

ANTISENSE OLIGOMERS FOR TREATMENT OF CONDITIONS AND DISEASES

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/811,511, filed on February 27, 2019 which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Nervous system disorders are often associated with channelopathy, characterized by the disturbed function of ion channels that mediate neuronal excitability, neuronal interactions, and brain functions at large. Mutations in the SCN1A gene, which is part of the SCN1A-SCN2A-SCN3A gene cluster that encodes alpha-pore forming subunits of the neuronal voltage gated sodium channel, are associated with development of disease number of diseases and conditions, such as Dravet Syndrome (DS) (Miller, et al., 1993-2015, GeneReviews, Eds. Pagon RA, et al. Seattle (WA): University of Washington, Seattle, Bookshelf ID: NBK1318, and Mulley, et al., 2005, Hum. Mutat. 25: 535-542).

SUMMARY

[0002a] In one aspect, the present disclosure refers to a method of modulating expression of Nav1.1 protein in a cell having a pre-mRNA that contains a non-sense mediated mRNA decay-inducing exon (NMD exon) and that encodes Nav1.1 protein, the method comprising contacting a therapeutic agent or a vector encoding the therapeutic agent to the cell, whereby the therapeutic agent modulates exclusion of the NMD exon from the pre-mRNA encoding Nav1.1 protein, thereby modulating a level of processed mRNA encoding Nav1.1 protein, and modulating expression of Nav1.1 protein in the cell, wherein the therapeutic agent binds to a targeted region of the pre-mRNA encoding Nav1.1, and wherein the targeted region is: from about 1000 nucleotides upstream from the 5' end of the NMD exon to about 100 nucleotides upstream from the 5' end of the NMD exon; or from about 100 nucleotides downstream of the 3' end of the NMD exon to about 1000 nucleotides downstream of the 3' end of the NMD exon.

[0002b] In another aspect, the present disclosure refers to a therapeutic agent or vector encoding a therapeutic agent for use in therapy, wherein the therapeutic agent modulates splicing of a non-sense mediated mRNA decay-inducing exon (NMD exon) from a pre-mRNA in a cell of the subject that contains the NMD exon and that encodes Nav1.1 protein, thereby modulating the level of processed mRNA encoding the Nav1.1 protein, and modulating expression of Nav1.1 protein in the cell of the subject; wherein the therapeutic agent binds to a targeted portion of the pre-mRNA encoding the Nav1.1 protein, and wherein the targeted portion is: from about 1000 nucleotides upstream from the

5' end of NMD exon to about 100 nucleotides upstream from the 5' end of the NMD exon; or from about 100 nucleotides downstream of the 3' end of the NMD exon to about 1000 nucleotides downstream of the 3' end of the NMD exon.

[0002c] In another aspect, the present disclosure refers to a use of a therapeutic agent or vector encoding a therapeutic agent in the manufacture of a medicament for the treatment of a disease or condition associated with haploinsufficiency of the *SCN1A* gene, wherein the therapeutic agent modulates splicing of a non-sense mediated mRNA decay-inducing exon (NMD exon) from a pre-mRNA in a cell of the subject that contains the NMD exon and that encodes Nav1.1 protein, thereby modulating the level of processed mRNA encoding the Nav1.1 protein, and modulating expression of Nav1.1 protein in the cell of the subject; wherein the therapeutic agent binds to a targeted portion of the pre-mRNA encoding the Nav1.1 protein, and wherein the targeted portion is: from about 1000 nucleotides upstream from the 5' end of NMD exon to about 100 nucleotides upstream from the 5' end of the NMD exon; or from about 100 nucleotides downstream of the 3' end of the NMD exon to about 1000 nucleotides downstream of the 3' end of the NMD exon.

[0002d] In another aspect, the present disclosure refers to a therapeutic agent or a vector encoding the therapeutic agent; wherein the therapeutic agent binds to a targeted portion of a pre-mRNA that contains a non-sense mediated RNA decay-inducing exon (NMD exon) and that encodes Nav1.1 protein, whereby the therapeutic agent modulates exclusion of the NMD exon from the pre-mRNA encoding Nav1.1, and wherein the targeted portion is: from about 1000 nucleotides upstream from the 5' end of an NMD exon to about 100 nucleotides upstream from the 5' end of the NMD exon; or from about 100 nucleotides downstream of the 3' end of the NMD exon to about 1000 nucleotides downstream of the 3' end of the NMD exon.

[0003] Disclosed herein, in certain examples, is a method of modulating expression of *SCN1A* protein in a cell having an mRNA that contains a non-sense mediated RNA decay-inducing exon (NMD exon mRNA) and encodes *SCN1A* protein, the method comprising contacting a therapeutic agent to the cell, whereby the therapeutic agent modulates splicing of the NMD exon from the NMD exon mRNA encoding *SCN1A* protein, thereby modulating the level of processed mRNA encoding *SCN1A* protein, and modulating expression of *SCN1A* protein in the cell, wherein the therapeutic agent binds to a targeted portion of the NMD exon mRNA encoding *SCN1A*, and wherein the targeted portion is: from about 1000 nucleotides upstream from the 5' end of an NMD-inducing exon (NIE) to about 100 nucleotides upstream from the 5' end of the NIE; or from about 100 nucleotides downstream of the 3' end of the NIE to about 1000 nucleotides downstream of the 3' end of the NIE. In some examples, the therapeutic agent interferes with binding of a factor involved in splicing of the NMD exon from a region of the targeted portion. In some

examples, the targeted portion is at most about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides upstream of 5' end of the NIE. In some examples, the targeted portion is at least about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides,

about 60 nucleotides, about 50 nucleotides, about 40 nucleotides, about 30 nucleotides, about 20 nucleotides, about 10 nucleotides, about 5 nucleotides, about 4 nucleotides, about 2 nucleotides, about 1 nucleotides upstream of 5' end of the NIE. In some examples, the targeted portion is at most about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides downstream of 3' end of the NIE. In some examples, the targeted portion is at least about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides, about 40 nucleotides, about 30 nucleotides, about 20 nucleotides, about 10 nucleotides, about 5 nucleotides, about 4 nucleotides, about 2 nucleotides, about 1 nucleotides downstream of 3' end of the NIE. In some examples, the therapeutic agent is an antisense oligomer (ASO). In some examples, the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% identity to any one of SEQ ID NOs: 12-731. In some examples, the therapeutic agent promotes exclusion of the NMD exon from the processed mRNA encoding SCN1A protein. In some examples, exclusion of the NMD exon from the processed mRNA encoding SCN1A 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 exclusion of the NMD exon from the processed mRNA encoding SCN1A protein in a control cell. In some examples, the therapeutic agent increases level of the processed mRNA encoding SCN1A protein in the cell. In some examples, an amount of the processed mRNA encoding SCN1A 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 an total amount of the processed mRNA encoding SCN1A protein in a control cell.

[0004] Disclosed herein, in certain examples, is a method of treating a disease or condition in a subject in need thereof by modulating expression of SCN1A protein in a cell of the subject, comprising: contacting the cell of the subject with a therapeutic agent that modulates splicing of a non-sense mediated mRNA decay-inducing exon (NMD exon) from an mRNA in the cell that contains the NMD exon and encodes SCN1A, thereby modulating the level of processed mRNA encoding the SCN1A protein, and modulating expression of SCN1A protein in the cell of the subject; wherein the therapeutic agent binds to a targeted portion of the NMD exon mRNA encoding SCN1A, and wherein the targeted portion is: from about 1000 nucleotides upstream from the 5' end of an NMD-inducing exon (NIE) to about 100 nucleotides upstream from the 5' end of the NIE; or from about 100 nucleotides downstream of the 3' end of the NIE to about 1000 nucleotides downstream of the 3' end of the NIE. In some examples, the therapeutic agent interferes with binding of a factor involved in splicing of the NMD exon from a region of the targeted portion. In some examples, the targeted portion is at most about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides upstream of 5' end of the NIE. In some examples, the targeted portion is at least about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides, about 40 nucleotides, about 30 nucleotides, about 20 nucleotides, about 10 nucleotides, about 5 nucleotides, about 4 nucleotides, about 2 nucleotides, about 1 nucleotides upstream of 5' end of the NIE. In some examples, the targeted portion is at most about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides downstream of 3' end of the NIE. In some examples, the targeted portion is at least about 800 nucleotides, about 700 nucleotides, about 600 nucleotides, about 500 nucleotides, about 400 nucleotides, about 300 nucleotides, about 200 nucleotides, about 100 nucleotides, about 80 nucleotides, about 70 nucleotides, about 60 nucleotides, about 50 nucleotides, about 40 nucleotides, about 30 nucleotides, about 20 nucleotides, about 10 nucleotides, about 5 nucleotides, about 4 nucleotides, about 2 nucleotides, about 1 nucleotides downstream of 3' end of the NIE. In some examples, the therapeutic agent is an antisense oligomer (ASO). In some examples, the ASO comprises a sequence that is at least about

80%, 85%, 90%, 95%, 97%, or 100% identity to any one of SEQ ID NOs: 12-731. In some examples, the therapeutic agent promotes exclusion of the NMD exon from the processed mRNA encoding SCN1A protein. In some examples, exclusion of the NMD exon from the processed mRNA encoding SCN1A 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 exclusion of the NMD exon from the processed mRNA encoding SCN1A protein in a control cell. In some examples, the therapeutic agent increases level of the processed mRNA encoding SCN1A protein in the cell. In some examples, an amount of the processed mRNA encoding SCN1A 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 an total amount of the processed mRNA encoding SCN1A protein in a control cell. In some examples, the disease or condition is induced by a loss-of-function mutation in *Na_v1.1*. In some examples, the disease or condition is associated with haploinsufficiency of the *SCN1A* gene, and wherein the subject has a first allele encoding a functional SCN1A, and a second allele from which SCN1A is not produced or produced at a reduced level, or a second allele encoding a nonfunctional SCN1A or a partially functional SCN1A. In some examples, the disease or condition is encephalopathy. In some examples, the encephalopathy is epileptic encephalopathy. In some examples, the disease or condition is Dravet Syndrome (DS); severe myoclonic epilepsy of infancy (SMEI)-borderland (SMEB); Febrile seizure (FS); epilepsy, generalized, with febrile seizures plus (GEFS+); epileptic encephalopathy, early infantile, 13; cryptogenic generalized epilepsy; cryptogenic focal epilepsy; myoclonic-astatic epilepsy; Lennox-Gastaut syndrome; West syndrome; idiopathic spasms; early myoclonic encephalopathy; progressive

myoclonic epilepsy; alternating hemiplegia of childhood; unclassified epileptic encephalopathy; sudden unexpected death in epilepsy (SUDEP); sick sinus syndrome 1; autism; or malignant migrating partial seizures of infancy. In some examples, GEFS+ is epilepsy, generalized, with febrile seizures plus, type 2. In some examples, the Febrile seizure is Febrile seizures, familial, 3A. In some examples, SMEB is SMEB without generalized spike wave (SMEB-SW), SMEB without myoclonic seizures (SMEB-M), SMEB lacking more than one feature of SMEI (SMEB-O), or intractable childhood epilepsy with generalized tonic-clonic seizures (ICEGTC).

[0005] Disclosed herein, in certain examples, is a method of modulating expression of SCN1A protein in a cell having an mRNA that contains a non-sense mediated RNA decay-inducing exon (NMD exon mRNA) and encodes SCN1A protein, the method comprising contacting a therapeutic agent to the cell, whereby the therapeutic agent modulates splicing of the NMD exon from the NMD exon mRNA encoding SCN1A protein, thereby modulating the level of processed mRNA encoding SCN1A protein, and modulating expression of SCN1A protein in the cell, wherein the therapeutic agent binds to a targeted portion of the NMD exon mRNA encoding SCN1A, and wherein the targeted portion is from about 1000 nucleotides upstream from the 5' end of an NMD-inducing exon (NIE) to about 1000 nucleotides downstream of the 3' end of the NIE.

[0006] Disclosed herein, in certain examples, is a method of treating a disease or condition in a subject in need thereof by modulating expression of SCN1A protein in a cell of the subject, comprising: contacting the cell of the subject with a therapeutic agent that modulates splicing of a non-sense mediated mRNA decay-inducing exon (NMD exon) from an mRNA in the cell that contains the NMD exon and encodes SCN1A, thereby modulating the level of processed mRNA encoding the SCN1A protein, and modulating expression of SCN1A protein in the cell of the subject; wherein the therapeutic agent binds to a targeted portion of the NMD exon mRNA encoding SCN1A, and wherein the targeted portion is from about 1000 nucleotides upstream from the 5' end of an NMD-inducing exon (NIE) to about 1000 nucleotides downstream of the 3' end of the NIE.

[0007] Disclosed herein, in certain examples, is an antisense oligomer (ASO) comprising a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% identity to any one of SEQ ID NOs: 12-731.

[0008] Disclosed herein, in certain examples, is an antisense oligomer (ASO) consisting of a sequence selected from SEQ ID NOs: 12-731.

[0009] Disclosed herein, in certain examples, is a method of treating a disease or condition in a subject in need thereof by modulating expression of SCN1A protein in a cell of the subject, comprising: contacting the cell of the subject with an ASO comprising a sequence that is at least about 80%, 85%,

90%, 95%, 97%, or 100% identity to any one of SEQ ID NOs: 12-731; or an ASO consisting of a sequence selected from SEQ ID NOs: 12-731.

[0010] Disclosed herein, in certain examples, is a kit comprising an ASO comprising a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% identity to any one of SEQ ID NOs: 12-731; or an ASO consisting of a sequence selected from SEQ ID NOs: 12-731.

INCORPORATION BY REFERENCE

[0011] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0013] FIG. 1 depicts a schematic representation of a target mRNA that contains a non-sense mediated RNA decay-inducing exon (NMD exon mRNA) and therapeutic agent-mediated exclusion of the nonsense-mediated mRNA decay-inducing exon to increase expression of the full-length target protein or functional RNA. **FIG. 1A** shows a cell divided into nuclear and cytoplasmic compartments. In the nucleus, a pre-mRNA transcript of a target gene undergoes splicing to generate mRNA, and this mRNA is exported to the cytoplasm and translated into target protein. For this target gene, some fraction of the mRNA contains a nonsense-mediated mRNA decay-inducing exon (NMD exon mRNA) that is degraded in the cytoplasm, thus leading to no target protein production. **FIG. 1B** shows an example of the same cell divided into nuclear and cytoplasmic compartments. Treatment with a therapeutic agent, such as an antisense oligomer (ASO), promotes the exclusion of the nonsense-mediated mRNA decay-inducing exon and results in an increase in mRNA, which is in turn translated into higher levels of target protein. **FIG. 1C** is a schematic representation of therapeutic ASO-mediated exclusion of a nonsense-mediated mRNA decay-inducing exon, which decreases non-productive mRNA and increases productive mRNA and increases expression of the full-length target protein from the productive mRNA.

[0014] FIG. 2 depicts identification of an exemplary nonsense-mediated mRNA decay (NMD)-inducing exon in the *SCN1A* gene. The identification of the NMD-inducing exon in the *SCN1A* gene using comparative genomics is shown, visualized in the UCSC genome browser. The upper panel

CLAIMS

What is claimed is:

1. A method of modulating expression of Nav1.1 protein in a cell having a pre-mRNA that contains a non-sense mediated mRNA decay-inducing exon (NMD exon) and that encodes Nav1.1 protein, the method comprising contacting a therapeutic agent or a vector encoding the therapeutic agent to the cell, whereby the therapeutic agent modulates exclusion of the NMD exon from the pre-mRNA encoding Nav1.1 protein, thereby modulating a level of processed mRNA encoding Nav1.1 protein, and modulating expression of Nav1.1 protein in the cell, wherein the therapeutic agent binds to a targeted region of the pre-mRNA encoding Nav1.1, and wherein the targeted region is: from about 1000 nucleotides upstream from the 5' end of the NMD exon to about 100 nucleotides upstream from the 5' end of the NMD exon; or from about 100 nucleotides downstream of the 3' end of the NMD exon to about 1000 nucleotides downstream of the 3' end of the NMD exon.
2. The method of claim 1, wherein the therapeutic agent interferes with binding of a factor involved in splicing of the NMD exon from a region of the targeted region.
3. The method of claim 1, wherein the targeted region is at most 500 nucleotides, upstream of 5' end of the NMD exon.
4. The method of claim 1, wherein the targeted region is at least 500 nucleotides upstream of 5' end of the NMD exon.
5. The method of claim 1, wherein the targeted region is at most 500 nucleotides downstream of 3' end of the NMD exon.
6. The method of claim 1, wherein the targeted region is at least 500 nucleotides downstream of 3' end of the NMD exon.
7. The method of any one of claims 1-6, wherein the NMD exon comprises a sequence with at least 95% sequence identity to SEQ ID NO: 7.
8. The method of any one of claims 1-7, wherein the targeted region is within an intronic sequence flanking the NMD exon.
9. The method of any one of claims 1-8, wherein the targeted region is comprised within sequence with at least 95% sequence identity to SEQ ID NO: 6.

10. The method of any one of claims 1-9, wherein the therapeutic agent is an antisense oligomer (ASO).
11. The method of claim 10, wherein the ASO comprises a sequence that is at least about 95% identical to any one of SEQ ID NOs: 12-731.
12. The method of any one of claims 1-11, wherein the therapeutic agent promotes exclusion of the NMD exon from the pre-mRNA.
13. The method of claim 12, wherein the therapeutic agent increases a level of the processed mRNA encoding Nav1.1 protein in the cell.
14. The method of claim 13, wherein the therapeutic agent increases a level of Nav1.1 protein in the cell.
15. The method of claim 14, wherein an amount of the Nav1.1 protein in the cell contacted with the therapeutic agent is increased at least 1.1-fold compared to a total amount of Nav1.1 protein in a control cell.
16. The method of any one of claims 1-15, wherein the ASO consists of a sequence selected from the group consisting of SEQ ID NOs: 72, 73, 76, 181, 220, 432, 433, 436, 541 and 580.
17. The method of any one of claims 1-16, wherein the method comprises contacting a vector encoding the therapeutic agent to the cell, wherein the vector is a viral vector.
18. A therapeutic agent or vector encoding a therapeutic agent for use in therapy, wherein the therapeutic agent modulates splicing of a non-sense mediated mRNA decay-inducing exon (NMD exon) from a pre-mRNA in a cell of the subject that contains the NMD exon and that encodes Nav1.1 protein, thereby modulating the level of processed mRNA encoding the Nav1.1 protein, and modulating expression of Nav1.1 protein in the cell of the subject; wherein the therapeutic agent binds to a targeted portion of the pre-mRNA encoding the Nav1.1 protein, and wherein the targeted portion is: from about 1000 nucleotides upstream from the 5' end of NMD exon to about 100 nucleotides upstream from the 5' end of the NMD exon; or from about 100 nucleotides downstream of the 3' end of the NMD exon to about 1000 nucleotides downstream of the 3' end of the NMD exon.
19. Use of a therapeutic agent or vector encoding a therapeutic agent in the manufacture of a medicament for the treatment of a disease or condition associated with haploinsufficiency of the *SCN1A* gene, wherein the therapeutic agent modulates splicing of a non-sense mediated mRNA

decay-inducing exon (NMD exon) from a pre-mRNA in a cell of the subject that contains the NMD exon and that encodes Nav1.1 protein, thereby modulating the level of processed mRNA encoding the Nav1.1 protein, and modulating expression of Nav1.1 protein in the cell of the subject; wherein the therapeutic agent binds to a targeted portion of the pre-mRNA encoding the Nav1.1 protein, and wherein the targeted portion is: from about 1000 nucleotides upstream from the 5' end of NMD exon to about 100 nucleotides upstream from the 5' end of the NMD exon; or from about 100 nucleotides downstream of the 3' end of the NMD exon to about 1000 nucleotides downstream of the 3' end of the NMD exon.

20. The use according to claim 19, wherein the disease or condition is associated with a loss-of-function mutation in Nav1.1 protein.
21. The use according to claim 19 or 20, wherein the subject has a first allele encoding a functional Nav1.1 protein, and a second allele from which Nav1.1 protein is not produced or produced at a reduced level, or a second allele encoding a nonfunctional Nav1.1 protein or a partially functional Nav1.1 protein.
22. The use according to any one of claims 19-21, wherein the disease or condition is Dravet Syndrome (DS); severe myoclonic epilepsy of infancy (SMEI)-borderland (SMEB); Febrile seizure (FS); Febrile seizures, familial, 3A; epilepsy, generalized, with febrile seizures plus (GEFS+); epilepsy, generalized, with febrile seizures plus, type 2; encephalopathy; epileptic encephalopathy, early infantile, 13; cryptogenic generalized epilepsy; cryptogenic focal epilepsy; myoclonic-astatic epilepsy; Lennox-Gastaut syndrome; West syndrome; idiopathic spasms; early myoclonic encephalopathy; progressive myoclonic epilepsy; alternating hemiplegia of childhood; unclassified epileptic encephalopathy; sudden unexpected death in epilepsy (SUDEP); sick sinus syndrome 1; autism; or malignant migrating partial seizures of infancy.
23. A therapeutic agent or a vector encoding the therapeutic agent; wherein the therapeutic agent binds to a targeted portion of a pre-mRNA that contains a non-sense mediated RNA decay-inducing exon (NMD exon) and that encodes Nav1.1 protein, whereby the therapeutic agent modulates exclusion of the NMD exon from the pre-mRNA encoding Nav1.1, and wherein the targeted portion is: from about 1000 nucleotides upstream from the 5' end of an NMD exon to about 100 nucleotides upstream from the 5' end of the NMD exon; or from about 100 nucleotides

downstream of the 3' end of the NMD exon to about 1000 nucleotides downstream of the 3' end of the NMD exon.