGAAATTCCCTGGACTGCATGG	1	5	49
(N20)NGG	8	48792160	-	AGTTCCTGGAGGAAATTCCCTGG	1	5	30
(N20)NGG	8	48792171	-	TTGAACCGCGGAGTTCCTGGAGG	1	3	16
(N20)NGG	8	48792174	-	TTATTGAACCGCGGAGTTCCTGG	1	1	3
(N20)NGG	8	48792183	-	TCCACATAATTATTGAACCGCGG	1	1	12
(N20)NGG	8	48794010	+	GTATCTTTTAATACAAGTCATGG	1	3	58
(N20)NGG	8	48794066	+	TCTACTTGCTGACACAAAGCTGG	1	2	39
(N20)NGG	8	48794081	+	AAAGCTGGATCTACATTTAAAGG	1	4	64
(N20)NGG	8	48793951	-	AAAGGAAGGAAAAGAAAAACAGG	16	314	5097
(N20)NGG	8	48793965	-	AGATGAATCAATCTAAAGGAAGG	1	5	137
(N20)NGG	8	48793969	-	ATACAGATGAATCAATCTAAAGG	1	4	92
(N20)NGG	8	48794017	-	TATATGTTGTAAAGACTTCAGGG	1	2	86
(N20)NGG	8	48794018	-	ATATATGTTGTAAAGACTTCAGG	1	6	66
(N20)NGG	8	48794472	+	ACTCACAACGAAATTGTCTCAGG	1	2	16
(N20)NGG	8	48794491	+	CAGGTGAGTGCCGTTTTGAACGG	1	1	17
(N20)NGG	8	48794513	+	GCATGTTAGACCAGAGCTTCAGG	1	1	21

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48794514	+	CATGTTAGACCAGAGCTTCAGGG	1	1	30
(N20)NGG	8	48794539	+	CGAGCAAACCAGAAACACCAAGG	1	3	39
(N20)NGG	8	48794573	+	CGACTACAATTCTGCAACACTGG	1	2	10
(N20)NGG	8	48794591	+	ACTGGAAGAAGTGTGATTCATGG	1	2	62
(N20)NGG	8	48794594	+	GGAAGAAGTGTGATTCATGGTGG	1	6	100
(N20)NGG	8	48794595	+	GAAGAAGTGTGATTCATGGTGGG	1	4	68
(N20)NGG	8	48794625	+	TTCCCCTCTCGAAACTAAAATGG	1	1	30
(N20)NGG	8	48794634	+	CGAAACTAAAATGGCAGTGCTGG	1	1	15
(N20)NGG	8	48794643	+	AATGGCAGTGCTGGCCTTACTGG	1	6	50
(N20)NGG	8	48794658	+	CTTACTGGCAAAAATTTTACAGG	1	3	63
(N20)NGG	8	48794479	-	GTCTAACATGCCGTTCAAAACGG	1	1	7
(N20)NGG	8	48794501	-	TTGCTCGCTCCCTGAAGCTCTGG	1	2	27
(N20)NGG	8	48794525	-	GTTTCAGTCCTTGGTGTTTCTGG	1	7	69
(N20)NGG	8	48794534	-	TAGTCGCAAGTTTCAGTCCTTGG	1	1	14
(N20)NGG	8	48794596	-	AGTTTCGAGAGGGGAATCTTTGG	1	1	17
(N20)NGG	8	48794605	-	TGCCATTTTAGTTTCGAGAGGGG	1	3	22
(N20)NGG	8	48794606	-	CTGCCATTTTAGTTTCGAGAGGG	1	1	22
(N20)NGG	8	48794607	-	ACTGCCATTTTAGTTTCGAGAGG	1	1	24
(N20)NGG	8	48794635	-	CTGTAAAATTTTTGCCAGTAAGG	2	5	93
(N20)NGG	8	48798540	+	GAGTCTTCTCCTGAACCCAGCGG	1	4	63
(N20)NGG	8	48798552	+	GAACCCAGCGGTGCTGTCCACGG	1	2	25
(N20)NGG	8	48798561	+	GGTGCTGTCCACGGCGTCCTTGG	1	2	19
(N20)NGG	8	48798562	+	GTGCTGTCCACGGCGTCCTTGGG	1	1	5
(N20)NGG	8	48798573	+	GGCGTCCTTGGGCAGCTCACAGG	1	4	27
(N20)NGG	8	48798574	+	GCGTCCTTGGGCAGCTCACAGGG	1	5	35

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48798598	+	AGCGTCATCCACTTCTCCCATGG	1	1	20
(N20)NGG	8	48798599	+	GCGTCATCCACTTCTCCCATGGG	1	2	13
(N20)NGG	8	48798600	+	CGTCATCCACTTCTCCCATGGGG	1	2	28
(N20)NGG	8	48798639	+	GTTCTCAGAAACGATCAACACGG	1	4	50
(N20)NGG	8	48798657	+	CACGGAATTATTGAAAAATCTGG	1	2	61
(N20)NGG	8	48798672	+	AAATCTGGATCTTGCTGTATTGG	1	6	96
(N20)NGG	8	48798693	+	GGAGCTCATGCAGTCTTCAGTGG	1	1	55
(N20)NGG	8	48798708	+	TTCAGTGGATAATACCAAAATGG	2	8	63
(N20)NGG	8	48798488	-	GCTCACACTGGGAAAAGAAAGG	1	7	95
(N20)NGG	8	48798499	-	ACTCACAAGGCGCTCACACTGGG	1	2	17
(N20)NGG	8	48798500	-	GACTCACAAGGCGCTCACACTGG	1	1	8
(N20)NGG	8	48798512	-	GGTTCAGGAGAAGACTCACAAGG	1	2	46
(N20)NGG	8	48798527	-	TGGACAGCACCGCTGGGTTCAGG	1	3	36
(N20)NGG	8	48798533	-	ACGCCGTGGACAGCACCGCTGGG	1	1	8
(N20)NGG	8	48798534	-	GACGCCGTGGACAGCACCGCTGG	1	2	6
(N20)NGG	8	48798547	-	TGAGCTGCCCAAGGACGCCGTGG	1	2	26
(N20)NGG	8	48798556	-	GCTGCCCTGTGAGCTGCCCAAGG	3	9	101
(N20)NGG	8	48798584	-	AATACTCCCCATGGGAGAAGTGG	1	2	37
(N20)NGG	8	48798592	-	GCTATAGAAATACTCCCCATGGG	1	3	21
(N20)NGG	8	48798593	-	AGCTATAGAAATACTCCCCATGG	1	2	34
(N20)NGG	8	48798700	-	GGGAAACTTTGTTACCATTTTGG	1	4	53
(N20)NGG	8	48800132	+	ACAGATTTGCATCATTCTGTTGG	3	10	73
(N20)NGG	8	48800152	+	TGGCACAGAACTTCTTTCCCTGG	1	7	55
(N20)NGG	8	48800162	+	CTTCTTTCCCTGGTTTATAAAGG	1	3	111
(N20)NGG	8	48800174	+	GTTTATAAAGGCATTGCCCCTGG	1	1	27

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48800224	+	AGACCTCAGTTGTAAGCAGCTGG	1	4	21
(N20)NGG	8	48800231	+	AGTTGTAAGCAGCTGGCCAGCGG	1	3	27
(N20)NGG	8	48800239	+	GCAGCTGGCCAGCGGACTTCTGG	1	2	26
(N20)NGG	8	48800258	+	CTGGAGTTAGCCTTTGCTTTTGG	1	3	44
(N20)NGG	8	48800261	+	GAGTTAGCCTTTGCTTTTGGAGG	1	4	52
(N20)NGG	8	48800266	+	AGCCTTTGCTTTTGGAGGACTGG	1	1	43
(N20)NGG	8	48800270	+	TTTGCTTTTGGAGGACTGGTAGG	1	3	49
(N20)NGG	8	48800099	-	ATGCAAATCTGTGGACTAAAAGG	1	3	62
(N20)NGG	8	48800108	-	AACAGAATGATGCAAATCTGTGG	1	6	89
(N20)NGG	8	48800147	-	GGCAATGCCTTTATAAACCAGGG	1	2	45
(N20)NGG	8	48800148	-	GGGCAATGCCTTTATAAACCAGG	1	1	31
(N20)NGG	8	48800168	-	ACACTGTCTCTCATCTCCAGGGG	1	3	83
(N20)NGG	8	48800169	-	GACACTGTCTCTCATCTCCAGGG	1	6	89
(N20)NGG	8	48800170	-	AGACACTGTCTCTCATCTCCAGG	1	3	99
(N20)NGG	8	48800194	-	TTACAACTGAGGTCTAGAGAAGG	1	3	50
(N20)NGG	8	48800205	-	TGGCCAGCTGCTTACAACTGAGG	1	1	35
(N20)NGG	8	48800225	-	GGCTAACTCCAGAAGTCCGCTGG	1	1	51
(N20)NGG	8	48800246	-	TACCAGTCCTCCAAAAGCAAAGG	1	3	49
(N20)NGG	8	48801085	+	TTGTCACATGGCCAGCATTGAGG	1	2	44
(N20)NGG	8	48801110	+	CTTTGTGCCGTCAACTTGTATGG	1	1	11
(N20)NGG	8	48801127	+	GTATGGCCCTGACGCGCAAGTGG	1	1	4
(N20)NGG	8	48801132	+	GCCCTGACGCGCAAGTGGACAGG	1	1	1
(N20)NGG	8	48801138	+	ACGCGCAAGTGGACAGGAGCAGG	1	1	4
(N20)NGG	8	48801142	+	GCAAGTGGACAGGAGCAGGCTGG	1	5	85
(N20)NGG	8	48801182	+	TGTAAACAGCTTCACAGAGCTGG	1	4	64

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48801183	+	GTAAACAGCTTCACAGAGCTGGG	1	3	49
(N20)NGG	8	48801211	+	GCATAATATATTACCGTCTCAGG	1	2	16
(N20)NGG	8	48801074	-	GGCACAAAGCTCCTCAATGCTGG	1	1	18
(N20)NGG	8	48801095	-	GTCAGGGCCATACAAGTTGACGG	1	1	18
(N20)NGG	8	48801111	-	TCCTGTCCACTTGCGCGTCAGGG	1	1	8
(N20)NGG	8	48801112	-	CTCCTGTCCACTTGCGCGTCAGG	1	1	7
(N20)NGG	8	48801158	-	AGCTCTGTGAAGCTGTTTACAGG	1	2	42
(N20)NGG	8	48801202	-	TAAGTTATAGTTACCTGAGACGG	1	2	38
(N20)NGG	8	48801586	+	TCTGTTACAGCTCCTGAAGAAGG	1	3	92
(N20)NGG	8	48801619	+	TACACACCTGATGAGAGTCCTGG	1	4	20
(N20)NGG	8	48801650	+	CTGTGTGAGCCCGCAAGCATAGG	1	2	29
(N20)NGG	8	48801662	+	GCAAGCATAGGTTTCAACATCGG	1	1	26
(N20)NGG	8	48801673	+	TTTCAACATCGGAGACGTCCAGG	1	1	3
(N20)NGG	8	48801679	+	CATCGGAGACGTCCAGGTTATGG	1	1	13
(N20)NGG	8	48801783	+	GAGAGAAAATAACAGCACAGAGG	1	9	175
(N20)NGG	8	48801786	+	AGAAAATAACAGCACACAGAGGTGG	2	12	229
(N20)NGG	8	48801787	+	GAAAATAACAGCACAGAGGTGGG	1	15	119
(N20)NGG	8	48801794	+	ACAGCACAGAGGTGGGTACTTGG	1	4	50
(N20)NGG	8	48801795	+	CAGCACAGAGGTGGGTACTTGGG	1	4	52
(N20)NGG	8	48801805	+	GTGGGTACTTGGGTCACAATCGG	1	1	14
(N20)NGG	8	48801806	+	TGGGTACTTGGGTCACAATCGGG	1	3	30
(N20)NGG	8	48801807	+	GGGTACTTGGGTCACAATCGGGG	1	2	8
(N20)NGG	8	48801576	-	TATTACACAAGTCCTTCTTCAGG	1	3	37
(N20)NGG	8	48801603	-	TCTGCACCAGGACTCTCATCAGG	1	3	38
(N20)NGG	8	48801615	-	GCTCACACAGCGTCTGCACCAGG	1	2	36

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48801637	-	ATGTTGAAACCTATGCTTGCGGG	1	1	23
(N20)NGG	8	48801638	-	GATGTTGAAACCTATGCTTGCGG	1	4	17
(N20)NGG	8	48801669	-	CAGGAAGATGAGCCATAACCTGG	2	8	38
(N20)NGG	8	48801688	-	ATCAGATTCACACAAACATCAGG	2	4	70
(N20)NGG	8	48801728	-	CTCTAGGATATCTTTGTATGGGG	1	1	35
(N20)NGG	8	48801729	-	TCTCTAGGATATCTTTGTATGGG	1	7	60
(N20)NGG	8	48801730	-	GTCTCTAGGATATCTTTGTATGG	1	2	32
(N20)NGG	8	48801744	-	TCTCTCTCAGATGGGTCTCTAGG	1	1	39
(N20)NGG	8	48801752	-	TGTTATTTTCTCTCTCAGATGGG	1	13	157
(N20)NGG	8	48801753	-	CTGTTATTTTCTCTCTCAGATGG	3	13	162
(N20)NGG	8	48802817	+	ACTTTAATATAATTGCTTCTAGG	3	18	179
(N20)NGG	8	48802852	+	GTCTTCACTTTTGAAAGCAGTGG	1	5	82
(N20)NGG	8	48802910	+	ATAGCAGCAGAAAAGTGCTTTGG	2	5	105
(N20)NGG	8	48802916	+	GCAGAAAAGTGCTTTGGCACTGG	1	1	30
(N20)NGG	8	48802917	+	CAGAAAAGTGCTTTGGCACTGGG	1	3	49
(N20)NGG	8	48802918	+	AGAAAAGTGCTTTGGCACTGGGG	2	4	61
(N20)NGG	8	48802925	+	TGCTTTGGCACTGGGGCAGCAGG	2	5	51
(N20)NGG	8	48802948	+	TAACAGAACAAGCCCACAAGAGG	1	3	40
(N20)NGG	8	48802949	+	AACAGAACAAGCCCACAAGAGGG	1	4	62
(N20)NGG	8	48802956	+	CAAGCCCACAAGAGGGAGAAAGG	1	5	71
(N20)NGG	8	48802984	+	CTACAGCAAATGCACCGTTGTGG	1	2	8
(N20)NGG	8	48802989	+	GCAAATGCACCGTTGTGGTCCGG	1	1	13
(N20)NGG	8	48802996	+	CACCGTTGTGGTCCGGATTATGG	1	2	4
(N20)NGG	8	48803029	+	GACTCTGCTAAACACCTCCCCGG	1	2	27
(N20)NGG	8	48803033	+	CTGCTAAACACCTCCCCGGAAGG	1	1	15

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48803037	+	TAAACACCTCCCCGGAAGGATGG	1	1	35
(N20)NGG	8	48803041	+	CACCTCCCCGGAAGGATGGAAGG	1	1	31
(N20)NGG	8	48803045	+	TCCCCGGAAGGATGGAAGGTAGG	1	2	29
(N20)NGG	8	48803064	+	TAGGCTGCTCTGTTAATTTGAGG	1	3	32
(N20)NGG	8	48802826	-	TGCTTTCAAAAGTGAAGACTGGG	1	8	102
(N20)NGG	8	48802827	-	CTGCTTTCAAAAGTGAAGACTGG	1	2	82
(N20)NGG	8	48802874	-	TGCTGCTATAATGTCATGCATGG	1	1	57
(N20)NGG	8	48802938	-	TGTACCTTTCTCCCTCTTGTGGG	1	5	80
(N20)NGG	8	48802939	-	TTGTACCTTTCTCCCTCTTGTGG	1	6	82
(N20)NGG	8	48802976	-	CTCCATAATCCGGACCACAACGG	1	1	8
(N20)NGG	8	48802986	-	TCGTGGTAAACTCCATAATCCGG	1	2	10
(N20)NGG	8	48803003	-	GGAGGTGTTTAGCAGAGTCGTGG	1	1	16
(N20)NGG	8	48803021	-	TACCTTCCATCCTTCCGGGGAGG	1	1	18
(N20)NGG	8	48803024	-	GCCTACCTTCCATCCTTCCGGGG	1	2	25
(N20)NGG	8	48803025	-	AGCCTACCTTCCATCCTTCCGGG	1	11	84
(N20)NGG	8	48803026	-	CAGCCTACCTTCCATCCTTCCGG	1	6	71
(N20)NGG	8	48805699	+	TTAATTTTGTTTCTTTTTTAAAGG	6	183	2613
(N20)NGG	8	48805721	+	GCAACAGATCCCCTAATTTGTGG	1	4	25
(N20)NGG	8	48805740	+	GTGGCTGAAAGATGTTCTCAAGG	1	2	48
(N20)NGG	8	48805747	+	AAAGATGTTCTCAAGGAAGAAGG	1	8	138
(N20)NGG	8	48805776	+	TTTTCTCATCAACACCTTTGAGG	2	7	90
(N20)NGG	8	48805777	+	TTTCTCATCAACACCTTTGAGGG	1	7	88
(N20)NGG	8	48805778	+	TTCTCATCAACACCTTTGAGGGG	1	3	53
(N20)NGG	8	48805779	+	TCTCATCAACACCTTTGAGGGGG	1	3	41
(N20)NGG	8	48805780	+	CTCATCAACACCTTTGAGGGGGG	2	5	35

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48805783	+	ATCAACACCTTTGAGGGGGGTGG	1	4	32
(N20)NGG	8	48805789	+	ACCTTTGAGGGGGGTGGCTGTGG	1	3	51
(N20)NGG	8	48805800	+	GGGTGGCTGTGGCCAGCCCTCGG	3	11	127
(N20)NGG	8	48805801	+	GGTGGCTGTGGCCAGCCCTCGGG	2	8	104
(N20)NGG	8	48805809	+	TGGCCAGCCCTCGGGCATCCTGG	2	3	38
(N20)NGG	8	48805834	+	CAGCCCACCCTCTTGTACTTCGG	2	3	34
(N20)NGG	8	48805835	+	AGCCCACCCTCTTGTACTTCGGG	1	1	23
(N20)NGG	8	48805836	+	GCCCACCCTCTTGTACTTCGGGG	1	2	22
(N20)NGG	8	48805837	+	CCCACCCTCTTGTACTTCGGGGG	1	2	27
(N20)NGG	8	48805853	+	TCGGGGGCCATTCAGCCTGCAGG	1	1	12
(N20)NGG	8	48805867	+	GCCTGCAGGCCACGCTATGCTGG	1	1	36
(N20)NGG	8	48805871	+	GCAGGCCACGCTATGCTGGCTGG	1	1	10
(N20)NGG	8	48805883	+	ATGCTGGCTGGACCTGCTCCTGG	1	5	48
(N20)NGG	8	48805892	+	GGACCTGCTCCTGGCCGCGTTGG	1	1	17
(N20)NGG	8	48805914	+	GAGTGCTACAACACGTTCATTGG	1	1	10
(N20)NGG	8	48805929	+	TTCATTGGCGAGAGAACTGTAGG	1	3	16
(N20)NGG	8	48805940	+	GAGAACTGTAGGAGCGCTCCAGG	1	1	9
(N20)NGG	8	48805947	+	GTAGGAGCGCTCCAGGTCCTAGG	1	1	16
(N20)NGG	8	48805951	+	GAGCGCTCCAGGTCCTAGGTAGG	1	2	15
(N20)NGG	8	48805971	+	AGGTCACCCTTGCCTTATTCTGG	1	6	87
(N20)NGG	8	48805708	-	ATCTTTCAGCCACAAATTAGGGG	2	6	56
(N20)NGG	8	48805709	-	CATCTTTCAGCCACAAATTAGGG	2	5	53
(N20)NGG	8	48805710	-	ACATCTTTCAGCCACAAATTAGG	1	4	58
(N20)NGG	8	48805768	-	GCCACAGCCACCCCCCTCAAAGG	2	2	67
(N20)NGG	8	48805790	-	GGGCCAGGATGCCCGAGGGCTGG	2	6	61

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48805794	-	GGCTGGGCCAGGATGCCCGAGGG	1	2	45
(N20)NGG	8	48805795	-	GGGCTGGGCCAGGATGCCCGAGG	1	8	103
(N20)NGG	8	48805805	-	ACAAGAGGGTGGGCTGGGCCAGG	1	12	157
(N20)NGG	8	48805810	-	GAAGTACAAGAGGGTGGGCTGGG	2	5	49
(N20)NGG	8	48805811	-	CGAAGTACAAGAGGGTGGGCTGG	1	2	27
(N20)NGG	8	48805815	-	CCCCCGAAGTACAAGAGGGTGGG	1	1	5
(N20)NGG	8	48805816	-	GCCCCCGAAGTACAAGAGGGTGG	1	1	9
(N20)NGG	8	48805819	-	ATGGCCCCCGAAGTACAAGAGGG	1	1	14
(N20)NGG	8	48805820	-	AATGGCCCCCGAAGTACAAGAGG	1	1	13
(N20)NGG	8	48805838	-	AGCGTGGCCTGCAGGCTGAATGG	1	2	29
(N20)NGG	8	48805846	-	GCCAGCATAGCGTGGCCTGCAGG	1	3	22
(N20)NGG	8	48805854	-	CAGGTCCAGCCAGCATAGCGTGG	1	1	17
(N20)NGG	8	48805873	-	ACTCCAACGCGGCCAGGAGCAGG	1	1	16
(N20)NGG	8	48805879	-	TGTAGCACTCCAACGCGGCCAGG	1	1	6
(N20)NGG	8	48805884	-	CGTGTTGTAGCACTCCAACGCGG	1	1	8
(N20)NGG	8	48805936	-	AGGGTGACCTACCTAGGACCTGG	1	1	11
(N20)NGG	8	48805942	-	AAGGCAAGGGTGACCTACCTAGG	1	1	24
(N20)NGG	8	48809722	+	AGTATGCTGTCTCTGTGCAGAGG	1	2	56
(N20)NGG	8	48809754	+	TTCCGCATCATTGTGTTTATTGG	1	1	28
(N20)NGG	8	48809760	+	ATCATTGTGTTTATTGGATCTGG	1	3	46
(N20)NGG	8	48809768	+	GTTTATTGGATCTGGTCAAGTGG	1	2	25
(N20)NGG	8	48809785	+	AAGTGGCTTTTAGCTCATTGTGG	1	1	31
(N20)NGG	8	48809786	+	AGTGGCTTTTAGCTCATTGTGGG	1	1	36
(N20)NGG	8	48809789	+	GGCTTTTAGCTCATTGTGGGAGG	1	1	28
(N20)NGG	8	48809854	+	AAATTCGTTCCTTTATTGCCAGG	1	3	34

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48809859	+	CGTTCCTTTATTGCCAGGTATGG	1	1	14
(N20)NGG	8	48809727	-	AAACACAATGATGCGGAAGGTGG	1	2	25
(N20)NGG	8	48809730	-	AATAAACACAATGATGCGGAAGG	1	2	31
(N20)NGG	8	48809734	-	ATCCAATAAACACAATGATGCGG	1	1	59
(N20)NGG	8	48809790	-	TTGTGTCGACATTCTGTCTGGGG	1	3	47
(N20)NGG	8	48809791	-	TTTGTGTCGACATTCTGTCTGGG	1	1	31
(N20)NGG	8	48809792	-	ATTTGTGTCGACATTCTGTCTGG	1	1	16
(N20)NGG	8	48809815	-	GAATTTATAAAAGAGTTCAATGG	1	5	162
(N20)NGG	8	48809841	-	ATTACCATACCTGGCAATAAAGG	1	5	55
(N20)NGG	8	48809850	-	GATATACAGATTACCATACCTGG	1	3	19
(N20)NGG	8	48811029	+	ATGTCTCTGTACTTGAGAACAGG	1	5	46
(N20)NGG	8	48811129	+	CAAAGAAACGACGTTTGCCGCGG	1	2	6
(N20)NGG	8	48811133	+	GAAACGACGTTTGCCGCGGTAGG	1	1	1
(N20)NGG	8	48811053	-	GATGCGGCATAGGTGATCAATGG	1	1	13
(N20)NGG	8	48811063	-	TCTTTTCAATGATGCGGCATAGG	1	1	22
(N20)NGG	8	48811069	-	CATGCTTCTTTTCAATGATGCGG	1	4	58
(N20)NGG	8	48811124	-	GGAAGCAAGATCACCTACCGCGG	1	1	18
(N20)NGG	8	48812932	+	TTTCCTATTCTTTATTTTACAGG	2	25	352
(N20)NGG	8	48812933	+	TTCCTATTCTTTATTTTACAGGG	2	12	304
(N20)NGG	8	48812948	+	TTACAGGGAAGAAGAGTCTCTGG	1	3	52
(N20)NGG	8	48812951	+	CAGGGAAGAAGAGTCTCTGGTGG	1	7	112
(N20)NGG	8	48812975	+	ACAGTTTGTGTTTGAAGCCTTGG	1	6	56
(N20)NGG	8	48812987	+	TGAAGCCTTGGTGATATACATGG	1	2	33
(N20)NGG	8	48812996	+	GGTGATATACATGGAGAGTCTGG	1	1	11
(N20)NGG	8	48813027	+	CATGCAGATGAGAAGTCCTTAGG	1	2	55

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48812913	-	TTCCCTGTAAAATAAAGAATAGG	2	16	246
(N20)NGG	8	48812970	-	ACTCTCCATGTATATCACCAAGG	1	1	24
(N20)NGG	8	48812997	-	CTTCTCATCTGCATGTGCTAAGG	1	2	63
(N20)NGG	8	48813021	-	ACTGAAGCAAAACGTACCTAAGG	1	1	25
(N20)NGG	8	48815128	+	AGGTCTCTTTGTTTGTTTCAGG	1	15	192
(N20)NGG	8	48815132	+	CTCTTTGTTTGTTTCAGGATGG	1	11	201
(N20)NGG	8	48815140	+	TTTGTTTCAGGATGGAATTGTGG	1	4	85
(N20)NGG	8	48815174	+	AGTACTTTAAGAGATTTTTGTGG	2	7	119
(N20)NGG	8	48815178	+	CTTTAAGAGATTTTTGTGGTCGG	1	7	99
(N20)NGG	8	48815202	+	GTATTCGAGAATTCCTTAAATGG	1	2	18
(N20)NGG	8	48815233	+	GCAAATAACACCACAGCAGCAGG	1	3	39
(N20)NGG	8	48815310	+	TTCACCCCAATGCTTTCAAGAGG	1	2	40
(N20)NGG	8	48815314	+	CCCCAATGCTTTCAAGAGGCTGG	1	3	23
(N20)NGG	8	48815315	+	CCCAATGCTTTCAAGAGGCTGGG	1	2	56
(N20)NGG	8	48815346	+	TTGCCTTTAATAATATCTACAGG	1	5	70
(N20)NGG	8	48815347	+	TGCCTTTAATAATATCTACAGGG	1	5	105
(N20)NGG	8	48815355	+	ATAATATCTACAGGGAATTCAGG	1	4	53
(N20)NGG	8	48815142	-	CTCTTAAAGTACTGTCAACAGGG	1	3	40
(N20)NGG	8	48815143	-	TCTCTTAAAGTACTGTCAACAGG	1	3	27
(N20)NGG	8	48815193	-	TTTGCTTAATGGACCATTTAAGG	1	4	43
(N20)NGG	8	48815204	-	CTGTGGTGTTATTTGCTTAATGG	2	4	63
(N20)NGG	8	48815221	-	GGACTCTTCTCCTGCTGCTGTGG	1	9	70
(N20)NGG	8	48815242	-	AAAAGCGATTTGGTGTTTACTGG	1	2	23
(N20)NGG	8	48815252	-	AAGTCGCTTGAAAAGCGATTTGG	1	1	6
(N20)NGG	8	48815280	-	AAGCATTGGGGTGAAGCGCAAGG	1	1	20

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48815292	-	CCAGCCTCTTGAAAGCATTGGGG	1	2	39
(N20)NGG	8	48815293	-	CCCAGCCTCTTGAAAGCATTGGG	1	5	60
(N20)NGG	8	48815294	-	TCCCAGCCTCTTGAAAGCATTGG	2	5	147
(N20)NGG	8	48815327	-	TTCCCTGTAGATATTATTAAAGG	1	6	82
(N20)NGG	8	48817428	+	TTTAATGGTATTGTTCTTCAGG	2	61	604
(N20)NGG	8	48817436	+	TATTGTTCTTCAGGTGACAAGG	1	1	63
(N20)NGG	8	48817475	+	TAGTTATGCAGCTGATTCACTGG	1	2	13
(N20)NGG	8	48817506	+	CAACAAGAAATTTGAAAGTCAGG	1	4	108
(N20)NGG	8	48817536	+	TGCCTTACTAGAAGCTATATTGG	1	3	16
(N20)NGG	8	48817449	-	TGAATCAGCTGCATAACTAGTGG	1	2	35
(N20)NGG	8	48817516	-	TACCAATATAGCTTCTAGTAAGG	1	1	16
(N20)NGG	8	48824969	+	CTGACCTCCTGGTCTGTTTTAGG	1	4	54
(N20)NGG	8	48824999	+	CTGTGAACTTTTACATAGCATGG	1	3	50
(N20)NGG	8	48825014	+	TAGCATGGTTATGTTTATGTTGG	1	2	59
(N20)NGG	8	48825015	+	AGCATGGTTATGTTTATGTTGGG	1	3	54
(N20)NGG	8	48825039	+	AAAGCCACGCAGATGCCAGAAGG	1	5	55
(N20)NGG	8	48825040	+	AAGCCACGCAGATGCCAGAAGGG	1	4	72
(N20)NGG	8	48825041	+	AGCCACGCAGATGCCAGAAGGGG	1	4	67
(N20)NGG	8	48825042	+	GCCACGCAGATGCCAGAAGGGGG	1	4	46
(N20)NGG	8	48825047	+	GCAGATGCCAGAAGGGGGACAGG	1	3	57
(N20)NGG	8	48825048	+	CAGATGCCAGAAGGGGGACAGGG	2	5	71
(N20)NGG	8	48825079	+	CCATGTACCAGCTCTATAAGCGG	1	3	21
(N20)NGG	8	48825122	+	ACTTGCCGTGTGATGTTGATCAGG	1	2	11
(N20)NGG	8	48825127	+	CGTGTGATGTTGATCAGGTAAGG	1	2	7
(N20)NGG	8	48825128	+	GTGTGATGTTGATCAGGTAAGGG	1	2	30

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48824951	-	GCAACCTAAAACAGACCAGGAGG	1	3	25
(N20)NGG	8	48824954	-	GCTGCAACCTAAAACAGACCAGG	1	3	23
(N20)NGG	8	48824976	-	CATGCTATGTAAAAGTTCACAGG	1	4	51
(N20)NGG	8	48825021	-	TCCCCCTTCTGGCATCTGCGTGG	1	2	22
(N20)NGG	8	48825032	-	GGGGCTCCCTGTCCCCCTTCTGG	1	5	68
(N20)NGG	8	48825051	-	ATAGAGCTGGTACATGGGTGGGG	1	1	24
(N20)NGG	8	48825052	-	TATAGAGCTGGTACATGGGTGGG	1	2	22
(N20)NGG	8	48825053	-	TTATAGAGCTGGTACATGGGTGG	1	1	20
(N20)NGG	8	48825056	-	CGCTTATAGAGCTGGTACATGGG	1	1	7
(N20)NGG	8	48825057	-	CCGCTTATAGAGCTGGTACATGG	1	1	4
(N20)NGG	8	48825064	-	GAAACGTCCGCTTATAGAGCTGG	1	1	2
(N20)NGG	8	48825086	-	CACGCAAGTCGAAGCAGCACAGG	1	2	8
(N20)NGG	8	48826495	+	TGAGATGATGAAGAGCTATGTGG	1	11	69
(N20)NGG	8	48826500	+	TGATGAAGAGCTATGTGGCCTGG	1	1	39
(N20)NGG	8	48826501	+	GATGAAGAGCTATGTGGCCTGGG	1	8	59
(N20)NGG	8	48826515	+	TGGCCTGGGACAGAGAGAAGCGG	2	9	195
(N20)NGG	8	48826564	+	GATGAAACCTGTCATTTTCCTGG	1	5	54
(N20)NGG	8	48826466	-	GCTCTTCATCATCTCATCTGAGG	2	3	57
(N20)NGG	8	48826496	-	CAGCCGCTTCTCTCTGTCCCAGG	2	10	95
(N20)NGG	8	48826531	-	ACAGGTTTCATCTCTCTAAAGGG	1	4	54
(N20)NGG	8	48826532	-	GACAGGTTTCATCTCTCTAAAGG	1	6	34
(N20)NGG	8	48826549	-	AACACATCCAGGAAAATGACAGG	1	5	92
(N20)NGG	8	48826560	-	CTCGAGGCAGGAACACATCCAGG	1	2	33
(N20)NGG	8	48826572	-	CTAATTCTGTGACTCGAGGCAGG	1	1	50
(N20)NGG	8	48826576	-	AGCGCTAATTCTGTGACTCGAGG	1	2	7

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48826604	-	TACTTTAGTTTGTCTGTCACTGG	1	1	37
(N20)NGG	8	48827939	+	ATTAGAGTAGTACAAATGCTTGG	1	2	32
(N20)NGG	8	48827948	+	GTACAAATGCTTGGATCTCTAGG	1	4	29
(N20)NGG	8	48827951	+	CAAATGCTTGGATCTCTAGGAGG	1	10	204
(N20)NGG	8	48827978	+	ATAAACAAAAATCTTCTGACAGG	1	8	137
(N20)NGG	8	48827900	-	TCTAATTCTTATTTCTTCTAAGG	2	22	266
(N20)NGG	8	48830855	+	TAGATGAGACCAAGAATAACTGG	1	2	47
(N20)NGG	8	48830856	+	AGATGAGACCAAGAATAACTGGG	1	6	61
(N20)NGG	8	48830876	+	GGGAAGTGTCAGCTCTTTCTCGG	1	6	57
(N20)NGG	8	48830877	+	GGAAGTGTCAGCTCTTTCTCGGG	1	4	50
(N20)NGG	8	48830890	+	CTTTCTCGGGCTGCCCAGAAAGG	1	5	36
(N20)NGG	8	48830904	+	CCAGAAAGGATTTAATAAAGTGG	1	5	118
(N20)NGG	8	48830842	-	TGACACTTCCCAGTTATTCTTGG	1	1	42
(N20)NGG	8	48830881	-	CACTTTATTAAATCCTTTCTGGG	2	5	135
(N20)NGG	8	48830882	-	CCACTTTATTAAATCCTTTCTGG	1	7	63
(N20)NGG	8	48830933	-	AAGGACTTCTTACTGATGAAAGG	1	7	51
(N20)NGG	8	48839756	+	TGTTTGTATTAACATACAGATGG	1	7	123
(N20)NGG	8	48839768	+	CATACAGATGGCTTTCAAACTGG	1	2	36
(N20)NGG	8	48839769	+	ATACAGATGGCTTTCAAACTGGG	1	4	66
(N20)NGG	8	48839789	+	GGGCCTGAGCTATACCCCCTTGG	1	4	20
(N20)NGG	8	48839799	+	TATACCCCCTTGGCAGAAGTAGG	1	1	14
(N20)NGG	8	48839821	+	GCCTGAATGCTCTAGAAGAATGG	1	3	32
(N20)NGG	8	48839882	+	CAAAGACATTCTCCCCTGCCTGG	1	2	42
(N20)NGG	8	48839886	+	GACATTCTCCCCTGCCTGGATGG	1	6	51
(N20)NGG	8	48839913	+	CTGAAGACTTCAGCCTTGTCAGG	1	4	39

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48839770	-	CTGCCAAGGGGGTATAGCTCAGG	1	2	11
(N20)NGG	8	48839781	-	CAGGCCTACTTCTGCCAAGGGGG	1	1	33
(N20)NGG	8	48839782	-	TCAGGCCTACTTCTGCCAAGGGG	1	1	31
(N20)NGG	8	48839783	-	TTCAGGCCTACTTCTGCCAAGGG	1	1	28
(N20)NGG	8	48839784	-	ATTCAGGCCTACTTCTGCCAAGG	1	2	32
(N20)NGG	8	48839800	-	ACCATTCTTCTAGAGCATTCAGG	1	1	30
(N20)NGG	8	48839852	-	GGGAGAATGTCTTTGTAATAAGG	1	5	68
(N20)NGG	8	48839872	-	TCAGGTATCCATCCAGGCAGGGG	1	3	40
(N20)NGG	8	48839873	-	TTCAGGTATCCATCCAGGCAGGG	1	3	36
(N20)NGG	8	48839874	-	CTTCAGGTATCCATCCAGGCAGG	1	1	23
(N20)NGG	8	48839878	-	AAGTCTTCAGGTATCCATCCAGG	1	2	27
(N20)NGG	8	48839890	-	CTGACAAGGCTGAAGTCTTCAGG	1	4	37
(N20)NGG	8	48839904	-	CTTCTAAACATTACCTGACAAGG	1	2	39
(N20)NGG	8	48840330	+	TACTGTCTTCTTTCTTGTTAAGG	1	12	166
(N20)NGG	8	48840333	+	TGTCTTCTTTCTTGTTAAGGTGG	1	7	123
(N20)NGG	8	48840369	+	GCAGTACAAAGATGAACTTTTGG	2	3	51
(N20)NGG	8	48840450	+	AGCCTACGTTCCTGCACTGCAGG	1	1	10
(N20)NGG	8	48840454	+	TACGTTCCTGCACTGCAGGTAGG	1	2	15
(N20)NGG	8	48840370	-	CAGAAGAAAGGTCAAACAAGAGG	1	5	107
(N20)NGG	8	48840382	-	GTGTGGCAAGGACAGAAGAAAGG	2	7	158
(N20)NGG	8	48840394	-	TTCAATGATGTTGTGTGGCAAGG	1	2	55
(N20)NGG	8	48840399	-	TCGAGTTCAATGATGTTGTGTGG	1	2	9
(N20)NGG	8	48840430	-	TACCTGCAGTGCAGGAACGTAGG	1	1	18
(N20)NGG	8	48840438	-	ACAACGCCTACCTGCAGTGCAGG	1	2	12
(N20)NGG	8	48841651	+	AACTTGCTGTTTTATTTGACAGG	2	10	99

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48841652	+	ACTTGCTGTTTTATTTGACAGGG	1	7	108
(N20)NGG	8	48841730	+	TTTGCTTTATTTGTGAAATTTGG	1	15	363
(N20)NGG	8	48841738	+	ATTTGTGAAATTTGGCAAAGAGG	2	13	136
(N20)NGG	8	48841660	-	GGAGAGTGTTTCAGACTCTTTGG	1	3	33
(N20)NGG	8	48841681	-	GAATACTTTTCTGGGTCTTCAGG	1	7	46
(N20)NGG	8	48841689	-	CAAAGCAAGAATACTTTTCTGGG	2	4	143
(N20)NGG	8	48841690	-	GCAAAGCAAGAATACTTTTCTGG	1	5	62
(N20)NGG	8	48842454	+	AAGCAGAATTTTTTGAACCATGG	2	31	630
(N20)NGG	8	48842455	+	AGCAGAATTTTTTGAACCATGGG	1	3	137
(N20)NGG	8	48842496	+	AATTAATTTTGCAATCTACAAGG	1	5	116
(N20)NGG	8	48842513	+	ACAAGGTTGCCCCTCATCAGTGG	1	3	19
(N20)NGG	8	48842572	+	CAAGAAAATAAAATATTTCGAGG	1	20	306
(N20)NGG	8	48842589	+	TCGAGGTGAGTCTTTCTTGCAGG	2	4	38
(N20)NGG	8	48842421	-	AAAATTCTGCTTGTTTCTCAGGG	1	13	160
(N20)NGG	8	48842422	-	AAAAATTCTGCTTGTTTCTCAGG	1	5	118
(N20)NGG	8	48842449	-	TATGAAAATGAGTACACCCATGG	1	5	50
(N20)NGG	8	48842500	-	TTGTAGAAACCACTGATGAGGGG	1	7	49
(N20)NGG	8	48842501	-	TTTGTAGAAACCACTGATGAGGG	1	4	90
(N20)NGG	8	48842502	-	ATTTGTAGAAACCACTGATGAGG	1	5	61
(N20)NGG	8	48842549	-	CTCGAAATATTTTATTTTCTTGG	1	21	221
(N20)NGG	8	48843235	+	CTACAATTACTCTTTAAGAATGG	1	3	78
(N20)NGG	8	48843243	+	ACTCTTTAAGAATGGAGATGAGG	1	7	67
(N20)NGG	8	48843250	+	AAGAATGGAGATGAGGCGCCTGG	1	4	41
(N20)NGG	8	48843257	+	GAGATGAGGCGCCTGGTGTTTGG	1	3	31
(N20)NGG	8	48843282	+	GATCCCAACTTCAGATCCAGCGG	2	2	31

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48843318	+	AGCTAAACCTAAAGATTTTTCGG	1	9	84
(N20)NGG	8	48843333	+	TTTTTCGGCTTTCATTAACCTGG	1	2	33
(N20)NGG	8	48843336	+	TTCGGCTTTCATTAACCTGGTGG	1	2	18
(N20)NGG	8	48843347	+	TTAACCTGGTGGAATTTTGCAGG	1	4	41
(N20)NGG	8	48843354	+	GGTGGAATTTTGCAGGTATTTGG	1	4	39
(N20)NGG	8	48843246	–	GTTGGGATCATCCAAACACCAGG	1	2	24
(N20)NGG	8	48843263	–	TAGCCGCTGGATCTGAAGTTGGG	1	1	10
(N20)NGG	8	48843264	–	TTAGCCGCTGGATCTGAAGTTGG	1	1	14
(N20)NGG	8	48843276	–	GCTGGATGCAAGTTAGCCGCTGG	1	1	5
(N20)NGG	8	48843294	–	GAAAAATCTTTAGGTTTAGCTGG	1	1	57
(N20)NGG	8	48843303	–	ATGAAAGCCGAAAAATCTTTAGG	1	2	39
(N20)NGG	8	48843329	–	AATACCTGCAAAATTCCACCAGG	1	3	53
(N20)NGG	8	48845579	+	TATTGTTTTTCTTTATTTTAAAGG	1	63	1249
(N20)NGG	8	48845693	+	TTTGAAGATTGTTGAGAAATTGG	1	6	137
(N20)NGG	8	48845721	+	ACACTTGAAATACAGACTGTTGG	1	3	40
(N20)NGG	8	48845722	+	CACTTGAAATACAGACTGTTGGG	1	2	54
(N20)NGG	8	48845723	+	ACTTGAAATACAGACTGTTGGGG	1	4	53
(N20)NGG	8	48845732	+	ACAGACTGTTGGGGAACAAGAGG	1	4	66
(N20)NGG	8	48845619	–	ATGATTCAGACTTTCACTGGAGG	1	1	44
(N20)NGG	8	48845622	–	TAAATGATTCAGACTTTCACTGG	1	5	68
(N20)NGG	8	48845667	–	TTTCTCAACAATCTTCAAAACGG	1	7	153
(N20)NGG	8	48846524	+	GTCATGCTGTCTTTCTGGCCAGG	1	1	29
(N20)NGG	8	48846525	+	TCATGCTGTCTTTCTGGCCAGGG	1	7	81
(N20)NGG	8	48846561	+	TCTGAAGACCACCGTGCTTCAGG	1	2	22
(N20)NGG	8	48846562	+	CTGAAGACCACCGTGCTTCAGGG	1	2	16

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48846563	+	TGAAGACCACCGTGCTTCAGGGG	1	1	18
(N20)NGG	8	48846576	+	GCTTCAGGGGAAGTCAGAACTGG	1	5	37
(N20)NGG	8	48846583	+	GGGAAGTCAGAACTGGCAAATGG	1	7	71
(N20)NGG	8	48846587	+	AGTCAGAACTGGCAAATGGAAGG	1	6	60
(N20)NGG	8	48846611	+	GCCCACATACAAAGACTACGTGG	1	1	11
(N20)NGG	8	48846650	+	CCTGAGCTCTGACCAGATGATGG	2	5	79
(N20)NGG	8	48846520	-	CAGATTCAGACTCAGGGCCCTGG	1	11	80
(N20)NGG	8	48846526	-	GGTCTTCAGATTCAGACTCAGGG	1	6	78
(N20)NGG	8	48846527	-	TGGTCTTCAGATTCAGACTCAGG	1	4	50
(N20)NGG	8	48846547	-	TGACTTCCCCTGAAGCACGGTGG	1	1	20
(N20)NGG	8	48846550	-	TTCTGACTTCCCCTGAAGCACGG	1	6	77
(N20)NGG	8	48846590	-	TCCACGTAGTCTTTGTATGTGGG	1	2	18
(N20)NGG	8	48846591	-	ATCCACGTAGTCTTTGTATGTGG	1	2	11
(N20)NGG	8	48846628	-	CCATCATCTGGTCAGAGCTCAGG	1	3	26
(N20)NGG	8	48846640	-	TGGTAAATGTTACCATCATCTGG	2	3	48
(N20)NGG	8	48847576	+	TTTTCTTTTTTCAGTGCATCAGG	1	14	294
(N20)NGG	8	48847577	+	TTTCTTTTTTCAGTGCATCAGGG	2	19	285
(N20)NGG	8	48847606	+	CAGAATATGTTCTAAACCAGTGG	2	4	56
(N20)NGG	8	48847618	+	TAAACCAGTGGTCCTTCCAAAGG	1	2	27
(N20)NGG	8	48847600	-	TTTACCTTTGGAAGGACCACTGG	1	4	57
(N20)NGG	8	48847608	-	ATTCAGAATTTACCTTTGGAAGG	1	6	102
(N20)NGG	8	48847612	-	TTAAATTCAGAATTTACCTTTGG	1	13	150
(N20)NGG	8	48848291	+	GTTTGCTGATTATTTCCGGTAGG	1	2	15
(N20)NGG	8	48848300	+	TTATTTCCGGTAGGTTCCTGAGG	1	1	21
(N20)NGG	8	48848318	+	TGAGGTGTATACTCCAGTTCTGG	1	1	22

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48848330	+	TCCAGTTCTGGAGCACCTCGTGG	1	1	20
(N20)NGG	8	48848378	+	GTACAGTCCAAAAATGCAGCTGG	1	1	30
(N20)NGG	8	48848402	+	GTGTTGCAGAGCCATAGTGAAGG	1	2	27
(N20)NGG	8	48848417	+	AGTGAAGGTGTTCCTAGCTTTGG	1	2	24
(N20)NGG	8	48848427	+	TTCCTAGCTTTGGCAGCAAAAGG	1	5	56
(N20)NGG	8	48848428	+	TCCTAGCTTTGGCAGCAAAAGGG	1	7	62
(N20)NGG	8	48848440	+	CAGCAAAAGGGCCAGTTCTCAGG	1	3	45
(N20)NGG	8	48848459	+	CAGGAATTGCATTAGTACTGTGG	1	2	53
(N20)NGG	8	48848460	+	AGGAATTGCATTAGTACTGTGGG	1	2	49
(N20)NGG	8	48848284	-	TATACACCTCAGGAACCTACCGG	1	2	14
(N20)NGG	8	48848294	-	AGAACTGGAGTATACACCTCAGG	1	2	22
(N20)NGG	8	48848309	-	ACCACGAGGTGCTCCAGAACTGG	1	4	9
(N20)NGG	8	48848323	-	TGTCTATCTGCATCACCACGAGG	1	2	13
(N20)NGG	8	48848350	-	GCATTTTTGGACTGTACTGTGGG	1	2	23
(N20)NGG	8	48848351	-	TGCATTTTTGGACTGTACTGTGG	1	4	39
(N20)NGG	8	48848363	-	CAACACACCAGCTGCATTTTTGG	2	5	47
(N20)NGG	8	48848391	-	AGCTAGGAACACCTTCACTATGG	1	1	19
(N20)NGG	8	48848407	-	GCCCTTTTGCTGCCAAAGCTAGG	2	4	48
(N20)NGG	8	48848429	-	CTAATGCAATTCCTGAGAACTGG	2	5	31
(N20)NGG	8	48848921	+	ACCTTTTCTAAAGCCGTGCAAGG	1	2	19
(N20)NGG	8	48849006	+	TTCCTCACCCAGACAGACACTGG	1	2	48
(N20)NGG	8	48848900	-	ACCTTGCACGGCTTTAGAAAAGG	1	3	13
(N20)NGG	8	48848912	-	TTTGCGTTTATAACCTTGCACGG	1	1	29
(N20)NGG	8	48848986	-	CACCAGTGTCTGTCTGGGTGAGG	1	6	146
(N20)NGG	8	48848991	-	GTCGTCACCAGTGTCTGTCTGGG	1	2	9

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48848992	-	GGTCGTCACCAGTGTCTGTCTGG	1	1	13
(N20)NGG	8	48849013	-	AGCTTGGCATCTGATAAACACGG	1	6	38
(N20)NGG	8	48849029	-	GCAACAGACTGGAGGAAGCTTGG	1	3	62
(N20)NGG	8	48849037	-	AGACGCTTGCAACAGACTGGAGG	1	3	15
(N20)NGG	8	48849040	-	GCAAGACGCTTGCAACAGACTGG	1	1	11
(N20)NGG	8	48849067	-	TTAGTTCACTTACTGTGTCAAGG	1	5	63
(N20)NGG	8	48852110	+	AATAAATATTATGTATTTGCAGG	3	18	262
(N20)NGG	8	48852122	+	GTATTTGCAGGTTTCTAATATGG	1	6	100
(N20)NGG	8	48852125	+	TTTGCAGGTTTCTAATATGGTGG	1	4	49
(N20)NGG	8	48852170	+	AAATAAACTGCAGTACTTTATGG	1	6	143
(N20)NGG	8	48852183	+	TACTTTATGGAGCAGTTTTATGG	1	6	154
(N20)NGG	8	48852200	+	TTATGGAATCATCAGAAATGTGG	1	2	66
(N20)NGG	8	48852215	+	AAATGTGGATTCGAACAACAAGG	1	3	35
(N20)NGG	8	48852237	+	GAGTTATCTATTGCTATCCGTGG	1	1	5
(N20)NGG	8	48852243	+	TCTATTGCTATCCGTGGATATGG	1	2	10
(N20)NGG	8	48852255	+	CGTGGATATGGACTTTTTGCAGG	1	2	6
(N20)NGG	8	48852232	-	CTGCAAAAAGTCCATATCCACGG	1	2	43
(N20)NGG	8	48855771	+	ATGGCATTTGCATTTGCAGCTGG	1	4	65
(N20)NGG	8	48855821	+	TCAGTTTAGCACCTGCCTTCTGG	1	5	37
(N20)NGG	8	48855859	+	TATTTGAAGTCTTGTTAAAGTGG	1	9	113
(N20)NGG	8	48855908	+	AAAAGCTGCACTTTCAGCCCTGG	1	3	58
(N20)NGG	8	48855926	+	CCTGGAATCCTTTCTGAAACAGG	2	13	97
(N20)NGG	8	48855778	-	GAGATGCATGCAGGGCAAATAGG	1	3	33
(N20)NGG	8	48855786	-	GCTAAACTGAGATGCATGCAGGG	1	1	16
(N20)NGG	8	48855787	-	TGCTAAACTGAGATGCATGCAGG	1	1	21

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48855810	-	CACGTAGTTGTCCAGAAGGCAGG	1	1	11
(N20)NGG	8	48855814	-	GAGACACGTAGTTGTCCAGAAGG	1	2	10
(N20)NGG	8	48855864	-	TTTCAATTCTACATTTGTGTGGG	2	8	158
(N20)NGG	8	48855865	-	TTTTCAATTCTACATTTGTGTGG	1	10	148
(N20)NGG	8	48855903	-	CTGTTTCAGAAAGGATTCCAGGG	1	7	72
(N20)NGG	8	48855904	-	CCTGTTTCAGAAAGGATTCCAGG	1	5	60
(N20)NGG	8	48855912	-	TTGTGGTACCTGTTTCAGAAAGG	1	1	35
(N20)NGG	8	48856443	+	AAGAGATATGCTGTGCCCTCAGG	1	3	35
(N20)NGG	8	48856447	+	GATATGCTGTGCCCTCAGGTAGG	1	2	21
(N20)NGG	8	48856465	+	GTAGGATTCTGTTTATAATGAGG	2	6	58
(N20)NGG	8	48856436	-	ATAAACAGAATCCTACCTGAGGG	1	3	56
(N20)NGG	8	48856437	-	TATAAACAGAATCCTACCTGAGG	1	3	45
(N20)NGG	8	48856549	+	CCCTAGATCCCCAGACTTCAAGG	1	5	61
(N20)NGG	8	48856550	+	CCTAGATCCCCAGACTTCAAGGG	1	1	27
(N20)NGG	8	48856574	+	GATTTTTAATTTTGTACTAAAGG	1	12	240
(N20)NGG	8	48856589	+	ACTAAAGGCAATTCGTCCTCAGG	1	2	10
(N20)NGG	8	48856593	+	AAGGCAATTCGTCCTCAGGTAGG	1	3	11
(N20)NGG	8	48856527	-	CCTTGAAGTCTGGGGATCTAGGG	1	1	35
(N20)NGG	8	48856528	-	CCCTTGAAGTCTGGGGATCTAGG	1	2	43
(N20)NGG	8	48856535	-	AAAATCTCCCTTGAAGTCTGGGG	1	4	74
(N20)NGG	8	48856536	-	AAAAATCTCCCTTGAAGTCTGGG	1	2	76
(N20)NGG	8	48856537	-	TAAAAATCTCCCTTGAAGTCTGG	1	3	64
(N20)NGG	8	48856583	-	AGTAATATTAATCCTACCTGAGG	1	2	42
(N20)NGG	8	48866218	+	AGAGCCCAAACTACCTGTTCTGG	1	3	21
(N20)NGG	8	48866222	+	CCCAAACTACCTGTTCTGGCAGG	1	3	26

FIG. 12

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48866233	+	TGTTCTGGCAGGATGTCTGAAGG	2	2	31
(N20)NGG	8	48866234	+	GTTCTGGCAGGATGTCTGAAGGG	1	5	78
(N20)NGG	8	48866235	+	TTCTGGCAGGATGTCTGAAGGGG	1	3	60
(N20)NGG	8	48866272	+	GTGCAACTTCACTAAGTCCATGG	1	3	17
(N20)NGG	8	48866279	+	TTCACTAAGTCCATGGAAGAAGG	2	15	82
(N20)NGG	8	48866289	+	CCATGGAAGAAGGTATTGCTTGG	1	3	32
(N20)NGG	8	48866200	-	CCTGCCAGAACAGGTAGTTTGGG	2	3	20
(N20)NGG	8	48866201	-	TCCTGCCAGAACAGGTAGTTTGG	3	4	21
(N20)NGG	8	48866209	-	TTCAGACATCCTGCCAGAACAGG	1	3	37
(N20)NGG	8	48866240	-	AGTGAAGTTGCACAGAAGTGAGG	2	6	91
(N20)NGG	8	48866267	-	CCAAGCAATACCTTCTTCCATGG	2	6	41
(N20)NGG	8	48866393	+	GAAAAAGTATATGAGCTCCTAGG	1	1	63
(N20)NGG	8	48866401	+	ATATGAGCTCCTAGGATTATTGG	1	5	34
(N20)NGG	8	48866402	+	TATGAGCTCCTAGGATTATTGGG	2	4	33
(N20)NGG	8	48866461	+	AAACCTGTTCCGCGCTTTTCTGG	1	1	10
(N20)NGG	8	48866462	+	AACCTGTTCCGCGCTTTTCTGGG	1	2	11
(N20)NGG	8	48866479	+	TCTGGGTGAACTTAAGACCCAGG	1	2	19
(N20)NGG	8	48866388	-	GAACTTCACCCAATAATCCTAGG	1	1	21
(N20)NGG	8	48866413	-	GCATTATTTATCATCTCACTAGG	1	6	60
(N20)NGG	8	48866442	-	CACCCAGAAAAGCGCGGAACAGG	1	1	8
(N20)NGG	8	48866448	-	TAAGTTCACCCAGAAAAGCGCGG	1	2	21
(N20)NGG	8	48866474	-	TCATAAAGTTCATCATACCTGGG	1	4	38
(N20)NGG	8	48866475	-	GTCATAAAGTTCATCATACCTGG	1	2	23
(N20)NGG	8	48866930	+	TTTTAGAAGTTCTAGACTCATGG	1	5	86
(N20)NGG	8	48866946	+	CTCATGGATGAATTTAAAATTGG	1	9	111

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48866970	+	GAATTATTTAGTAAATTCTATGG	2	6	170
(N20)NGG	8	48867006	+	AAAAAAAAAATACCAGATACAGG	9	181	2285
(N20)NGG	8	48866996	-	AAATGCATCTCACCTGTATCTGG	1	3	35
(N20)NGG	8	48868493	+	TAAATGTAAAATTCCAGCCCTGG	3	11	94
(N20)NGG	8	48868508	+	AGCCCTGGACCTTCTTATTAAGG	3	7	43
(N20)NGG	8	48868428	-	AACACTGGTACAAGTGTTCTAGG	1	7	53
(N20)NGG	8	48868443	-	TCTATCTTTTGTATAAACACTGG	4	6	81
(N20)NGG	8	48868484	-	TTAATAAGAAGGTCCAGGGCTGG	2	6	50
(N20)NGG	8	48868488	-	TACCTTAATAAGAAGGTCCAGGG	1	3	33
(N20)NGG	8	48868489	-	TTACCTTAATAAGAAGGTCCAGG	1	1	29
(N20)NGG	8	48868495	-	ACATAATTACCTTAATAAGAAGG	1	4	86
(N20)NGG	8	48869787	+	ATGTATTTTCTTAGAAAAAATGG	5	45	588
(N20)NGG	8	48869788	+	TGTATTTTCTTAGAAAAAATGGG	2	29	518
(N20)NGG	8	48869823	+	ACCTTACTCTGTTGAAATTAAGG	1	2	36
(N20)NGG	8	48869753	-	AGAAAATACATAAAAACTTTAGG	2	29	537
(N20)NGG	8	48869789	-	CAGAGTAAGGTGCGATCTTCTGG	1	1	8
(N20)NGG	8	48869802	-	ACCTTAATTTCAACAGAGTAAGG	1	1	47
(N20)NGG	8	48869950	+	TTAGTTTTTTCCAGAGATTTCGG	2	12	158
(N20)NGG	8	48869969	+	TCGGTTTGCTTGTATTTGTCCGG	2	5	89
(N20)NGG	8	48870008	+	TTGAAGTAAGTTGACAATTTTGG	1	5	73
(N20)NGG	8	48869938	-	TACAAGCAAACCGAAATCTCTGG	1	4	14
(N20)NGG	8	48869966	-	CAATACTGTTGAGTGACTTCCGG	3	3	30
(N20)NGG	8	48872530	+	CGCGCGGGAGCGGGACTCGGCGG	1	2	20
(N20)NGG	8	48872535	+	GGGAGCGGGACTCGGCGGCATGG	1	2	34
(N20)NGG	8	48872538	+	AGCGGGACTCGGCGGCATGGCGG	1	2	8

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48872539	+	GCGGGACTCGGCGGCATGGCGGG	1	1	11
(N20)NGG	8	48872545	+	CTCGGCGGCATGGCGGGCTCCGG	1	2	11
(N20)NGG	8	48872551	+	GGCATGGCGGGCTCCGGAGCCGG	1	2	26
(N20)NGG	8	48872573	+	GTGTGCGTTGCTCCCTGCTGCGG	1	4	47
(N20)NGG	8	48872580	+	TTGCTCCCTGCTGCGGCTGCAGG	1	4	73
(N20)NGG	8	48872598	+	GCAGGAGACCTTGTCCGCTGCGG	1	2	14
(N20)NGG	8	48872608	+	TTGTCCGCTGCGGACCGCTGCGG	1	1	5
(N20)NGG	8	48872619	+	GGACCGCTGCGGTGCTGCCCTGG	1	1	23
(N20)NGG	8	48872623	+	CGCTGCGGTGCTGCCCTGGCCGG	1	4	30
(N20)NGG	8	48872641	+	GCCGGTCATCAACTGATCCGCGG	1	1	1
(N20)NGG	8	48872646	+	TCATCAACTGATCCGCGGCCTGG	1	1	5
(N20)NGG	8	48872647	+	CATCAACTGATCCGCGGCCTGGG	1	1	64
(N20)NGG	8	48872648	+	ATCAACTGATCCGCGGCCTGGGG	1	1	3
(N20)NGG	8	48872652	+	ACTGATCCGCGGCCTGGGGCAGG	1	1	23
(N20)NGG	8	48872679	+	CGTCCTGAGCAGCAGCCCCGCGG	1	3	29
(N20)NGG	8	48872685	+	GAGCAGCAGCCCCGCGGTGCTGG	2	5	34
(N20)NGG	8	48872686	+	AGCAGCAGCCCCGCGGTGCTGGG	1	4	35
(N20)NGG	8	48872689	+	AGCAGCCCCGCGGTGCTGGGTGG	1	4	57
(N20)NGG	8	48872690	+	GCAGCCCCGCGGTGCTGGGTGGG	1	2	36
(N20)NGG	8	48872696	+	CCGCGGTGCTGGGTGGGTACCGG	2	7	22
(N20)NGG	8	48872706	+	GGGTGGGTACCGGCCCGAGCTGG	1	3	18
(N20)NGG	8	48872707	+	GGTGGGTACCGGCCCGAGCTGGG	1	2	6
(N20)NGG	8	48872542	-	GGAGCAACGCACACCGGCTCCGG	1	2	15
(N20)NGG	8	48872548	-	CAGCAGGGAGCAACGCACACCGG	2	9	105
(N20)NGG	8	48872563	-	GGTCTCCTGCAGCCGCAGCAGGG	1	4	51

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	8	48872564	-	AGGTCTCCTGCAGCCGCAGCAGG	1	3	50
(N20)NGG	8	48872584	-	GCAGCGGTCCGCAGCGGACAAGG	1	1	5
(N20)NGG	8	48872590	-	AGCACCGCAGCGGTCCGCAGCGG	1	1	10
(N20)NGG	8	48872600	-	CGGCCAGGGCAGCACCGCAGCGG	2	3	40
(N20)NGG	8	48872614	-	GATCAGTTGATGACCGGCCAGGG	1	1	8
(N20)NGG	8	48872615	-	GGATCAGTTGATGACCGGCCAGG	1	2	15
(N20)NGG	8	48872620	-	GCCGCGGATCAGTTGATGACCGG	1	1	4
(N20)NGG	8	48872636	-	CGCATTCCTGCCCCAGGCCGCGG	1	1	33
(N20)NGG	8	48872642	-	TCAGGACGCATTCCTGCCCCAGG	1	4	31
(N20)NGG	8	48872660	-	GCACCGCGGGGCTGCTGCTCAGG	1	1	32
(N20)NGG	8	48872672	-	GGTACCCACCCAGCACCGCGGGG	1	3	18
(N20)NGG	8	48872673	-	CGGTACCCACCCAGCACCGCGGG	1	5	15
(N20)NGG	8	48872674	-	CCGGTACCCACCCAGCACCGCGG	1	2	16

FIG. 12

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36594881	+	AGCCTCTTTCCCACCCACCTTGG	1	8	94
(N20)NGG	11	36594882	+	GCCTCTTTCCCACCCACCTTGGG	1	2	65
(N20)NGG	11	36594937	+	CACATATTAAATTTTCAGAATGG	1	20	258
(N20)NGG	11	36594955	+	AATGGAAATTTAAGCTGTTCCGG	1	7	80
(N20)NGG	11	36594956	+	ATGGAAATTTAAGCTGTTCCGGG	1	13	156
(N20)NGG	11	36594995	+	GACACCTGAAGAAGCTCAAAAGG	1	2	47
(N20)NGG	11	36595004	+	AGAAGCTCAAAAGGAAAAGAAGG	3	24	430
(N20)NGG	11	36595016	+	GGAAAAGAAGGATTCCTTTGAGG	1	8	108
(N20)NGG	11	36595017	+	GAAAAGAAGGATTCCTTTGAGGG	1	11	268
(N20)NGG	11	36595018	+	AAAAGAAGGATTCCTTTGAGGGG	1	7	95
(N20)NGG	11	36595031	+	CTTTGAGGGGAAACCCTCTCTGG	1	3	23
(N20)NGG	11	36595052	+	GGAGCAATCTCCAGCAGTCCTGG	1	1	24
(N20)NGG	11	36595058	+	ATCTCCAGCAGTCCTGGACAAGG	1	3	46
(N20)NGG	11	36595065	+	GCAGTCCTGGACAAGGCTGATGG	1	2	44
(N20)NGG	11	36595149	+	CACGACAACGAGAAAGCAAGAGG	1	1	19
(N20)NGG	11	36595197	+	CGACATCTCTGCCGCATCTGTGG	1	1	9
(N20)NGG	11	36595198	+	GACATCTCTGCCGCATCTGTGGG	1	1	14
(N20)NGG	11	36595228	+	TTAGAGCTGATGAGCACAACAGG	1	2	26
(N20)NGG	11	36595245	+	AACAGGAGATATCCAGTCCATGG	1	2	83
(N20)NGG	11	36595253	+	ATATCCAGTCCATGGTCCTGTGG	1	3	21
(N20)NGG	11	36595257	+	CCAGTCCATGGTCCTGTGGATGG	1	5	41
(N20)NGG	11	36595269	+	CCTGTGGATGGTAAAACCCTAGG	1	3	43
(N20)NGG	11	36595286	+	CCTAGGCCTTTTACGAAAGAAGG	1	1	24
(N20)NGG	11	36595306	+	AGGAAAAGAGAGCTACTTCCTGG	1	2	55
(N20)NGG	11	36595310	+	AAAGAGAGCTACTTCCTGGCCGG	1	2	48

FIG. 13

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36595325	+	CTGGCCGGACCTCATTGCCAAGG	1	1	18
(N20)NGG	11	36595333	+	ACCTCATTGCCAAGGTTTTCCGG	1	4	35
(N20)NGG	11	36595346	+	GGTTTTCCGGATCGATGTGAAGG	1	1	1
(N20)NGG	11	36595393	+	CTGAGTTCTGCCATAACTGCTGG	1	2	40
(N20)NGG	11	36595408	+	ACTGCTGGAGCATCATGCACAGG	1	4	26
(N20)NGG	11	36595433	+	GTTTAGCAGTGCCCCATGTGAGG	1	1	13
(N20)NGG	11	36595447	+	CATGTGAGGTTTACTTCCCGAGG	1	1	12
(N20)NGG	11	36595460	+	CTTCCCGAGGAACGTGACCATGG	1	3	24
(N20)NGG	11	36595465	+	CGAGGAACGTGACCATGGAGTGG	1	2	15
(N20)NGG	11	36595510	+	ACATCTGCAACACTGCCCGTCGG	1	1	12
(N20)NGG	11	36595511	+	CATCTGCAACACTGCCCGTCGGG	1	1	9
(N20)NGG	11	36595512	+	ATCTGCAACACTGCCCGTCGGGG	1	1	10
(N20)NGG	11	36595522	+	CTGCCCGTCGGGGACTCAAGAGG	1	1	14
(N20)NGG	11	36595616	+	TCAGCACAAGAGAAGAGCTCAGG	1	6	78
(N20)NGG	11	36595621	+	ACAAGAGAAGAGCTCAGGCAAGG	1	9	140
(N20)NGG	11	36595634	+	TCAGGCAAGGATCAGCAGCAAGG	1	2	57
(N20)NGG	11	36595697	+	TAGTACCAAGCTCCTTGCAGTGG	1	2	25
(N20)NGG	11	36595754	+	CCAGATCTGTGAACACATTCTGG	2	6	47
(N20)NGG	11	36595766	+	ACACATTCTGGCTGACCCTGTGG	1	4	40
(N20)NGG	11	36595795	+	ACTGTAAGCATGTCTTTTGCCGG	1	6	108
(N20)NGG	11	36595796	+	CTGTAAGCATGTCTTTTGCCGGG	1	2	51
(N20)NGG	11	36595826	+	TCTCAGATGCCTCAAAGTCATGG	1	4	63
(N20)NGG	11	36595827	+	CTCAGATGCCTCAAAGTCATGGG	1	3	49
(N20)NGG	11	36595874	+	TCCATGCTTCCCTACTGACCTGG	1	2	33
(N20)NGG	11	36595919	+	GAGCGTCTTGAATTCCCTGATGG	1	1	19

FIG. 13

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36595949	+	TCCAGCAAAAGAGTGCAATGAGG	1	4	46
(N20)NGG	11	36595952	+	AGCAAAAGAGTGCAATGAGGAGG	2	4	92
(N20)NGG	11	36595961	+	GTGCAATGAGGAGGTCAGTTTGG	1	3	36
(N20)NGG	11	36595994	+	TCACCACATCTCAAGTCACAAGG	1	2	48
(N20)NGG	11	36596028	+	ATTTTTGTGCACATTAATAAAGG	1	11	171
(N20)NGG	11	36596029	+	TTTTTGTGCACATTAATAAAGGG	1	9	142
(N20)NGG	11	36596030	+	TTTTGTGCACATTAATAAAGGGG	1	4	85
(N20)NGG	11	36596031	+	TTTGTGCACATTAATAAAGGGGG	1	3	57
(N20)NGG	11	36596035	+	TGCACATTAATAAAGGGGGCCGG	1	1	18
(N20)NGG	11	36596065	+	AACATCTTCTGTCGCTGACTCGG	1	1	21
(N20)NGG	11	36596083	+	CTCGGAGAGCTCAGAAGCACCGG	1	2	28
(N20)NGG	11	36596089	+	GAGCTCAGAAGCACCGGCTGAGG	2	5	54
(N20)NGG	11	36596090	+	AGCTCAGAAGCACCGGCTGAGGG	2	4	23
(N20)NGG	11	36596133	+	GCCTTTGCTGACAAAGAAGAAGG	1	4	63
(N20)NGG	11	36596136	+	TTTGCTGACAAAGAAGAAGGTGG	2	11	153
(N20)NGG	11	36596174	+	GTGCATGACCTTGTTCCTGCTGG	1	2	26
(N20)NGG	11	36596182	+	CCTTGTTCCTGCTGGCTCTGAGG	1	19	168
(N20)NGG	11	36596183	+	CTTGTTCCTGCTGGCTCTGAGGG	1	8	75
(N20)NGG	11	36596188	+	TCCTGCTGGCTCTGAGGGCGAGG	1	6	64
(N20)NGG	11	36596200	+	TGAGGGCGAGGAATGAGCACAGG	1	4	38
(N20)NGG	11	36596216	+	GCACAGGCAAGCTGATGAGCTGG	1	5	35
(N20)NGG	11	36596219	+	CAGGCAAGCTGATGAGCTGGAGG	1	5	67
(N20)NGG	11	36596231	+	TGAGCTGGAGGCCATCATGCAGG	1	8	235
(N20)NGG	11	36596232	+	GAGCTGGAGGCCATCATGCAGGG	3	247	3384
(N20)NGG	11	36596237	+	GGAGGCCATCATGCAGGGAAAGG	1	1	66

FIG. 13

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36596238	+	GAGGCCATCATGCAGGGAAAGGG	1	6	65
(N20)NGG	11	36596244	+	ATCATGCAGGGAAAGGGCTCTGG	1	3	42
(N20)NGG	11	36596267	+	CCTGCAGCCAGCTGTTTGCTTGG	2	7	76
(N20)NGG	11	36596320	+	GTCAGTACCACAAGATGTACAGG	1	1	13
(N20)NGG	11	36596340	+	AGGACTGTGAAAGCCATCACAGG	1	2	41
(N20)NGG	11	36596341	+	GGACTGTGAAAGCCATCACAGGG	1	2	33
(N20)NGG	11	36596374	+	TTCAGCCTTTGCATGCCCTTCGG	1	5	58
(N20)NGG	11	36596387	+	TGCCCTTCGGAATGCTGAGAAGG	1	2	41
(N20)NGG	11	36596400	+	GCTGAGAAGGTACTTCTGCCAGG	1	2	53
(N20)NGG	11	36596419	+	CAGGCTACCACCACTTTGAGTGG	2	2	37
(N20)NGG	11	36596460	+	GTGTCTTCCAGCACTGATGTTGG	1	3	41
(N20)NGG	11	36596472	+	ACTGATGTTGGCATTATTGATGG	2	13	67
(N20)NGG	11	36596473	+	CTGATGTTGGCATTATTGATGGG	1	7	68
(N20)NGG	11	36596481	+	GGCATTATTGATGGGCTGTCTGG	1	2	25
(N20)NGG	11	36596498	+	GTCTGGACTATCATCCTCTGTGG	1	2	17
(N20)NGG	11	36596513	+	CTCTGTGGATGATTACCCAGTGG	1	3	31
(N20)NGG	11	36596530	+	CAGTGGACACCATTGCAAAGAGG	1	3	39
(N20)NGG	11	36596552	+	GTTCCGCTATGATTCAGCTTTGG	1	1	12
(N20)NGG	11	36596567	+	AGCTTTGGTGTCTGCTTTGATGG	2	7	76
(N20)NGG	11	36596573	+	GGTGTCTGCTTTGATGGACATGG	1	3	44
(N20)NGG	11	36596588	+	GGACATGGAAGAAGACATCTTGG	1	3	73
(N20)NGG	11	36596592	+	ATGGAAGAAGACATCTTGGAAGG	1	3	87
(N20)NGG	11	36596628	+	GACCTTGATGATTACCTGAATGG	1	3	23
(N20)NGG	11	36596642	+	CCTGAATGGCCCCTTCACTGTGG	1	3	46
(N20)NGG	11	36596645	+	GAATGGCCCCTTCACTGTGGTGG	1	1	31

FIG. 13

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36596651	+	CCCCTTCACTGTGGTGGTGAAGG	1	2	62
(N20)NGG	11	36596664	+	GTGGTGAAGGAGTCTTGTGATGG	1	2	30
(N20)NGG	11	36596669	+	GAAGGAGTCTTGTGATGGAATGG	2	5	69
(N20)NGG	11	36596670	+	AAGGAGTCTTGTGATGGAATGGG	1	4	63
(N20)NGG	11	36596691	+	GGAGACGTGAGTGAGAAGCATGG	1	2	58
(N20)NGG	11	36596692	+	GAGACGTGAGTGAGAAGCATGGG	1	3	33
(N20)NGG	11	36596697	+	GTGAGTGAGAAGCATGGGAGTGG	1	5	111
(N20)NGG	11	36596698	+	TGAGTGAGAAGCATGGGAGTGGG	1	6	95
(N20)NGG	11	36596717	+	TGGGCCTGTAGTTCCAGAAAAGG	1	4	62
(N20)NGG	11	36596840	+	CAAGCCATTGTGCCTTATGCTGG	1	4	34
(N20)NGG	11	36596899	+	TGAGTCCTCTCATTGCTGAGAGG	1	12	64
(N20)NGG	11	36596900	+	GAGTCCTCTCATTGCTGAGAGGG	1	4	47
(N20)NGG	11	36596903	+	TCCTCTCATTGCTGAGAGGGAGG	1	5	58
(N20)NGG	11	36596936	+	CAGTGAATTAATGCTTGAGCTGG	1	3	44
(N20)NGG	11	36596937	+	AGTGAATTAATGCTTGAGCTGGG	1	2	71
(N20)NGG	11	36596940	+	GAATTAATGCTTGAGCTGGGAGG	1	3	74
(N20)NGG	11	36596950	+	TTGAGCTGGGAGGCATTCTCCGG	1	2	44
(N20)NGG	11	36596971	+	GGACTTTCAAGTTCATCTTCAGG	1	3	48
(N20)NGG	11	36596972	+	GACTTTCAAGTTCATCTTCAGGG	1	4	98
(N20)NGG	11	36596973	+	ACTTTCAAGTTCATCTTCAGGGG	1	7	69
(N20)NGG	11	36596979	+	AAGTTCATCTTCAGGGGCACCGG	1	3	35
(N20)NGG	11	36597001	+	GCTATGATGAAAAACTTGTGCGG	1	2	53
(N20)NGG	11	36597002	+	CTATGATGAAAAACTTGTGCGGG	1	2	42
(N20)NGG	11	36597008	+	TGAAAAACTTGTGCGGGAAGTGG	1	2	18
(N20)NGG	11	36597012	+	AAACTTGTGCGGGAAGTGGAAGG	1	1	20

FIG. 13

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36597020	+	GCGGGAAGTGGAAGGCCTCGAGG	1	1	27
(N20)NGG	11	36597027	+	GTGGAAGGCCTCGAGGCTTCTGG	1	1	17
(N20)NGG	11	36597068	+	TCTTTGTGATGCCACCCGTCTGG	1	2	16
(N20)NGG	11	36597125	+	CAGAAGCCATGCTGAGAACCTGG	3	7	92
(N20)NGG	11	36597137	+	TGAGAACCTGGAACGTTATGAGG	1	1	10
(N20)NGG	11	36597142	+	ACCTGGAACGTTATGAGGTCTGG	1	2	11
(N20)NGG	11	36597170	+	CAACCCTTACCATGAGTCTGTGG	1	1	19
(N20)NGG	11	36597181	+	ATGAGTCTGTGGAAGAACTGCGG	1	4	75
(N20)NGG	11	36597182	+	TGAGTCTGTGGAAGAACTGCGGG	1	4	70
(N20)NGG	11	36597187	+	CTGTGGAAGAACTGCGGGATCGG	1	1	26
(N20)NGG	11	36597188	+	TGTGGAAGAACTGCGGGATCGGG	1	1	16
(N20)NGG	11	36597195	+	GAACTGCGGGATCGGGTGAAAGG	1	1	29
(N20)NGG	11	36597196	+	AACTGCGGGATCGGGTGAAAGGG	1	1	5
(N20)NGG	11	36597197	+	ACTGCGGGATCGGGTGAAAGGGG	1	1	10
(N20)NGG	11	36597258	+	GATGCACTCCCACTGTGACATTGG	1	2	33
(N20)NGG	11	36597300	+	AAGATCTTCCAGCTAGAGATAGG	1	3	39
(N20)NGG	11	36597301	+	AGATCTTCCAGCTAGAGATAGGG	1	6	55
(N20)NGG	11	36597302	+	GATCTTCCAGCTAGAGATAGGGG	2	5	50
(N20)NGG	11	36597335	+	GAATCCCAATGCTTCCAAAGAGG	1	2	31
(N20)NGG	11	36597340	+	CCAATGCTTCCAAAGAGGAAAGG	1	7	60
(N20)NGG	11	36597346	+	CTTCCAAAGAGGAAAGGAAAAGG	1	41	458
(N20)NGG	11	36597349	+	CCAAAGAGGAAAGGAAAAGGTGG	2	39	523
(N20)NGG	11	36597353	+	AGAGGAAAGGAAAAGGTGGCAGG	3	11	305
(N20)NGG	11	36597362	+	GAAAAGGTGGCAGGCCACACTGG	1	5	53
(N20)NGG	11	36597376	+	CCACACTGGACAAGCATCTCCGG	1	3	24

FIG. 13

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36597406	+	TGAACCTCAAACCAATCATGAGG	1	1	35
(N20)NGG	11	36597414	+	AAACCAATCATGAGGATGAATGG	1	5	72
(N20)NGG	11	36597427	+	GGATGAATGGCAACTTTGCCAGG	1	3	24
(N20)NGG	11	36597452	+	GCTCATGACCAAAGAGACTGTGG	1	2	39
(N20)NGG	11	36597482	+	TTGTGAGTTAATTCCTTCCGAGG	1	1	16
(N20)NGG	11	36597487	+	AGTTAATTCCTTCCGAGGAGAGG	1	1	13
(N20)NGG	11	36597494	+	TCCTTCCGAGGAGAGGCACGAGG	1	1	28
(N20)NGG	11	36597502	+	AGGAGAGGCACGAGGCTCTGAGG	1	3	69
(N20)NGG	11	36597503	+	GGAGAGGCACGAGGCTCTGAGGG	1	1	43
(N20)NGG	11	36597512	+	CGAGGCTCTGAGGGAGCTGATGG	1	3	43
(N20)NGG	11	36597541	+	ACCTGAAGATGAAACCAGTATGG	1	3	36
(N20)NGG	11	36597643	+	TTTCTACGAAGTTCAAGTATAGG	1	2	51
(N20)NGG	11	36597650	+	GAAGTTCAAGTATAGGTATGAGG	2	3	35
(N20)NGG	11	36597651	+	AAGTTCAAGTATAGGTATGAGGG	1	3	35
(N20)NGG	11	36597683	+	CAATTATTTTCACAAAACCCTGG	1	5	94
(N20)NGG	11	36597709	+	ATGTTCCTGAAATTATTGAGAGG	1	4	79
(N20)NGG	11	36597710	+	TGTTCCTGAAATTATTGAGAGGG	1	8	155
(N20)NGG	11	36597714	+	CCTGAAATTATTGAGAGGGATGG	1	2	50
(N20)NGG	11	36597723	+	ATTGAGAGGGATGGCTCCATTGG	1	2	17
(N20)NGG	11	36597724	+	TTGAGAGGGATGGCTCCATTGGG	1	1	17
(N20)NGG	11	36597725	+	TGAGAGGGATGGCTCCATTGGGG	1	4	41
(N20)NGG	11	36597730	+	GGGATGGCTCCATTGGGGCATGG	1	4	21
(N20)NGG	11	36597731	+	GGATGGCTCCATTGGGGCATGGG	1	1	19
(N20)NGG	11	36597740	+	CATTGGGGCATGGGCAAGTGAGG	1	3	33
(N20)NGG	11	36597741	+	ATTGGGGCATGGGCAAGTGAGGG	1	3	41

FIG. 13

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36597753	+	GCAAGTGAGGGAAATGAGTCTGG	1	5	114
(N20)NGG	11	36597769	+	AGTCTGGTAACAAACTGTTTAGG	1	4	43
(N20)NGG	11	36597778	+	ACAAACTGTTTAGGCGCTTCCGG	1	1	16
(N20)NGG	11	36597793	+	GCTTCCGGAAAATGAATGCCAGG	1	1	17
(N20)NGG	11	36597815	+	GCAGTCCAAATGCTATGAGATGG	1	3	34
(N20)NGG	11	36597838	+	AAGATGTCCTGAAACACCACTGG	1	1	36
(N20)NGG	11	36597900	+	CATAATGCATTAAAAACCTCTGG	1	3	60
(N20)NGG	11	36597901	+	ATAATGCATTAAAAACCTCTGGG	2	8	86
(N20)NGG	11	36597920	+	TGGGTTTACCATGAACCCTCAGG	1	3	17
(N20)NGG	11	36597930	+	ATGAACCCTCAGGCAAGCTTAGG	1	2	27
(N20)NGG	11	36597931	+	TGAACCCTCAGGCAAGCTTAGGG	1	1	17
(N20)NGG	11	36597932	+	GAACCCTCAGGCAAGCTTAGGGG	1	2	16
(N20)NGG	11	36597942	+	GCAAGCTTAGGGGACCCATTAGG	1	2	12
(N20)NGG	11	36597950	+	AGGGGACCCATTAGGCATAGAGG	1	3	22
(N20)NGG	11	36597959	+	ATTAGGCATAGAGGACTCTCTGG	1	1	20
(N20)NGG	11	36597977	+	TCTGGAAAGCCAAGATTCAATGG	1	7	61
(N20)NGG	11	36594861	-	TCCCAAGGTGGGTGGGAAAGAGG	1	6	90
(N20)NGG	11	36594868	-	AACTGAGTCCCAAGGTGGGTGGG	1	6	113
(N20)NGG	11	36594869	-	GAACTGAGTCCCAAGGTGGGTGG	2	6	82
(N20)NGG	11	36594872	-	GCAGAACTGAGTCCCAAGGTGGG	1	4	61
(N20)NGG	11	36594873	-	GGCAGAACTGAGTCCCAAGGTGG	1	6	100
(N20)NGG	11	36594876	-	TGGGGCAGAACTGAGTCCCAAGG	1	5	98
(N20)NGG	11	36594894	-	TGGGTGCTGAATTTCATCTGGGG	2	8	65
(N20)NGG	11	36594895	-	GTGGGTGCTGAATTTCATCTGGG	2	2	49
(N20)NGG	11	36594896	-	TGTGGGTGCTGAATTTCATCTGG	1	4	38

FIG. 13

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36594913	-	ATTCTGAAAATTTAATATGTGGG	1	22	290
(N20)NGG	11	36594914	-	CATTCTGAAAATTTAATATGTGG	3	11	173
(N20)NGG	11	36594952	-	TCTTTTCAAAGGATCTCACCCGG	1	2	51
(N20)NGG	11	36594963	-	TTCTTCAGGTGTCTTTTCAAAGG	2	12	161
(N20)NGG	11	36594977	-	TTTTCCTTTTGAGCTTCTTCAGG	1	11	187
(N20)NGG	11	36595008	-	CAGAGAGGGTTTCCCCTCAAAGG	1	4	28
(N20)NGG	11	36595022	-	GCTGGAGATTGCTCCAGAGAGGG	1	4	56
(N20)NGG	11	36595023	-	TGCTGGAGATTGCTCCAGAGAGG	1	2	43
(N20)NGG	11	36595040	-	TCAGCCTTGTCCAGGACTGCTGG	1	4	49
(N20)NGG	11	36595048	-	TCTGACCATCAGCCTTGTCCAGG	2	2	47
(N20)NGG	11	36595073	-	AACAATGGCTGAGTTGGGACTGG	1	5	52
(N20)NGG	11	36595078	-	CTTTTAACAATGGCTGAGTTGGG	1	6	95
(N20)NGG	11	36595079	-	GCTTTTAACAATGGCTGAGTTGG	1	3	58
(N20)NGG	11	36595088	-	TTAGGGTGGGCTTTTAACAATGG	1	2	34
(N20)NGG	11	36595101	-	TTTCTTTGAAAACTTAGGGTGGG	1	13	130
(N20)NGG	11	36595102	-	ATTTCTTTGAAAACTTAGGGTGG	1	5	108
(N20)NGG	11	36595105	-	GAAATTTCTTTGAAAACTTAGGG	2	22	293
(N20)NGG	11	36595106	-	TGAAATTTCTTTGAAAACTTAGG	1	22	312
(N20)NGG	11	36595159	-	GATGTCGAAGGTTGGCTTGATGG	1	3	18
(N20)NGG	11	36595167	-	GCGGCAGAGATGTCGAAGGTTGG	1	1	6
(N20)NGG	11	36595171	-	AGATGCGGCAGAGATGTCGAAGG	1	2	15
(N20)NGG	11	36595186	-	TAAAAGAATTCCCACAGATGCGG	1	7	91
(N20)NGG	11	36595235	-	CCATCCACAGGACCATGGACTGG	1	5	75
(N20)NGG	11	36595240	-	TTTACCATCCACAGGACCATGG	1	3	46
(N20)NGG	11	36595247	-	CCTAGGGTTTTACCATCCACAGG	1	2	16

FIG. 13

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36595263	-	CTTCTTTCGTAAAAGGCCTAGGG	1	5	27
(N20)NGG	11	36595264	-	CCTTCTTTCGTAAAAGGCCTAGG	1	1	19
(N20)NGG	11	36595270	-	TCTTTTCCTTCTTTCGTAAAAGG	1	10	194
(N20)NGG	11	36595302	-	CTTGGCAATGAGGTCCGGCCAGG	1	1	10
(N20)NGG	11	36595307	-	AAAACCTTGGCAATGAGGTCCGG	1	4	52
(N20)NGG	11	36595312	-	TCCGGAAAACCTTGGCAATGAGG	1	1	12
(N20)NGG	11	36595320	-	CACATCGATCCGGAAAACCTTGG	1	2	6
(N20)NGG	11	36595330	-	CATCTGCCTTCACATCGATCCGG	1	2	11
(N20)NGG	11	36595363	-	TATGGCAGAACTCAGTGGGGTGG	1	1	59
(N20)NGG	11	36595366	-	AGTTATGGCAGAACTCAGTGGGG	1	4	34
(N20)NGG	11	36595367	-	CAGTTATGGCAGAACTCAGTGGG	1	3	39
(N20)NGG	11	36595368	-	GCAGTTATGGCAGAACTCAGTGG	1	4	57
(N20)NGG	11	36595381	-	GCATGATGCTCCAGCAGTTATGG	1	1	19
(N20)NGG	11	36595422	-	CGGGAAGTAAACCTCACATGGGG	1	1	16
(N20)NGG	11	36595423	-	TCGGGAAGTAAACCTCACATGGG	1	2	18
(N20)NGG	11	36595424	-	CTCGGGAAGTAAACCTCACATGG	1	3	16
(N20)NGG	11	36595441	-	ACTCCATGGTCACGTTCCTCGGG	1	5	19
(N20)NGG	11	36595442	-	CACTCCATGGTCACGTTCCTCGG	1	3	28
(N20)NGG	11	36595455	-	TGTGTGGGGGTGCCACTCCATGG	1	4	35
(N20)NGG	11	36595468	-	TGTCACAGGATGGTGTGTGGGGG	2	5	97
(N20)NGG	11	36595469	-	ATGTCACAGGATGGTGTGTGGGG	1	5	63
(N20)NGG	11	36595470	-	GATGTCACAGGATGGTGTGTGGG	1	4	48
(N20)NGG	11	36595471	-	AGATGTCACAGGATGGTGTGTGG	1	5	57
(N20)NGG	11	36595478	-	GTGTTGCAGATGTCACAGGATGG	1	8	106
(N20)NGG	11	36595482	-	GGCAGTGTTGCAGATGTCACAGG	2	2	39

FIG. 13

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36595503	-	CTTCCTCTTGAGTCCCCGACGGG	1	3	13
(N20)NGG	11	36595504	-	TCTTCCTCTTGAGTCCCCGACGG	1	2	24
(N20)NGG	11	36595535	-	TTTTTGCTGAGCTGCAAGTTTGG	1	2	52
(N20)NGG	11	36595576	-	GCTGACGGGCTTGTCTTGCTTGG	1	3	74
(N20)NGG	11	36595590	-	AGCTCTTCTCTTGTGCTGACGGG	2	3	38
(N20)NGG	11	36595591	-	GAGCTCTTCTCTTGTGCTGACGG	1	2	44
(N20)NGG	11	36595653	-	AAGATGTATCTTACTGCAGTTGG	1	2	43
(N20)NGG	11	36595680	-	GAAGTCCACTGCAAGGAGCTTGG	1	3	26
(N20)NGG	11	36595687	-	GCTCTGGGAAGTCCACTGCAAGG	1	4	41
(N20)NGG	11	36595702	-	TGGATTTCACAAAGTGCTCTGGG	1	2	66
(N20)NGG	11	36595703	-	ATGGATTTCACAAAGTGCTCTGG	1	3	41
(N20)NGG	11	36595722	-	TTCACAGATCTGGCAGGAGATGG	1	13	151
(N20)NGG	11	36595728	-	AATGTGTTCACAGATCTGGCAGG	1	4	43
(N20)NGG	11	36595732	-	CCAGAATGTGTTCACAGATCTGG	2	6	47
(N20)NGG	11	36595759	-	GCTTACAGTTGGTCTCCACAGGG	1	1	23
(N20)NGG	11	36595760	-	TGCTTACAGTTGGTCTCCACAGG	1	1	20
(N20)NGG	11	36595770	-	GCAAAAGACATGCTTACAGTTGG	1	2	51
(N20)NGG	11	36595792	-	GGCATCTGAGAATGCAGACCCGG	1	5	50
(N20)NGG	11	36595813	-	AATAGCTGCCCATGACTTTGAGG	1	7	48
(N20)NGG	11	36595838	-	AAGCATGGATATCGGCAAGAGGG	1	1	23
(N20)NGG	11	36595839	-	GAAGCATGGATATCGGCAAGAGG	1	2	22
(N20)NGG	11	36595846	-	CAGTAGGGAAGCATGGATATCGG	1	2	47
(N20)NGG	11	36595853	-	TCCAGGTCAGTAGGGAAGCATGG	1	5	59
(N20)NGG	11	36595861	-	CTGGACTCTCCAGGTCAGTAGGG	1	3	39
(N20)NGG	11	36595862	-	ACTGGACTCTCCAGGTCAGTAGG	2	5	17

FIG. 13

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36595870	-	AGGACTTCACTGGACTCTCCAGG	1	3	35
(N20)NGG	11	36595880	-	ACGCTCAGAAAGGACTTCACTGG	1	1	22
(N20)NGG	11	36595890	-	GGAATTCAAGACGCTCAGAAAGG	1	1	23
(N20)NGG	11	36595911	-	TGCTGGACATTTCACCATCAGGG	1	3	48
(N20)NGG	11	36595912	-	TTGCTGGACATTTCACCATCAGG	1	2	30
(N20)NGG	11	36595928	-	TCCTCATTGCACTCTTTTGCTGG	1	3	33
(N20)NGG	11	36595975	-	ATTCCTTGTGACTTGAGATGTGG	1	3	32
(N20)NGG	11	36596032	-	ACAGAAGATGTTGGCGGGGCCGG	1	2	60
(N20)NGG	11	36596036	-	AGCGACAGAAGATGTTGGCGGGG	1	2	21
(N20)NGG	11	36596037	-	CAGCGACAGAAGATGTTGGCGGG	1	2	23
(N20)NGG	11	36596038	-	TCAGCGACAGAAGATGTTGGCGG	1	2	30
(N20)NGG	11	36596041	-	GAGTCAGCGACAGAAGATGTTGG	1	8	54
(N20)NGG	11	36596080	-	GCAGCTTGAGCTCCCTCAGCCGG	1	3	40
(N20)NGG	11	36596112	-	ACCTTCTTCTTTGTCAGCAAAGG	1	4	50
(N20)NGG	11	36596148	-	CAGGAACAAGGTCATGCACACGG	1	4	56
(N20)NGG	11	36596160	-	CCTCAGAGCCAGCAGGAACAAGG	2	19	201
(N20)NGG	11	36596167	-	TCCTCGCCCTCAGAGCCAGCAGG	1	2	41
(N20)NGG	11	36596220	-	AGAGCCCTTTCCCTGCATGATGG	1	1	46
(N20)NGG	11	36596245	-	CCAAGCAAACAGCTGGCTGCAGG	3	4	45
(N20)NGG	11	36596252	-	CGGATGGCCAAGCAAACAGCTGG	1	1	16
(N20)NGG	11	36596268	-	GAGGAAGGTGTTGACACGGATGG	1	3	37
(N20)NGG	11	36596272	-	AGCTGAGGAAGGTGTTGACACGG	1	5	72
(N20)NGG	11	36596283	-	GTACTGACTGCAGCTGAGGAAGG	1	7	57
(N20)NGG	11	36596287	-	TGTGGTACTGACTGCAGCTGAGG	1	5	65
(N20)NGG	11	36596305	-	TCACAGTCCTGTACATCTTGTGG	1	2	36

FIG. 13

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36596331	-	AAAAATCTGTCTCCCTGTGATGG	1	2	100
(N20)NGG	11	36596357	-	GCATTCCGAAGGGCATGCAAAGG	1	1	10
(N20)NGG	11	36596367	-	TACCTTCTCAGCATTCCGAAGGG	1	1	35
(N20)NGG	11	36596368	-	GTACCTTCTCAGCATTCCGAAGG	1	1	11
(N20)NGG	11	36596396	-	CACTCAAAGTGGTGGTAGCCTGG	2	3	19
(N20)NGG	11	36596404	-	GTGGCTGCCACTCAAAGTGGTGG	1	1	30
(N20)NGG	11	36596407	-	GAGGTGGCTGCCACTCAAAGTGG	1	5	53
(N20)NGG	11	36596423	-	GAAGACACATTCTTCAGAGGTGG	1	4	82
(N20)NGG	11	36596426	-	CTGGAAGACACATTCTTCAGAGG	2	5	70
(N20)NGG	11	36596445	-	AATAATGCCAACATCAGTGCTGG	1	4	41
(N20)NGG	11	36596490	-	CACTGGGTAATCATCCACAGAGG	2	2	27
(N20)NGG	11	36596506	-	TCTTTGCAATGGTGTCCACTGGG	1	5	24
(N20)NGG	11	36596507	-	CTCTTTGCAATGGTGTCCACTGG	1	2	24
(N20)NGG	11	36596517	-	ATAGCGGAACCTCTTTGCAATGG	1	1	10
(N20)NGG	11	36596533	-	ACACCAAAGCTGAATCATAGCGG	1	2	35
(N20)NGG	11	36596601	-	CAGGTAATCATCAAGGTCTTGGG	1	1	26
(N20)NGG	11	36596602	-	TCAGGTAATCATCAAGGTCTTGG	1	3	33
(N20)NGG	11	36596608	-	GGCCATTCAGGTAATCATCAAGG	1	1	17
(N20)NGG	11	36596620	-	CCACAGTGAAGGGGCCATTCAGG	1	3	33
(N20)NGG	11	36596629	-	CCTTCACCACCACAGTGAAGGGG	1	3	62
(N20)NGG	11	36596630	-	TCCTTCACCACCACAGTGAAGGG	1	2	52
(N20)NGG	11	36596631	-	CTCCTTCACCACCACAGTGAAGG	1	5	79
(N20)NGG	11	36596699	-	ACTGCCTTTTCTGGAACTACAGG	2	2	53
(N20)NGG	11	36596708	-	GAAAAACGGACTGCCTTTTCTGG	1	1	27
(N20)NGG	11	36596722	-	TCATGATTGTGAATGAAAAACGG	1	8	141

FIG. 13

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36596757	-	TTTCACATTCTGAGAGCTGTGGG	1	4	66
(N20)NGG	11	36596758	-	CTTTCACATTCTGAGAGCTGTGG	3	9	85
(N20)NGG	11	36596793	-	ACACAGTTCAGAGTTAGGTTTGG	1	4	32
(N20)NGG	11	36596798	-	TTGCAACACAGTTCAGAGTTAGG	2	11	62
(N20)NGG	11	36596822	-	TCTGCCAGCATAAGGCACAATGG	1	2	34
(N20)NGG	11	36596830	-	CAGACTCATCTGCCAGCATAAGG	1	1	36
(N20)NGG	11	36596854	-	GGATGGCAGTCAGCGTCTCGTGG	1	3	11
(N20)NGG	11	36596871	-	AGCAATGAGAGGACTCAGGATGG	1	5	97
(N20)NGG	11	36596875	-	TCTCAGCAATGAGAGGACTCAGG	1	2	55
(N20)NGG	11	36596882	-	GCCTCCCTCTCAGCAATGAGAGG	1	2	42
(N20)NGG	11	36596904	-	CATTAATTCACTGCTCTTCATGG	1	4	108
(N20)NGG	11	36596947	-	TGAAGATGAACTTGAAAGTCCGG	1	2	94
(N20)NGG	11	36596976	-	CACAAGTTTTTCATCATAGCCGG	1	1	28
(N20)NGG	11	36597013	-	AGACTGAGCCAGAAGCCTCGAGG	1	3	42
(N20)NGG	11	36597057	-	TTGAGAGGCTTCCAGACGGGTGG	1	3	30
(N20)NGG	11	36597060	-	ATTTTGAGAGGCTTCCAGACGGG	1	4	31
(N20)NGG	11	36597061	-	GATTTTGAGAGGCTTCCAGACGG	1	5	64
(N20)NGG	11	36597072	-	GTGGAAGACAAGATTTTGAGAGG	1	3	81
(N20)NGG	11	36597091	-	CATGGCTTCTGGTTATAGAGTGG	1	6	44
(N20)NGG	11	36597102	-	CAGGTTCTCAGCATGGCTTCTGG	1	5	76
(N20)NGG	11	36597109	-	AACGTTCCAGGTTCTCAGCATGG	1	3	20
(N20)NGG	11	36597121	-	GCCAGACCTCATAACGTTCCAGG	1	1	11
(N20)NGG	11	36597147	-	CACAGACTCATGGTAAGGGTTGG	1	2	29
(N20)NGG	11	36597151	-	CTTCCACAGACTCATGGTAAGGG	1	5	41
(N20)NGG	11	36597152	-	TCTTCCACAGACTCATGGTAAGG	1	5	38

FIG. 13

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36597157	-	GCAGTTCTTCCACAGACTCATGG	1	5	54
(N20)NGG	11	36597209	-	GAAGGGACTGTCTCAATGAAAGG	1	3	40
(N20)NGG	11	36597226	-	AGTGGAGTGCATCTATGGAAGGG	1	2	31
(N20)NGG	11	36597227	-	CAGTGGAGTGCATCTATGGAAGG	1	2	21
(N20)NGG	11	36597231	-	GTCACAGTGGAGTGCATCTATGG	1	9	59
(N20)NGG	11	36597244	-	CTGCATTGCCAATGTCACAGTGG	1	5	50
(N20)NGG	11	36597286	-	ACACTTCCCCTATCTCTAGCTGG	1	1	24
(N20)NGG	11	36597317	-	CTTTCCTCTTTGGAAGCATTGGG	1	7	102
(N20)NGG	11	36597318	-	CCTTTCCTCTTTGGAAGCATTGG	1	3	74
(N20)NGG	11	36597327	-	CCACCTTTTCCTTTCCTCTTTGG	3	18	318
(N20)NGG	11	36597354	-	CCGGAGATGCTTGTCCAGTGTGG	1	1	11
(N20)NGG	11	36597373	-	GTTTGAGGTTCATCTTCTTCCGG	1	5	47
(N20)NGG	11	36597388	-	TCATCCTCATGATTGGTTTGAGG	1	3	36
(N20)NGG	11	36597395	-	TTGCCATTCATCCTCATGATTGG	1	2	34
(N20)NGG	11	36597423	-	CTCTTTGGTCATGAGCTTCCTGG	1	5	59
(N20)NGG	11	36597438	-	AACTGCATCCACAGTCTCTTTGG	1	6	70
(N20)NGG	11	36597473	-	GCCTCGTGCCTCTCCTCGGAAGG	1	3	21
(N20)NGG	11	36597477	-	CAGAGCCTCGTGCCTCTCCTCGG	1	4	45
(N20)NGG	11	36597520	-	GCCATACTGGTTTCATCTTCAGG	1	1	32
(N20)NGG	11	36597533	-	GGGCATGATGATCGCCATACTGG	1	2	5
(N20)NGG	11	36597553	-	ATTCTGGGCACTCTTTAGCAGGG	1	2	35
(N20)NGG	11	36597554	-	GATTCTGGGCACTCTTTAGCAGG	2	4	32
(N20)NGG	11	36597568	-	TGTACTGGCAGAGGGATTCTGGG	1	2	31
(N20)NGG	11	36597569	-	CTGTACTGGCAGAGGGATTCTGG	1	1	23
(N20)NGG	11	36597576	-	ATTGAAACTGTACTGGCAGAGGG	1	3	38

FIG. 13

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36597577	-	AATTGAAACTGTACTGGCAGAGG	1	7	44
(N20)NGG	11	36597583	-	GCTGTGAATTGAAACTGTACTGG	1	1	19
(N20)NGG	11	36597619	-	TATACTTGAACTTCGTAGAAAGG	1	1	37
(N20)NGG	11	36597660	-	CAGGGTTTTGTGAAAATAATTGG	1	7	98
(N20)NGG	11	36597678	-	AATTTCAGGAACATGGGCCAGGG	1	4	44
(N20)NGG	11	36597679	-	TAATTTCAGGAACATGGGCCAGG	1	3	36
(N20)NGG	11	36597684	-	CTCAATAATTTCAGGAACATGGG	1	4	74
(N20)NGG	11	36597685	-	TCTCAATAATTTCAGGAACATGG	1	9	114
(N20)NGG	11	36597692	-	CCATCCCTCTCAATAATTTCAGG	1	2	35
(N20)NGG	11	36597717	-	CTCACTTGCCCATGCCCCAATGG	1	3	38
(N20)NGG	11	36597775	-	ACTGCCTGGCATTCATTTTCCGG	1	4	45
(N20)NGG	11	36597789	-	CTCATAGCATTTGGACTGCCTGG	1	1	18
(N20)NGG	11	36597798	-	ATCTTCCATCTCATAGCATTTGG	1	4	51
(N20)NGG	11	36597823	-	TGTACAACCAGTGGTGTTTCAGG	1	1	24
(N20)NGG	11	36597832	-	ATTTGGAGGTGTACAACCAGTGG	1	1	24
(N20)NGG	11	36597846	-	AAACTTCTGGAGGTATTTGGAGG	1	6	76
(N20)NGG	11	36597849	-	CATAAACTTCTGGAGGTATTTGG	1	2	42
(N20)NGG	11	36597856	-	GAGCATTCATAAACTTCTGGAGG	1	5	79
(N20)NGG	11	36597859	-	TATGAGCATTCATAAACTTCTGG	1	4	38
(N20)NGG	11	36597894	-	AGGGTTCATGGTAAACCCAGAGG	1	6	39
(N20)NGG	11	36597906	-	TAAGCTTGCCTGAGGGTTCATGG	1	1	25
(N20)NGG	11	36597913	-	GGTCCCCTAAGCTTGCCTGAGGG	1	2	21
(N20)NGG	11	36597914	-	GGGTCCCCTAAGCTTGCCTGAGG	1	3	18
(N20)NGG	11	36597934	-	GAGAGTCCTCTATGCCTAATGGG	1	1	9
(N20)NGG	11	36597935	-	AGAGAGTCCTCTATGCCTAATGG	1	3	21

FIG. 13

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36614186	+	AACATAGCCTTAATTCAGCCAGG	1	3	29
(N20)NGG	11	36614210	+	TTCTCACTGATGAATTTTGATGG	1	24	221
(N20)NGG	11	36614228	+	GATGGACAAGTTTTCTTCTTTGG	1	4	80
(N20)NGG	11	36614237	+	GTTTTCTTCTTTGGACAAAAAGG	1	13	170
(N20)NGG	11	36614241	+	TCTTCTTTGGACAAAAAGGCTGG	1	8	67
(N20)NGG	11	36614264	+	CCCAAAAGATCCTGCCCCACTGG	1	3	46
(N20)NGG	11	36614278	+	CCCCACTGGAGTTTTCCATCTGG	1	4	38
(N20)NGG	11	36614326	+	GAAGCCTACAATTTTCTCTAAGG	1	5	38
(N20)NGG	11	36614378	+	CCAGCCACTTGCACATTCAAAGG	1	3	30
(N20)NGG	11	36614386	+	TTGCACATTCAAAGGCAGCTTGG	2	3	40
(N20)NGG	11	36614417	+	AAGCATCAATACATCATCCATGG	1	2	28
(N20)NGG	11	36614420	+	CATCAATACATCATCCATGGAGG	1	1	22
(N20)NGG	11	36614421	+	ATCAATACATCATCCATGGAGGG	1	3	30
(N20)NGG	11	36614440	+	AGGGAAAACACCAAACAATGAGG	1	3	105
(N20)NGG	11	36614491	+	TGTTTGCAAGAACAACAAAAAGG	1	16	224
(N20)NGG	11	36614521	+	TCGCTGCACAGAGAAAGACTTGG	1	2	30
(N20)NGG	11	36614525	+	TGCACAGAGAAAGACTTGGTAGG	1	4	54
(N20)NGG	11	36614549	+	GATGTTCCTGAAGCCAGATATGG	1	8	46
(N20)NGG	11	36614566	+	ATATGGTCATTCCATTAATGTGG	1	4	45
(N20)NGG	11	36614579	+	ATTAATGTGGTGTACAGCCGAGG	1	1	8
(N20)NGG	11	36614580	+	TTAATGTGGTGTACAGCCGAGGG	1	1	11
(N20)NGG	11	36614590	+	GTACAGCCGAGGGAAAAGTATGG	1	5	223
(N20)NGG	11	36614591	+	TACAGCCGAGGGAAAAGTATGGG	1	2	20
(N20)NGG	11	36614603	+	AAAAGTATGGGTGTTCTCTTTGG	1	2	60
(N20)NGG	11	36614606	+	AGTATGGGTGTTCTCTTTGGAGG	1	2	40

FIG. 14

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36614649	+	CCCACAGAACCACAGAAAAATGG	2	11	170
(N20)NGG	11	36614686	+	CTGCCTGCCCTGTGTTTTCCTGG	3	8	106
(N20)NGG	11	36614689	+	CCTGCCCTGTGTTTTCCTGGTGG	1	8	117
(N20)NGG	11	36614702	+	TTCCTGGTGGATTTTGAATTTGG	1	3	72
(N20)NGG	11	36614703	+	TCCTGGTGGATTTTGAATTTGGG	1	7	123
(N20)NGG	11	36614737	+	ATACATTCTTCCAGAACTTCAGG	1	5	73
(N20)NGG	11	36614741	+	ATTCTTCCAGAACTTCAGGATGG	1	4	73
(N20)NGG	11	36614742	+	TTCTTCCAGAACTTCAGGATGGG	1	4	69
(N20)NGG	11	36614792	+	AATGACACCATCTATATTTTAGG	1	18	113
(N20)NGG	11	36614795	+	GACACCATCTATATTTTAGGAGG	1	3	49
(N20)NGG	11	36614820	+	ATTCACTTGCCAATAATATCCGG	1	2	47
(N20)NGG	11	36614844	+	CTGCCAACCTGTACAGAATAAGG	1	3	42
(N20)NGG	11	36614845	+	TGCCAACCTGTACAGAATAAGGG	1	2	36
(N20)NGG	11	36614860	+	AATAAGGGTTGATCTTCCCCTGG	1	2	22
(N20)NGG	11	36614861	+	ATAAGGGTTGATCTTCCCCTGGG	1	1	27
(N20)NGG	11	36614894	+	GTGAATTGCACAGTCTTGCCAGG	1	2	25
(N20)NGG	11	36614897	+	AATTGCACAGTCTTGCCAGGAGG	1	5	39
(N20)NGG	11	36614957	+	AATGATGAATTTGTTATTGTTGG	2	8	158
(N20)NGG	11	36614960	+	GATGAATTTGTTATTGTTGGTGG	1	6	90
(N20)NGG	11	36615013	+	CTGCAACATCATCTCTTTAGAGG	1	5	78
(N20)NGG	11	36615040	+	CAAGATAGAAATTCGTGAGATGG	1	5	34
(N20)NGG	11	36615054	+	GTGAGATGGAGACCCCAGATTGG	1	1	40
(N20)NGG	11	36615084	+	ACATTAAGCACAGCAAGATATGG	1	7	62
(N20)NGG	11	36615089	+	AAGCACAGCAAGATATGGTTTGG	1	2	49
(N20)NGG	11	36615100	+	GATATGGTTTGGAAGCAACATGG	1	2	48

FIG. 14

site type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36615101	+	ATATGGTTTGGAAGCAACATGGG	1	3	96
(N20)NGG	11	36615107	+	TTTGGAAGCAACATGGGAAATGG	1	8	210
(N20)NGG	11	36615122	+	GGAAATGGAACTGTTTTTCTTGG	1	14	119
(N20)NGG	11	36615131	+	ACTGTTTTTCTTGGCATACCAGG	1	2	51
(N20)NGG	11	36615158	+	AATAAACAAGTTGTTTCAGAAGG	2	6	109
(N20)NGG	11	36615251	+	CAAACATCAACAGAAGATCCAGG	1	4	57
(N20)NGG	11	36615252	+	AAACATCAACAGAAGATCCAGGG	1	8	97
(N20)NGG	11	36615253	+	AACATCAACAGAAGATCCAGGGG	1	4	72
(N20)NGG	11	36615317	+	GCAGAAGCAAATAGTTTTGATGG	1	3	92
(N20)NGG	11	36615374	+	GAAGAAGATGAGTCTGAGACAGG	1	7	125
(N20)NGG	11	36615381	+	ATGAGTCTGAGACAGGCTACTGG	1	2	29
(N20)NGG	11	36615409	+	ATGCTGCCCTACTTGTGATGTGG	1	5	48
(N20)NGG	11	36615423	+	GTGATGTGGATATCAACACTTGG	1	5	19
(N20)NGG	11	36615424	+	TGATGTGGATATCAACACTTGGG	1	1	31
(N20)NGG	11	36615479	+	GCCATGATCTACTGCTCTCATGG	1	3	39
(N20)NGG	11	36615480	+	CCATGATCTACTGCTCTCATGGG	1	2	31
(N20)NGG	11	36615481	+	CATGATCTACTGCTCTCATGGGG	1	3	22
(N20)NGG	11	36615485	+	ATCTACTGCTCTCATGGGGATGG	1	2	37
(N20)NGG	11	36615486	+	TCTACTGCTCTCATGGGGATGGG	1	3	34
(N20)NGG	11	36615492	+	GCTCTCATGGGGATGGGCACTGG	1	3	36
(N20)NGG	11	36615493	+	CTCTCATGGGGATGGGCACTGGG	2	3	45
(N20)NGG	11	36615511	+	CTGGGTCCATGCTCAGTGCATGG	1	4	50
(N20)NGG	11	36615517	+	CCATGCTCAGTGCATGGATCTGG	1	3	34
(N20)NGG	11	36615548	+	ACACTCATCCATCTGTCAGCAGG	1	7	46
(N20)NGG	11	36615580	+	GTATTACTGCAATGAGCATGTGG	1	4	77

FIG. 14

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36615659	+	ATGAAATCCCTCCGTAAAAAGG	1	3	25
(N20)NGG	11	36615665	+	TCCCTCCGTAAAAAGGTTCTGG	1	1	10
(N20)NGG	11	36615705	+	CCAAGAAATCCTTTCTTAGAAGG	1	5	71
(N20)NGG	11	36614171	-	TGAGAAGCCTGGCTGAATTAAGG	1	5	54
(N20)NGG	11	36614182	-	AAATTCATCAGTGAGAAGCCTGG	2	3	61
(N20)NGG	11	36614242	-	CCAGTGGGGCAGGATCTTTTGGG	1	3	50
(N20)NGG	11	36614243	-	TCCAGTGGGGCAGGATCTTTTGG	1	1	27
(N20)NGG	11	36614252	-	ATGGAAAACTCCAGTGGGGCAGG	1	6	47
(N20)NGG	11	36614256	-	CCAGATGGAAAACTCCAGTGGGG	1	3	58
(N20)NGG	11	36614257	-	TCCAGATGGAAAACTCCAGTGGG	1	3	70
(N20)NGG	11	36614258	-	ATCCAGATGGAAAACTCCAGTGG	1	7	85
(N20)NGG	11	36614271	-	GGTTATGCTTTACATCCAGATGG	1	2	21
(N20)NGG	11	36614292	-	TTGTAGGCTTCAGTTTGACATGG	1	3	44
(N20)NGG	11	36614308	-	GAATCCTTAGAGAAAATTGTAGG	1	6	86
(N20)NGG	11	36614330	-	GCGAAGAGGAGGGAGGTAGCAGG	1	9	101
(N20)NGG	11	36614337	-	CTGGGTAGCGAAGAGGAGGGAGG	1	6	94
(N20)NGG	11	36614340	-	TGGCTGGGTAGCGAAGAGGAGGG	1	3	67
(N20)NGG	11	36614341	-	GTGGCTGGGTAGCGAAGAGGAGG	1	4	55
(N20)NGG	11	36614344	-	CAAGTGGCTGGGTAGCGAAGAGG	1	3	21
(N20)NGG	11	36614355	-	CTTTGAATGTGCAAGTGGCTGGG	1	4	37
(N20)NGG	11	36614356	-	CCTTTGAATGTGCAAGTGGCTGG	1	2	29
(N20)NGG	11	36614360	-	GCTGCCTTTGAATGTGCAAGTGG	1	7	72
(N20)NGG	11	36614412	-	TGTTTGGTGTTTTCCCTCCATGG	1	5	88
(N20)NGG	11	36614428	-	TTATCTGAAACCTCATTGTTTGG	1	7	60
(N20)NGG	11	36614533	-	GAATGACCATATCTGGCTTCAGG	2	3	36

FIG. 14

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36614540	-	ATTAATGGAATGACCATATCTGG	1	2	35
(N20)NGG	11	36614555	-	TCGGCTGTACACCACATTAATGG	1	2	5
(N20)NGG	11	36614574	-	GAACACCCATACTTTTCCCTCGG	1	2	29
(N20)NGG	11	36614620	-	TCTGTGGTTCTGTGGGTAGAAGG	1	5	78
(N20)NGG	11	36614627	-	CCATTTTCTGTGGTTCTGTGGG	1	6	144
(N20)NGG	11	36614628	-	TCCATTTTCTGTGGTTCTGTGG	1	9	120
(N20)NGG	11	36614636	-	TACACTATTCCATTTTTCTGTGG	1	8	105
(N20)NGG	11	36614667	-	CCACCAGGAAAACACAGGGCAGG	1	7	95
(N20)NGG	11	36614671	-	AAATCCACCAGGAAAACACAGGG	1	12	140
(N20)NGG	11	36614672	-	AAAATCCACCAGGAAAACACAGG	1	8	96
(N20)NGG	11	36614682	-	ACCCAAATTCAAAATCCACCAGG	1	6	79
(N20)NGG	11	36614725	-	GATAGCCCATCCTGAAGTTCTGG	1	1	16
(N20)NGG	11	36614765	-	AATATAGATGGTGTCATTTTTGG	1	3	110
(N20)NGG	11	36614777	-	ATGTCCTCCTAAAATATAGATGG	2	8	100
(N20)NGG	11	36614807	-	GTTGGCAGGCCGGATATTATTGG	1	1	7
(N20)NGG	11	36614817	-	TTCTGTACAGGTTGGCAGGCCGG	1	8	194
(N20)NGG	11	36614821	-	CTTATTCTGTACAGGTTGGCAGG	1	1	23
(N20)NGG	11	36614825	-	AACCCTTATTCTGTACAGGTTGG	1	2	21
(N20)NGG	11	36614829	-	GATCAACCCTTATTCTGTACAGG	1	1	11
(N20)NGG	11	36614854	-	TTCACAGCTGGGCTACCCAGGGG	2	4	54
(N20)NGG	11	36614855	-	ATTCACAGCTGGGCTACCCAGGG	1	1	32
(N20)NGG	11	36614856	-	AATTCACAGCTGGGCTACCCAGG	1	2	25
(N20)NGG	11	36614865	-	AGACTGTGCAATTCACAGCTGGG	1	1	42
(N20)NGG	11	36614866	-	AAGACTGTGCAATTCACAGCTGG	1	2	43
(N20)NGG	11	36614890	-	CTGGAGACAGAGATTCCTCCTGG	1	4	80

FIG. 14

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36614909	-	AGTTTGAGTCAGGATTGCACTGG	1	4	23
(N20)NGG	11	36614919	-	CATCATTGTTAGTTTGAGTCAGG	1	1	31
(N20)NGG	11	36615044	-	AATGTCTGGGGTCCAATCTGGGG	1	5	30
(N20)NGG	11	36615045	-	TAATGTCTGGGGTCCAATCTGGG	1	3	22
(N20)NGG	11	36615046	-	TTAATGTCTGGGGTCCAATCTGG	1	2	21
(N20)NGG	11	36615056	-	CTTGCTGTGCTTAATGTCTGGGG	1	5	54
(N20)NGG	11	36615057	-	TCTTGCTGTGCTTAATGTCTGGG	1	2	70
(N20)NGG	11	36615058	-	ATCTTGCTGTGCTTAATGTCTGG	1	1	36
(N20)NGG	11	36615127	-	ACAACTTGTTTATTGTCTCCTGG	1	5	70
(N20)NGG	11	36615247	-	TCAAAGGGAGTGGAATCCCCTGG	1	3	23
(N20)NGG	11	36615257	-	TTCAGAGTCTTCAAAGGAGTGG	1	6	79
(N20)NGG	11	36615262	-	AATTCTTCAGAGTCTTCAAAGGG	1	13	151
(N20)NGG	11	36615263	-	AAATTCTTCAGAGTCTTCAAAGG	1	7	122
(N20)NGG	11	36615335	-	TTCTTCATCATCTTCATTATAGG	2	21	338
(N20)NGG	11	36615393	-	TGATATCCACATCACAAGTAGGG	1	2	30
(N20)NGG	11	36615394	-	TTGATATCCACATCACAAGTAGG	1	5	26
(N20)NGG	11	36615427	-	TTGAGCTCAGTTGAATAGAATGG	1	3	42
(N20)NGG	11	36615454	-	TGAGAGCAGTAGATCATGGCGGG	1	3	43
(N20)NGG	11	36615455	-	ATGAGAGCAGTAGATCATGGCGG	1	4	44
(N20)NGG	11	36615458	-	CCCATGAGAGCAGTAGATCATGG	1	3	29
(N20)NGG	11	36615495	-	CCAGATCCATGCACTGAGCATGG	1	1	44
(N20)NGG	11	36615534	-	TGTTGCTTCCTGCTGACAGATGG	1	3	89
(N20)NGG	11	36615604	-	TTTAAGGGTAGGACTCTTTGGGG	1	2	36
(N20)NGG	11	36615605	-	TTTTAAGGGTAGGACTCTTTGGG	1	8	46
(N20)NGG	11	36615606	-	TTTTTAAGGGTAGGACTCTTTGG	1	2	54

FIG. 14

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	11	36615615	-	TTGGAGGCTTTTTTAAGGGTAGG	1	5	52
(N20)NGG	11	36615619	-	TTCATTGGAGGCTTTTTTAAGGG	2	9	98
(N20)NGG	11	36615620	-	TTTCATTGGAGGCTTTTTTAAGG	2	11	101
(N20)NGG	11	36615631	-	TTACGGAGGGATTTCATTGGAGG	1	2	11
(N20)NGG	11	36615634	-	TTTTTACGGAGGGATTTCATTGG	1	3	24
(N20)NGG	11	36615644	-	TCCAGAACCTTTTTTACGGAGGG	1	1	20
(N20)NGG	11	36615645	-	TTCCAGAACCTTTTTTACGGAGG	1	2	19
(N20)NGG	11	36615648	-	TTTTTCCAGAACCTTTTTTACGG	1	12	219
(N20)NGG	11	36615679	-	CTAAGAAAGGATTTCTTGGCAGG	2	4	86
(N20)NGG	11	36615683	-	CCTTCTAAGAAAGGATTTCTTGG	1	8	100
(N20)NGG	11	36615692	-	ATCAAACAACCTTCTAAGAAAGG	1	5	63

FIG. 14

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98340496	+	GCAGGTTTCGGGAGGCCCAGGGG	1	3	38
(N20)NGG	2	98340514	+	AGGGGCGATGCCAGACCCCGCGG	1	1	18
(N20)NGG	2	98340536	+	GCGCACCTGCCCTTCTTCTACGG	1	1	16
(N20)NGG	2	98340556	+	CGGCAGCATCTCGCGTGCCGAGG	1	1	5
(N20)NGG	2	98340562	+	CATCTCGCGTGCCGAGGCCGAGG	1	1	3
(N20)NGG	2	98340577	+	GGCCGAGGAGCACCTGAAGCTGG	1	5	72
(N20)NGG	2	98340580	+	CGAGGAGCACCTGAAGCTGGCGG	1	17	373
(N20)NGG	2	98340581	+	GAGGAGCACCTGAAGCTGGCGGG	1	11	352
(N20)NGG	2	98340586	+	GCACCTGAAGCTGGCGGGCATGG	1	3	69
(N20)NGG	2	98340589	+	CCTGAAGCTGGCGGGCATGGCGG	1	2	52
(N20)NGG	2	98340593	+	AAGCTGGCGGGCATGGCGGACGG	1	2	20
(N20)NGG	2	98340594	+	AGCTGGCGGGCATGGCGGACGGG	1	2	18
(N20)NGG	2	98340628	+	GCGCCAGTGCCTGCGCTCGCTGG	1	2	13
(N20)NGG	2	98340629	+	CGCCAGTGCCTGCGCTCGCTGGG	1	2	17
(N20)NGG	2	98340632	+	CAGTGCCTGCGCTCGCTGGGCGG	1	1	19
(N20)NGG	2	98340698	+	CCCATCGAGCGCCAGCTCAACGG	1	3	14
(N20)NGG	2	98340716	+	AACGGCACCTACGCCATTGCCGG	1	2	4
(N20)NGG	2	98340719	+	GGCACCTACGCCATTGCCGGCGG	2	2	10
(N20)NGG	2	98340734	+	GCCGGCGGCAAAGCGCACTGTGG	1	2	10
(N20)NGG	2	98340739	+	CGGCAAAGCGCACTGTGGACCGG	1	1	7
(N20)NGG	2	98340776	+	TTCTACTCGCGCGACCCCGACGG	1	1	1
(N20)NGG	2	98340777	+	TCTACTCGCGCGACCCCGACGGG	1	1	1
(N20)NGG	2	98340810	+	ACCTGCGCAAGCCGTGCAACCGG	1	1	9
(N20)NGG	2	98340817	+	CAAGCCGTGCAACCGGCCGTCGG	1	1	3
(N20)NGG	2	98340818	+	AAGCCGTGCAACCGGCCGTCGGG	1	1	1

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98340835	+	GTCGGGCCTCGAGCCGCAGCCGG	1	21	58
(N20)NGG	2	98340836	+	TCGGGCCTCGAGCCGCAGCCGGG	1	20	58
(N20)NGG	2	98340837	+	CGGGCCTCGAGCCGCAGCCGGGG	1	2	49
(N20)NGG	2	98340838	+	GGGCCTCGAGCCGCAGCCGGGGG	1	22	81
(N20)NGG	2	98340865	+	CGACTGCCTGCGAGACGCCATGG	1	1	8
(N20)NGG	2	98340891	+	GTGACTACGTGCGCCAGACGTGG	1	1	3
(N20)NGG	2	98340898	+	CGTGCGCCAGACGTGGAAGCTGG	1	1	6
(N20)NGG	2	98340901	+	GCGCCAGACGTGGAAGCTGGAGG	1	1	18
(N20)NGG	2	98340917	+	CTGGAGGTGAGAGCGCAGCCTGG	1	2	78
(N20)NGG	2	98340918	+	TGGAGGTGAGAGCGCAGCCTGGG	1	6	72
(N20)NGG	2	98340919	+	GGAGGTGAGAGCGCAGCCTGGGG	1	6	109
(N20)NGG	2	98340924	+	TGAGAGCGCAGCCTGGGGCGCGG	1	1	51
(N20)NGG	2	98340925	+	GAGAGCGCAGCCTGGGGCGCGGG	1	5	53
(N20)NGG	2	98340489	-	CGGGGTCTGGCATCGCCCCTGGG	1	3	22
(N20)NGG	2	98340490	-	GCGGGGTCTGGCATCGCCCCTGG	1	1	13
(N20)NGG	2	98340502	-	GGCAGGTGCGCCGCGGGGTCTGG	1	2	34
(N20)NGG	2	98340507	-	AGAAGGGCAGGTGCGCCGCGGGG	1	1	23
(N20)NGG	2	98340508	-	AAGAAGGGCAGGTGCGCCGCGGG	1	3	19
(N20)NGG	2	98340509	-	GAAGAAGGGCAGGTGCGCCGCGG	1	5	35
(N20)NGG	2	98340519	-	TGCTGCCGTAGAAGAAGGGCAGG	1	1	24
(N20)NGG	2	98340523	-	GAGATGCTGCCGTAGAAGAAGGG	1	3	41
(N20)NGG	2	98340524	-	CGAGATGCTGCCGTAGAAGAAGG	1	1	10
(N20)NGG	2	98340551	-	CTTCAGGTGCTCCTCGGCCTCGG	1	5	94
(N20)NGG	2	98340557	-	CGCCAGCTTCAGGTGCTCCTCGG	1	3	47
(N20)NGG	2	98340567	-	CCGCCATGCCCGCCAGCTTCAGG	1	1	34

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98340600	-	AGCGCAGGCACTGGCGCAGCAGG	1	2	21
(N20)NGG	2	98340609	-	CGCCCAGCGAGCGCAGGCACTGG	1	1	18
(N20)NGG	2	98340615	-	CATAGCCGCCCAGCGAGCGCAGG	1	1	7
(N20)NGG	2	98340666	-	GGCGCTCGATGGGAAAGTGGTGG	1	2	17
(N20)NGG	2	98340669	-	GCTGGCGCTCGATGGGAAAGTGG	1	2	8
(N20)NGG	2	98340676	-	CCGTTGAGCTGGCGCTCGATGGG	1	1	3
(N20)NGG	2	98340677	-	GCCGTTGAGCTGGCGCTCGATGG	1	1	9
(N20)NGG	2	98340687	-	TGGCGTAGGTGCCGTTGAGCTGG	1	1	11
(N20)NGG	2	98340701	-	TTTGCCGCCGGCAATGGCGTAGG	1	1	2
(N20)NGG	2	98340707	-	GTGCGCTTTGCCGCCGGCAATGG	1	1	1
(N20)NGG	2	98340713	-	TCCACAGTGCGCTTTGCCGCCGG	1	2	15
(N20)NGG	2	98340736	-	TAGAACTCGCAGAGCTCTGCCGG	1	2	17
(N20)NGG	2	98340768	-	GGTTGCAGGGCAGCCCGTCGGGG	1	2	14
(N20)NGG	2	98340769	-	AGGTTGCAGGGCAGCCCGTCGGG	1	1	20
(N20)NGG	2	98340770	-	CAGGTTGCAGGGCAGCCCGTCGG	1	4	23
(N20)NGG	2	98340781	-	CACGGCTTGCGCAGGTTGCAGGG	1	1	10
(N20)NGG	2	98340782	-	GCACGGCTTGCGCAGGTTGCAGG	1	1	8
(N20)NGG	2	98340789	-	GCCGGTTGCACGGCTTGCGCAGG	1	1	5
(N20)NGG	2	98340799	-	AGGCCCGACGGCCGGTTGCACGG	1	1	4
(N20)NGG	2	98340807	-	GCGGCTCGAGGCCCGACGGCCGG	1	1	12
(N20)NGG	2	98340811	-	GGCTGCGGCTCGAGGCCCGACGG	1	2	28
(N20)NGG	2	98340819	-	AGACCCCCGGCTGCGGCTCGAGG	1	3	13
(N20)NGG	2	98340826	-	CAGTCGAAGACCCCCGGCTGCGG	1	2	7
(N20)NGG	2	98340832	-	CGCAGGCAGTCGAAGACCCCCGG	1	1	12
(N20)NGG	2	98340849	-	CACGCACCATGGCGTCTCGCAGG	1	1	9

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98340860	-	GCGCACGTAGTCACGCACCATGG	1	1	4
(N20)NGG	2	98340882	-	TCACCTCCAGCTTCCACGTCTGG	2	3	41
(N20)NGG	2	98341554	+	CTCCTCGCCTCTCCTTTTCTAGG	1	7	162
(N20)NGG	2	98341555	+	TCCTCGCCTCTCCTTTTCTAGGG	1	2	71
(N20)NGG	2	98341560	+	GCCTCTCCTTTTCTAGGGCGAGG	1	1	33
(N20)NGG	2	98341566	+	CCTTTTCTAGGGCGAGGCCCTGG	1	4	21
(N20)NGG	2	98341572	+	CTAGGGCGAGGCCCTGGAGCAGG	1	2	38
(N20)NGG	2	98341587	+	GGAGCAGGCCATCATCAGCCAGG	1	5	39
(N20)NGG	2	98341596	+	CATCATCAGCCAGGCCCCGCAGG	1	2	32
(N20)NGG	2	98341599	+	CATCAGCCAGGCCCCGCAGGTGG	2	6	80
(N20)NGG	2	98341620	+	GGAGAAGCTCATTGCTACGACGG	1	2	19
(N20)NGG	2	98341631	+	TTGCTACGACGGCCCACGAGCGG	1	1	1
(N20)NGG	2	98341640	+	CGGCCCACGAGCGGATGCCCTGG	1	1	4
(N20)NGG	2	98341665	+	CCACAGCAGCCTGACGCGTGAGG	1	2	24
(N20)NGG	2	98341668	+	CAGCAGCCTGACGCGTGAGGAGG	2	3	18
(N20)NGG	2	98341690	+	GCCGAGCGCAAACTTTACTCTGG	1	1	3
(N20)NGG	2	98341691	+	CCGAGCGCAAACTTTACTCTGGG	1	1	2
(N20)NGG	2	98341692	+	CGAGCGCAAACTTTACTCTGGGG	1	1	5
(N20)NGG	2	98341705	+	TACTCTGGGGCGCAGACCGACGG	1	1	6
(N20)NGG	2	98341722	+	CGACGGCAAGTTCCTGTATGTGG	1	4	7
(N20)NGG	2	98341723	+	GACGGCAAGTTCCTGTATGTGGG	1	1	9
(N20)NGG	2	98341724	+	ACGGCAAGTTCCTGTATGTGGGG	1	3	16
(N20)NGG	2	98341729	+	AAGTTCCTGTATGTGGGGCCCGG	1	2	26
(N20)NGG	2	98341730	+	AGTTCCTGTATGTGGGGCCCGGG	1	4	45
(N20)NGG	2	98341736	+	TGTATGTGGGGCCCGGGATTTGG	1	2	26

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98341737	+	GTATGTGGGGCCCGGGATTTGGG	1	2	21
(N20)NGG	2	98341531	-	CTAGAAAAGGAGAGGCGAGGAGG	1	6	100
(N20)NGG	2	98341534	-	GCCCTAGAAAAGGAGAGGCGAGG	1	1	30
(N20)NGG	2	98341539	-	GCCTCGCCCTAGAAAAGGAGAGG	1	2	23
(N20)NGG	2	98341544	-	CCAGGGCCTCGCCCTAGAAAAGG	1	3	30
(N20)NGG	2	98341561	-	GCTGATGATGGCCTGCTCCAGGG	3	6	53
(N20)NGG	2	98341562	-	GGCTGATGATGGCCTGCTCCAGG	1	7	52
(N20)NGG	2	98341573	-	CTGCGGGGCCTGGCTGATGATGG	1	1	41
(N20)NGG	2	98341583	-	GCTTCTCCACCTGCGGGGCCTGG	1	7	75
(N20)NGG	2	98341588	-	AATGAGCTTCTCCACCTGCGGGG	1	2	33
(N20)NGG	2	98341589	-	CAATGAGCTTCTCCACCTGCGGG	2	11	57
(N20)NGG	2	98341590	-	GCAATGAGCTTCTCCACCTGCGG	2	6	33
(N20)NGG	2	98341621	-	GTACCAGGGCATCCGCTCGTGGG	1	1	5
(N20)NGG	2	98341622	-	GGTACCAGGGCATCCGCTCGTGG	1	1	9
(N20)NGG	2	98341635	-	GTCAGGCTGCTGTGGTACCAGGG	1	2	53
(N20)NGG	2	98341636	-	CGTCAGGCTGCTGTGGTACCAGG	1	2	49
(N20)NGG	2	98341643	-	CCTCACGCGTCAGGCTGCTGTGG	1	2	25
(N20)NGG	2	98341652	-	GCTCGGCCTCCTCACGCGTCAGG	1	4	9
(N20)NGG	2	98341669	-	CCCAGAGTAAAGTTTGCGCTCGG	1	1	6
(N20)NGG	2	98341699	-	CACATACAGGAACTTGCCGTCGG	1	2	19
(N20)NGG	2	98341712	-	AAATCCCGGGCCCCACATACAGG	1	2	12
(N20)NGG	2	98349345	+	ATCCCCTCCCTTCCCCTGCCAGG	1	19	323
(N20)NGG	2	98349351	+	TCCCTTCCCCTGCCAGGCTGAGG	4	40	380
(N20)NGG	2	98349357	+	CCCCTGCCAGGCTGAGGCCGCGG	1	8	116
(N20)NGG	2	98349361	+	TGCCAGGCTGAGGCCGCGGAAGG	1	2	53

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with_NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98349367	+	GCTGAGGCCGCGGAAGGAGCAGG	1	4	92
(N20)NGG	2	98349368	+	CTGAGGCCGCGGAAGGAGCAGGG	1	4	72
(N20)NGG	2	98349395	+	TACGCCCTGTCCCTCATCTATGG	1	1	10
(N20)NGG	2	98349396	+	ACGCCCTGTCCCTCATCTATGGG	1	1	12
(N20)NGG	2	98349403	+	GTCCCTCATCTATGGGAAGACGG	1	4	37
(N20)NGG	2	98349433	+	CTACCTCATCAGCCAAGACAAGG	1	1	45
(N20)NGG	2	98349436	+	CCTCATCAGCCAAGACAAGGCGG	2	4	58
(N20)NGG	2	98349437	+	CTCATCAGCCAAGACAAGGCGGG	1	4	45
(N20)NGG	2	98349457	+	GGGCAAGTACTGCATTCCCGAGG	1	2	10
(N20)NGG	2	98349458	+	GGCAAGTACTGCATTCCCGAGGG	1	2	12
(N20)NGG	2	98349480	+	GCACCAAGTTTGACACGCTCTGG	1	1	6
(N20)NGG	2	98349484	+	CAAGTTTGACACGCTCTGGCAGG	1	2	14
(N20)NGG	2	98349488	+	TTTGACACGCTCTGGCAGGTAGG	1	1	18
(N20)NGG	2	98349325	–	AGCCTGGCAGGGGAAGGGAGGGG	2	25	373
(N20)NGG	2	98349326	–	CAGCCTGGCAGGGGAAGGGAGGG	3	31	429
(N20)NGG	2	98349327	–	TCAGCCTGGCAGGGGAAGGGAGG	3	26	293
(N20)NGG	2	98349330	–	GCCTCAGCCTGGCAGGGGAAGGG	1	17	236
(N20)NGG	2	98349331	–	GGCCTCAGCCTGGCAGGGGAAGG	1	20	289
(N20)NGG	2	98349335	–	CCGCGGCCTCAGCCTGGCAGGGG	1	8	55
(N20)NGG	2	98349336	–	TCCGCGGCCTCAGCCTGGCAGGG	1	6	108
(N20)NGG	2	98349337	–	TTCCGCGGCCTCAGCCTGGCAGG	1	2	211
(N20)NGG	2	98349341	–	CTCCTTCCGCGGCCTCAGCCTGG	2	3	38
(N20)NGG	2	98349352	–	TATGTGCCCTGCTCCTTCCGCGG	1	1	23
(N20)NGG	2	98349377	–	CTTCCCATAGATGAGGGACAGGG	1	4	42
(N20)NGG	2	98349378	–	TCTTCCCATAGATGAGGGACAGG	1	4	39

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98349383	-	CACCGTCTTCCCATAGATGAGGG	1	2	15
(N20)NGG	2	98349384	-	ACACCGTCTTCCCATAGATGAGG	1	2	16
(N20)NGG	2	98349408	-	TGTCTTGGCTGATGAGGTAGTGG	1	1	46
(N20)NGG	2	98349414	-	CCGCCTTGTCTTGGCTGATGAGG	1	3	27
(N20)NGG	2	98349423	-	AGTACTTGCCCGCCTTGTCTTGG	1	2	7
(N20)NGG	2	98349451	-	GTGTCAAACTTGGTGCCCTCGGG	1	2	24
(N20)NGG	2	98349452	-	CGTGTCAAACTTGGTGCCCTCGG	1	1	9
(N20)NGG	2	98349461	-	CTGCCAGAGCGTGTCAAACTTGG	1	1	11
(N20)NGG	2	98349590	+	AGCTGCCTGCTCCCTGCAGCTGG	3	18	173
(N20)NGG	2	98349593	+	TGCCTGCTCCCTGCAGCTGGTGG	2	17	246
(N20)NGG	2	98349611	+	GGTGGAGTATCTGAAGCTGAAGG	1	2	37
(N20)NGG	2	98349614	+	GGAGTATCTGAAGCTGAAGGCGG	1	8	102
(N20)NGG	2	98349618	+	TATCTGAAGCTGAAGGCGGACGG	1	1	26
(N20)NGG	2	98349619	+	ATCTGAAGCTGAAGGCGGACGGG	1	1	15
(N20)NGG	2	98349638	+	CGGGCTCATCTACTGCCTGAAGG	1	2	15
(N20)NGG	2	98349641	+	GCTCATCTACTGCCTGAAGGAGG	1	1	25
(N20)NGG	2	98349675	+	AGCAGTGCCAGCAACGCCTCAGG	1	2	25
(N20)NGG	2	98349681	+	GCCAGCAACGCCTCAGGTGACGG	1	2	27
(N20)NGG	2	98349688	+	ACGCCTCAGGTGACGGCAGCAGG	1	2	18
(N20)NGG	2	98349691	+	CCTCAGGTGACGGCAGCAGGCGG	1	8	67
(N20)NGG	2	98349692	+	CTCAGGTGACGGCAGCAGGCGGG	1	5	55
(N20)NGG	2	98349695	+	AGGTGACGGCAGCAGGCGGGCGG	1	1	57
(N20)NGG	2	98349696	+	GGTGACGGCAGCAGGCGGGCGGG	1	3	65
(N20)NGG	2	98349699	+	GACGGCAGCAGGCGGGCGGGCGG	1	8	90
(N20)NGG	2	98349573	-	CTCCACCAGCTGCAGGGAGCAGG	1	9	119

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98349579	-	CAGATACTCCACCAGCTGCAGGG	1	6	51
(N20)NGG	2	98349580	-	TCAGATACTCCACCAGCTGCAGG	1	2	30
(N20)NGG	2	98349631	-	TGTTGGGGCAGGCCTCCTTCAGG	1	3	55
(N20)NGG	2	98349642	-	GCTGGCACTGCTGTTGGGGCAGG	2	14	102
(N20)NGG	2	98349646	-	CGTTGCTGGCACTGCTGTTGGGG	1	3	37
(N20)NGG	2	98349647	-	GCGTTGCTGGCACTGCTGTTGGG	1	2	10
(N20)NGG	2	98349648	-	GGCGTTGCTGGCACTGCTGTTGG	1	2	37
(N20)NGG	2	98349660	-	GCCGTCACCTGAGGCGTTGCTGG	1	3	7
(N20)NGG	2	98349669	-	CCGCCTGCTGCCGTCACCTGAGG	1	2	41
(N20)NGG	2	98349759	+	ACTGTCCCTTCTGCTCCCCCAGG	2	2	83
(N20)NGG	2	98349760	+	CTGTCCCTTCTGCTCCCCCAGGG	1	15	191
(N20)NGG	2	98349761	+	TGTCCCTTCTGCTCCCCCAGGGG	1	9	119
(N20)NGG	2	98349814	+	CCACGTTGACTCATGTGAGTTGG	1	1	15
(N20)NGG	2	98349815	+	CACGTTGACTCATGTGAGTTGGG	1	1	21
(N20)NGG	2	98349816	+	ACGTTGACTCATGTGAGTTGGGG	1	1	11
(N20)NGG	2	98349817	+	CGTTGACTCATGTGAGTTGGGGG	1	1	14
(N20)NGG	2	98349824	+	TCATGTGAGTTGGGGGCACCTGG	1	3	19
(N20)NGG	2	98349742	-	CAGCCCCTGGGGGAGCAGAAGGG	3	9	111
(N20)NGG	2	98349743	-	GCAGCCCCTGGGGGAGCAGAAGG	1	17	144
(N20)NGG	2	98349752	-	GTGGGAGCAGCAGCCCCTGGGGG	2	13	169
(N20)NGG	2	98349753	-	TGTGGGAGCAGCAGCCCCTGGGG	4	17	142
(N20)NGG	2	98349754	-	GTGTGGGAGCAGCAGCCCCTGGG	2	10	79
(N20)NGG	2	98349755	-	AGTGTGGGAGCAGCAGCCCCTGG	1	7	80
(N20)NGG	2	98349770	-	GATGGGTGGGCTGGGAGTGTGGG	1	13	158
(N20)NGG	2	98349771	-	GGATGGGTGGGCTGGGAGTGTGG	3	30	323

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98349778	-	TCAACGTGGATGGGTGGGCTGGG	1	3	15
(N20)NGG	2	98349779	-	GTCAACGTGGATGGGTGGGCTGG	1	1	22
(N20)NGG	2	98349783	-	ATGAGTCAACGTGGATGGGTGGG	1	2	16
(N20)NGG	2	98349784	-	CATGAGTCAACGTGGATGGGTGG	1	2	20
(N20)NGG	2	98349787	-	TCACATGAGTCAACGTGGATGGG	1	2	22
(N20)NGG	2	98349788	-	CTCACATGAGTCAACGTGGATGG	1	1	29
(N20)NGG	2	98349792	-	CCAACTCACATGAGTCAACGTGG	1	1	14
(N20)NGG	2	98350040	+	ATCGACACCCTCAACTCAGATGG	1	1	8
(N20)NGG	2	98350058	+	GATGGATACACCCCTGAGCCAGG	1	2	16
(N20)NGG	2	98350065	+	ACACCCCTGAGCCAGGTGAGCGG	2	9	67
(N20)NGG	2	98350066	+	CACCCCTGAGCCAGGTGAGCGGG	1	7	84
(N20)NGG	2	98350072	+	TGAGCCAGGTGAGCGGGCAGAGG	3	13	83
(N20)NGG	2	98350075	+	GCCAGGTGAGCGGGCAGAGGTGG	1	7	113
(N20)NGG	2	98350076	+	CCAGGTGAGCGGGCAGAGGTGGG	1	5	102
(N20)NGG	2	98350077	+	CAGGTGAGCGGGCAGAGGTGGGG	1	21	161
(N20)NGG	2	98349982	-	TAAAGGCCACAGGGTCAGCAAGG	1	5	59
(N20)NGG	2	98349991	-	CTCTGAGGCTAAAGGCCACAGGG	1	1	57
(N20)NGG	2	98349992	-	TCTCTGAGGCTAAAGGCCACAGG	1	5	54
(N20)NGG	2	98349999	-	CGATTCGTCTCTGAGGCTAAAGG	1	1	6
(N20)NGG	2	98350006	-	AGGGTGTCGATTCGTCTCTGAGG	1	1	9
(N20)NGG	2	98350025	-	GGTGTATCCATCTGAGTTGAGGG	1	2	18
(N20)NGG	2	98350026	-	GGGTGTATCCATCTGAGTTGAGG	2	2	13
(N20)NGG	2	98350046	-	TGCCCGCTCACCTGGCTCAGGGG	2	10	61
(N20)NGG	2	98350047	-	CTGCCCGCTCACCTGGCTCAGGG	5	7	48
(N20)NGG	2	98350048	-	TCTGCCCGCTCACCTGGCTCAGG	1	3	45

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98350054	-	CCCACCTCTGCCCGCTCACCTGG	1	6	108
(N20)NGG	2	98351010	+	TAACGTCCCCAGACAAACCGCGG	1	1	10
(N20)NGG	2	98351023	+	CAAACCGCGGCCGATGCCCATGG	1	1	3
(N20)NGG	2	98351062	+	GAGCCCCTACAGCGACCCAGAGG	1	4	27
(N20)NGG	2	98351071	+	CAGCGACCCAGAGGAGCTCAAGG	2	2	45
(N20)NGG	2	98351126	+	CTCATAGCTGACATTGAACTTGG	1	9	44
(N20)NGG	2	98351132	+	GCTGACATTGAACTTGGCTGCGG	1	5	51
(N20)NGG	2	98351141	+	GAACTTGGCTGCGGCAACTTTGG	1	1	18
(N20)NGG	2	98351155	+	CAACTTTGGCTCAGTGCGCCAGG	1	1	10
(N20)NGG	2	98351156	+	AACTTTGGCTCAGTGCGCCAGGG	1	1	9
(N20)NGG	2	98351180	+	GTGTACCGCATGCGCAAGTATGG	1	1	2
(N20)NGG	2	98351195	+	AAGTATGGCCGCCCCTGCCGTGG	1	1	5
(N20)NGG	2	98351198	+	TATGGCCGCCCCTGCCGTGGTGG	1	1	8
(N20)NGG	2	98351199	+	ATGGCCGCCCCTGCCGTGGTGGG	1	1	11
(N20)NGG	2	98350965	-	TGCGTGCTGGGCACACACAGCGG	2	11	66
(N20)NGG	2	98350977	-	CTGGGGACGTTATGCGTGCTGGG	1	1	5
(N20)NGG	2	98350978	-	TCTGGGGACGTTATGCGTGCTGG	1	1	4
(N20)NGG	2	98350994	-	CATCGGCCGCGGTTTGTCTGGGG	1	1	4
(N20)NGG	2	98350995	-	GCATCGGCCGCGGTTTGTCTGGG	1	1	1
(N20)NGG	2	98350996	-	GGCATCGGCCGCGGTTTGTCTGG	1	1	4
(N20)NGG	2	98351005	-	GTGTCCATGGGCATCGGCCGCGG	1	2	14
(N20)NGG	2	98351011	-	ACGCTCGTGTCCATGGGCATCGG	1	3	8
(N20)NGG	2	98351017	-	TCATACACGCTCGTGTCCATGGG	1	1	3
(N20)NGG	2	98351018	-	CTCATACACGCTCGTGTCCATGG	1	1	4
(N20)NGG	2	98351043	-	GCTCCTCTGGGTCGCTGTAGGGG	1	1	17

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98351044	-	AGCTCCTCTGGGTCGCTGTAGGG	1	1	14
(N20)NGG	2	98351045	-	GAGCTCCTCTGGGTCGCTGTAGG	1	1	18
(N20)NGG	2	98351055	-	TCTTGTCCTTGAGCTCCTCTGGG	2	4	50
(N20)NGG	2	98351056	-	TTCTTGTCCTTGAGCTCCTCTGG	1	4	76
(N20)NGG	2	98351085	-	TGAGGAGGTTATCGCGCTTCAGG	1	1	5
(N20)NGG	2	98351100	-	GTTCAATGTCAGCTATGAGGAGG	2	2	39
(N20)NGG	2	98351103	-	CAAGTTCAATGTCAGCTATGAGG	1	4	82
(N20)NGG	2	98351151	-	TGCGCATGCGGTACACGCCCTGG	1	1	6
(N20)NGG	2	98351163	-	GGCGGCCATACTTGCGCATGCGG	1	1	3
(N20)NGG	2	98351712	+	CTCCCGTGGCCGGGTCGGGCAGG	1	4	22
(N20)NGG	2	98351728	+	GGGCAGGAAGCAGATCGACGTGG	1	1	11
(N20)NGG	2	98351737	+	GCAGATCGACGTGGCCATCAAGG	1	1	12
(N20)NGG	2	98351749	+	GGCCATCAAGGTGCTGAAGCAGG	1	3	46
(N20)NGG	2	98351750	+	GCCATCAAGGTGCTGAAGCAGGG	1	4	59
(N20)NGG	2	98351755	+	CAAGGTGCTGAAGCAGGGCACGG	1	6	83
(N20)NGG	2	98351761	+	GCTGAAGCAGGGCACGGAGAAGG	1	5	75
(N20)NGG	2	98351770	+	GGGCACGGAGAAGGCAGACACGG	2	6	109
(N20)NGG	2	98351788	+	CACGGAAGAGATGATGCGCGAGG	1	1	6
(N20)NGG	2	98351809	+	GGCGCAGATCATGCACCAGCTGG	1	1	11
(N20)NGG	2	98351829	+	TGGACAACCCCTACATCGTGCGG	2	2	12
(N20)NGG	2	98351837	+	CCCTACATCGTGCGGCTCATTGG	1	2	8
(N20)NGG	2	98351848	+	GCGGCTCATTGGCGTCTGCCAGG	1	1	7
(N20)NGG	2	98351854	+	CATTGGCGTCTGCCAGGCCGAGG	1	1	13
(N20)NGG	2	98351866	+	CCAGGCCGAGGCCCTCATGCTGG	1	4	40
(N20)NGG	2	98351872	+	CGAGGCCCTCATGCTGGTCATGG	1	5	28

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98351878	+	CCTCATGCTGGTCATGGAGATGG	1	3	47
(N20)NGG	2	98351882	+	ATGCTGGTCATGGAGATGGCTGG	1	5	46
(N20)NGG	2	98351883	+	TGCTGGTCATGGAGATGGCTGGG	1	2	54
(N20)NGG	2	98351884	+	GCTGGTCATGGAGATGGCTGGGG	1	6	80
(N20)NGG	2	98351885	+	CTGGTCATGGAGATGGCTGGGGG	1	4	70
(N20)NGG	2	98351888	+	GTCATGGAGATGGCTGGGGGCGG	1	7	115
(N20)NGG	2	98351889	+	TCATGGAGATGGCTGGGGGCGGG	1	8	89
(N20)NGG	2	98351908	+	CGGGCCGCTGCACAAGTTCCTGG	1	2	7
(N20)NGG	2	98351912	+	CCGCTGCACAAGTTCCTGGTCGG	1	1	14
(N20)NGG	2	98351919	+	ACAAGTTCCTGGTCGGCAAGAGG	1	2	23
(N20)NGG	2	98351929	+	GGTCGGCAAGAGGTGAGCACCGG	1	5	15
(N20)NGG	2	98351930	+	GTCGGCAAGAGGTGAGCACCGGG	1	1	16
(N20)NGG	2	98351933	+	GGCAAGAGGTGAGCACCGGGTGG	1	6	79
(N20)NGG	2	98351934	+	GCAAGAGGTGAGCACCGGGTGGG	2	52	403
(N20)NGG	2	98351939	+	AGGTGAGCACCGGGTGGGCCCGG	2	3	70
(N20)NGG	2	98351689	-	CTGCCCGACCCGGCCACGGGAGG	1	4	29
(N20)NGG	2	98351692	-	TTCCTGCCCGACCCGGCCACGGG	1	3	22
(N20)NGG	2	98351693	-	CTTCCTGCCCGACCCGGCCACGG	1	2	31
(N20)NGG	2	98351699	-	GATCTGCTTCCTGCCCGACCCGG	1	2	16
(N20)NGG	2	98351729	-	GCCCTGCTTCAGCACCTTGATGG	1	12	54
(N20)NGG	2	98351802	-	CGATGTAGGGGTTGTCCAGCTGG	1	2	14
(N20)NGG	2	98351814	-	CAATGAGCCGCACGATGTAGGGG	1	2	10
(N20)NGG	2	98351815	-	CCAATGAGCCGCACGATGTAGGG	1	2	7
(N20)NGG	2	98351816	-	GCCAATGAGCCGCACGATGTAGG	1	2	6
(N20)NGG	2	98351844	-	CCAGCATGAGGGCCTCGGCCTGG	2	4	42

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98351849	-	CATGACCAGCATGAGGGCCTCGG	5	9	61
(N20)NGG	2	98351855	-	CATCTCCATGACCAGCATGAGGG	1	6	51
(N20)NGG	2	98351856	-	CCATCTCCATGACCAGCATGAGG	1	3	58
(N20)NGG	2	98351890	-	CCGACCAGGAACTTGTGCAGCGG	1	1	11
(N20)NGG	2	98351904	-	GTGCTCACCTCTTGCCGACCAGG	1	2	13
(N20)NGG	2	98353935	+	CCCGCCTTCCCCGCCACCCCAGG	1	18	237
(N20)NGG	2	98353936	+	CCGCCTTCCCCGCCACCCCAGGG	1	12	127
(N20)NGG	2	98353939	+	CCTTCCCCGCCACCCCAGGGAGG	1	18	120
(N20)NGG	2	98353960	+	GGAGATCCCTGTGAGCAATGTGG	1	2	40
(N20)NGG	2	98353978	+	TGTGGCCGAGCTGCTGCACCAGG	1	4	32
(N20)NGG	2	98353987	+	GCTGCTGCACCAGGTGTCCATGG	1	4	54
(N20)NGG	2	98353988	+	CTGCTGCACCAGGTGTCCATGGG	1	3	44
(N20)NGG	2	98353989	+	TGCTGCACCAGGTGTCCATGGGG	1	2	43
(N20)NGG	2	98354002	+	GTCCATGGGGATGAAGTACCTGG	1	1	14
(N20)NGG	2	98354005	+	CATGGGGATGAAGTACCTGGAGG	1	5	46
(N20)NGG	2	98354032	+	GAACTTTGTGCACCGTGACCTGG	2	5	25
(N20)NGG	2	98354035	+	CTTTGTGCACCGTGACCTGGCGG	1	3	28
(N20)NGG	2	98354053	+	GGCGGCCCGCAACGTCCTGCTGG	1	1	10
(N20)NGG	2	98354061	+	GCAACGTCCTGCTGGTTAACCGG	1	1	5
(N20)NGG	2	98354087	+	TACGCCAAGATCAGCGACTTTGG	1	2	4
(N20)NGG	2	98354104	+	CTTTGGCCTCTCCAAAGCACTGG	3	15	103
(N20)NGG	2	98354105	+	TTTGGCCTCTCCAAAGCACTGGG	2	15	169
(N20)NGG	2	98353912	-	CTGGGGTGGCGGGGAAGGCGGGG	2	10	188
(N20)NGG	2	98353913	-	CCTGGGGTGGCGGGGAAGGCGGG	1	11	172
(N20)NGG	2	98353914	-	CCCTGGGGTGGCGGGGAAGGCGG	1	13	216

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98353917	-	CCTCCCTGGGGTGGCGGGGAAGG	1	14	129
(N20)NGG	2	98353921	-	ATCTCCTCCCTGGGGTGGCGGGG	1	3	59
(N20)NGG	2	98353922	-	GATCTCCTCCCTGGGGTGGCGGG	1	3	48
(N20)NGG	2	98353923	-	GGATCTCCTCCCTGGGGTGGCGG	1	8	75
(N20)NGG	2	98353926	-	CAGGGATCTCCTCCCTGGGGTGG	3	6	79
(N20)NGG	2	98353929	-	TCACAGGGATCTCCTCCCTGGGG	1	4	63
(N20)NGG	2	98353930	-	CTCACAGGGATCTCCTCCCTGGG	1	4	54
(N20)NGG	2	98353931	-	GCTCACAGGGATCTCCTCCCTGG	1	3	66
(N20)NGG	2	98353944	-	GCTCGGCCACATTGCTCACAGGG	1	2	15
(N20)NGG	2	98353945	-	AGCTCGGCCACATTGCTCACAGG	1	2	11
(N20)NGG	2	98353961	-	GGACACCTGGTGCAGCAGCTCGG	1	1	44
(N20)NGG	2	98353974	-	ACTTCATCCCCATGGACACCTGG	1	1	34
(N20)NGG	2	98353982	-	CTCCAGGTACTTCATCCCCATGG	1	3	62
(N20)NGG	2	98353998	-	GCACAAAGTTCTTCTCCTCCAGG	1	1	59
(N20)NGG	2	98354022	-	CGTTGCGGGCCGCCAGGTCACGG	1	4	17
(N20)NGG	2	98354028	-	GCAGGACGTTGCGGGCCGCCAGG	1	2	12
(N20)NGG	2	98354036	-	GTTAACCAGCAGGACGTTGCGGG	1	1	8
(N20)NGG	2	98354037	-	GGTTAACCAGCAGGACGTTGCGG	1	2	13
(N20)NGG	2	98354046	-	CGTAGTGCCGGTTAACCAGCAGG	1	1	4
(N20)NGG	2	98354058	-	CGCTGATCTTGGCGTAGTGCCGG	1	1	5
(N20)NGG	2	98354069	-	GAGGCCAAAGTCGCTGATCTTGG	1	4	21
(N20)NGG	2	98354088	-	CGGCACCCAGTGCTTTGGAGAGG	1	1	22
(N20)NGG	2	98354093	-	GTCGTCGGCACCCAGTGCTTTGG	1	1	2
(N20)NGG	2	98354108	-	TACAGTGTAGTAGCTGTCGTCGG	1	1	6
(N20)NGG	2	98354219	+	AGCAGCATCTCCCCCTCCCCAGG	1	12	172

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98354232	+	CCTCCCCAGGCCCGCTCAGCAGG	2	5	89
(N20)NGG	2	98354233	+	CTCCCCAGGCCCGCTCAGCAGGG	2	3	65
(N20)NGG	2	98354239	+	AGGCCCGCTCAGCAGGGAAGTGG	1	9	57
(N20)NGG	2	98354251	+	CAGGGAAGTGGCCGCTCAAGTGG	1	2	25
(N20)NGG	2	98354305	+	TCTCCAGCCGCAGCGATGTCTGG	1	1	16
(N20)NGG	2	98354313	+	CGCAGCGATGTCTGGAGCTATGG	1	3	16
(N20)NGG	2	98354314	+	GCAGCGATGTCTGGAGCTATGGG	1	1	18
(N20)NGG	2	98354315	+	CAGCGATGTCTGGAGCTATGGGG	1	2	22
(N20)NGG	2	98354326	+	GGAGCTATGGGGTCACCATGTGG	1	4	27
(N20)NGG	2	98354327	+	GAGCTATGGGGTCACCATGTGGG	1	4	146
(N20)NGG	2	98354330	+	CTATGGGGTCACCATGTGGGAGG	1	4	33
(N20)NGG	2	98354343	+	ATGTGGGAGGCCTTGTCCTACGG	1	4	43
(N20)NGG	2	98354360	+	CTACGGCCAGAAGCCCTACAAGG	1	1	15
(N20)NGG	2	98354364	+	GGCCAGAAGCCCTACAAGGCAGG	1	1	28
(N20)NGG	2	98354369	+	GAAGCCCTACAAGGCAGGCGCGG	1	1	29
(N20)NGG	2	98354370	+	AAGCCCTACAAGGCAGGCGCGGG	1	3	29
(N20)NGG	2	98354376	+	TACAAGGCAGGCGCGGGCAGAGG	1	1	24
(N20)NGG	2	98354380	+	AGGCAGGCGCGGGCAGAGGCAGG	2	10	164
(N20)NGG	2	98354383	+	CAGGCGCGGGCAGAGGCAGGTGG	1	13	325
(N20)NGG	2	98354384	+	AGGCGCGGGCAGAGGCAGGTGGG	2	7	89
(N20)NGG	2	98354195	-	TGGGGAGGGGGAGATGCTGCTGG	2	16	233
(N20)NGG	2	98354207	-	GCTGAGCGGGCCTGGGGAGGGGG	1	11	178
(N20)NGG	2	98354208	-	TGCTGAGCGGGCCTGGGGAGGGG	1	6	97
(N20)NGG	2	98354209	-	CTGCTGAGCGGGCCTGGGGAGGG	1	8	98
(N20)NGG	2	98354210	-	CCTGCTGAGCGGGCCTGGGGAGG	2	6	88

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98354213	-	TTCCCTGCTGAGCGGGCCTGGGG	2	5	35
(N20)NGG	2	98354214	-	CTTCCCTGCTGAGCGGGCCTGGG	1	4	29
(N20)NGG	2	98354215	-	ACTTCCCTGCTGAGCGGGCCTGG	2	3	19
(N20)NGG	2	98354220	-	CGGCCACTTCCCTGCTGAGCGGG	1	7	53
(N20)NGG	2	98354221	-	GCGGCCACTTCCCTGCTGAGCGG	1	2	38
(N20)NGG	2	98354240	-	TCGGGTGCGTACCACTTGAGCGG	1	1	3
(N20)NGG	2	98354258	-	TTGCGGAAGTTGATGCATTCGGG	1	1	8
(N20)NGG	2	98354259	-	CTTGCGGAAGTTGATGCATTCGG	1	1	14
(N20)NGG	2	98354275	-	CGCTGCGGCTGGAGAACTTGCGG	1	2	28
(N20)NGG	2	98354286	-	GCTCCAGACATCGCTGCGGCTGG	1	1	18
(N20)NGG	2	98354290	-	CATAGCTCCAGACATCGCTGCGG	1	3	32
(N20)NGG	2	98354319	-	GTAGGACAAGGCCTCCCACATGG	1	5	35
(N20)NGG	2	98354331	-	GGGCTTCTGGCCGTAGGACAAGG	1	1	13
(N20)NGG	2	98354337	-	CTTGTAGGGCTTCTGGCCGTAGG	1	2	30
(N20)NGG	2	98354344	-	CGCCTGCCTTGTAGGGCTTCTGG	1	4	32
(N20)NGG	2	98354351	-	CTGCCCGCGCCTGCCTTGTAGGG	1	1	16
(N20)NGG	2	98354352	-	TCTGCCCGCGCCTGCCTTGTAGG	1	1	13
(N20)NGG	2	98354467	+	CGGCTTGAGCAGAAGATGAAAGG	1	1	28
(N20)NGG	2	98354468	+	GGCTTGAGCAGAAGATGAAAGGG	1	4	67
(N20)NGG	2	98354472	+	TGAGCAGAAGATGAAAGGGCCGG	1	13	112
(N20)NGG	2	98354475	+	GCAGAAGATGAAAGGGCCGGAGG	1	5	89
(N20)NGG	2	98354481	+	GATGAAAGGGCCGGAGGTCATGG	1	3	32
(N20)NGG	2	98354496	+	GGTCATGGCCTTCATCGAGCAGG	1	1	11
(N20)NGG	2	98354497	+	GTCATGGCCTTCATCGAGCAGGG	2	3	15
(N20)NGG	2	98354504	+	CCTTCATCGAGCAGGGCAAGCGG	1	1	22

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98354508	+	CATCGAGCAGGGCAAGCGGATGG	1	1	9
(N20)NGG	2	98354561	+	ACGCACTCATGAGTGACTGCTGG	1	2	16
(N20)NGG	2	98354583	+	GATCTACAAGTGAGTGCCAGTGG	1	1	24
(N20)NGG	2	98354584	+	ATCTACAAGTGAGTGCCAGTGGG	1	1	15
(N20)NGG	2	98354585	+	TCTACAAGTGAGTGCCAGTGGGG	1	3	24
(N20)NGG	2	98354588	+	ACAAGTGAGTGCCAGTGGGGAGG	1	5	47
(N20)NGG	2	98354589	+	CAAGTGAGTGCCAGTGGGGAGGG	2	8	87
(N20)NGG	2	98354590	+	AAGTGAGTGCCAGTGGGGAGGGG	1	9	90
(N20)NGG	2	98354442	-	TTCATCTTCTGCTCAAGCCGGGG	1	2	24
(N20)NGG	2	98354443	-	TTTCATCTTCTGCTCAAGCCGGG	1	2	63
(N20)NGG	2	98354444	-	CTTTCATCTTCTGCTCAAGCCGG	1	4	60
(N20)NGG	2	98354469	-	TCGATGAAGGCCATGACCTCCGG	1	2	22
(N20)NGG	2	98354482	-	CCGCTTGCCCTGCTCGATGAAGG	1	1	8
(N20)NGG	2	98354513	-	GTTCGGGTGGACACTCTGGTGGG	1	2	11
(N20)NGG	2	98354514	-	AGTTCGGGTGGACACTCTGGTGG	1	1	12
(N20)NGG	2	98354517	-	TACAGTTCGGGTGGACACTCTGG	1	1	6
(N20)NGG	2	98354526	-	ATGAGTGCGTACAGTTCGGGTGG	1	3	8
(N20)NGG	2	98354529	-	CTCATGAGTGCGTACAGTTCGGG	1	1	10
(N20)NGG	2	98354530	-	ACTCATGAGTGCGTACAGTTCGG	1	1	8
(N20)NGG	2	98355837	+	GGATGTACCCCACGCCCCACAGG	1	1	14
(N20)NGG	2	98355840	+	TGTACCCCACGCCCCCACAGGTGG	1	2	36
(N20)NGG	2	98355841	+	GTACCCCACGCCCCCACAGGTGGG	1	1	27
(N20)NGG	2	98355844	+	CCCCACGCCCCCACAGGTGGGAGG	1	6	68
(N20)NGG	2	98355868	+	TCGCCCCGACTTCCTGACCGTGG	1	1	11
(N20)NGG	2	98355901	+	GCGAGCCTGTTACTACAGCCTGG	1	2	9

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98355910	+	TTACTACAGCCTGGCCAGCAAGG	1	23	811
(N20)NGG	2	98355913	+	CTACAGCCTGGCCAGCAAGGTGG	1	8	291
(N20)NGG	2	98355917	+	AGCCTGGCCAGCAAGGTGGAAGG	1	21	551
(N20)NGG	2	98355918	+	GCCTGGCCAGCAAGGTGGAAGGG	1	18	453
(N20)NGG	2	98355926	+	AGCAAGGTGGAAGGGCCCCCAGG	1	3	41
(N20)NGG	2	98355940	+	GCCCCCAGGCAGCACACAGAAGG	3	6	109
(N20)NGG	2	98355946	+	AGGCAGCACACAGAAGGCTGAGG	1	9	127
(N20)NGG	2	98355976	+	TGCCTGAGCTCCCGCTGCCCAGG	2	5	59
(N20)NGG	2	98355977	+	GCCTGAGCTCCCGCTGCCCAGGG	1	10	89
(N20)NGG	2	98355978	+	CCTGAGCTCCCGCTGCCCAGGGG	1	6	83
(N20)NGG	2	98355812	-	GTGGGGCGTGGGGTACATCCAGG	1	1	28
(N20)NGG	2	98355822	-	CCTCCCACCTGTGGGGCGTGGGG	1	3	58
(N20)NGG	2	98355823	-	TCCTCCCACCTGTGGGGCGTGGG	1	2	33
(N20)NGG	2	98355824	-	ATCCTCCCACCTGTGGGGCGTGG	1	2	30
(N20)NGG	2	98355829	-	GGGCGATCCTCCCACCTGTGGGG	1	1	27
(N20)NGG	2	98355830	-	GGGGCGATCCTCCCACCTGTGGG	1	2	16
(N20)NGG	2	98355831	-	CGGGGCGATCCTCCCACCTGTGG	1	2	28
(N20)NGG	2	98355849	-	GCTCCACGGTCAGGAAGTCGGGG	1	1	13
(N20)NGG	2	98355850	-	TGCTCCACGGTCAGGAAGTCGGG	1	2	15
(N20)NGG	2	98355851	-	CTGCTCCACGGTCAGGAAGTCGG	1	2	26
(N20)NGG	2	98355858	-	GCATGCGCTGCTCCACGGTCAGG	1	2	9
(N20)NGG	2	98355863	-	GGCTCGCATGCGCTGCTCCACGG	1	2	11
(N20)NGG	2	98355884	-	GCTGGCCAGGCTGTAGTAACAGG	1	2	38
(N20)NGG	2	98355897	-	GCCCTTCCACCTTGCTGGCCAGG	1	5	65
(N20)NGG	2	98355902	-	TGGGGGCCCTTCCACCTTGCTGG	1	3	41

FIG. 15

site_type	site_chromosome	site_start_nucleotide	site_strand	target_site_sequence_with NGG	genome_wide_hits_with_1_or_less_mismatches	genome_wide_hits_with_2_or_less_mismatches	genome_wide_hits_with_3_or_less_mismatches
(N20)NGG	2	98355919	-	GCCTTCTGTGTGCTGCCTGGGGG	1	5	102
(N20)NGG	2	98355920	-	AGCCTTCTGTGTGCTGCCTGGGG	1	6	93
(N20)NGG	2	98355921	-	CAGCCTTCTGTGTGCTGCCTGGG	1	7	119
(N20)NGG	2	98355922	-	TCAGCCTTCTGTGTGCTGCCTGG	1	5	76
(N20)NGG	2	98355950	-	GGCAGCGGGAGCTCAGGCACAGG	1	6	57
(N20)NGG	2	98355956	-	CCCCTGGGCAGCGGGAGCTCAGG	1	3	66

FIG. 15

1 MDKKYSIGLD IGTNSVGWAV ITDEYKVPSK KFKVLGNTDR HSIKKNLIGA LLFDSGETAE

61 ATRLKRTARR RYTRRKNRIC YLQEIFSNEM AKVDDSFFHR LEESFLVEED KKHERHPIFG

121 NIVDEVAYHE KYPTIYHLRK KLVDSTDKAD LRLIYLALAH MIKFRGHFLI EGDLNPDNSD

181 VDKLFIQLVQ TYNQLFEENP INASGVDAKA ILSARLSKSR RLENLIAQLP GEKKNGLFGN

241 LIALSLGLTP NFKSNFDLAE DAKLQLSKDT YDDDLDNLLA QIGDQYADLF LAAKNLSDAI

301 LLSDILRVNT EITKAPLSAS MIKRYDEHHQ DLTLLKALVR QQLPEKYKEI FFDQSKNGYA

361 GYIDGGASQE EFYKFIKPIL EKMDGTEELL VKLNREDLLR KQRTFDNGSI PHQIHLGELH

421 AILRRQEDFY PFLKDNREKI EKILTFRIPY YVGPLARGNS RFAWMTRKSE ETITPWNFEE

481 VVDKGASAQS FIERMTNFDK NLPNEKVLPK HSLLYEYFTV YNELTKVKYV TEGMRKPAFL

541 SGEQKKAIVD LLFKTNRKVT VKQLKEDYFK KIECFDSVEI SGVEDRFNAS LGTYHDLLKI

601 IKDKDFLDNE ENEDILEDIV LTLTLFEDRE MIEERLKTYA HLFDDKVMKQ LKRRRYTGWG

661 RLSRKLINGI RDKQSGKTIL DFLKSDGFAN RNFMQLIHDD SLTFKEDIQK AQVSGQGDSL

721 HEHIANLAGS PAIKKGILQT VKVVDELVKV MGRHKPENIV IEMARENQTT QKGQKNSRER

781 MKRIEEGIKE LGSQILKEHP VENTQLQNEK LYLYYLQNGR DMYVDQELDI NRLSDYDVDH

841 IVPQSFLKDD SIDNKVLTRS DKNRGKSDNV PSEEVVKKMK NYWRQLLNAK LITQRKFDNL

901 TKAERGGLSE LDKAGFIKRQ LVETRQITKH VAQILDSRMN TKYDENDKLI REVKVITLKS

961 KLVSDFRKDF QFYKVREINN YHHAHDAYLN AVVGTALIKK YPKLESEFVY GDYKVYDVRK

1021 MIAKSEQEIG KATAKYFFYS NIMNFFKTEI TLANGEIRKR PLIETNGETG EIVWDKGRDF

1081 ATVRKVLSMP QVNIVKKTEV QTGGFSKESI LPKRNSDKLI ARKKDWDPKK YGGFDSPTVA

1141 YSVLVVAKVE KGKSKKLKSV KELLGITIME RSSFEKNPID FLEAKGYKEV KKDLIIKLPK

1201 YSLFELENGR KRMLASAGEL QKGNELALPS KYVNFLYLAS HYEKLKGSPE DNEQKQLFVE

1261 QHKHYLDEII EQISEFSKRV ILADANLDKV LSAYNKHRDK PIREQAENII HLFTLTNLGA

1321 PAAFKYFDTT IDRKRYTSTK EVLDATLIHQ SITGLYETRI DLSQLGGD (SEQ ID NO: 298)

FIG. 16