

COMPOSITIONS AND METHODS FOR MODULATING SPLICING AND PROTEIN EXPRESSION

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/888,887, filed August 19, 2019, and U.S. Provisional Application No. 63/049,262, filed July 08, 2020, each of which is incorporated herein by reference in its entirety.

REFERENCE TO SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on August 19, 2020, is named 47991-727_601_SL.txt and is 17,694,293 bytes in size.

BACKGROUND

[0003] Alternative splicing events in genes can lead to non-productive or less productive mRNA transcripts, and therapeutic agents which can target the alternative splicing events in genes can modulate the expression level of functional proteins in patients and/or inhibit aberrant protein expression. Such therapeutic agents can be used to treat a condition or disease caused by protein deficiency.

SUMMARY

[003a] In one aspect, disclosed herein is a composition comprising a non-sense mediated RNA decay alternative exon (NSAE)-modulating agent that interacts with a target motif within a pre-processed mRNA transcript to modulate splicing at an alternative 5' or 3' splice site of a pre-processed mRNA transcript in a cell, thereby promoting inclusion of a canonical exon in a processed mRNA transcript that is processed from the pre-processed mRNA transcript, and promoting exclusion of an alternative exon from the pre-processed mRNA transcript in the cell, wherein the target motif is located: (i) in an intronic region between two canonical exons, (ii) in one of the two canonical exons, or (iii) in a region spanning both an intron and canonical exon; and wherein the alternative exon comprises: (1) only a portion of a canonical exon, or (2) a canonical exon and at least a portion of an intron upstream of the canonical exon and adjacent to the canonical exon.

[003b] In another aspect, disclosed herein is the use of the composition disclosed herein in manufacturing a medicament for treating or preventing a disease or condition in a subject in need thereof, wherein the disease or condition is a disease or condition caused by a deficient amount or activity of the target protein.

[003c] In another aspect, disclosed herein is the use of the composition disclosed herein in manufacturing a medicament for modulating expression of the target protein.

[003d] In yet another aspect, disclosed herein is a pharmaceutical composition comprising the composition disclosed herein, and a pharmaceutically acceptable excipient and/or a delivery vehicle.

[003e] In yet another aspect, disclosed herein is a composition comprising a non-sense mediated RNA decay alternative exon (NSAE)-modulating agent that interacts with a target motif within a pre-processed

mRNA transcript to modulate splicing at an alternative 5' or 3' splice site of a pre-processed mRNA transcript, thereby modulating inclusion of a canonical exon in a processed mRNA transcript that is processed from the pre-processed mRNA transcript, and modulating exclusion of an alternative exon from the pre-processed mRNA transcript, wherein the target motif is located: (i) in an intronic region between two canonical exons, (ii) in one of the two canonical exons, or (iii) in a region spanning both an intron and canonical exon; and wherein the alternative exon comprises: (1) only a portion of a canonical exon, or (2) a canonical exon and at least a portion of an intron adjacent to the canonical exon.

[003f] In yet another aspect, disclosed herein is a composition comprising a modified antisense oligonucleotide sequence or a viral delivery system encoding a polynucleotide comprising an antisense oligonucleotide sequence, wherein the antisense oligonucleotide sequence has at least about 80% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 1-165 and 1301-10225.

[003g] In yet another aspect, disclosed herein in the use of the composition disclosed herein in manufacturing a medicament for treating or preventing a disease or condition in a subject in need thereof, wherein the disease or condition is a disease or condition caused by a deficient amount or activity of the target protein.

[003h] In yet another aspect, disclosed herein is the composition disclosed herein for use in therapy.

[0004] In some aspectsexamples, provided herein is a composition comprising a non-sense mediated RNA decay alternative exon (NSAE)-modulating agent that interacts with a target motif within a pre-processed mRNA transcript to modulate exclusion of an NSAE from a processed mRNA transcript and to modulate inclusion of a canonical exon in the processed mRNA transcript, wherein the target motif is located (i) in an intronic region between two canonical exons, (ii) in one of the two canonical exons, or (iii) in a region spanning both an intron and canonical exon; and wherein the NSAE comprises (i) only a portion of a canonical exon, or (ii) a canonical exon and at least a portion of an intron adjacent to the canonical exon; wherein the NSAE-modulating agent modulates exclusion of an NSAE from the processed mRNA transcript and modulates inclusion of a canonical exon in the processed mRNA transcript.

[0005] In some aspectsexamples, provided herein is a composition comprising a non-sense mediated RNA decay alternative exon (NSAE)-modulating agent that modulates expression of a target protein in a cell comprising a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein and comprises: an alternative nonsense mediated RNA decay-inducing (NMD) exon comprising an alternative 5' splice site downstream of the 5' splice site of a canonical exon and within the canonical exon, or upstream of the 5' splice site of the canonical exon and within an intron, wherein the NSAE-modulating agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 5' alternative splice site, wherein the splicing of the pre-mRNA at the 5' alternative splice site modulates the expression of the target protein in a cell.

[0006] In some [aspectsexamples](#), provided herein is a composition comprising a non-sense mediated RNA decay alternative exon (NSAE)-modulating agent that modulates expression of a target protein in a cell comprising a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein and comprises: an alternative nonsense mediated RNA decay-inducing (NMD) exon comprising an alternative 3' splice site upstream of the 3' splice site of a canonical exon and within the canonical exon, or downstream of the 3' splice site of the canonical exon and within an intron, wherein the NSAE-modulating agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 3' alternative splice site, and wherein the splicing of the pre-mRNA at the 3' alternative splice site modulates the expression of the target protein in a cell.

[0007] In some [aspectsexamples](#), provided herein is a composition comprising a non-sense mediated RNA decay alternative 5' or 3' splice site (NSASS)-modulating agent that interacts with a target motif within a pre-processed mRNA transcript to modulate splicing at an alternative 5' or 3' splice site of a pre-processed mRNA transcript and to modulate inclusion of a canonical exon in a processed mRNA transcript that is processed from the pre-processed mRNA transcript, wherein the target motif is located in an intronic region between two canonical exons, in one of the two canonical exons, or in a region spanning both an intron and canonical exon; wherein modulating splicing at the alternative 5' or 3' splice site of the pre-processed mRNA transcript modulates exclusion of an alternative exon from the processed mRNA transcript, wherein the alternative exon comprises only a portion of a canonical exon, or a canonical exon and at least a portion of an intron adjacent to the canonical exon; and wherein the NSASS-modulating agent modulates exclusion of the alternative exon from the processed mRNA transcript and modulates inclusion of a canonical exon in the processed mRNA transcript.

[0008] In some [aspectsexamples](#), provided herein is a composition comprising a non-sense mediated RNA decay alternative 5' or 3' splice site (NSASS)-modulating agent that modulates expression of a target protein in a cell comprising a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein, wherein the pre-mRNA comprises an alternative exon comprising an alternative 5' splice site downstream of the 5' splice site of a canonical exon and within the canonical exon, or upstream of the 5' splice site of the canonical exon and within an intron; wherein the NSASS-modulating agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 5' alternative splice site, wherein the splicing of the pre-mRNA at the 5' alternative splice site modulates the expression of the target protein in a cell.

[0009] In some [aspectsexamples](#), provided herein is a composition comprising a non-sense mediated RNA decay alternative exon (NSASS)-modulating agent that modulates expression of a target protein in a cell comprising a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein, wherein the pre-mRNA comprises an alternative exon comprising an alternative 3' splice site upstream of the 3' splice site of a canonical exon and within the canonical exon, or downstream of the 3' splice site of the canonical exon and within an intron, wherein the NSASS-modulating agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 3'

alternative splice site, and wherein the splicing of the pre-mRNA at the 3' alternative splice site modulates the expression of the target protein in a cell.

[0010] In some [embodimentsexamples](#), the agent is a small molecule. In some [embodimentsexamples](#) the agent is a polypeptide. In some [embodimentsexamples](#), the polypeptide is a nucleic acid binding protein. In some [embodimentsexamples](#), the nucleic acid binding protein contains a TAL-effector or zinc finger binding domain. In some [embodimentsexamples](#), the nucleic acid binding protein is a Cas family protein. In some [embodimentsexamples](#), the polypeptide is accompanied by or complexed with one or more nucleic acid molecules. In some [embodimentsexamples](#), the Agent is an antisense oligomer (ASO) complementary to the targeted region of the pre-mRNA. In some [embodimentsexamples](#), the Agent is at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, complementary to the targeted region of the pre-mRNA encoding the target protein. In some [embodimentsexamples](#), the Agent is an antisense oligomer, and wherein the Agent comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage. In some [embodimentsexamples](#), the Agent is an antisense oligomer, and wherein the Agent comprises a phosphorodiamidate morpholino. In some [embodimentsexamples](#), the Agent is an antisense oligomer, and wherein the Agent comprises a locked nucleic acid. In some [embodimentsexamples](#), the Agent is an antisense oligomer, and wherein the Agent comprises a peptide nucleic acid. In some [embodimentsexamples](#), the Agent is an antisense oligomer, and wherein the Agent comprises a 2'- O-methyl. In some [embodimentsexamples](#), the Agent is an antisense oligomer, and wherein the Agent comprises a 2'-Fluoro, or a 2'-O-methoxyethyl moiety. In some [embodimentsexamples](#), the Agent is an antisense oligomer, and wherein the Agent comprises at least one modified sugar moiety. In some [embodimentsexamples](#), each sugar moiety is a modified sugar moiety. In some [embodimentsexamples](#), the Agent is an antisense oligomer, and wherein the Agent consists of from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases. Described herein, in some [aspectsexamples](#), is a composition of a nucleic acid molecule that encodes for the NSAE-modulating agent. In some [embodimentsexamples](#), the nucleic acid molecule is incorporated into a viral delivery system. In some [embodimentsexamples](#), the viral delivery system is an adenovirus-associated vector.

[0011] In some [aspectsexamples](#), provided herein is a method of modulating protein expression, comprising: (a) contacting a non-sense mediated RNA decay alternative exon (NSAE)-modulating agent to a target motif within a pre-processed mRNA transcript, wherein the NSAE comprises (i) only a portion of a canonical exon, or (ii) a canonical exon and at least a portion of an intron adjacent to the canonical exon; (b) processing a mRNA transcript from the pre-processed mRNA transcript thereby forming a processed mRNA transcript, wherein the NSAE-modulating agent modulates exclusion of an NSAE from the

processed mRNA transcript and modulates inclusion of the canonical exon in the processed mRNA transcript; and (c) translating the processed mRNA transcript wherein the exclusion of the NSAE and inclusion of the canonical exon modulates protein expression relative to the protein expression of an equivalent mRNA transcript comprising the NSAE instead of the canonical exon. In some [embodimentsexamples](#), the target motif is located in an intronic region between two canonical exons. In some [embodimentsexamples](#), the target motif is located in one of the two canonical exons. In some [embodimentsexamples](#), the target motif is located in a region spanning both an intron and a canonical exon.

[0012] In some [aspectsexamples](#), provided herein is a method of modulating expression of a target protein by a cell having a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein and comprises: an alternative nonsense mediated RNA decay-inducing (NMD) exon comprising an alternative 3' splice site upstream of the 3' splice site of a canonical exon and within the canonical exon, or downstream of the 3' splice site of the canonical exon and within an intron, the method comprising contacting a non-sense mediated RNA decay alternative exon (NSAE)-modulating agent to the cell, wherein the non-sense mediated RNA decay alternative exon (NSAE)-modulating agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 3' alternative splice site, and wherein the splicing of the pre-mRNA at the 3' alternative splice site modulates the expression of the target protein.

[0013] In some [aspectsexamples](#), provided herein is a method of modulating expression of a target protein by a cell having a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein and comprises: an alternative nonsense mediated RNA decay-inducing (NMD) exon comprising an alternative 5' splice site downstream of the 5' splice site of a canonical exon and within the canonical exon, or upstream of the 5' splice site of the canonical exon and within an intron, the method comprising contacting a non-sense mediated RNA decay alternative exon (NSAE)-modulating agent to the cell, wherein the non-sense mediated RNA decay alternative exon (NSAE)-modulating agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 5' alternative splice site, and wherein the splicing of the pre-mRNA at the 5' alternative splice site modulates the expression of the target protein.

[0014] In some [embodimentsexamples](#), the non-sense mediated RNA decay alternative exon (NSAE)-modulating agent binds to a targeted portion of the pre-processed mRNA transcript. In some [embodimentsexamples](#), the wherein the non-sense mediated RNA decay alternative exon (NSAE)-modulating agent binds to a factor involved in splicing of the NSAE or NMD exon. In some [embodimentsexamples](#), the wherein the non-sense mediated RNA decay alternative exon (NSAE)-modulating agent inhibits activity of a factor involved in splicing of the NMD exon. In some [embodimentsexamples](#), the wherein the non-sense mediated RNA decay alternative exon (NSAE)-modulating agent interferes with binding of a factor involved in splicing of the NMD exon to a region of the targeted portion of the pre-processed mRNA transcript. In some [embodimentsexamples](#), modulation of splicing of the pre-mRNA increases the expression of the target protein. In some [embodimentsexamples](#), the level the target protein in the cell is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1

to about 5-fold, about 1.1 to about 6- fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the level of processed mRNA encoding the target protein in a control cell. In some [embodimentsexamples](#), modulation of splicing of the pre-mRNA increases production of the processed mRNA encoding the target protein. In some [embodimentsexamples](#), the level of processed mRNA encoding the target protein in the cell contacted with the therapeutic agent is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6- fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the level of processed mRNA encoding the target protein in a control cell. In some [embodimentsexamples](#), the target protein is the canonical isoform of the protein. In some [embodimentsexamples](#), the target protein is SynGAP1. In some [embodimentsexamples](#), the target protein is any one selected from the group consisting of ABCA5, ABCA7, ABCC3, ABCC5, ABCC8, ABCD1, ABR, ACAD9, ACAP1, ACOX2, ACSF3, ACTN4, ADAM17, ADAMTS13, AKR1E2, ALAD, ALG3, ANKRD29, ANKS3, ANO4, AP3B2, AP3M1, AP5Z1, ARNTL, ASAP3, ATRX, BBS2, BBS4, BRD9, CALM3, CARS1, CASP9, CATSPER1, CCDC40, CCDC88B, CD4, CD58, CES2, CHFR, CLCN2, CNOT3, CNTROB, COL5A3, CPSF1, CSPP1, CTF1, CTH, CYP3A5, DAB2IP, DBN1, DDX51, DEAF1, DGKE, DHDDS, DMKN, DNHD1, DOCK8, DOK5, EIF2B5, ELAC2, ELP1, ENTPD4, ESRRA, ESS2, ETAA1, ETHE1, FANCA, FASTK, FASTKD3, FPGS, FREM1, GAS8, GCK, GGA1, GGA3, GGT1, GLMN, GON4L, GRB14, HDAC3, HELQ, HP1BP3, HPS1, HPS4, IDUA, IFT122, IL17RC, IMPDH1, INVS, IRF3, KCTD3, KLKB1, KYAT1, LAMC3, LDAH, LIMS2, MALT1, MAP3K7, MAPK13, MCAT, MCEE, MPI, MSTO1, NBEAL2, NLE1, NLRC5, NOM1, NOP58, NPHP1, NPR1, NUP188, OSGEP, PABPC4, PCOLCE, PHKA2, PIDD1, PKD1, PLA2G6, PLD2, PLEKHG5, PNPO, POLE, PON2, PRMT7, PRODH, PRPF3, PRPF4, PYCR1, RAD52, REXO1, RFX5, RHBDF2, RMND1, ROBO3, RPGRI1, RTTN, RUFY3, SEMA3B, SEMA3F, SH2D3A, SIK3, SIRT3, SKIV2L, SLC2A13, SLC12A7, SLC22A3, SLC25A13, SLC25A37, SLC27A5, SLC30A9, SLC30A10, SMPD1, SMTN, SNRPB, SP140, STAMBP, STXBP2, SULF2, SYNGAP1, SYNJ2, TAZ, TBL2, TDRD7, TECPR2, TFB1M, TM6SF1, TNK2, TOE1, TOR1B, TRAPPC6B, TRIP4, TRMT2A, TRMU, TRPV4, TTC19, TYMP, UMPS, UROD, WDR11, WDR62, WIPI1, WRAP53, XPO1, YY1AP1, and ZC3H14. In some [embodimentsexamples](#), the non-sense mediated RNA decay alternative exon (NSAE)-modulating agent is a composition described herein.

[0015] In some [aspectsexamples](#), provided herein is a pharmaceutical composition comprising: a therapeutic agent comprising a composition described herein; and a pharmaceutically acceptable excipient and/or a delivery vehicle.

[0016] In some [aspectsexamples](#), provided herein is a method of treating or preventing a disease or condition in a subject in need thereof, the method comprising: administering to the subject a pharmaceutical composition described herein.

[0017] In some [aspectsexamples](#), provided herein is a method of treating or preventing a disease or condition in a subject in need thereof, the method comprising: administering to the subject a pharmaceutical composition comprising: (a) a non-sense mediated RNA decay alternative exon (NSAE)-modulating agent that interacts with a target motif within a pre-processed mRNA transcript to modulate exclusion of an NSAE from a processed mRNA transcript and to modulate inclusion of a canonical exon in the processed mRNA transcript, wherein the NSAE comprises (i) only a portion of a canonical exon, or (ii) a canonical exon and at least a portion of an intron adjacent to the canonical exon; and (b) a pharmaceutically acceptable excipient and/or a delivery vehicle, wherein the disease or condition is treated or prevented in the subject by the administration of the NSAE-modulating agent by a modulation in expression of a protein translated from the processed mRNA transcript.

[0018] In some [aspectsexamples](#), provided herein is a method of treating a disease or condition in a subject in need thereof by modulating expression of a target protein in a cell of the subject, wherein the cell of the subject has a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein and comprises: (a) an exon followed by an intron flanking a 3' splice site of the exon; and (b) an alternative nonsense mediated RNA decay-inducing (NMD) exon comprising an alternative 3' splice site upstream of the 3' splice site of the exon and within the exon, or downstream of the 3' splice site of the exon and within the intron, the method comprising contacting a therapeutic agent to the cell, wherein the therapeutic agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 3' alternative splice site, and wherein the splicing of the pre-mRNA at the 3' alternative splice site modulates the expression of the target protein in the cell of the subject.

[0019] In some [aspectsexamples](#), provided herein is a method of treating a disease or condition in a subject in need thereof by modulating expression of a target protein in a cell of the subject, wherein the cell of the subject has a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein and comprises: (a) an exon preceded by an intron flanking a 5' splice site of the exon; and (b) an alternative nonsense mediated RNA decay-inducing (NMD) exon comprising an alternative 5' splice site downstream of the 5' splice site of the exon and within the exon, or upstream of the 5' splice site of the exon and within the intron, the method comprising contacting a therapeutic agent to the cell, wherein the therapeutic agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 5' alternative splice site, and wherein the splicing of the pre-mRNA at the 5' alternative splice site modulates the expression of the target protein in the cell of the subject.

[0020] In some [embodimentexamples](#) the disease is autosomal dominant mental retardation, epileptic encephalopathy, or autism. In some [embodimentexamples](#), the disease or the condition is caused by a deficient

amount or activity of the target protein. In some [embodimentsexamples](#), the therapeutic agent increases the level of the processed mRNA encoding the target protein in the cell. In some [embodimentsexamples](#), the therapeutic agent increases the expression of the target protein in the cell. In some [embodimentsexamples](#), the level of processed mRNA encoding the target protein in the cell contacted with the therapeutic agent is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the level of processed mRNA encoding the target protein in a control cell. In some [embodimentsexamples](#), the level the target protein in the cell is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the level of processed mRNA encoding the target protein in a control cell. In some [embodimentsexamples](#), the method further comprises assessing mRNA levels or expression levels of the target protein. In some [embodimentsexamples](#), the method further comprises assessing the subject's genome for at least one genetic mutation associated with the disease.

[0021] In some [embodimentsexamples](#), the disease or the condition is caused by an excess amount or activity of the target protein. In some [embodimentsexamples](#), the therapeutic agent decreases the level of the processed mRNA encoding the target protein in the cell. In some [embodimentsexamples](#), the therapeutic agent decreases the expression of the target protein in the cell. In some [embodimentsexamples](#), the level of processed mRNA encoding the target protein in the cell contacted with the therapeutic agent is decreased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the level of processed mRNA encoding the target protein in a control cell. In some [embodimentsexamples](#), the level the target protein in the cell is decreased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about

2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the level of processed mRNA encoding the target protein in a control cell.

[0022] In some [embodimentsexamples](#), at least one genetic mutation is within a locus of a gene associated with the disease. In some [embodimentsexamples](#), at least one genetic mutation is within a locus associated with expression of a gene associated with the disease. In some [embodimentsexamples](#), at least one genetic mutation is within the SYNGAP1 gene locus. In some [embodimentsexamples](#), at least one genetic mutation is within a locus associated with SYNGAP1 gene expression. In some [embodimentsexamples](#), at least one genetic mutation is within a target gene locus, wherein the target gene locus is any one selected from the group consisting of ABCA5, ABCA7, ABCC3, ABCC5, ABCC8, ABCD1, ABR, ACAD9, ACAP1, ACOX2, ACSF3, ACTN4, ADAM17, ADAMTS13, AKR1E2, ALAD, ALG3, ANKRD29, ANKS3, ANO4, AP3B2, AP3M1, AP5Z1, ARNTL, ASAP3, ATRX, BBS2, BBS4, BRD9, CALM3, CARS1, CASP9, CATSPER1, CCDC40, CCDC88B, CD4, CD58, CES2, CHFR, CLCN2, CNOT3, CNTROB, COL5A3, CPSF1, CSPP1, CTF1, CTH, CYP3A5, DAB2IP, DBN1, DDX51, DEAF1, DGKE, DHDDS, DMKN, DNHD1, DOCK8, DOK5, EIF2B5, ELAC2, ELP1, ENTPD4, ESRRA, ESS2, ETAA1, ETHE1, FANCA, FASTK, FASTKD3, FPGS, FREM1, GAS8, GCK, GGA1, GGA3, GGT1, GLMN, GON4L, GRB14, HDAC3, HELQ, HP1BP3, HPS1, HPS4, IDUA, IFT122, IL17RC, IMPDH1, INVS, IRF3, KCTD3, KLKB1, KYAT1, LAMC3, LDAH, LIMS2, MALT1, MAP3K7, MAPK13, MCAT, MCEE, MPI, MSTO1, NBEAL2, NLE1, NLRC5, NOM1, NOP58, NPHP1, NPR1, NUP188, OSGEP, PABPC4, PCOLCE, PHKA2, PIDD1, PKD1, PLA2G6, PLD2, PLEKHG5, PNPO, POLE, PON2, PRMT7, PRODH, PRPF3, PRPF4, PYCR1, RAD52, REXO1, RFX5, RHBDF2, RMND1, ROBO3, RPGRIP1, RTTN, RUFY3, SEMA3B, SEMA3F, SH2D3A, SIK3, SIRT3, SKIV2L, SLC2A13, SLC12A7, SLC22A3, SLC25A13, SLC25A37, SLC27A5, SLC30A9, SLC30A10, SMPD1, SMTN, SNRBP, SP140, STAMBP, STXBP2, SULF2, SYNGAP1, SYNJ2, TAZ, TBL2, TDRD7, TECPR2, TFB1M, TM6SF1, TNK2, TOE1, TOR1B, TRAPPC6B, TRIP4, TRMT2A, TRMU, TRPV4, TTC19, TYMP, UMPS, UROD, WDR11, WDR62, WIPI1, WRAP53, XPO1, YY1AP1, and ZC3H14 gene locus. In some [embodimentsexamples](#), at least one genetic mutation is within a locus associated with a target gene expression, wherein the target gene is any one selected from the group consisting of ABCA5, ABCA7, ABCC3, ABCC5, ABCC8, ABCD1, ABR, ACAD9, ACAP1, ACOX2, ACSF3, ACTN4, ADAM17, ADAMTS13, AKR1E2, ALAD, ALG3, ANKRD29, ANKS3, ANO4, AP3B2, AP3M1, AP5Z1, ARNTL, ASAP3, ATRX, BBS2, BBS4, BRD9, CALM3, CARS1, CASP9, CATSPER1, CCDC40, CCDC88B, CD4, CD58, CES2, CHFR, CLCN2, CNOT3, CNTROB, COL5A3, CPSF1, CSPP1, CTF1, CTH, CYP3A5, DAB2IP, DBN1, DDX51, DEAF1, DGKE, DHDDS, DMKN, DNHD1, DOCK8, DOK5, EIF2B5, ELAC2, ELP1, ENTPD4,

ESRRA, ESS2, ETAA1, ETHE1, FANCA, FASTK, FASTKD3, FPGS, FREM1, GAS8, GCK, GGA1, GGA3, GGT1, GLMN, GON4L, GRB14, HDAC3, HELQ, HP1BP3, HPS1, HPS4, IDUA, IFT122, IL17RC, IMPDH1, INVS, IRF3, KCTD3, KLKB1, KYAT1, LAMC3, LDAH, LIMS2, MALT1, MAP3K7, MAPK13, MCAT, MCEE, MPI, MSTO1, NBEAL2, NLE1, NLRC5, NOM1, NOP58, NPHP1, NPR1, NUP188, OSGEP, PABPC4, PCOLCE, PHKA2, PIDD1, PKD1, PLA2G6, PLD2, PLEKHG5, PNPO, POLE, PON2, PRMT7, PRODH, PRPF3, PRPF4, PYCR1, RAD52, REXO1, RFX5, RHBDF2, RMND1, ROBO3, RPGRIP1, RTTN, RUFY3, SEMA3B, SEMA3F, SH2D3A, SIK3, SIRT3, SKIV2L, SLC2A13, SLC12A7, SLC22A3, SLC25A13, SLC25A37, SLC27A5, SLC30A9, SLC30A10, SMPD1, SMTN, SNRPB, SP140, STAMBP, STXBP2, SULF2, SYNGAP1, SYNJ2, TAZ, TBL2, TDRD7, TECPR2, TFB1M, TM6SF1, TNK2, TOE1, TOR1B, TRAPPC6B, TRIP4, TRMT2A, TRMU, TRPV4, TTC19, TYMP, UMPS, UROD, WDR11, WDR62, WIPI1, WRAP53, XPO1, YY1AP1, and ZC3H14 genes. In some [embodimentsexamples](#), the subject is a human. In some [embodimentsexamples](#), the subject is a non-human animal. In some [embodimentsexamples](#), the subject is a fetus, an embryo, or a child. In some [embodimentsexamples](#), the cell or the cells is ex vivo, or in a tissue, or organ ex vivo. In some [embodimentsexamples](#), the therapeutic agent is administered to the subject by intracerebroventricular injection, intraperitoneal injection, intramuscular injection, intrathecal injection, subcutaneous injection, oral administration, synovial injection, intravitreal administration, subretinal injection, topical application, implantation, or intravenous injection.

[0023] In some [aspectsexamples](#), provided herein is a therapeutic agent for use in a method described herein.

[0024] In some [aspectsexamples](#), provided herein is a pharmaceutical composition comprising a therapeutic agent described herein and a pharmaceutically acceptable excipient.

[0025] In some [aspectsexamples](#), provided herein is a method of treating a subject in need thereof, comprising administering a pharmaceutical composition described herein by intracerebroventricular injection, intraperitoneal injection, intramuscular injection, intrathecal injection, subcutaneous injection, oral administration, synovial injection, intravitreal administration, subretinal injection, topical application, implantation, or intravenous injection to the subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] Figure 1A depicts an exemplary schematic depicting a wild type cell expressing a pre-mRNA that is alternatively spliced to generate a productive mRNA and a non-productive mRNA. While the non-productive mRNA is degraded by NMD, the productive mRNA is translated into normal protein levels.

[0027] Figure 1B depicts an exemplary schematic depicting a wild type cell treated with a TANGO (Targeted Augmentation of Nuclear Gene Output) ASO targeting the non-productive AS event (e.g. exon inclusion) that prevents the inclusion of the non-productive exon and leads to an increase of the productive mRNA. Increased level of the productive mRNA results in increased protein level beyond 100%.

[0028] Figure 1C depicts an exemplary schematic depicting an example of a haploinsufficient cell containing a wild-type allele (orange) and a mutant allele (red). Both alleles express a pre-mRNA that is alternatively spliced to generate a productive mRNA and a non-productive mRNA. While the non-

CLAIMS

1. A composition comprising a non-sense mediated RNA decay alternative exon (NSAE)-modulating agent that interacts with a target motif within a pre-processed mRNA transcript to modulate splicing at an alternative 5' or 3' splice site of a pre-processed mRNA transcript in a cell, thereby promoting inclusion of a canonical exon in a processed mRNA transcript that is processed from the pre-processed mRNA transcript, and promoting exclusion of an alternative exon from the pre-processed mRNA transcript in the cell,

wherein the target motif is located:

(i) in an intronic region between two canonical exons,

(ii) in one of the two canonical exons, or

(iii) in a region spanning both an intron and canonical exon; and

wherein the alternative exon comprises:

(1) only a portion of a canonical exon, or

(2) a canonical exon and at least a portion of an intron upstream of the canonical exon and adjacent to the canonical exon.

~~exclusion of an NSAE from a processed mRNA transcript and to modulate inclusion of a canonical exon in the processed mRNA transcript, wherein the target motif is located:~~

~~(i) — in an intronic region between two canonical exons,~~

~~(ii) — in one of the two canonical exons, or~~

~~(iii) — in a region spanning both an intron and canonical exon;~~

~~wherein the NSAE comprises:~~

~~(a) — only a portion of a canonical exon, or~~

~~(b) — a canonical exon and at least a portion of an intron adjacent to the canonical exon; and~~

~~wherein the NSAE modulating agent modulates exclusion of an NSAE from the processed mRNA transcript and modulates inclusion of a canonical exon in the processed mRNA transcript.~~

~~2. — The composition of claim 1, wherein the NSAE modulating agent promotes exclusion of an NSAE from the processed mRNA transcript and promotes inclusion of a canonical exon in the processed mRNA transcript.~~

~~3. — The composition of claim 1, wherein the processed mRNA transcript encodes a target protein and the NSAE modulating agent increases expression of a target protein in a cell containing the pre-processed mRNA transcript.~~

~~4. — The composition of claim 3, wherein the target protein is selected from the group consisting of ABCA5, ABCA7, ABCC3, ABCC5, ABCC8, ABCD1, ABR, ACAD9, ACAP1, ACOX2, ACSF3, ACTN4, ADAM17, ADAMTS13, AKR1E2, ALAD, ALG3, ANKRD29, ANKS3, ANO4, AP3B2, AP3M1, AP5Z1, ARNTL, ASAP3, ATRX, BBS2, BBS4, BRD9, CALM3, CARS1, CASP9, CATSPER1, CCDC40,~~

CCDC88B, CD4, CD58, CES2, CHFR, CLCN2, CNOT3, CNTROB, COL5A3, CPSF1, CSPP1, CTF1, CTH, CYP3A5, DAB2IP, DBN1, DDX51, DEAF1, DGKE, DHDDS, DMKN, DNHD1, DOCK8, DOK5, EIF2B5, ELAC2, ELP1, ENTPD4, ESRRA, ESS2, ETAA1, ETHE1, FANCA, FASTK, FASTKD3, FPGS, FREM1, GAS8, GCK, GGA1, GGA3, GGT1, GLMN, GON4L, GRB14, HDAC3, HELQ, HP1BP3, HPS1, HPS4, IDUA, IFT122, IL17RC, IMPDH1, INVS, IRF3, KCTD3, KLKB1, KYAT1, LAMC3, LDAH, LIMS2, MALT1, MAP3K7, MAPK13, MCAT, MCEE, MPI, MSTO1, NBEAL2, NLE1, NLRC5, NOM1, NOP58, NPHP1, NPR1, NUP188, OSGEP, PABPC4, PCOLCE, PHKA2, PIDD1, PKD1, PLA2G6, PLD2, PLEKHG5, PNPO, POLE, PON2, PRMT7, PRODH, PRPF3, PRPF4, PYCR1, RAD52, REXO1, RFX5, RHBDF2, RMND1, ROBO3, RRGRI1, RRTN, RUFY3, SEMA3B, SEMA3F, SH2D3A, SIK3, SIRT3, SKIV2L, SLC2A13, SLC12A7, SLC22A3, SLC25A13, SLC25A37, SLC27A5, SLC30A9, SLC30A10, SMPD1, SMTN, SNRPB, SP140, STAMBP, STXBP2, SULF2, SYNGAP1, SYNJ2, TAZ, TBL2, TDRD7, TECPR2, TFB1M, TM6SF1, TNK2, TOE1, TOR1B, TRAPPC6B, TRIP4, TRMT2A, TRMU, TRPV4, TTC19, TYMP, UMPS, UROD, WDR11, WDR62, WIP1, WRAP53, XPO1, YY1AP1, and ZC3H14.

5. ——— A composition comprising a non-sense mediated RNA decay alternative 5' or 3' splice site (NSASS)-modulating agent that interacts with a target motif within a pre-processed mRNA transcript to modulate splicing at an alternative 5' or 3' splice site of a pre-processed mRNA transcript and to modulate inclusion of a canonical exon in a processed mRNA transcript that is processed from the pre-processed mRNA transcript, wherein the target motif is located:

- (i) in an intronic region between two canonical exons;
- (ii) in one of the two canonical exons; or
- (iii) in a region spanning both an intron and canonical exon;

wherein modulating splicing at the alternative 5' or 3' splice site of the pre-processed mRNA transcript modulates exclusion of an alternative exon from the processed mRNA transcript, wherein the alternative exon comprises:

- (a) only a portion of a canonical exon; or
- (b) a canonical exon and at least a portion of an intron adjacent to the canonical exon; and wherein the NSASS-modulating agent modulates exclusion of the alternative exon from the processed mRNA transcript and modulates inclusion of a canonical exon in the processed mRNA transcript.

62. The composition of claim 5, wherein the NSASS-modulating agent promotes exclusion of the alternative exon from the processed mRNA transcript and promotes inclusion of a canonical exon in the processed mRNA transcript.

7. ——— The composition of claim 51, wherein the processed mRNA transcript encodes a target protein, and wherein the NSASS/NSAE-modulating agent increases expression of the target protein in the cell, a target protein in a cell containing the pre-processed mRNA transcript.

8. — The composition of claim 7, wherein the target protein is selected from the group consisting of ABCA5, ABCA7, ABCC3, ABCC5, ABCC8, ABCD1, ABR, ACAD9, ACAP1, ACOX2, ACSF3, ACTN4, ADAM17, ADAMTS13, AKR1E2, ALAD, ALC3, ANKRD29, ANKS3, ANO4, AP3B2, AP3M1, AP5Z1, ARNTL, ASAP3, ATRX, BBS2, BBS4, BRD9, CALM3, CARS1, CASP9, CATSPER1, CCDC40, CCDC88B, CD4, CD58, CES2, CHFR, CLCN2, CNOT3, CNTROB, COL5A3, CPSF1, CSPP1, CTF1, CTH, CYP3A5, DAB2IP, DBN1, DDX51, DEAF1, DGKE, DHDDS, DMKN, DNHD1, DOCK8, DOK5, EIF2B5, ELAC2, ELP1, ENTPD4, ESRRA, ESS2, ETAA1, ETHE1, FANCA, FASTK, FASTKD3, FPGS, FREM1, GAS8, GCK, GGA1, GGA3, GGT1, GLMN, GON4L, GRB14, HDAC3, HELQ, HP1BP3, HPS1, HPS4, IDUA, IFT122, IL17RC, IMPDH1, INVS, IRF3, KCTD3, KLKB1, KYAT1, LAMC3, LDAH, LIMS2, MALT1, MAP3K7, MAPK13, MCAT, MCEE, MPI, MSTO1, NBEAL2, NLE1, NLRC5, NOM1, NOP58, NPHP1, NPR1, NUP188, OSGEP, PABPC4, PCOLCE, PHKA2, PIDD1, PKD1, PLA2G6, PLD2, PLEKHG5, PNPO, POLE, PON2, PRMT7, PRODH, PRPF3, PRPF4, PYCR1, RAD52, REXO1, RFX5, RHBDF2, RMND1, ROBO3, RCGRIP1, RTTN, RUFY3, SEMA3B, SEMA3F, SH2D3A, SIK3, SIRT3, SKIV2L, SLC2A13, SLC12A7, SLC22A3, SLC25A13, SLC25A37, SLC27A5, SLC30A9, SLC30A10, SMPD1, SMTN, SNRPB, SP140, STAMBP, STXBP2, SULF2, SYNGAP1, SYNJ2, TAZ, TBL2, TDRD7, TECPR2, TFB1M, TM6SF1, TNK2, TOE1, TOR1B, TRAPPC6B, TRIP4, TRMT2A, TRMU, TRPV4, TTC19, TYMP, UMPS, UROD, WDR11, WDR62, WIP1, WRAP53, XPO1, YY1AP1, and ZC3H14.

9. — A composition comprising a non-sense mediated RNA decay alternative exon (NSAE)-modulating agent that modulates expression of a target protein in a cell comprising a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein, wherein the pre-mRNA comprises:
an alternative nonsense mediated RNA decay inducing (NMD) exon comprising an alternative 5' splice site downstream of the 5' splice site of a canonical exon and within the canonical exon, or upstream of the 5' splice site of the canonical exon and within an intron;
wherein the NSAE-modulating agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 5' alternative splice site, wherein the splicing of the pre-mRNA at the 5' alternative splice site modulates the expression of the target protein in a cell.

103. The composition of claim 91, wherein the target protein is selected from the group consisting of ABCC3, ABCC5, ABCC8, ACOX2, ACSF3, ADAM17, ADAMTS13, ALAD, ANKS3, ANO4, AP3B2, AP5Z1, ARNTL, BBS2, BRD9, CALM3, CARS1, CASP9, CD58, CHFR, CLCN2, CNOT3, CNTROB, CTF1, CYP3A5, DHDDS, DNHD1, ENTPD4, ESRRA, ESS2, ETAA1, FASTKD3, FREM1, GAS8, GGA3, GGT1, GLMN, GRB14, HDAC3, HP1BP3, HPS4, IDUA, IFT122, IMPDH1, KCTD3, KYAT1, MAP3K7, NBEAL2, NOP58, NPHP1, NUP188, PHKA2, PIDD1, PKD1, PLA2G6, PLD2, PLEKHG5, PRMT7, PRODH, PRPF3, PRPF4, RAD52, REXO1, RFX5, RUFY3, SEMA3B, SEMA3F, SH2D3A, SIRT3, SKIV2L, SLC25A13, SLC2A13, SLC30A10, SLC30A9, SMTN, STXBP2, SYNGAP1, TBL2, TECPR2, TNK2, TOE1, TRMT2A, TRPV4, UROD, WDR62, WRAP53 and XPO1.

~~114.~~ The composition of claim ~~9 or 10~~1, wherein the ~~splicing of the pre-mRNA at the 5' alternative 3'~~ splice site ~~increases the expression of the target protein in a cell.~~

~~12.~~—The composition of claim~~10~~, wherein~~flanks~~ the alternative nonsense-mediated RNA decay-inducing (NMD) exon ~~comprises an alternative 5', is downstream of a 3' splice site downstream of flanking the 5' splice site of a canonical exon, and is~~ within the canonical exon.

~~135.~~ The composition of claim ~~10~~1, wherein the ~~alternative 3' splice site flanks the alternative exon, is upstream of a 3' splice site flanking the canonical exon, and is within the intron immediately upstream of the canonical exon.~~~~alternative nonsense-mediated RNA decay-inducing (NMD) exon comprises an alternative 5' splice site upstream of the 5' splice site of the canonical exon and within an intron.~~

~~14.~~—A composition comprising a non-sense mediated RNA decay alternative 5' or 3' splice site (NSASS)-modulating agent that modulates expression of a target protein in a cell comprising a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein, wherein the pre-mRNA comprises:
an alternative exon comprising an alternative 5' splice site downstream of the 5' splice site of a canonical exon and within the canonical exon, or upstream of the 5' splice site of the canonical exon and within an intron;

wherein the NSASS-modulating agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 5' alternative splice site, wherein the splicing of the pre-mRNA at the 5' alternative splice site modulates the expression of the target protein in a cell.

~~15.~~—The composition of claim 14, wherein the target protein is selected from the group consisting of ABCC3, ABCC5, ABCC8, ACOX2, ACSF3, ADAM17, ADAMTS13, ALAD, ANKS3, ANO4, AP3B2, AP5Z1, ARNTL, BBS2, BRD9, CALM3, CARS1, CASP9, CD58, CHFR, CLCN2, CNOT3, CNTROB, CTF1, CYP3A5, DHDDS, DNHD1, ENTPD4, ESRRA, ESS2, ETAA1, FASTKD3, FREM1, GAS8, GGA3, GGT1, GLMN, GRB14, HDAC3, HP1BP3, HPS4, IDUA, IFT122, IMPDH1, KCTD3, KYAT1, MAP3K7, NBEAL2, NOP58, NPHP1, NUP188, PHKA2, PIDD1, PKD1, PLA2G6, PLD2, PLEKHG5, PRMT7, PRODH, PRPF3, PRPF4, RAD52, REXO1, RFX5, RUFY3, SEMA3B, SEMA3F, SH2D3A, SIRT3, SKIV2L, SLC25A13, SLC2A13, SLC30A10, SLC30A9, SMTN, STXBP2, SYNGAP1, TBL2, TECPR2, TNK2, TOE1, TRMT2A, TRPV4, UROD, WDR62, WRAP53 and XPO1.

~~16.~~—The composition of claim 14 or 15, wherein the splicing of the pre-mRNA at the 5' alternative splice site ~~increases the expression of the target protein in a cell.~~

~~17.~~—The composition of claim 15, wherein the pre-mRNA comprises an alternative exon comprising an alternative 5' splice site downstream of the 5' splice site of a canonical exon and within the canonical exon.

~~18.~~—The composition of claim 15, wherein the pre-mRNA comprises an alternative exon comprising an alternative 5' splice site upstream of the 5' splice site of the canonical exon and within an intron.

19. — A composition comprising a non-sense mediated RNA decay alternative exon (NSAE)-modulating agent that modulates expression of a target protein in a cell comprising a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein, wherein the pre-mRNA comprises

an alternative nonsense mediated RNA decay inducing (NMD) exon comprising an alternative 3' splice site upstream of the 3' splice site of a canonical exon and within the canonical exon, or downstream of the 3' splice site of the canonical exon and within an intron, wherein the NSAE-modulating agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 3' alternative splice site, and wherein the splicing of the pre-mRNA at the 3' alternative splice site modulates the expression of the target protein in a cell.

20. — The composition of claim 19, wherein the target protein is selected from the group consisting of ABCA5, ABCA7, ABCD1, ABR, ACAD9, ACAP1, ACTN4, ADAMTS13, AKR1E2, ALG3, ANKRD29, AP3M1, ASAP3, ATRX, BBS4, CATSPER1, CCDC40, CCDC88B, CD4, CES2, COL5A3, CPSF1, CSPP1, CTH, DAB2IP, DBN1, DDX51, DEAF1, DGKE, DMKN, DOCK8, DOK5, EIF2B5, ELAC2, ELP1, ETHE1, FANCA, FASTK, FPGS, GAS8, GCK, GGA1, GON4L, HELQ, HPS1, IL17RC, INVS, IRF3, KLKB1, LAMC3, LDAH, LIMS2, MALT1, MAPK13, MCAT, MCEE, MPI, MSTO1, NLE1, NLRC5, NOM1, NPR1, OSGEP, PABPC4, PCOLCE, PLD2, PNPO, POLE, PON2, PYCR1, RAD52, RHBDF2, RMND1, ROBO3, RPGRI1, RPTN, SIK3, SLC12A7, SLC22A3, SLC25A37, SLC27A5, SMPD1, SNRNPB, SP140, STAMBP, SULF2, SYNJ2, TAZ, TDRD7, TFB1M, TM6SF1, TOR1B, TRAPPC6B, TRIP4, TRMU, TTC19, TYMP, UMPS, WDR11, WIP1, YY1AP1 and ZC3H14.

6. — The composition of claim 1, wherein the NSAE-modulating agent is a small molecule or a polypeptide.

~~21. — The composition of claim 19 or 20, wherein the splicing of the pre-mRNA at the 3' alternative splice site increases the expression of the target protein in a cell.~~

22. — The composition of claim 20, wherein the alternative nonsense mediated RNA decay inducing (NMD) exon comprises an alternative 3' splice site upstream of the 3' splice site of a canonical exon and within the canonical exon.

~~23. — The composition of claim 20, wherein the alternative nonsense mediated RNA decay inducing (NMD) exon comprises an alternative 3' splice site downstream of the 3' splice site of the canonical exon and within an intron.~~

24. — A composition comprising a non-sense mediated RNA decay alternative 5' or 3' splice site (NSASS)-modulating agent that modulates expression of a target protein in a cell comprising a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein, wherein the pre-mRNA comprises an alternative exon comprising an alternative 3' splice site upstream of the 3' splice site of a canonical exon and within the canonical exon, or downstream of the 3' splice site of the canonical exon and within an intron,

wherein the NSAE-modulating agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 3' alternative splice site, and wherein the splicing of the pre-mRNA at the 3' alternative splice site modulates the expression of the target protein in a cell.

25. — The composition of claim 24, wherein the target protein is selected from the group consisting of ABCA5, ABCA7, ABCD1, ABR, ACAD9, ACAP1, ACTN4, ADAMTS13, AKR1E2, ALG3, ANKRD29, AP3M1, ASAP3, ATRX, BBS4, CATSPER1, CCDC40, CCDC88B, CD4, CES2, COL5A3, CPSF1, CSPP1, CTH, DAB2IP, DBN1, DDX51, DEAF1, DGKE, DMKN, DOCK8, DOK5, EIF2B5, ELAC2, ELP1, ETHE1, FANCA, FASTK, FPGS, GAS8, GCK, GGA1, GON4L, HELQ, HPS1, IL17RC, INVS, IRF3, KLKB1, LAMC3, LDAH, LIMS2, MALT1, MAPK13, MCAT, MCEE, MPI, MSTO1, NLE1, NLRC5, NOM1, NPR1, OSGEP, PABPC4, PCOLCE, PLD2, PNPO, POLE, PON2, PYCR1, RAD52, RHBDF2, RMND1, ROBO3, RPRIP1, RPTN, SIK3, SLC12A7, SLC22A3, SLC25A37, SLC27A5, SMPD1, SNRNPB, SP140, STAMBP, SULF2, SYNJ2, TAZ, TDRD7, TFB1M, TM6SF1, TOR1B, TRAPPC6B, TRIP4, TRMU, TTC19, TYMP, UMPS, WDR11, WIP1, YY1AP1 and ZC3H14.

26. — The composition of claim 24 or 25, wherein the splicing of the pre-mRNA at the 3' alternative splice site increases the expression of the target protein in a cell.

27. — The composition of claim 25, wherein the pre-mRNA comprises an alternative exon comprising an alternative 3' splice site upstream of the 3' splice site of a canonical exon and within the canonical exon.

28. — The composition of claim 25, wherein the pre-mRNA comprises an alternative exon comprising an alternative 3' splice site downstream of the 3' splice site of the canonical exon and within an intron.

29. — The composition of any one of claims 1-28, wherein the agent is a small molecule.

~~30. — The composition of any one of claims 1-28, wherein the agent is a polypeptide.~~

31. The composition of claim 30, wherein the polypeptide NSAE-modulating agent is a nucleic acid binding protein.

32. The composition of claim 31, wherein the nucleic acid binding protein contains a TAL-effector or zinc finger binding domain.

33. — The composition of claim 31, wherein the nucleic acid binding protein is a Cas family protein.

34. The composition of claim 31, wherein the polypeptide is accompanied by or complexed with one or more nucleic acid molecules.

NSAE-modulating agent. — The composition of any one of claims 1-28, wherein the agent is an antisense oligomer (ASO), or a viral delivery system encoding the antisense oligomer.

10. The composition of claim 9, wherein the antisense oligomer is at least 75% complementary to the targeted region/target motif of the pre-mRNA encoding the target protein.

~~3611.~~ The composition of claim ~~359~~, wherein the NSAE-modulating agent is ~~at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, complementary to the targeted region of the pre-mRNA encoding the target protein.~~

~~37.~~ ~~The composition of claim 35 or 36, antisense oligomer, and~~ wherein the ~~agent~~antisense oligomer comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage.

~~3812.~~ The composition of ~~any one of claims 35-37~~claim 9, wherein the NSAE-modulating agent ~~is the antisense oligomer, and wherein the antisense oligomer~~ comprises a phosphorodiamidate morpholino, ~~or~~

~~39.~~ ~~The composition of any one of claims 35-38, wherein the agent comprises~~ a locked nucleic acid.

~~40.~~ ~~The composition of any one of claims 35-39, wherein the agent comprises a~~, or a peptide nucleic acid.

~~4113.~~ The composition of ~~any one of claims 35-40~~claim 9, wherein the ~~agent~~NSAE-modulating agent is the antisense oligomer, and wherein the antisense oligomer comprises a 2'-O-methyl-, moiety, a 2'-Fluoro moiety, or a 2'-O-methoxyethyl moiety.

~~4214.~~ The composition of ~~any one of claims 35-41~~claim 9, wherein the NSAE-modulating agent ~~comprises~~ a 2'-Fluoro, or a 2'-O-methoxyethyl moiety.

~~43.~~ ~~The composition of any one of claims 35-42, wherein is the agent~~antisense oligomer, and wherein the antisense oligomer comprises at least one modified sugar moiety.

~~4415.~~ The composition of claim ~~439~~, wherein ~~each sugar moiety is a modified sugar moiety.~~

~~45.~~ ~~The composition of any one of claims 1-28 or 35-44, wherein the agent is an antisense oligomer, and wherein the agent consists of from 8 to 50 nucleobases, 8 to 40 nucleobases, 8 to 35 nucleobases, 8 to 30 nucleobases, 8 to 25 nucleobases, 8 to 20 nucleobases, 8 to 15 nucleobases, 9 to 50 nucleobases, 9 to 40 nucleobases, 9 to 35 nucleobases, 9 to 30 nucleobases, 9 to 25 nucleobases, 9 to 20 nucleobases, 9 to 15 nucleobases, 10 to 50 nucleobases, 10 to 40 nucleobases, 10 to 35 nucleobases, 10 to 30 nucleobases, 10 to 25 nucleobases, 10 to 20 nucleobases, 10 to 15 nucleobases, 11 to 50 nucleobases, 11 to 40 nucleobases, 11 to 35 nucleobases, 11 to 30 nucleobases, 11 to 25 nucleobases, 11 to 20 nucleobases, 11 to 15 nucleobases, 12 to 50 nucleobases, 12 to 40 nucleobases, 12 to 35 nucleobases, 12 to 30 nucleobases, 12 to 25 nucleobases, 12 to 20 nucleobases, or 12 to 15 nucleobases.~~

16. The composition of claim 1, wherein target protein is SYNGAP1 protein, and wherein the pre-mRNA comprises a sequence selected from the group consisting of premrna_ENST00000293748.9, premrna_ENST00000418600.7, premrna_ENST00000428982.4, premrna_ENST00000449372.7, premrna_ENST00000470232.1, premrna_ENST00000479510.2, premrna_ENST00000628646.2, premrna_ENST00000629380.3, premrna_ENST00000635885.1, premrna_ENST00000636075.1, premrna_ENST00000636116.1, premrna_ENST00000636146.1, premrna_ENST00000636193.1, premrna_ENST00000636436.1, premrna_ENST00000636443.1, premrna_ENST00000636640.1,

premrna ENST00000636731.1, premrna ENST00000636905.1, premrna ENST00000637052.1, premrna ENST00000637194.1, premrna ENST00000637490.1, premrna ENST00000637587.1, premrna ENST00000637671.1, premrna ENST00000637721.1, premrna ENST00000637911.1, premrna ENST00000638127.1, premrna ENST00000638142.2, premrna ENST00000644458.1, premrna ENST00000645250.1, and premrna ENST00000646630.1.

17. The composition of claim 1, wherein target protein is SYNGAP1 protein, and wherein the target motif of the pre-mRNA comprises a sequence with at least 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to a region comprising at least 8 contiguous nucleic acids of a sequence selected from the group consisting of SEQ ID NOs: 166-169 and 980-983, and complements thereof.

18. The composition of claim 1, wherein target protein is SYNGAP1 protein, and wherein the target motif of the SYNGAP1 pre-mRNA comprises a sequence that is complementary to at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 contiguous nucleic acids of a sequence selected from the group consisting of SEQ ID NOs: 1-165 and 4300-4352, and a complement thereof.

19. The composition of claim 1, wherein the NSAE-modulating agent comprises a sequence that comprises has at least about 80% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 1-165 and 4300-4352.

20. Use of the composition of any one of claims 1 to 19 in manufacturing a medicament for treating or preventing a disease or condition in a subject in need thereof, wherein the disease or condition is a disease or condition caused by a deficient amount or activity of the target protein.

21. The use according to claim 20, wherein the disease or condition is autosomal dominant mental retardation, epileptic encephalopathy, or autism.~~46. The composition of any one of claims 1-28 or 35-44, wherein.~~

~~47. A composition comprising a nucleic acid molecule that encodes for the agent according to the composition of any one of claims 1-28 or 30-46.~~

~~48. The composition of claim 47, wherein the nucleic acid molecule is incorporated into a viral delivery system.~~

~~49. The composition of claim 48, wherein the viral delivery system is an adenovirus-associated vector.~~

~~50. A method of modulating protein expression, comprising:~~

~~(a) contacting a non-sense mediated RNA decay alternative exon (NSAE)-modulating agent to a target motif within a pre-processed mRNA transcript;~~

~~wherein the NSAE comprises~~

~~(i) only a portion of a canonical exon, or~~

~~(ii) a canonical exon and at least a portion of an intron adjacent to the canonical exon;~~

(b) processing a mRNA transcript from the pre-processed mRNA transcript thereby forming a processed mRNA transcript, wherein the NSAE-modulating agent modulates exclusion of an NSAE from the processed mRNA transcript and modulates inclusion of the canonical exon in the processed mRNA transcript; and
(c) translating the processed mRNA transcript wherein the exclusion of the NSAE and inclusion of the canonical exon modulates target protein expression relative to the target protein expression of an equivalent mRNA transcript comprising the NSAE instead of the canonical exon.

51. — The method of claim 50, wherein the target motif is located in an intronic region between two canonical exons.

52. — The method of claim 50

22. — The use according to claim 20, wherein the NSAE-modulating agent increases the level of the processed mRNA encoding the target protein in the cell, target motif is located in one of the two canonical exons.

53. — The method of claim 50, wherein the target motif is located in a region spanning both an intron and a canonical exon.

54. — The method of claim 50, wherein the target protein is selected from the group consisting of ABCA5, ABCA7, ABCC3, ABCC5, ABCC8, ABCD1, ABR, ACAD9, ACAP1, ACOX2, ACSF3, ACTN4, ADAM17, ADAMTS13, AKR1E2, ALAD, ALG3, ANKRD29, ANKS3, ANO4, AP3B2, AP3M1, AP5Z1, ARNTL, ASAP3, ATRX, BBS2, BBS4, BRD9, CALM3, CARS1, CASP9, CATSPER1, CCDC40, CCDC88B, CD4, CD58, CES2, CHFR, CLCN2, CNOT3, CNTROB, COL5A3, CPSF1, CSPP1, CTF1, CTH, CYP3A5, DAB2IP, DBN1, DDX51, DEAF1, DGKE, DHDDS, DMKN, DNHD1, DOCK8, DOK5, EIF2B5, ELAC2, ELP1, ENTPD4, ESRRB, ESS2, ETAA1, ETHE1, FANCA, FASTK, FASTKD3, FPGS, FREM1, GAS8, GCK, GGA1, GGA3, GGT1, GLMN, GON4L, GRB14, HDAC3, HELQ, HP1BP3, HPS1, HPS4, IDUA, IFT122, IL17RC, IMPDH1, INVS, IRF3, KCTD3, KLKB1, KYAT1, LAMC3, LDAH, LIMS2, MALT1, MAP3K7, MAPK13, MCAT, MCEE, MPI, MSTO1, NBEAL2, NLE1, NLRC5, NOM1, NOP58, NPHP1, NPR1, NUP188, OSGEP, PABPC4, PCOLCE, PHKA2, PIDD1, PKD1, PLA2G6, PLD2, PLEKHG5, PNPO, POLE, PON2, PRMT7, PRODH, PRPF3, PRPF4, PYCR1, RAD52, REXO1, RFX5, RHBDF2, RMND1, ROBO3, RPGRI1, RPTN, RUFY3, SEMA3B, SEMA3F, SH2D3A, SIK3, SIRT3, SKIV2L, SLC2A13, SLC12A7, SLC22A3, SLC25A13, SLC25A37, SLC27A5, SLC30A9, SLC30A10, SMPD1, SMTN, SNRNP, SP140, STAMBP, STXB2, SULF2, SYNGAP1, SYNJ2, TAZ, TBL2, TDRD7, TECPR2, TFB1M, TM6SF1, TNK2, TOE1, TOR1B, TRAPPC6B, TRIP4, TRMT2A, TRMU, TRPV4, TTC19, TYMP, UMPS, UROD, WDR11, WDR62, WIP1, WRAP53, XPO1, YY1AP1, and ZC3H14.

55. — A method of modulating expression of a target protein by a cell having a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein, wherein the pre-mRNA comprises:

an alternative nonsense mediated RNA decay inducing (NMD) exon comprising an alternative 3' splice site upstream of the 3' splice site of a canonical exon and within the canonical exon, or downstream of the 3' splice site of the canonical exon and within an intron;

the method comprising contacting a non-sense mediated RNA decay alternative exon (NSAE) modulating agent to the cell, wherein the non-sense mediated RNA decay alternative exon (NSAE) modulating agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 3' alternative splice site, and wherein the splicing of the pre-mRNA at the 3' alternative splice site modulates the expression of the target protein.

56.—— The method of claim 55, wherein the target protein is selected from the group consisting of ABCA5, ABCA7, ABCD1, ABR, ACAD9, ACAP1, ACTN4, ADAMTS13, AKR1E2, ALG3, ANKRD29, AP3M1, ASAP3, ATRX, BBS4, CATSPER1, CCDC40, CCDC88B, CD4, CES2, COL5A3, CPSF1, CSPP1, CTH, DAB2IP, DBN1, DDX51, DEAF1, DGKE, DMKN, DOCK8, DOK5, EIF2B5, ELAC2, ELP1, ETHE1, FANCA, FASTK, FPGS, GAS8, GCK, GGA1, GON4L, HELQ, HPS1, IL17RC, INVS, IRF3, KLKB1, LAMC3, LDAH, LIMS2, MALT1, MAPK13, MCAT, MCEE, MPI, MSTO1, NLE1, NLRC5, NOM1, NPR1, OSGEP, PABPC4, PCOLCE, PLD2, PNPO, POLE, PON2, PYCR1, RAD52, RHBDF2, RMND1, ROBO3, RPGRI1, RPTN, SIK3, SLC12A7, SLC22A3, SLC25A37, SLC27A5, SMPD1, SNRPB, SP140, STAMBP, SULF2, SYNJ2, TAZ, TDRD7, TFB1M, TM6SF1, TOR1B, TRAPPC6B, TRIP4, TRMU, TTC19, TYMP, UMPS, WDR11, WIP1, YY1AP1 and ZC3H14.

57.—— A method of modulating expression of a target protein by a cell having a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein, wherein the pre-mRNA comprises:
an alternative nonsense mediated RNA decay inducing (NMD) exon comprising an alternative 5' splice site downstream of the 5' splice site of a canonical exon and within the canonical exon, or upstream of the 5' splice site of the canonical exon and within an intron;
the method comprising contacting a non-sense mediated RNA decay alternative exon (NSAE) modulating agent to the cell, wherein the non-sense mediated RNA decay alternative exon (NSAE) modulating agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 5' alternative splice site, and wherein the splicing of the pre-mRNA at the 5' alternative splice site modulates the expression of the target protein.

58.—— The method of claim 57, wherein the target protein is selected from the group consisting of ABCC3, ABCC5, ABCC8, ACOX2, ACSF3, ADAM17, ADAMTS13, ALAD, ANKS3, ANO4, AP3B2, AP5Z1, ARNTL, BBS2, BRD9, CALM3, CARS1, CASP9, CD58, CHFR, CLCN2, CNOT3, CNTROB, CTF1, CYP3A5, DHDDS, DNHD1, ENTPD4, ESRRA, ESS2, ETAA1, FASTKD3, FREM1, GAS8, GGA3, GGT1, GLMN, GRB14, HDAC3, HP1BP3, HPS4, IDUA, IFT122, IMPDH1, KCTD3, KYAT1, MAP3K7, NBEAL2, NOP58, NPHP1, NUP188, PHKA2, PIDD1, PKD1, PLA2G6, PLD2, PLEKHG5, PRMT7, PRODH, PRPF3, PRPF4, RAD52, REXO1, RFX5, RUFY3, SEMA3B, SEMA3F, SH2D3A, SIRT3,

SKIV2L, SLC25A13, SLC2A13, SLC30A10, SLC30A9, SMTN, STXBP2, SYNGAP1, TBL2, TECPR2, TNK2, TOE1, TRMT2A, TRPV4, UROD, WDR62, WRAP53 and XPO1.

59. — ~~The method of any one of claims 55-58, wherein the non-sense mediated RNA decay alternative exon (NSAE)-modulating agent binds to a targeted portion of the pre-processed mRNA transcript.~~

60. — ~~The method of any one of claims 55-59, wherein the wherein the non-sense mediated RNA decay alternative exon (NSAE)-modulating agent binds to a factor involved in splicing of the NSAE or NMD-exon.~~

61. — ~~The method of any one of claims 55-60, wherein the wherein the non-sense mediated RNA decay alternative exon (NSAE)-modulating agent inhibits activity of a factor involved in splicing of the NMD-exon.~~

62. — ~~The method of any one of claims 55-61, wherein the wherein the non-sense mediated RNA decay alternative exon (NSAE)-modulating agent interferes with binding of a factor involved in splicing of the NMD-exon to a region of the targeted portion of the pre-processed mRNA transcript.~~

63. — ~~The method of any one of claims 50-62, wherein modulation of splicing of the pre-mRNA increases the expression of the target protein.~~

64. — ~~The method of claim 63, wherein the level the target protein in the cell is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the level of processed mRNA encoding the target protein in a control cell.~~

23. The 65. ~~The method of any one of claims 50-62, wherein modulation of splicing of the pre-mRNA increases production of the processed mRNA encoding the target protein.~~

66. — ~~The method of use according to claim 65~~22, wherein the level of processed mRNA encoding the target protein in the cell contacted with the ~~therapeutic~~NSAE-modulating agent is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the level of processed mRNA encoding the target protein in a control cell that is not contacted with the NSAE-modulating agent.

~~67~~24. The method of any one of claims 50-66 use according to claim 20, wherein the NSAE-modulating agent increases the expression of the target protein in the cell, target protein is the canonical isoform of the protein.

68.——The method of any one of claims 50-67, wherein the target protein is SynGAP1.

69.——The method of any one of claims 50-67, wherein the target protein is any one selected from the group consisting of ABCA5, ABCA7, ABCC3, ABCC5, ABCC8, ABCD1, ABR, ACAD9, ACAP1, ACOX2, ACSF3, ACTN4, ADAM17, ADAMTS13, AKR1E2, ALAD, ALG3, ANKRD29, ANKS3, ANO4, AP3B2, AP3M1, AP5Z1, ARNTL, ASAP3, ATRX, BBS2, BBS4, BRD9, CALM3, CARS1, CASP9, CATSPER1, CCDC40, CCDC88B, CD4, CD58, CES2, CHFR, CLCN2, CNOT3, CNTROB, COL5A3, CPSF1, CSPP1, CTF1, CTH, CYP3A5, DAB2IP, DBN1, DDX51, DEAF1, DGKE, DHDDS, DMKN, DNHD1, DOCK8, DOK5, EIF2B5, ELAC2, ELP1, ENTPD4, ESRRA, ESS2, ETAA1, ETHE1, FANCA, FASTK, FASTKD3, FPGS, FREM1, GAS8, GCK, GGA1, GGA3, GGT1, GLMN, GON4L, GRB14, HDAC3, HELQ, HP1BP3, HPS1, HPS4, IDUA, IFT122, IL17RC, IMPDH1, INVS, IRF3, KCTD3, KLKB1, KYAT1, LAMC3, LDAH, LIMS2, MALT1, MAP3K7, MAPK13, MCAT, MCEE, MPI, MSTO1, NBEAL2, NLE1, NLRC5, NOM1, NOP58, NPHP1, NPR1, NUP188, OSGEP, PABPC4, PCOLCE, PHKA2, PIDD1, PKD1, PLA2G6, PLD2, PLEKHG5, PNPO, POLE, PON2, PRMT7, PRODH, PRPF3, PRPF4, PYCR1, RAD52, REXO1, RFX5, RHBDF2, RMND1, ROBO3, RCGRIP1, RTTN, RUFY3, SEMA3B, SEMA3F, SH2D3A, SIK3, SIRT3, SKIV2L, SLC2A13, SLC12A7, SLC22A3, SLC25A13, SLC25A37, SLC27A5, SLC30A9, SLC30A10, SMPD1, SMTN, SNRPB, SP140, STAMBP, STXBP2, SULF2, SYNGAP1, SYNJ2, TAZ, TBL2, TDRD7, TECPR2, TFB1M, TM6SF1, TNK2, TOE1, TOR1B, TRAPPC6B, TRIP4, TRMT2A, TRMU, TRPV4, TTC19, TYMP, UMPS, UROD, WDR11, WDR62, WIP1, WRAP53, XPO1, YY1AP1, and ZC3H14.

70.——The method of any one of claims 50-68, wherein the non-sense mediated RNA decay alternative exon (NSAE) modulating agent is the composition of any one of claims 1-49.

71.——A pharmaceutical composition comprising a therapeutic agent comprising the composition of any one of claims 1-49; and a pharmaceutically acceptable excipient and/or a delivery vehicle.

72.——A method of treating or preventing a disease or condition in a subject in need thereof, the method comprising: administering to the subject a pharmaceutical composition of claim 71 to a subject in need thereof.

73.——A method of treating or preventing a disease or condition in a subject in need thereof, the method comprising: administering to the subject a pharmaceutical composition comprising:

(a) a non-sense mediated RNA decay alternative exon (NSAE) modulating agent that interacts with a target motif within a pre-processed mRNA transcript to modulate exclusion of an NSAE from a processed mRNA transcript and to modulate inclusion of a canonical exon in the processed mRNA transcript, wherein the NSAE comprises

(i) only a portion of a canonical exon; or

(ii) a canonical exon and at least a portion of an intron adjacent to the canonical exon; and

(b) a pharmaceutically acceptable excipient and/or a delivery vehicle,

~~wherein the disease or condition is treated or prevented in the subject by the administration of the NSAE-modulating agent by a modulation in expression of a target protein translated from the processed mRNA transcript.~~

~~7425. The method of use according to claim 24, wherein the level of the target protein in the cell contacted with the NSAE-modulating agent is increased about 1.1 to about 10-fold, about 1.5 to about 10-fold, about 2 to about 10-fold, about 3 to about 10-fold, about 4 to about 10-fold, about 1.1 to about 5-fold, about 1.1 to about 6-fold, about 1.1 to about 7-fold, about 1.1 to about 8-fold, about 1.1 to about 9-fold, about 2 to about 5-fold, about 2 to about 6-fold, about 2 to about 7-fold, about 2 to about 8-fold, about 2 to about 9-fold, about 3 to about 6-fold, about 3 to about 7-fold, about 3 to about 8-fold, about 3 to about 9-fold, about 4 to about 7-fold, about 4 to about 8-fold, about 4 to about 9-fold, at least about 1.1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at least about 3.5-fold, at least about 4-fold, at least about 5-fold, or at least about 10-fold, compared to the level of the target protein in a control cell that is not contacted with the NSAE-modulating agent.~~

~~73, wherein the target protein is selected from the group consisting of ABCA5, ABCA7, ABCC3, ABCC5, ABCC8, ABCD1, ABR, ACAD9, ACAP1, ACOX2, ACSF3, ACTN4, ADAM17, ADAMTS13, AKR1E2, ALAD, ALG3, ANKRD29, ANKS3, ANO4, AP3B2, AP3M1, AP5Z1, ARNTL, ASAP3, ATRX, BBS2, BBS4, BRD9, CALM3, CARS1, CASP9, CATSPER1, CCDC40, CCDC88B, CD4, CD58, CES2, CHFR, CLCN2, CNOT3, CNTROB, COL5A3, CPSF1, CSPP1, CTF1, CTH, CYP3A5, DAB2IP, DBN1, DDX51, DEAF1, DGKE, DHDDS, DMKN, DNHD1, DOCK8, DOK5, EIF2B5, ELAC2, ELP1, ENTPD4, ESRRA, ESS2, ETAA1, ETHE1, FANCA, FASTK, FASTKD3, FPGS, FREM1, GAS8, GCK, GGA1, GGA3, GGT1, GLMN, GON4L, GRB14, HDAC3, HELQ, HP1BP3, HPS1, HPS4, IDUA, IFT122, IL17RC, IMPDH1, INVS, IRF3, KCTD3, KLKB1, KYAT1, LAMC3, LDAH, LIMS2, MALT1, MAP3K7, MAPK13, MCAT, MCEE, MPI, MSTO1, NBEAL2, NLE1, NLRC5, NOM1, NOP58, NPHP1, NPR1, NUP188, OSGEP, PABPC4, PCOLCE, PHKA2, PIDD1, PKD1, PLA2G6, PLD2, PLEKHG5, PNPO, POLE, PON2, PRMT7, PRODH, PRPF3, PRPF4, PYCR1, RAD52, REXO1, RFX5, RHBDF2, RMND1, ROBO3, RPGRI1, RPTN, RUFY3, SEMA3B, SEMA3F, SH2D3A, SIK3, SIRT3, SKIV2L, SLC2A13, SLC12A7, SLC22A3, SLC25A13, SLC25A37, SLC27A5, SLC30A9, SLC30A10, SMPD1, SMTN, SNRBP, SP140, STAMBP, STXBP2, SULF2, SYNGAP1, SYNJ2, TAZ, TBL2, TDRD7, TECPR2, TFB1M, TM6SF1, TNK2, TOE1, TOR1B, TRAPPC6B, TRIP4, TRMT2A, TRMU, TRPV4, TTC19, TYMP, UMPS, UROD, WDR11, WDR62, WIP1, WRAP53, XPO1, YY1AP1, and ZC3H14.~~

~~75. A method of treating a disease or condition in a subject in need thereof by modulating expression of a target protein in a cell of the subject, wherein the cell of the subject has a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein, wherein the pre-mRNA comprises:~~

~~(a) a canonical exon followed by a canonical intron flanking a 3' splice site of the canonical exon; and~~

(b) an alternative nonsense-mediated RNA decay-inducing (NMD) exon comprising an alternative 3' splice site upstream of the 3' splice site of the canonical exon and within the canonical exon, or downstream of the 3' splice site of the canonical exon and within the canonical intron,

the method comprising contacting a therapeutic agent to the cell, wherein the therapeutic agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 3' alternative splice site, and wherein the splicing of the pre-mRNA at the 3' alternative splice site modulates the expression of the target protein in the cell of the subject.

76.—— The method of claim 75, wherein the target protein is selected from the group consisting of ABCA5, ABCA7, ABCD1, ABR, ACAD9, ACAP1, ACTN4, ADAMTS13, AKR1E2, ALG3, ANKRD29, AP3M1, ASAP3, ATRX, BBS4, CATSPER1, CCDC40, CCDC88B, CD4, CES2, COL5A3, CPSF1, CSPP1, CTH, DAB2IP, DBN1, DDX51, DEAF1, DGKE, DMKN, DOCK8, DOK5, EIF2B5, ELAC2, ELP1, ETHE1, FANCA, FASTK, FPGS, GAS8, GCK, GGA1, GON4L, HELQ, HPS1, IL17RC, INVS, IRF3, KLKB1, LAMC3, LDAH, LIMS2, MALT1, MAPK13, MCAT, MCEE, MPI, MSTO1, NLE1, NLRC5, NOM1, NPR1, OSGEP, PABPC4, PCOLCE, PLD2, PNPO, POLE, PON2, PYCR1, RAD52, RHBDF2, RMND1, ROBO3, RPGRIPI, RTTN, SIK3, SLC12A7, SLC22A3, SLC25A37, SLC27A5, SMPD1, SNRPB, SP140, STAMBP, SULF2, SYNJ2, TAZ, TDRD7, TFB1M, TM6SF1, TOR1B, TRAPPC6B, TRIP4, TRMU, TTC19, TYMP, UMPS, WDR11, WIP1, YY1AP1 and ZC3H14.

77.—— A method of treating a disease or condition in a subject in need thereof by modulating expression of a target protein in a cell of the subject, wherein the cell of the subject has a pre-processed mRNA transcript (pre-mRNA) that encodes the target protein, wherein the pre-mRNA comprises:

(a) a canonical exon preceded by a canonical intron flanking a 5' splice site of the canonical exon; and

(b) an alternative nonsense-mediated RNA decay-inducing (NMD) exon comprising an alternative 5' splice site downstream of the 5' splice site of the canonical exon and within the canonical exon, or upstream of the 5' splice site of the canonical exon and within the canonical intron,

the method comprising contacting a therapeutic agent to the cell, wherein the therapeutic agent modulates processing of an mRNA transcript from the pre-processed mRNA transcript by modulating splicing of the pre-mRNA at the 5' alternative splice site, and wherein the splicing of the pre-mRNA at the 5' alternative splice site modulates the expression of the target protein in the cell of the subject.

78.—— The method of claim 77, wherein the target protein is selected from the group consisting of ABCC3, ABCC5, ABCC8, ACOX2, ACSF3, ADAM17, ADAMTS13, ALAD, ANKS3, ANO4, AP3B2, AP5Z1, ARNTL, BBS2, BRD9, CALM3, CARS1, CASP9, CD58, CHFR, CLCN2, CNOT3, CNTROB, CTF1, CYP3A5, DHDDS, DNHD1, ENTPD4, ESRRA, ESS2, ETAA1, FASTKD3, FREM1, GAS8, GGA3, GGT1, GLMN, GRB14, HDAC3, HP1BP3, HPS4, IDUA, IFT122, IMPDH1, KCTD3, KYAT1, MAP3K7, NBEAL2, NOP58, NPHP1, NUP188, PHKA2, PIDD1, PKD1, PLA2G6, PLD2, PLEKHG5, PRMT7, PRODH, PRPF3, PRPF4, RAD52, REXO1, RFX5, RUFY3, SEMA3B, SEMA3F, SH2D3A, SIRT3,

SKIV2L, SLC25A13, SLC2A13, SLC30A10, SLC30A9, SMTN, STXBP2, SYNGAP1, TBL2, TECPR2, TNK2, TOE1, TRMT2A, TRPV4, UROD, WDR62, WRAP53 and XPO1.

79. — The method of any one of claims 72-78, wherein the disease is autosomal dominant mental retardation, epileptic encephalopathy, or autism.

80. — The method of any one of claims 72-79, wherein the disease or the condition is caused by a deficient amount or activity of the target protein.

81. — The method of any one of claims 72-80, wherein the therapeutic agent increases the level of the processed mRNA encoding the target protein in the cell.

82. — The method of any one of claims 72-81, wherein the therapeutic agent increases the expression of the target protein in the cell.

83. — The method of any one of claims 72-82, wherein the level of processed mRNA encoding the target protein in the cell contacted with the therapeutic agent is increased about 1.1 to about 10 fold, about 1.5 to about 10 fold, about 2 to about 10 fold, about 3 to about 10 fold, about 4 to about 10 fold, about 1.1 to about 5 fold, about 1.1 to about 6 fold, about 1.1 to about 7 fold, about 1.1 to about 8 fold, about 1.1 to about 9 fold, about 2 to about 5 fold, about 2 to about 6 fold, about 2 to about 7 fold, about 2 to about 8 fold, about 2 to about 9 fold, about 3 to about 6 fold, about 3 to about 7 fold, about 3 to about 8 fold, about 3 to about 9 fold, about 4 to about 7 fold, about 4 to about 8 fold, about 4 to about 9 fold, at least about 1.1 fold, at least about 1.5 fold, at least about 2 fold, at least about 2.5 fold, at least about 3 fold, at least about 3.5 fold, at least about 4 fold, at least about 5 fold, or at least about 10 fold, compared to the level of processed mRNA encoding the target protein in a control cell.

84. — The method of any one of claims 72-83, wherein the level the target protein in the cell is increased about 1.1 to about 10 fold, about 1.5 to about 10 fold, about 2 to about 10 fold, about 3 to about 10 fold, about 4 to about 10 fold, about 1.1 to about 5 fold, about 1.1 to about 6 fold, about 1.1 to about 7 fold, about 1.1 to about 8 fold, about 1.1 to about 9 fold, about 2 to about 5 fold, about 2 to about 6 fold, about 2 to about 7 fold, about 2 to about 8 fold, about 2 to about 9 fold, about 3 to about 6 fold, about 3 to about 7 fold, about 3 to about 8 fold, about 3 to about 9 fold, about 4 to about 7 fold, about 4 to about 8 fold, about 4 to about 9 fold, at least about 1.1 fold, at least about 1.5 fold, at least about 2 fold, at least about 2.5 fold, at least about 3 fold, at least about 3.5 fold, at least about 4 fold, at least about 5 fold, or at least about 10 fold, compared to the level of processed mRNA encoding the target protein in a control cell.

85. — The method of any one of claims 72-84, wherein the method further comprises assessing mRNA levels or expression levels of the target protein.

86. — The method of any one of claims 72-85, wherein the method further comprises assessing the subject's genome for at least one genetic mutation associated with the disease.

87. — The method of claim 86. — The use according to claim 20, wherein at least one genetic mutation is within a locus of a gene associated with the disease.

~~8827.~~ The ~~method of use according to~~ claim ~~8620~~, wherein at least one genetic mutation is within a locus associated with expression of a gene associated with the disease.

~~8928.~~ The ~~method of use according to~~ claim ~~8620~~, wherein at least one genetic mutation is within the SYNGAP1 gene locus.

~~9029.~~ The ~~method of use according to~~ claim ~~8620~~, wherein at least one genetic mutation is within a locus associated with SYNGAP1 gene expression.

~~30. 91. The method of claim 86, wherein at least one genetic mutation is within a target gene locus, wherein the target gene locus is any one selected from the group consisting of ABCA5, ABCA7, ABCC3, ABCC5, ABCC8, ABCD1, ABR, ACAD9, ACAP1, ACOX2, ACSF3, ACTN4, ADAM17, ADAMTS13, AKR1E2, ALAD, ALG3, ANKRD29, ANKS3, ANO4, AP3B2, AP3M1, AP5Z1, ARNTL, ASAP3, ATRX, BBS2, BBS4, BRD9, CALM3, CARS1, CASP9, CATSPER1, CCDC40, CCDC88B, CD4, CD58, CES2, CHFR, CLCN2, CNOT3, CNTROB, COL5A3, CPSF1, CSPP1, CTF1, CTH, CYP3A5, DAB2IP, DBN1, DDX51, DEAF1, DGKE, DHDDS, DMKN, DNHD1, DOCK8, DOK5, EIF2B5, ELAC2, ELP1, ENTPD4, ESRRA, ESS2, ETAA1, ETHE1, FANCA, FASTK, FASTKD3, FPGS, FREM1, GAS8, GCK, GGA1, GGA3, GGT1, GLMN, GON4L, GRB14, HDAC3, HELQ, HP1BP3, HPS1, HPS4, IDUA, IFT122, IL17RC, IMPDH1, INVS, IRF3, KCTD3, KLKB1, KYAT1, LAMC3, LDAH, LIMS2, MALT1, MAP3K7, MAPK13, MCAT, MCEE, MPI, MSTO1, NBEAL2, NLE1, NLRC5, NOM1, NOP58, NPHP1, NPR1, NUP188, OSGEP, PABPC4, PCOLCE, PHKA2, PIDD1, PKD1, PLA2G6, PLD2, PLEKHG5, PNPO, POLE, PON2, PRMT7, PRODH, PRPF3, PRPF4, PYCR1, RAD52, REXO1, RFX5, RHBDF2, RMND1, ROBO3, RPGRI1, RPTN, RUFY3, SEMA3B, SEMA3F, SH2D3A, SIK3, SIRT3, SKIV2L, SLC2A13, SLC12A7, SLC22A3, SLC25A13, SLC25A37, SLC27A5, SLC30A9, SLC30A10, SMPD1, SMTN, SNRPB, SP140, STAMBP, STXBP2, SULF2, SYNGAP1, SYNJ2, TAZ, TBL2, TDRD7, TECPR2, TFB1M, TM6SF1, TNK2, TOE1, TOR1B, TRAPPC6B, TRIP4, TRMT2A, TRMU, TRPV4, TTC19, TYMP, UMPS, UROD, WDR11, WDR62, WIPI1, WRAP53, XPO1, YY1AP1, and ZC3H14 gene locus.~~

~~92. The method of claim 86, wherein at least one genetic mutation is within a locus associated with a target gene expression, wherein the target gene is any one selected from the group consisting of ABCA5, ABCA7, ABCC3, ABCC5, ABCC8, ABCD1, ABR, ACAD9, ACAP1, ACOX2, ACSF3, ACTN4, ADAM17, ADAMTS13, AKR1E2, ALAD, ALG3, ANKRD29, ANKS3, ANO4, AP3B2, AP3M1, AP5Z1, ARNTL, ASAP3, ATRX, BBS2, BBS4, BRD9, CALM3, CARS1, CASP9, CATSPER1, CCDC40, CCDC88B, CD4, CD58, CES2, CHFR, CLCN2, CNOT3, CNTROB, COL5A3, CPSF1, CSPP1, CTF1, CTH, CYP3A5, DAB2IP, DBN1, DDX51, DEAF1, DGKE, DHDDS, DMKN, DNHD1, DOCK8, DOK5, EIF2B5, ELAC2, ELP1, ENTPD4, ESRRA, ESS2, ETAA1, ETHE1, FANCA, FASTK, FASTKD3, FPGS, FREM1, GAS8, GCK, GGA1, GGA3, GGT1, GLMN, GON4L, GRB14, HDAC3, HELQ, HP1BP3, HPS1, HPS4, IDUA, IFT122, IL17RC, IMPDH1, INVS, IRF3, KCTD3, KLKB1, KYAT1, LAMC3, LDAH, LIMS2, MALT1, MAP3K7, MAPK13, MCAT, MCEE, MPI, MSTO1, NBEAL2, NLE1, NLRC5, NOM1, NOP58, NPHP1,~~

NPR1, NUP188, OSGEP, PABPC4, PCOLCE, PHKA2, PIDD1, PKD1, PLA2G6, PLD2, PLEKHG5, PNPO, POLE, PON2, PRMT7, PRODH, PRPF3, PRPF4, PYCR1, RAD52, REXO1, RFX5, RHBDF2, RMND1, ROBO3, RPGRI1, RTTN, RUFY3, SEMA3B, SEMA3F, SH2D3A, SIK3, SIRT3, SKIV2L, SLC2A13, SLC12A7, SLC22A3, SLC25A13, SLC25A37, SLC27A5, SLC30A9, SLC30A10, SMPD1, SMTN, SNRPB, SP140, STAMBP, STXBP2, SULF2, SYNGAP1, SYNJ2, TAZ, TBL2, TDRD7, TECPR2, TFB1M, TM6SF1, TNK2, TOE1, TOR1B, TRAPPC6B, TRIP4, TRMT2A, TRMU, TRPV4, TTC19, TYMP, UMPS, UROD, WDR11, WDR62, WIP1, WRAP53, XPO1, YY1AP1, and ZC3H14 genes.

93. ~~The method of any one of claims 72-92, wherein the subject is a human.~~

94. ~~The method of any one of claims 72-92, wherein the subject is a non-human animal.~~

95. ~~The method of any one of claims 72-93, wherein the subject is a fetus, an embryo, or a child.~~

96. ~~The method of any one of claims 72-95, wherein the cell or the cells is ex vivo, or in a tissue, or organ ex vivo.~~

97. ~~The method of any one of claims 72-96, wherein the therapeutic agent~~The use according to claim 20,
wherein the subject is a human.

31. The use according to claim 20, wherein the composition is administered to the subject by intracerebroventricular injection, intraperitoneal injection, intramuscular injection, intrathecal injection, subcutaneous injection, oral administration, synovial injection, intravitreal administration, subretinal injection, topical application, implantation, or intravenous injection.

98. ~~A therapeutic agent for use in the method~~32. Use of the composition of any one of claims ~~72-97~~1
to 19 in manufacturing a medicament for modulating expression of the target protein.

9933. A pharmaceutical composition comprising the ~~therapeutic agent of claim 98~~composition of any one of
claims 1 to 19, and a pharmaceutically acceptable excipient and/or a delivery vehicle.

34. A composition comprising a non-sense mediated RNA decay alternative exon (NSAE)-modulating agent that interacts with a target motif within a pre-processed mRNA transcript to modulate splicing at an alternative 5' or 3' splice site of a pre-processed mRNA transcript, thereby modulating inclusion of a canonical exon in a processed mRNA transcript that is processed from the pre-processed mRNA transcript, and modulating exclusion of an alternative exon from the pre-processed mRNA transcript,

wherein the target motif is located: (i) in an intronic region between two canonical exons, (ii) in one of the two canonical exons, or (iii) in a region spanning both an intron and canonical exon; and

wherein the alternative exon comprises:

(1) only a portion of a canonical exon, or

(2) a canonical exon and at least a portion of an intron adjacent to the canonical exon.

~~35.~~100. ~~A method of~~A composition comprising a modified antisense oligonucleotide sequence or a viral delivery system encoding a polynucleotide comprising an antisense oligonucleotide sequence, wherein

the antisense oligonucleotide sequence has at least about 80% sequence identity to a sequence selected from the group consisting of SEQ ID NOs: 1-165 and 1301-10225.

36. Use of the composition of claim 34 or 35 in manufacturing a medicament for treating or preventing a disease or condition in a subject in need thereof, comprising administering the pharmaceutical composition of wherein the disease or condition is a disease or condition caused by a deficient amount or activity of the target protein.

37. The use according to claim 99 by intracerebroventricular injection, intraperitoneal 36, wherein the disease or condition is autosomal dominant mental retardation, epileptic encephalopathy or autism.

38. The use according to claim 37, wherein the disease or condition is autosomal dominant mental retardation.

39. The composition of any one of claims 1 to 38 for use in therapy.

injection, intramuscular injection, intrathecal injection, subcutaneous injection, oral administration, synovial injection, intravitreal administration, subretinal injection, topical application, implantation, or intravenous injection to the subject.