

CLAIMS

What is claimed is:

1. A method of treating a Autosomal Dominant Mental Retardation 5 (MRD5) or Dravet Syndrome (DS) in a subject in need thereof, by increasing the expression of a target protein or functional RNA by cells of the subject, wherein the cells have a retained-intron-containing pre-mRNA (RIC pre-mRNA), the RIC pre-mRNA comprising a retained intron, an exon flanking the 5' splice site, an exon flanking the 3' splice site, and wherein the RIC pre-mRNA encodes the target protein or functional RNA, the method comprising contacting the cells of the subject with an antisense oligomer (ASO) complementary to a targeted portion of the RIC pre-mRNA encoding the target protein or functional RNA, whereby the retained intron is constitutively spliced from the RIC pre-mRNA encoding the target protein or functional RNA, thereby increasing the level of mRNA encoding the target protein or functional RNA, and increasing the expression of the target protein or functional RNA in the cells of the subject.
2. A method of increasing expression of a target protein, wherein the target protein is SYNGAP1 or SCN1A, by cells having a retained-intron-containing pre-mRNA (RIC pre-mRNA), the RIC pre-mRNA comprising a retained intron, an exon flanking the 5' splice site of the retained intron, an exon flanking the 3' splice site of the retained intron, and wherein the RIC pre-mRNA encodes SYNGAP1 or SCN1A protein, the method comprising contacting the cells with an antisense oligomer (ASO) complementary to a targeted portion of the RIC pre-mRNA encoding SYNGAP1 or SCN1A protein, whereby the retained intron is constitutively spliced from the RIC pre-mRNA encoding SYNGAP1 or SCN1A protein, thereby increasing the level of mRNA encoding SYNGAP1 or SCN1A protein, and increasing the expression of SYNGAP1 or SCN1A protein in the cells.
3. The method of claim 1, wherein the method is a method of treating MRD5 and the target protein is SYNGAP1, or the method is a method of treating DS and the target protein is SCN1A.
4. The method of claim 1, wherein the target protein or the functional RNA is a compensating protein or a compensating functional RNA that functionally augments or replaces a target protein or functional RNA that is deficient in amount or activity in the subject.
5. The method of claim 2, wherein the cells are in or from a subject having a condition caused by a deficient amount or activity of SYNGAP1 or SCN1A protein.
6. The method of any one of claims 1 to 5, wherein the deficient amount of the target protein is caused by haploinsufficiency of the target protein, wherein the subject has a first allele encoding a functional target protein, and a second allele from which the target protein is not produced, or a second allele encoding a nonfunctional target protein, and wherein the antisense oligomer binds to a targeted portion of a RIC pre-mRNA transcribed from the first allele.

7. The method of any one of claims 1 to 5, wherein the subject has a condition caused by a disorder resulting from a deficiency in the amount or function of the target protein, wherein the subject has

- (a) a first mutant allele from which
 - (i) the target protein is produced at a reduced level compared to production from a wild-type allele,
 - (ii) the target protein is produced in a form having reduced function compared to an equivalent wild-type protein, or
 - (iii) the target protein is not produced, and
- (b) a second mutant allele from which
 - (i) the target protein is produced at a reduced level compared to production from a wild-type allele,
 - (ii) the target protein is produced in a form having reduced function compared to an equivalent wild-type protein, or
 - (iii) the target protein is not produced, and

wherein when the subject has a first mutant allele (a)(iii), the second mutant allele is (b)(i) or (b)(ii), and wherein when the subject has a second mutant allele (b)(iii), the first mutant allele is (a)(i) or (a)(ii), and wherein the RIC pre-mRNA is transcribed from either the first mutant allele that is (a)(i) or (a)(ii), and/or the second allele that is (b)(i) or (b)(ii).

8. The method of claim 7, wherein the target protein is produced in a form having reduced function compared to the equivalent wild-type protein.

9. The method of claim 7, wherein the target protein is produced in a form that is fully-functional compared to the equivalent wild-type protein.

10. The method of any of claims 1 to 9, wherein the targeted portion of the RIC pre-mRNA is in the retained intron within the region +6 relative to the 5' splice site of the retained intron to -16 relative to the 3' splice site of the retained intron.

11. The method of any of claims 1 to 9, wherein the targeted portion of the RIC pre-mRNA is in the retained intron within:

- (a) the region +6 to +499 relative to the 5' splice site of the retained intron; or
- (b) the region -16 to -496 relative to the 3' splice site of the retained intron.

12. The method of any of claims 1 to 9, wherein the targeted portion of the RIC pre-mRNA is within:

- (a) the region +2e to -4e in the exon flanking the 5' splice site of the retained intron; or
- (b) the region +2e to -4e in the exon flanking the 3' splice site of the retained intron.

13. The method of any of claims 1 to 9, wherein the targeted portion of the RIC pre-mRNA is within:
- (a) the region -4e to -1,054e relative to the 5' splice site of the retained intron;
 - (b) the region +6 to +499 relative to the 5' splice site of the retained intron;
 - (c) the region -16 to -496 relative to the 3' splice site of the retained intron; or
 - (d) the region +2e to +1,912e relative to the 3' splice site of the retained intron.
14. The method of any one of claims 1 to 13, wherein the target protein is SCN1A.
15. The method of claim 14, wherein the RIC pre-mRNA comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 4-7.
16. The method of claim 14, wherein the RIC pre-mRNA is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to SEQ ID NO: 1.
17. The method of claim 14, wherein the targeted portion of the RIC 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 SEQ ID NO: 2593.
18. The method of claim 14, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 10-1037.
19. The method of claim 14, wherein the targeted portion of the RIC pre-mRNA is within the region -264e to +496 relative to the 5' splice site of the retained intron 21 or within the region -496 to +37e relative to the 3' splice site of the retained intron 21.
20. The method of claim 19, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 10-266 or 524-1037.
21. The method of claim 14, wherein the targeted portion of the RIC pre-mRNA is within the region -264e to -4e relative to the 5' splice site of the retained intron 21.
22. The method of claim 21, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 10-62, 524-576, or 781-833.
23. The method of claim 14, wherein the targeted portion of the RIC pre-mRNA is in retained intron 21 within the region +6 to +496 relative to the 5' splice site of the retained intron 21.
24. The method of claim 23, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 63-162, 577-675, or 834-932.

25. The method of claim 14, wherein the targeted portion of the RIC pre-mRNA is in retained intron 21 within the region -16 to -496 relative to the 3' splice site of the retained intron 21.
26. The method of claim 25, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 163-258, 676-772, or 933-1029.
27. The method of claim 14, wherein the targeted portion of the RIC pre-mRNA is within the region +2e to +37e relative to the 3' splice site of the retained intron 21.
28. The method of claim 27, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 259-266, 773-780, or 1030-1037.
29. The method of claim 14, wherein the targeted portion of the RIC pre-mRNA is within the region -264e to +496 relative to the 5' splice site of the retained intron 23 or within the region -496 to +37e relative to the 3' splice site of the retained intron 23.
30. The method of claim 29, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 267-523.
31. The method of claim 14, wherein the targeted portion of the RIC pre-mRNA is within the region -264e to -4e relative to the 5' splice site of the retained intron 23.
32. The method of claim 31, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 267-319.
33. The method of claim 14, wherein the targeted portion of the RIC pre-mRNA is in retained intron 23 within the region +6 to +496 relative to the 5' splice site of the retained intron 23.
34. The method of claim 33, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 320-418.
35. The method of claim 14, wherein the targeted portion of the RIC pre-mRNA is in retained intron 23 within the region -16 to -496 relative to the 3' splice site of the retained intron 23.
36. The method of claim 35, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 419-515.
37. The method of claim 14, wherein the targeted portion of the RIC pre-mRNA is within the region +2e to +37e relative to the 3' splice site of the retained intron 23.
38. The method of claim 37, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 516-523.

39. The method of any one of claims 1 to 13, wherein the target protein is SYNGAP1.
40. The method of claim 39, wherein the RIC pre-mRNA comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 8 or 9.
41. The method of claim 39, wherein the RIC pre-mRNA is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to SEQ ID NO: 2 or 3.
42. The method of claim 39, wherein the targeted portion of the RIC 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 SEQ ID NO: 2592, 2594, or 2595.
43. The method of claim 39, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1038-2591.
44. The method of claim 39, wherein the targeted portion of the RIC pre-mRNA is within the region -73e to +499 relative to the 5' splice site of the retained intron 18 or within the region -496 to +1,912e relative to the 3' splice site of the retained intron 19.
45. The method of claim 44, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1038-1509 or 1815- 2286.
46. The method of claim 39, wherein the targeted portion of the RIC pre-mRNA is within the region -73e to -4e relative to the 5' splice site of the retained intron 18.
47. The method of claim 44, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1038-1050 or 1815-1827.
48. The method of claim 39, wherein the targeted portion of the RIC pre-mRNA is in retained intron 18 within the region +6 to +499 relative to the 5' splice site of the retained intron 18.
49. The method of claim 48, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1051-1136 or 1828-1913.
50. The method of claim 39, wherein the targeted portion of the RIC pre-mRNA is in retained intron 19 within the region -16 to -496 relative to the 3' splice site of the retained intron 19.
51. The method of claim 50, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1137-1228 or 1914-2005.
52. The method of claim 39, wherein the targeted portion of the RIC pre-mRNA is within the region +17e to +1,912e relative to the 3' splice site of the retained intron 19.

53. The method of claim 52, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1229-1509 or 2006-2286.
54. The method of claim 39, wherein the targeted portion of the RIC pre-mRNA is within the region -1,054e to +251 relative to the 5' splice site of the retained intron 15 or within the region -256 to +157e relative to the 3' splice site of the retained intron 15.
55. The method of claim 54, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1510-1814 or 2287-2591.
56. The method of claim 39, wherein the targeted portion of the RIC pre-mRNA is within the region -4e to -1,054e relative to the 5' splice site of the retained intron 15.
57. The method of claim 56, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1510-1686 or 2287-2463.
58. The method of claim 39, wherein the targeted portion of the RIC pre-mRNA is in retained intron 15 within the region +6 to +251 relative to the 5' splice site of the retained intron 15.
59. The method of claim 58, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1687-1736 or 2464-2513.
60. The method of claim 39, wherein the targeted portion of the RIC pre-mRNA is in retained intron 15 within the region -16 to -256 relative to the 3' splice site of the retained intron 15.
61. The method of claim 60, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1737-1785 or 2514-2562.
62. The method of claim 39, wherein the targeted portion of the RIC pre-mRNA is within the region +2e to +157e relative to the 3' splice site of the retained intron 15.
63. The method of claim 62, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1786-1814 or 2563-2591.
64. The method of any one of claims 1 to 63, wherein the antisense oligomer does not increase the amount of the target protein or the functional RNA by modulating alternative splicing of pre-mRNA transcribed from a gene encoding the functional RNA or target protein.
65. The method of any one of claims 1 to 64, wherein the antisense oligomer does not increase the amount of the target protein or the functional RNA by modulating aberrant splicing resulting from mutation of the gene encoding the target protein or the functional RNA.

66. The method of any one of claims 1 to 65, wherein the RIC pre-mRNA was produced by partial splicing of a full-length pre-mRNA or partial splicing of a wild-type pre-mRNA.

67. The method of any one of claims 1 to 66, wherein the mRNA encoding the target protein or functional RNA is a full-length mature mRNA, or a wild-type mature mRNA.

68. The method of any one of claims 1 to 67, wherein the target protein produced is full-length protein, or wild-type protein.

69. The method of any one of claims 1 to 68, wherein the total amount of the mRNA encoding the target protein or functional RNA produced in the cell contacted with the antisense oligomer 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 total amount of the mRNA encoding the target protein or functional RNA produced in a control cell.

70. The method of one any of claims 1 to 69, wherein the total amount of target protein produced by the cell contacted with the antisense oligomer 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 total amount of target protein produced by a control cell.

71. The method of any of one claims 1 to 70, wherein the antisense oligomer comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage.

72. The method of any one of claims 1 to 71, wherein the antisense oligomer comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl, a 2'-Fluoro, or a 2'-O-methoxyethyl moiety.

73. The method of any one of claims 1 to 72, wherein the antisense oligomer comprises at least one modified sugar moiety.

74. The method of claim 73, wherein each sugar moiety is a modified sugar moiety.
75. The method of any one of claims 1 to 74, wherein the antisense oligomer 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.
76. The method of any one of claims 1 to 75, wherein the antisense oligomer is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or 100%, complementary to the targeted portion of the RIC pre-mRNA encoding the protein.
77. The method of any one of claims 1 to 76, wherein the cell comprises a population of RIC pre-mRNAs transcribed from the gene encoding the target protein or functional RNA, wherein the population of RIC pre-mRNAs comprises two or more retained introns, and wherein the antisense oligomer binds to the most abundant retained intron in the population of RIC pre-mRNAs.
78. The method of claim 77, whereby the binding of the antisense oligomer to the most abundant retained intron induces splicing out of the two or more retained introns from the population of RIC pre-mRNAs to produce mRNA encoding the target protein or functional RNA.
79. The method of any one of claims 1 to 78, wherein the cell comprises a population of RIC pre-mRNAs transcribed from the gene encoding the target protein or functional RNA, wherein the population of RIC pre-mRNAs comprises two or more retained introns, and wherein the antisense oligomer binds to the second most abundant retained intron in the population of RIC pre-mRNAs.
80. The method of claim 79, whereby the binding of the antisense oligomer to the second most abundant retained intron induces splicing out of the two or more retained introns from the population of RIC pre-mRNAs to produce mRNA encoding the target protein or functional RNA.
81. The method of any of claims 1 to 80, wherein the method further comprises assessing SYNGAP1 or SCN1A protein expression.
82. The method of any of claims 1 to 81, wherein MRD5 is treated and wherein the antisense oligomer binds to a targeted portion of a *SYNGAP1* RIC pre-mRNA, wherein the targeted portion is within a sequence selected from SEQ ID NOs: 1038-2591, or wherein DS is treated and wherein the antisense oligomer binds to a targeted portion of a *SCN1A* RIC pre-mRNA, wherein the targeted portion is

within a sequence selected from SEQ ID NOs: 10-1037.

83. The method of any of claims 1 to 82, wherein the subject is a human.
84. The method of any of claims 1 to 82, wherein the subject is a non-human animal.
85. The method of any of claims 1 to 83, wherein the subject is a fetus, an embryo, or a child.
86. The method of any of claims 1 to 85, wherein the cells are *ex vivo*.
87. The method of any of claims 1 to 86, wherein the antisense oligomer is administered by intrathecal injection, intracerebroventricular injection, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection of the subject.
88. The method of any of claims 1 to 87, wherein the 9 nucleotides at -3e to -1e of the exon flanking the 5' splice site and +1 to +6 of the retained intron, are identical to the corresponding wild-type sequence.
89. The method of any of claims 1 to 88, wherein the 16 nucleotides at -15 to -1 of the retained intron and +1e of the exon flanking the 3' splice site are identical to the corresponding wild-type sequence.
90. An antisense oligomer as used in a method of any of claims 1 to 89.
91. An antisense oligomer comprising a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 10-2591.
92. A pharmaceutical composition comprising the antisense oligomer of claim 90 or 91 and a pharmaceutically acceptable excipient, diluent, or carrier.
93. A method of treating a subject in need thereof, by administering the pharmaceutical composition of claim 92 by intrathecal injection, intracerebroventricular injection, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection.
94. A composition comprising an antisense oligomer for use in a method of increasing expression of a target protein or a functional RNA by cells to treat MRD5 or DS in a subject in need thereof, associated with a deficient protein or deficient functional RNA, wherein the deficient protein or deficient functional RNA is deficient in amount or activity in the subject, wherein the antisense oligomer enhances constitutive splicing of a retained intron-containing pre-mRNA (RIC pre-mRNA) encoding the target protein or the functional RNA, wherein the target protein is:
 - (a) the deficient protein; or
 - (b) a compensating protein which functionally augments or replaces the deficient protein or in the subject;

and wherein the functional RNA is:

- (c) the deficient RNA; or
- (d) a compensating functional RNA which functionally augments or replaces the deficient functional RNA in the subject;

wherein the RIC pre-mRNA comprises a retained intron, an exon flanking the 5' splice site and an exon flanking the 3' splice site, and wherein the retained intron is spliced from the RIC pre-mRNA encoding the target protein or the functional RNA, thereby increasing production or activity of the target protein or the functional RNA in the subject.

95. A composition comprising an antisense oligomer for use in a method of treating a condition associated with SYNGAP1 or SCN1A protein in a subject in need thereof, the method comprising the step of increasing expression of SYNGAP1 or SCN1A protein by cells of the subject, wherein the cells have a retained-intron-containing pre-mRNA (RIC pre-mRNA) comprising a retained intron, an exon flanking the 5' splice site of the retained intron, an exon flanking the 3' splice site of the retained intron, and wherein the RIC pre-mRNA encodes the SYNGAP1 or SCN1A protein, the method comprising contacting the cells with the antisense oligomer, whereby the retained intron is constitutively spliced from the RIC pre-mRNA transcripts encoding SYNGAP1 or SCN1A protein, thereby increasing the level of mRNA encoding SYNGAP1 or SCN1A protein, and increasing the expression of SYNGAP1 or SCN1A protein, in the cells of the subject.

96. The composition of claim 95, wherein the condition is a disease or disorder.

97. The composition of claim 96, wherein the disease or disorder is AD mental retardation 5 or Dravet syndrome.

98. The composition of claim 97, wherein the target protein and RIC pre-mRNA are encoded by the *SYNGAP1* or *SCN1A* gene.

99. The composition of any of claims 94 to 98, wherein the antisense oligomer targets a portion of the RIC pre-mRNA that is in the retained intron within the region +6 relative to the 5' splice site of the retained intron to -16 relative to the 3' splice site of the retained intron.

100. The composition of any of claims 94 to 98, wherein the antisense oligomer targets a portion of the RIC pre-mRNA that is in the retained intron within:

- (a) the region +6 to +499 relative to the 5' splice site of the retained intron; or
- (b) the region -16 to -496 relative to the 3' splice site of the retained intron.

101. The composition of any of claims 94 to 98, wherein the antisense oligomer targets a portion of the RIC pre-mRNA that is within the region about 100 nucleotides downstream of the 5' splice site of the at least one retained intron, to about 100 nucleotides upstream of the 3' splice site of the at least one retained intron.

102. The composition of any of claims 94 to 98, wherein the targeted portion of the RIC pre-mRNA is within:

- (a) the region +2e to -4e in the exon flanking the 5' splice site of the retained intron; or
- (b) the region +2e to -4e in the exon flanking the 3' splice site of the retained intron.

103. The composition of any of claims 94 to 98, wherein the targeted portion of the RIC pre-mRNA is within:

- (a) the region -4e to -1,054e relative to the 5' splice site of the retained intron;
- (b) the region +6 to +499 relative to the 5' splice site of the retained intron;
- (c) the region -16 to -496 relative to the 3' splice site of the retained intron; or
- (d) the region +2e to +1,912e relative to the 3' splice site of the retained intron.

104. The composition of any one of claims 94 to 98, wherein the target protein is SCN1A.

105. The composition of claim 104, wherein the RIC pre-mRNA comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 4-7.

106. The composition of claim 104, wherein the RIC pre-mRNA is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to SEQ ID NO: 1.

107. The composition of claim 104, wherein the targeted portion of the RIC 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 SEQ ID NO: 2593.

108. The composition of claim 104, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 10-1037.

109. The composition of claim 104, wherein the targeted portion of the RIC pre-mRNA is within the region -264e to +496 relative to the 5' splice site of the retained intron 21 or within the region -496 to +37e relative to the 3' splice site of the retained intron 21.

110. The composition of claim 109, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 10-266 or 524-1037.

111. The composition of claim 104, wherein the targeted portion of the RIC pre-mRNA is within the region -264e to -4e relative to the 5' splice site of the retained intron 21.

112. The composition of claim 111, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 10-62, 524-576, or 781-833.

113. The composition of claim 104, wherein the targeted portion of the RIC pre-mRNA is in retained intron 21 within the region +6 to +496 relative to the 5' splice site of the retained intron 21.
114. The composition of claim 113, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 63-162, 577-675, or 834-932.
115. The composition of claim 104, wherein the targeted portion of the RIC pre-mRNA is in retained intron 21 within the region -16 to -496 relative to the 3' splice site of the retained intron 21.
116. The composition of claim 115, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 163-258, 676-772, or 933-1029.
117. The composition of claim 104, wherein the targeted portion of the RIC pre-mRNA is within the region +2e to +37e relative to the 3' splice site of the retained intron 21.
118. The composition of claim 117, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 259-266, 773-780, or 1030-1037.
119. The composition of claim 104, wherein the targeted portion of the RIC pre-mRNA is within the region -264e to +496 relative to the 5' splice site of the retained intron 23 or within the region -496 to +37e relative to the 3' splice site of the retained intron 23.
120. The composition of claim 119, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 267-523.
121. The composition of claim 104, wherein the targeted portion of the RIC pre-mRNA is within the region -264e to -4e relative to the 5' splice site of the retained intron 23.
122. The composition of claim 121, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 267-319.
123. The composition of claim 104, wherein the targeted portion of the RIC pre-mRNA is in retained intron 23 within the region +6 to +496 relative to the 5' splice site of the retained intron 23.
124. The composition of claim 123, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 320-418.
125. The composition of claim 104, wherein the targeted portion of the RIC pre-mRNA is in retained intron 23 within the region -16 to -496 relative to the 3' splice site of the retained intron 23.

126. The composition of claim 125, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 419-515.
127. The composition of claim 104, wherein the targeted portion of the RIC pre-mRNA is within the region +2e to +37e relative to the 3' splice site of the retained intron 23.
128. The composition of claim 127, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 516-523.
129. The composition of any one of claims 94 to 98, wherein the target protein is SYNGAP1.
130. The composition of claim 129, wherein the RIC pre-mRNA comprises a sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to any one of SEQ ID NOs: 8 or 9.
131. The composition of claim 129, wherein the RIC pre-mRNA is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 97%, or 100% sequence identity to SEQ ID NO: 2 or 3.
132. The composition of claim 129, wherein the targeted portion of the RIC 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 SEQ ID NO: 2592, 2594, or 2595.
133. The composition of claim 129, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1038-2591.
134. The composition of claim 129, wherein the targeted portion of the RIC pre-mRNA is within the region -73e to +499 relative to the 5' splice site of the retained intron 18 or within the region -496 to +1,912e relative to the 3' splice site of the retained intron 19.
135. The composition of claim 134, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1038-1509 or 1815-2286.
136. The composition of claim 129, wherein the targeted portion of the RIC pre-mRNA is within the region -73e to -4e relative to the 5' splice site of the retained intron 18.
137. The composition of claim 136, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1038-1050 or 1815-1827.
138. The composition of claim 129, wherein the targeted portion of the RIC pre-mRNA is in retained intron 18 within the region +6 to +499 relative to the 5' splice site of the retained intron 18.
139. The composition of claim 138, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1051-1136 or 1828-1913.

140. The composition of claim 129, wherein the targeted portion of the RIC pre-mRNA is in retained intron 19 within the region -16 to -496 relative to the 3' splice site of the retained intron 19.
141. The composition of claim 140, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1137-1228 or 1914-2005.
142. The composition of claim 129, wherein the targeted portion of the RIC pre-mRNA is within the region +17e to +1,912e relative to the 3' splice site of the retained intron 19.
143. The composition of claim 142, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1229-1509 or 2006-2286.
144. The composition of claim 129, wherein the targeted portion of the RIC pre-mRNA is within the region -1,054e to +251 relative to the 5' splice site of the retained intron 15 or within the region -256 to +157e relative to the 3' splice site of the retained intron 15.
145. The composition of claim 144, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1510-1814 or 2287-2591.
146. The composition of claim 129, wherein the targeted portion of the RIC pre-mRNA is within the region -4e to -1,054e relative to the 5' splice site of the retained intron 15.
147. The composition of claim 146, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1510-1686 or 2287-2463.
148. The composition of claim 129, wherein the targeted portion of the RIC pre-mRNA is in retained intron 15 within the region +6 to +251 relative to the 5' splice site of the retained intron 15.
149. The composition of claim 148, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1687-1736 or 2464-2513.
150. The composition of claim 129, wherein the targeted portion of the RIC pre-mRNA is in retained intron 15 within the region -16 to -256 relative to the 3' splice site of the retained intron 15.
151. The composition of claim 150, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1737-1785 or 2514-2562.
152. The composition of claim 129, wherein the targeted portion of the RIC pre-mRNA is within the region +2e to +157e relative to the 3' splice site of the retained intron 15.
153. The composition of claim 152, wherein the ASO comprises a sequence that is at least about 80%, 85%, 90%, 95%, 97%, or 100% complimentary to any one of SEQ ID NOs: 1786-1814 or 2563-2591.

154. The composition of any one of claims 94 to 153 wherein the antisense oligomer does not increase the amount of target protein or functional RNA by modulating alternative splicing of the pre-mRNA transcribed from a gene encoding the target protein or functional RNA.
155. The composition of any one of claims 94 to 154, wherein the antisense oligomer does not increase the amount of the functional RNA or functional protein by modulating aberrant splicing resulting from mutation of the gene encoding the target protein or functional RNA.
156. The composition of any one of claims 94 to 155, wherein the RIC pre-mRNA was produced by partial splicing from a full-length pre-mRNA or a wild-type pre-mRNA.
157. The composition of any one of claims 94 to 156, wherein the mRNA encoding the target protein or functional RNA is a full-length mature mRNA, or a wild-type mature mRNA.
158. The composition of any one of claims 94 to 157, wherein the target protein produced is full-length protein, or wild-type protein.
159. The composition of any one of claims 94 to 158, wherein the retained intron is a rate-limiting intron.
160. The composition of any one of claims 94 to 159 wherein said retained intron is the most abundant retained intron in said RIC pre-mRNA.
161. The composition of any one of claims 94 to 159, wherein the retained intron is the second most abundant retained intron in said RIC pre-mRNA.
162. The composition of any one of claims 94 to 161, wherein the antisense oligomer comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage.
163. The composition of any of claims 94 to 162 wherein said antisense oligomer is an antisense oligonucleotide.
164. The composition of any of claims 94 to 163, wherein the antisense oligomer comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl, a 2'-Fluoro, or a 2'-O-methoxyethyl moiety.
165. The composition of any of claims 94 to 164, wherein the antisense oligomer comprises at least one modified sugar moiety.
166. The composition of claim 165, wherein each sugar moiety is a modified sugar moiety.
167. The composition of any of claims 94 to 166, wherein the antisense oligomer 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.

168. A pharmaceutical composition comprising the antisense oligomer of any of the compositions of claims 94 to 167, and a pharmaceutically acceptable excipient, diluent, or carrier.

169. A method of treating a subject in need thereof, by administering the pharmaceutical composition of claim 168 by intrathecal injection, intracerebroventricular injection, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection.

170. A pharmaceutical composition comprising: an antisense oligomer that hybridizes to a target sequence of a *SCN1A* or *SYNGAP1* mRNA transcript, wherein the *SCN1A* or *SYNGAP1* mRNA transcript comprises a retained intron, wherein the antisense oligomer induces splicing out of the retained intron from the *SCN1A* or *SYNGAP1* mRNA transcript; and a pharmaceutically acceptable excipient, diluent, or carrier.

171. The pharmaceutical composition of claim 170, wherein the *SCN1A* or *SYNGAP1* mRNA transcript is a *SCN1A* or *SYNGAP1* RIC pre-mRNA transcript.

172. The pharmaceutical composition of claim 170 or 171, wherein the targeted portion of the *SCN1A* or *SYNGAP1* RIC pre-mRNA transcript is in the retained intron within the region +500 relative to the 5' splice site of the retained intron to -500 relative to the 3' spliced site of the retained intron.

173. The pharmaceutical composition of claim 170 or 171, wherein the *SCN1A* or *SYNGAP1* RIC pre-mRNA transcript is encoded by a genetic sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to any one of SEQ ID NOs: 1-3.

174. The pharmaceutical composition of claim 170 or 171, wherein the *SCN1A* or *SYNGAP1* RIC pre-mRNA transcript comprises a sequence with at least about 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to any one of SEQ ID NOs: 4-9.

175. The pharmaceutical composition of claim 170, wherein the antisense oligomer comprises a backbone modification comprising a phosphorothioate linkage or a phosphorodiamidate linkage.

176. The pharmaceutical composition of claim 170, wherein the antisense oligomer is an antisense oligonucleotide.

177. The pharmaceutical composition of claim 170, wherein the antisense oligomer comprises a phosphorodiamidate morpholino, a locked nucleic acid, a peptide nucleic acid, a 2'-O-methyl, a 2'-Fluoro, or a 2'-O-methoxyethyl moiety.

178. The pharmaceutical composition of claim 170, wherein the antisense oligomer comprises at least one modified sugar moiety.

179. The pharmaceutical composition of claim 170, wherein the antisense oligomer comprises 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.

180. The pharmaceutical composition of claim 170 or 171, wherein the antisense oligomer is at least 80%, at least 85%, at least 90%, at least 95%, at least 98%, at least 99%, or is 100% complementary to a targeted portion of the *SCN1A* or *SYNGAP1* RIC pre-mRNA transcript.

181. The pharmaceutical composition of claim 170 or 171 wherein the targeted portion of the *SCN1A* or *SYNGAP1* RIC pre-mRNA transcript is within a sequence selected from SEQ ID NOs: 2592-2595.

182. The pharmaceutical composition of claim 170, wherein the antisense oligomer comprises a nucleotide sequence that is at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 10-2591.

183. The pharmaceutical composition of claim 170, wherein the antisense oligomer comprises a nucleotide sequence selected from SEQ ID NOs: 10-2591.

184. The pharmaceutical composition of any one of the claims 170-183, wherein the pharmaceutical composition is formulated for intrathecal injection, intracerebroventricular injection, intraperitoneal injection, intramuscular injection, subcutaneous injection, or intravenous injection.

185. A method of inducing processing of a deficient *SCN1A* or *SYNGAP1* mRNA transcript to facilitate removal of a retained intron to produce a fully processed *SCN1A* or *SYNGAP1* mRNA transcript that encodes a functional form of a *SCN1A* or *SYNGAP1* protein, the method comprising:

- (a) contacting an antisense oligomer to a target cell of a subject;
- (b) hybridizing the antisense oligomer to the deficient *SCN1A* or *SYNGAP1* mRNA transcript,

wherein the deficient *SCN1A* or *SYNGAP1* mRNA transcript is capable of encoding the functional form of a SCN1A or SYNGAP1 protein and comprises at least one retained intron;

- (c) removing the at least one retained intron from the deficient *SCN1A* or *SYNGAP1* mRNA transcript to produce the fully processed *SCN1A* or *SYNGAP1* mRNA transcript that encodes the functional form of SCN1A or SYNGAP1 protein; and
- (d) translating the functional form of SCN1A or SYNGAP1 protein from the fully processed *SCN1A* or *SYNGAP1* mRNA transcript.

186. The method of claim 185, wherein the retained intron is an entire retained intron.

187. The method of claim 185, wherein the deficient *SCN1A* or *SYNGAP1* mRNA transcript is a *SCN1A* or *SYNGAP1* pre-mRNA transcript.

188. A method of treating a subject having a condition caused by a deficient amount or activity of SCN1A or SYNGAP1 protein comprising administering to the subject an antisense oligomer comprising a nucleotide sequence with at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to any one of SEQ ID NOs: 10-2591.