

SUMMARY

In an aspect of the present disclosure, there is provided a use of a UNC13A cryptic exon splice variant specific inhibitor in the manufacture of a medicament for reducing expression of a UNC13A cryptic exon splice variant in a cell, wherein:

(a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the UNC13A cryptic exon splice variant mature mRNA transcript; and

(b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide.

In another aspect of the present disclosure, there is provided a use of a UNC13A cryptic exon splice variant specific inhibitor in the manufacture of a medicament for reducing phosphorylated TAR-DNA binding protein-43 (TDP-43) in a cell, wherein:

(a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the UNC13A cryptic exon splice variant mature mRNA transcript; and

(b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide.

In a further aspect of the present disclosure, there is provided a use of a UNC13A cryptic exon splice variant specific inhibitor in the manufacture of a medicament for treating TAR-DNA binding protein-43 (TDP-43) proteinopathy in a subject, wherein:

(a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the UNC13A cryptic exon splice variant mature mRNA transcript; and

(b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide.

In another aspect of the present disclosure, there is provided a use of an UNC13A cryptic exon splice variant specific inhibitor in the manufacture of a medicament for treating a subject that has been identified as having a *UNC13A* gene mutation in intron 20-21, wherein:

(a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the *UNC13A* cryptic exon splice variant mature mRNA transcript; and

(b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide.

In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising an antisense oligonucleotide having 15-40 bases and comprising a base sequence that has at least 80% identity to any one of SEQ ID NOS: 13-90, 92-219, 221-298, 300-377, and 423-640, and a pharmaceutically acceptable excipient.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising an antisense oligonucleotide having:

(a) 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:650;

(b) 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO: 651;

(c) 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:652;

(d) 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:653; or

(e) 18-21 bases that are complementary to SEQ ID NO:654; and a pharmaceutically acceptable excipient.

In a further aspect of the present disclosure, there is provided a modified antisense oligonucleotide having 15-40 bases and comprising a base sequence that has at least 80% identity to any one of SEQ ID NOS: 13-90, 92-219, 221- 298, 300-377, and 423-640.

In another aspect of the present disclosure, there is provided a modified antisense oligonucleotide having 15-40 bases, wherein the base sequence is complementary to:

(a) the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:641; or

(b) the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:642.

In a further aspect of the present disclosure, there is provided a kit comprising an UNC13A cryptic exon splice variant specific antisense oligonucleotide having 15-40 bases and comprising a base sequence that has at least 80% identity to any one of SEQ ID NOS: 13-90, 92-219, 221-298, 300-377, and 423-640.

In another aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein, or a modified antisense oligonucleotide disclosed herein, or a kit disclosed herein, for use in therapy.

In one example, the present disclosure provides a method of reducing expression of a UNC13A cryptic exon splice variant in a cell comprising administering a UNC13A cryptic exon splice variant specific inhibitor, wherein: (a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the UNC13A cryptic exon splice variant mature mRNA transcript; and (b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide.

In another example, the present disclosure provides a method of reducing phosphorylated TAR-DNA binding protein-43 (TDP-43) in a cell comprising administering a UNC13A cryptic exon splice variant specific inhibitor, wherein: (a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the UNC13A cryptic exon splice variant mature mRNA transcript; and (b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide.

In another example, the present disclosure provides a method of treating TAR-DNA binding protein-43 (TDP-43) proteinopathy in a subject comprising administering a UNC13A cryptic exon splice variant specific inhibitor to the subject, wherein: (a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the UNC13A cryptic exon splice variant mature mRNA transcript; and (b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide.

In yet another example, the present disclosure provides a method of treating a subject that has been identified as having a UNC13A gene mutation in intron 20-21 comprising administering an UNC13A cryptic exon splice variant specific inhibitor to the subject, wherein: (a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the UNC13A cryptic exon splice variant mature mRNA transcript; and (b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide.

In examples, the cryptic exon comprises the base sequence of SEQ ID NO:5 or SEQ ID NO:6.

In examples, the UNC13A cryptic exon splice variant comprises SEQ ID NO:7 or SEQ ID NO:8.

In examples, the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide that is complementary to: (a) the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:641; or (b) the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:642.

In examples, the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide that is complementary to: (a) the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:643; or (b) the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:644.

In examples, the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide that is complementary to: (a) the exon 20 splice donor site region in a preprocessed mRNA encoding UNC13A; (b) the cryptic exon splice acceptor site region in a preprocessed mRNA encoding UNC13A; (c) the cryptic exon splice donor site region in a preprocessed mRNA encoding UNC13A; or (d) the exon 21 splice acceptor site region in a preprocessed mRNA encoding UNC13A.

In examples, the exon 20 splice donor site region in the preprocessed mRNA encoding UNC13A comprises or consists of SEQ ID NO:12; the cryptic exon splice acceptor site region in the preprocessed mRNA encoding UNC13A comprises or consists of SEQ ID NO:91; the cryptic exon splice donor site region in the preprocessed mRNA encoding UNC13A comprises or consists of SEQ ID NO:220; or the exon 21 splice acceptor site region in the preprocessed mRNA encoding UNC13A comprises or consists of SEQ ID NO:299.

In examples, the antisense oligonucleotide has 15-40 bases. In examples, the antisense oligonucleotide has 20-30 bases. In examples, the antisense oligonucleotide has 18-25 bases. In examples, the antisense oligonucleotide has 18-22 bases.

In examples, the antisense oligonucleotide has a base sequence that has at least 80%, 85%, 90%, or 95% identity to any one of SEQ ID NOS:13-90, 92-219, 221-298, 300-377, and 423-640. In examples, the antisense oligonucleotide has a base sequence comprising or consisting of any one of SEQ ID NOS: 13-90, 92-219, 221-298,

300-377, and 423-640. In examples, the antisense oligonucleotide has a base sequence comprising or consisting of any one of SEQ ID NOS:423-432, 439-443, 491-498, 502-507, and 513-514.

In examples, the antisense oligonucleotide: (a) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:650; (b) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO: 651; (c) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:652; (d) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:653; or

(e) has 18-21 bases that are complementary to SEQ ID NO:654.

In examples, the antisense oligonucleotide is a modified antisense oligonucleotide. In examples, the modified antisense oligonucleotide comprises a 2'OMe antisense oligonucleotide, 2' O-Methoxyethyl antisense oligonucleotide, phosphorothioate antisense oligonucleotide, or LNA antisense oligonucleotide.

The present disclosure also provides a pharmaceutical composition comprising an antisense oligonucleotide having 15-40 bases and comprising a base sequence that has at least 80% identity to any one of SEQ ID NOS: 13-90, 92-219, 221-298, 300-377, and 423-640, and a pharmaceutically acceptable excipient.

The present disclosure also provides a pharmaceutical composition comprising an antisense oligonucleotide having: (a) 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:650; (b) 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO: 651; (c) 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:652; (d) 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:653; or (e) 18-21 bases that are complementary to SEQ ID NO:654; and a pharmaceutically acceptable excipient.

In another example, the present disclosure provides a modified antisense oligonucleotide having 15-40 bases and comprising a base sequence that has at least 80% identity to any one of SEQ ID NOS: 13-90, 92-219, 221-298, 300-377, and 423-640.

In yet another example, the present disclosure provides a modified antisense oligonucleotide having 15-40 bases, wherein wherein the base sequence is complementary to: (a) the 5' end of the cryptic exon having a sequence set forth in SEQ

CLAIMS

1. Use of a UNC13A cryptic exon splice variant specific inhibitor in the manufacture of a medicament for reducing expression of a UNC13A cryptic exon splice variant in a cell, wherein:

(a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the UNC13A cryptic exon splice variant mature mRNA transcript; and

(b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide.

2. The use of claim 1 wherein the cryptic exon comprises the base sequence of SEQ ID NO:5 or SEQ ID NO:6.

3. The use of claim 1 or 2, wherein the UNC13A cryptic exon splice variant comprises SEQ ID NO:7 or SEQ ID NO:8.

4. The use of any one of claims 1-3, wherein the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide that is complementary to:

(a) the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:641; or (b) the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:642.

5. The use of any one of claims 1-4, wherein the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide that is complementary to:

(a) the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:643; or (b) the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:644.

6. The use of any one of claims 1-3, wherein the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide that is complementary

to:

- (a) the exon 20 splice donor site region in a preprocessed mRNA encoding UNC13A;
- (b) the cryptic exon splice acceptor site region in a preprocessed mRNA encoding UNC13A;
- (c) the cryptic exon splice donor site region in a preprocessed mRNA encoding UNC13A; or
- (d) the exon 21 splice acceptor site region in a preprocessed mRNA encoding UNC13A.

7. The use of claim 6, wherein:

- (a) the exon 20 splice donor site region in the preprocessed mRNA encoding UNC13A comprises or consists of SEQ ID NO:12;
- (b) the cryptic exon splice acceptor site region in the preprocessed mRNA encoding UNC13A comprises or consists of SEQ ID NO:91;
- (c) the cryptic exon splice donor site region in the preprocessed mRNA encoding UNC13A comprises or consists of SEQ ID NO:220; or
- (d) the exon 21 splice acceptor site region in the preprocessed mRNA encoding UNC13A comprises or consists of SEQ ID NO:299.

8. The use of any one of claims 1-7, wherein the antisense oligonucleotide has 15-40 bases.

9. The use of claim 8, wherein the antisense oligonucleotide has 20-30 bases.

10. The use of claim 8, wherein the antisense oligonucleotide has 18-25 bases.

11. The use of claim 8, wherein the antisense oligonucleotide has 18-22 bases.

12. The use of any one of claims 1-11, wherein the antisense oligonucleotide has a base sequence that has at least 80%, 85%, 90%, or 95% identity to any one of SEQ ID NOS:13-90, 92-219, 221-298, 300-377, and 423-640.

13. The use of claim 12, wherein the antisense oligonucleotide has a base sequence comprising or consisting of any one of SEQ ID NOS: 13-90, 92-219, 221-298, 300-377, and 423-640.

14. The use of claim 13, wherein the antisense oligonucleotide has a base sequence comprising or consisting of any one of SEQ ID NOS:423-432, 439-443, 491- 498, 502-507, and 513-514.

15. The use of any one of claims 1-14, wherein the antisense oligonucleotide:

(a) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:650;

(b) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO: 651;

(c) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:652;

(d) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:653; or

(e) has 18-21 bases that are complementary to SEQ ID NO:654.

16. The use of any one of claims 1-15, wherein the antisense oligonucleotide is a modified antisense oligonucleotide.

17. The use of claim 16, wherein the modified antisense oligonucleotide comprises a 2'OMe antisense oligonucleotide, 2' O-Methoxyethyl antisense oligonucleotide, phosphorothioate antisense oligonucleotide, or LNA antisense oligonucleotide.

18. The use of any one of claims 1-17, wherein the cell is within a subject.

19. The use of any one of claims 1-18, wherein the subject is identified as having an *UNC13A* gene mutation in intron 20-21, optionally wherein the *UNC13A* gene mutation comprises rs12608932 (hg38 chr19:17,641,880 A→C), rs12973192 (hg38 chr19: 17,642,430 C→G), rs56041637 (hg38 chr19:17,642,033-17,642,056 0-2

CATC repeats → 3-5 CATC repeats), and rs62121687 (hg38 chr19:17,642,351 C→ A), or any combination thereof.

20. Use of a UNC13A cryptic exon splice variant specific inhibitor in the manufacture of a medicament for reducing phosphorylated TAR-DNA binding protein-43 (TDP-43) in a cell, wherein:

(a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the UNC13A cryptic exon splice variant mature mRNA transcript; and

(b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide.

21. The use of claim 20 wherein the cryptic exon comprises the base sequence of SEQ ID NO:5 or SEQ ID NO:6.

22. The use of claim 20 or 21, wherein the UNC13A cryptic exon splice variant comprises SEQ ID NO:7 or SEQ ID NO:8.

23. The use of any one of claims 20-22, wherein the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide that is complementary to:

(a) the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:641; or (b) the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:642.

24. The use of any one of claims 20-23, wherein the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide that is complementary to:

(a) the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:643; or (b) the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:644.

25. The use of any one of claims 20-22, wherein the UNC13A cryptic exon

splice variant specific inhibitor comprises an antisense oligonucleotide that is complementary to:

- (a) the exon 20 splice donor site region in a preprocessed mRNA encoding UNC13A;
- (b) the cryptic exon splice acceptor site region in a preprocessed mRNA encoding UNC13A;
- (c) the cryptic exon splice donor site region in a preprocessed mRNA encoding UNC13A; or
- (d) the exon 21 splice acceptor site region in a preprocessed mRNA encoding UNC13A.

26. The use of claim 25, wherein:

- (a) the exon 20 splice donor site region in the preprocessed mRNA encoding UNC13A comprises or consists of SEQ ID NO:12;
- (b) the cryptic exon splice acceptor site region in the preprocessed mRNA encoding UNC13A comprises or consists of SEQ ID NO:91;
- (c) the cryptic exon splice donor site region in the preprocessed mRNA encoding UNC13A comprises or consists of SEQ ID NO:220; or
- (d) the exon 21 splice acceptor site region in the preprocessed mRNA encoding UNC13A comprises or consists of SEQ ID NO:299.

27. The use of any one of claims 16-26, wherein the antisense oligonucleotide has 15-40 bases.

28. The use of claim 27, wherein the antisense oligonucleotide has 20-30 bases.

29. The use of claim 27, wherein the antisense oligonucleotide has 18-25 bases.

30. The use of claim 27, wherein the antisense oligonucleotide has 18-22 bases.

31. The use of any one of claims 16-30, wherein the antisense oligonucleotide has a base sequence that has at least 80% identity to any one of SEQ ID NOS: 13-90, 92-219, 221-298, 300-377, and 423-640.

32. The use of claim 31, wherein the antisense oligonucleotide has a base sequence comprising or consisting of any one of SEQ ID NOS: 13-90, 92-219, 221-298, 300-377, and 423-640.

33. The use of claim 32, wherein the antisense oligonucleotide has a base sequence comprising or consisting of any one of SEQ ID NOS:423-432, 439-443, 491- 498, 502-507, and 513-514.

34. The use of any one of claims 16-33, wherein the antisense oligonucleotide:

(a) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:650;

(b) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO: 651;

(c) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:652;

(d) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:653; or

(e) has 18-21 bases that are complementary to SEQ ID NO:654.

35. The use of any one of claims 16-34, wherein the antisense oligonucleotide is a modified antisense oligonucleotide.

36. The use of claim 35, wherein the modified antisense oligonucleotide comprises a 2'OMe antisense oligonucleotide, 2' O-Methoxyethyl antisense oligonucleotide, phosphorothioate antisense oligonucleotide, or LNA antisense oligonucleotide.

37. The use of any one of claims 16-36, wherein the cell is within a subject.

38. Use of a UNC13A cryptic exon splice variant specific inhibitor in the manufacture of a medicament for treating TAR-DNA binding protein-43 (TDP-43) proteinopathy in a subject, wherein:

(a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the UNC13A cryptic exon splice variant mature mRNA transcript; and

(b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide.

39. Use of an UNC13A cryptic exon splice variant specific inhibitor in the manufacture of a medicament for treating a subject that has been identified as having a *UNC13A* gene mutation in intron 20-21, wherein:

(a) the UNC13A cryptic exon splice variant comprises a cryptic exon between exon 20 and exon 21 of the *UNC13A* cryptic exon splice variant mature mRNA transcript; and

(b) the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide.

40. The use of claim 39, wherein the *UNC13A* gene mutation comprises rs12608932 (hg38 chr19:17,641,880 A→C), rs12973192 (hg38 chr19: 17,642,430 C→G), rs56041637 (hg38 chr19:17,642,033-17,642,056 0-2 CATC repeats → 3-5 CATC repeats), and rs62121687 (hg38 chr19:17,642,351 C→ A), or any combination thereof

41. The use of claim 39 or 40, wherein the subject has decreased expression of TDP-43.

42. A pharmaceutical composition comprising an antisense oligonucleotide having 15-40 bases and comprising a base sequence that has at least 80% identity to any one of SEQ ID NOS: 13-90, 92-219, 221-298, 300-377, and 423-640, and a pharmaceutically acceptable excipient.

43. A pharmaceutical composition comprising an antisense oligonucleotide having:
(a) 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:650;

(b) 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID

NO: 651;

(c) 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:652;

(d) 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:653; or

(e) 18-21 bases that are complementary to SEQ ID NO:654;
and a pharmaceutically acceptable excipient.

44. The pharmaceutical composition of claim 42 or 43, wherein the antisense oligonucleotide has 20-30 bases.

45. The pharmaceutical composition of any one of claims 42-44, wherein the antisense oligonucleotide is a modified antisense oligonucleotide.

46. The pharmaceutical composition of claim 45, wherein the modified antisense oligonucleotide comprises a 2'OMe antisense oligonucleotide, 2' O-Methoxyethyl antisense oligonucleotide, phosphorothioate antisense oligonucleotide, or LNA antisense oligonucleotide.

47. The pharmaceutical composition of any one of claims 42-46, wherein the antisense oligonucleotide is complementary to:

(a) the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:641; or (b) the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:642.

48. The pharmaceutical composition of any one of claims 42-47, wherein the UNC13A cryptic exon splice variant specific inhibitor comprises an antisense oligonucleotide that is complementary to:

(a) the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:643; or (b) the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:644.

49. A modified antisense oligonucleotide having 15-40 bases and comprising a base

sequence that has at least 80% identity to any one of SEQ ID NOS: 13-90, 92-219, 221-298, 300-377, and 423-640.

50. The modified antisense oligonucleotide of claim 49, wherein the antisense oligonucleotide has a base sequence comprising or consisting of any one of SEQ ID NOS: 13-90, 92-219, 221-298, 300-377, and 423-640.

51. The modified antisense oligonucleotide of claim 50, wherein the antisense oligonucleotide has a base sequence comprising or consisting of any one of SEQ ID NOS: 423-432, 439-443, 491-498, 502-507, and 513-514.

52. The modified antisense oligonucleotide of any one of claims 49-51, wherein the modified antisense oligonucleotide comprises a 2'OMe antisense oligonucleotide, 2' O-Methoxyethyl antisense oligonucleotide, phosphorothioate antisense oligonucleotide, or LNA antisense oligonucleotide.

53. A modified antisense oligonucleotide having 15-40 bases, wherein the base sequence is complementary to:

(a) the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:641; or (b) the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:642.

54. The modified antisense oligonucleotide of claim 53, wherein the antisense oligonucleotide that is complementary to:

(a) the 5' end of the UNC13A cryptic exon having a sequence set forth in SEQ ID NO:643; or

(b) the 3' end of the UNC13A cryptic exon having a sequence set forth in SEQ ID NO:644.

55. The modified antisense oligonucleotide of claim 53 or 54, wherein the antisense oligonucleotide:

(a) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:650;

(b) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO: 651;

(c) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:652;

(d) has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:653; or

(e) has 18-21 bases that are complementary to SEQ ID NO:654.

56. The modified antisense oligonucleotide of any one of claims 53-55, wherein the antisense oligonucleotide has a base sequence comprising or consisting of any one of SEQ ID NOS:423-432, 439-443, 491-498, 502-507, and 513-514.

57. The modified antisense oligonucleotide of any one of claims 49-56, wherein the antisense oligonucleotide has 18-25 bases.

58. The modified antisense oligonucleotide of claim 57, wherein the antisense oligonucleotide has 18-22 bases.

59. The modified antisense oligonucleotide of any one of claims 49-56, wherein the antisense oligonucleotide has 20-30 bases.

60. A kit comprising an UNC13A cryptic exon splice variant specific antisense oligonucleotide having 15-40 bases and comprising a base sequence that has at least 80% identity to any one of SEQ ID NOS: 13-90, 92-219, 221-298, 300-377, and 423-640.

61. A pharmaceutical composition of any one of claims 42-48, or a modified antisense oligonucleotide of any one of claims 49-59, or a kit of claim 60, for use in therapy.