

COMPOSITIONS AND METHODS FOR TREATING TDP-43 PROTEINOPATHY

STATEMENT REGARDING SEQUENCE LISTING

The Sequence Listing associated with this application is provided in text format in lieu of a paper copy, and is hereby incorporated by reference into the specification.

- 5 The name of the text file containing the Sequence Listing is
630264_403WO_SEQUENCE_LISTING.txt. The text file is 243 KB, was created on
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BACKGROUND

- The hallmark pathological feature of neurodegenerative diseases amyotrophic
10 lateral sclerosis (ALS) and frontotemporal dementia (FTD) is the depletion of RNA-
binding protein TDP-43 from the nucleus of neurons in the brain and spinal cord. TDP-
43, encoded by *TARDBP*, is an abundant, ubiquitously expressed RNA-binding protein
that normally localizes to the nucleus. It plays a role in fundamental RNA processing
activities including RNA transcription, alternative splicing, and RNA transport (1).
15 TDP-43 can bind to thousands of pre-messenger RNA/mRNA targets (2, 3). Reduction
in TDP-43 from an otherwise normal adult nervous system alters the splicing or
expression levels of more than 1,500 RNAs, including long intron-containing
transcripts (2). A major splicing regulatory function of TDP-43 is to repress the
inclusion of cryptic exons during splicing (4–7). Unlike normal conserved exons, these
20 cryptic exons are lurking in introns and normally excluded from mature mRNAs. When
TDP-43 is depleted from cells, these cryptic exons get spliced into messenger RNAs,
often introducing frame shifts and premature termination or even nonsense-mediated
decay of the mRNA. However, cryptic splicing events that are key for disease remains
to be identified. Thus, the discovery of cryptic splicing targets that are regulated by
25 TDP-43 and also play a role in the pathogenesis of TDP-43 proteinopathies as
therapeutic targets is needed.

SUMMARY

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

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

5 In embodiments, 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.

10 In embodiments, 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.

15 In embodiments, 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.

20 In embodiments, 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.

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

30 In embodiments, 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 embodiments, 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 embodiments, 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 embodiments, the antisense oligonucleotide: (a) has 18-30 bases, 18-25
5 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.

10 In embodiments, the antisense oligonucleotide is a modified antisense oligonucleotide. In embodiments, 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
15 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
20 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.

25 In another aspect, 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 aspect, the present disclosure provides a modified antisense
30 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

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

The present disclosure also provides kits comprising the UNC13A cryptic exon splice variant specific antisense oligonucleotide of the present disclosure.

5 BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

FIGS. 1A-1J. Nuclear depletion of TDP-43 causes cryptic exon inclusion in *UNC13A* RNA and reduced expression of UNC13A protein. FIG. 1A: Splicing analyses were performed on RNA-sequencing results generated from TDP-43-positive and TDP-43-negative neuronal nuclei isolated from frontal cortices of 7 FTD/FTD-ALS
 10 patients. FACS, fluorescent-activated cell sorting. **FIG. 1B:** 65 alternatively spliced genes identified by both MAJIQ ($P(\Delta\Psi > 0.1) > 0.95$)($\Delta\Psi$, changes of local splicing variations between two conditions) and LeafCutter ($P < 0.05$). **FIG. 1C:** Visualization of RNA-sequencing alignment between exon 20 and exon 21 in *UNC13A* (hg38). Libraries were generated as described in (FIG. 1A). CE, cryptic exon. **FIG. 1D:** iCLIP
 15 for TDP-43 indicates that TDP-43 binds to intron 20-21. An example of a region in intron 20-21 that is frequently bound by TDP-43. TDP-43 binding motif (UG)_n is highlighted in orange. **FIG. 1E and FIG. 1H:** RT-qPCR confirmed the inclusion of cryptic exon in *UNC13A* mRNA upon TDP-43 depletion in SH-SY5Y cells (5 independent cell culture experiments for each condition) (FIG. 1E) and in 3
 20 independent induced motor neurons (iMNs) (4 independent cell culture experiments for each iMN) (**FIG. 1H**). The locations of the primers spanning the cryptic exon associated region are shown. RPLP0 were used to normalize qRT-PCR. (two sided-Welch Two Sample t-test, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$; mean $\pm$ s.e.m.). **FIG. 1F and FIG. 1I:** Immunoblotting of UNC13A protein and TDP-
 25 43 in SH-SY5Y cells (FIG. 1F) and iMNs (FIG. 1I) treated with Scramble shRNA or TDP-43 shRNA (n=3). GAPDH served as a loading control. **FIG. 1G:** Quantification of the blots in (**FIG. 1F**) (two-sided Welch Two Sample t-test, * $P < 0.05$, ** $P < 0.01$). **FIG. 1J:** RT-qPCR (n=5) analyses confirmed the inclusion of *UNC13A* cryptic exon upon TDP-43 depletion in neurons derived from human iPS cells (3 independent cell culture

experiments). RPLP0 and GAPDH were used to normalize qRT-PCR (two sided-Welch Two Sample t-test; ***P < 0.001, ****P<0.0001; mean $\pm$ s.e.m.).

FIGS. 2A-2D. *UNC13A* cryptic exon inclusion in human TDP-43 proteinopathies. FIG. 2A: *UNC13A* cryptic exon expression level is significantly increased in the frontal cortices of FTLD-TDP patients. The qRT-PCR primer pair used for cryptic exon detection is shown on top. GAPDH and RPLP0 were used to normalize qRT-PCR (two-tailed Mann-Whitney test, ****P<0.0001; error bars represent 95% confidence intervals). **FIG. 2B:** *UNC13A* cryptic exon is detected in nearly 50% of frontal cortical tissues and temporal cortical tissues from neuropathologically confirmed FTLD-TDP patients in NYGC ALS Consortium cohort. The cryptic exon is also notably absent in tissues from healthy controls, FTLD-FUS, FTLD-TAU and ALS-SOD1 patients. **FIG. 2C:** *UNC13A* cryptic exon signal is positively correlated with phosphorylated TDP-43 levels in frontal cortices of FTLD-TDP patients in Mayo Clinic brain bank (Spearman's rho = 0.572, p-value <0.0001). Data points are colored according to patients' reported genetic mutations. **FIG. 2D:** Spearman's correlations between *UNC13A* cryptic exon signal and phosphorylated TDP-43 levels. Rows colored in green indication the correlation within each genetic mutation group. Rows colored in blue shows the correlation within each disease group.

FIGS. 3A-3B. *UNC13A* cryptic splicing is a pathological feature in human brain associated with loss of nuclear TDP-43. FIG. 3A: BaseScope™ *in situ* hybridization and immunofluorescence was performed on sections from the medial frontal pole. Representative images illustrate the presence of *UNC13A* cryptic exons (arrowheads) in neurons showing depletion of nuclear TDP-43. Neurons with normal nuclear TDP-43, in patients and controls, show no cryptic exons (arrows). **FIG. 3B:** Representative images showing expression of *UNC13A* mRNA in layer 2-3 neurons from the medial frontal pole. BaseScope™ *in situ* hybridization was used to visualize *UNC13A* mRNA, using probes that target the canonical exon20/21 junction, and combined with immunofluorescence for TDP-43 and NeuN. *UNC13A* mRNA expression is restricted to neurons (arrows). Images are maximum intensity projections of a confocal image Z-stack. Scale bar equals 10 μ m.

FIGS. 4A-4J. Risk haplotype associated with ALS/FTD susceptibility potentiates cryptic exon inclusion when TDP-43 is dysfunctional. FIG. 4A: LocusZoom plot showing SNPs associated with ALS/FTD in *UNC13A*. rs12608932, the most significant GWAS hit is chosen to be the reference. Other SNPs are colored based on their levels of linkage equilibrium with rs12608932 in EUR population. The two SNPs in intron 20-21 (black triangles), rs12608932 and rs12973192 are in strong linkage disequilibrium. **FIG. 4B:** There is a higher inclusion of the risk allele (G) at rs12973192 in *UNC13A* splice variant (two-sided paired t-test, $**P = 0.0094$). Both simple linear regression model (**FIG. 4C**) and multiple regression model (**FIG. 4D**) show a strong correlation between the abundance of *UNC13A* cryptic exon and the number of risk alleles. Normality of residuals is tested by Shapiro-Wilk normality test (p-value = 0.2604). **FIG. 4D:** Summary results of the multiple regression analysis using the number of risk alleles at rs12973192, TDP-43 phosphorylation levels, sex, reported genetic mutations as predictor variables. Rows colored in the same color indicate factors within the same variable. Normality of residuals is tested by Shapiro-Wilk normality test (p-value = 0.1751). **FIG. 4E:** Diagram of the location of rs56041637 relative to the two known GWAS hits and *UNC13A* cryptic exon. **FIG. 4F:** Design of *UNC13A* cryptic exon minigene reporter constructs and the location of the primer pair used for RT-PCR. Transcription of GFP and mCherry is controlled by a bidirectional promoter (blue). Black triangles represent the locations of genetic variants as shown in (E). **FIG. 4G:** Splicing of the minigenes was assessed in WT and TDP-43^{-/-} HEK293T cells. HEK293T cells do not endogenously express *UNC13A*. The PCR products represented by each band are marked to the left of each gel. In addition to the inclusion of cryptic exon (b), some splice variants have inclusion of the longer version of the cryptic exon (c) (FIG. 5) or the complete intron upstream of the cryptic exon (d). The risk allele-carrying minigene showed an almost complete loss of canonical splicing product (a) and an increase in alternatively spliced products. **FIG. 4H:** In HeLa cells expressing a different *UNC13A* minigene reporter, depletion of TDP-43 by siRNA (and cycloheximide (CHX) treatment), resulted in inclusion of the cryptic exon, which can be rescued by over-expressing TDP-43 protein (GFP-TDP-43) but not by the RNA-binding deficient mutant TDP-43 (GFP-TDP-43-5FL). **FIG. 4I:** Survival curves of

FTLD-TDP patients stratified based on the number of the risk haplotypes they carry (0, 1, or 2). Patients who are heterozygous and homozygous for the risk haplotype had shorter survival time after disease onset (n= 205, Mayo Clinic brain bank) (Score (logrank) test, p-value = 0.01). Dash lines mark the median survival for each genotype.

- 5 The effect of the risk haplotype is modeled as an additive model using Cox multivariable analysis adjusted for genetic mutations, sex and age at onset. The risk table is shown at the bottom. Summary results of the analysis are in **Fig. 15A. FIG. 4J:** Model of how UNC13A protein expression level is most significantly decreased in patients who both carry the UNC13A risk haplotype and exhibit TDP-43 pathology.
- 10 **FIG. 5A-5D. Splicing analysis using MAJIQ demonstrates inclusion of the cryptic exon between exon 20 and exon 21 of *UNC13A*. FIGS. 5A and 5B:** Depletion of TDP-43 introduces two alternative 3' splicing acceptors in the intron 20-21: one is at chr19:17642591($\Delta\Psi=0.05184$) and the other one is at chr19:17642541($\Delta\Psi=0.48865$). **FIG. 5C and 5D:** An alternative 5' splicing donor is also introduced at chr19:17642414 ($\Delta\Psi=0.772$). Since much higher usage of the chr19:17642541 3' splicing acceptor was observed (**FIG. 5B**), the 128 bp cryptic exon defined by this 3' splicing acceptor and the alternative 5' splicing donor (**FIG. 5C**) became the focus. **FIGS. 5A and 5C** are splice graphs showing the inclusion of the cryptic exon (CE) between exon 20 and exon 21 of *UNC13A*. **FIGS. 5B and 5D:** are violin plots corresponding to **FIGS. 5A and 5C**, respectively. Each violin in (**FIGS. 5B and 5D**) represents the posterior probability distribution of the expected relative inclusion (PSI or Ψ) for the color matching junction in the splice graph. The tails of each violin represent the 10 th and 90 th percentile. The box represents the interquartile range with the line in the middle indicating the median. The white circles mark the expected PSI ($E[\Psi]$). The change in the relative inclusion
- 25 level of each junction between two conditions is referred to as $\Delta\Psi$ or $\Delta\Psi(12)$.

- FIGS 6A-6D. Intron 20-21 of *UNC13A* is conserved among most primates.** The Primates Multiz Alignment & Conservation track on UCSC(39) genome browser (<http://genome.ucsc.edu>) includes 20 mammals, 17 of which are primates. **FIG. 6A:** Exon 20 and exon 21 of *UNC13A* is well conserved among mammals. However, intron 20-21 (**FIG. 6B**), the cryptic exon (**FIG. 6C**), and the splicing acceptor site upstream of
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the cryptic exon (FIG. 6C) and splicing donor site downstream of the cryptic exon (FIG. 6D) are only conserved in primates.

FIGS. 7A-7B. Depletion of TDP-43 from induced motor neurons (iMN) leads to cryptic exon inclusion in UNC13A. FIG. 7A: RT-PCR confirmed the expression of the cryptic exon-containing *UNC13A* mRNA isoforms upon TDP-43 depletion in three independent iMNs (4 independent cell culture experiments for each iMN and condition). In addition to the splice variant containing the cryptic exon, inclusion of a longer version of the cryptic exon was detected (FIG. 5A) and the complete intron upstream of the cryptic exon (FIG. 4G). The PCR products represented by each band are marked to the left of each gel. The location of the PCR primer pair used is shown on top of each gel image. FIG. 7B: The PCR primer pairs spanning the cryptic exon and exon 21 junction confirms cryptic exon inclusion only occurs upon TDP-43 knockdown.

FIG. 8. Total *UNC13A* transcripts do not change significantly in the frontal cortices of most FTLD-TDP patients in Mayo Clinic brain bank. A decrease in total *UNC13A* transcript was observed in FTD patients with no reported genetic mutations and FTD patients with GRN mutations. This may be due to specific pathologies that are currently unclear. The qRT-PCR primer pair used for the detection is shown on top. GAPDH and RPLP0 were used to normalize qRT-PCR (two tailed Mann-Whitney test, ns: $P > 0.05$; ** $P < 0.01$; **** $P < 0.0001$; error bars represent 95% confidence intervals).

FIG 9. *UNC13A* cryptic exon can also be detected in disease relevant tissues of ALS/FTLD, ALS-TDP and ALS/AD patients. The diagnoses of these patients are not neuropathologically confirmed. Therefore, it is unclear whether TDP-43 mislocalization is present in these patients. ALS patients were categorized based on whether they harbor *SOD1* mutations (ALS-SOD1 vs. ALS-TDP). ALS-AD refers to ALS patients with suspected Alzheimer's disease. ALS-FTLD refers to patients who have concurrent FTD and ALS.

FIGS. 10A-10H. *UNC13A* cryptic exon signal and total *UNC13A* signal is correlated with phosphorylated TDP-43 levels in frontal cortices of FTLD-TDP patients in Mayo Clinic brain bank. FIG. 10A: *UNC13A* cryptic exon signal is positively correlated with phosphorylated TDP-43 levels in frontal cortices of FTLD-

TDP patients in Mayo Clinic Brain bank (Spearman's $\rho = 0.572$, p-value < 0.0001). Data points are colored according to patients' disease types. **FIGS. 10B and 10C:** Total UNC13A signal is negatively correlated with phosphorylated TDP-43 levels in the same samples. Data points are colored according to patients' reported genetic mutations (FIG. 10B) and disease types (FIG. 10C) respectively. **FIG. 10D:** Spearman's correlations between total *UNC13A* signal and phosphorylated TDP-43 levels. Rows colored in green shows the correlation within each genetic mutation group. Rows colored in blue shows the correlation within each disease group. **FIGS. 10E-10H:** Scatter plots using untransformed data as input. **FIGS. 10E-10F:** Cryptic exon signal vs. phosphorylated TDP-43 levels. **FIG. 10G-10H:** Total UNC13A signal vs. phosphorylated TDP-42 levels. qRT-PCR primer pair is shown on top of each panel.

FIGS. 11A-11E. *UNC13A* cryptic splicing is associated with loss of nuclear TDP-43 in human brain. **FIG. 11A:** The design of the *UNC13A* e20/CE BaseScope™ probe targeting the alternatively spliced *UNC13A* transcript. **FIG. 11B:** The design of the *UNC13A* e20/e21 BaseScope™ probe targeting canonical *UNC13A* transcript. Each “Z” binds to the transcript independently. Both “Z”s have to be in close proximity for successful signal amplification, ensuring binding specificity. **FIG. 11C:** BaseScope™ *in situ* hybridization and immunofluorescence was performed on sections from the medial frontal pole. Representative images illustrate the presence of *UNC13A* cryptic exons (arrowheads) in neurons showing depletion of nuclear TDP-43 and cytoplasmic aggregation. Neurons with normal nuclear TDP-43, in patients and controls, show no cryptic exons (arrows). **FIG. 11D:** Representative images showing expression of *UNC13A* mRNA in layer 2-3 neurons from the medial frontal pole. BaseScope *in situ* hybridization was used to visualize *UNC13A* mRNA, using probes that target the exon20-exon 21 junction, and combined with immunofluorescence for TDP-43 and NeuN. *UNC13A* mRNA expression is restricted to neurons (arrows). Images are maximum intensity projections of a confocal image Z-stack. Scale bar equals 10 μm . **FIG. 11E:** Six non-overlapping Z-stack images from layer 2-3 of medial frontal pole were captured, per subject, using a 63X oil objective and flattened into a maximum intensity projection image. Puncta counts per image were derived using the “analyze particle” plugin in ImageJ. Each data point represents the number of *UNC13A* cryptic

exon puncta in a single image. The abundance of cryptic exons varies between patients but always exceeds the technical background of the assay, as observed in controls. Data are presented as mean +/- standard deviation.

FIGS. 12A-12C. The levels of cryptic exon inclusion are influenced by the genotype at rs12973192. **FIG. 12A:** Visualization of RNA-seq alignment between exon 20 and exon 21 of *UNC13A*. The RNA-seq libraries were generated from TDP-43 negative neuronal nuclei as described in FIG. 1A. **FIG. 12B:** Samples that are heterozygous (C/G) or homozygous (G/G) at rs12973192 have higher relative inclusion (Ψ) of the cryptic exon with the exception of SRR8571945. **FIG. 12C:** The percentages of C and G alleles in the *UNC13A* spliced variants in TDP-43 depleted iMNs and SRR8571950 neuronal nuclei. Exact binomial test was done for each replicate to test whether the observed difference in percentages differ from what was expected if both alleles are equally included in the cryptic exon.

FIG. 13A-13F. The abundance of *UNC13A* cryptic exon is associated with the number of risk alleles. Simple linear regression model (**FIG. 13A**) and multiple regression model (**FIG. 13B**) using untransformed data show a strong correlation between the abundance of *UNC13A* cryptic exon and the number of risk alleles. **FIG. 13B:** Summary results of the multiple regression analysis using the number of risk alleles, TDP-43 phosphorylation levels, sex, reported genetic mutations as predictor variables. Rows colored in the same color indicate factors within the same variable. **FIGS. 13C and 13E:** Simple linear regression models and **FIGS. 13D and 13F:** multiple regression models using transformed (FIGS. 13A and 13D) and untransformed (E and F) data show the abundance of total *UNC13A* mRNA transcript is not significantly correlated with the number of risk alleles at rs12971392 in the patient carries. This could be a result of the expression of *UNC13A* from neurons that are not affected by TDP-43 pathology as shown in **FIG. 3B** and **FIG. 11D**. The normality of residuals is tested by Shapiro-Wilk normality test and the results are shown at the bottom of each panel. The qPCR primer pair used for the detection is shown on top of each panel.

FIG. 14. rs56041637 and rs62121687 are in strong linkage disequilibrium with both GWAS hits in intron 20-21 of *UNC13A*. Using genetic variants identified

in whole genome sequencing data from 297 ALS patients of European descent (July 2020, Answer ALS), we looked for other genetic variants in intron 20-21 that were not represented in the previous GWASs. Along the axes of the heatmap are all loci that show variation among the 297 patients. Each tile represents the Bonferroni-adjusted p-value from Chi-square test. P-values less than 0.05 are shown in yellow and others are shown in blue or gray. The blue and red blocks highlight the associations of rs12608932 and rs12973192 with other genetic variants in intron 20-21 respectively. Significant associations that are common to both are circled out in black. Two additional SNPs, rs56041637 (Bonferroni-adjusted p-value <0.0001 with rs12608932, Bonferroni-adjusted p-value <0.0001 with rs12973192), and rs62121687 (Bonferroni-adjusted p-value <0.0001 with rs12608932, Bonferroni-adjusted p <0.0001 with rs12973192) were found that are in LD with both. However, since rs62121687 was included in the GWAS and has a p-value of 0.0186585 (36), it was excluded from further analysis

FIGS. 15A-15E. *UNC13A* risk haplotype reduces the survival time of FTLT-DTP patients. FIG. 15A: Summary results of Cox multivariable analysis (adjusted for genetic mutations, sex and age at onset) of an additive model. **FIGS. 15B and 15D:** Survival curves of FTLT-DTP patients (n= 205, Mayo Clinic Brain bank), according to a dominant model (FIG. 15B) and a recessive model (FIG. 15C) and their corresponding risk tables. Summary results of Cox multivariable analysis (adjusted for genetic mutations, sex and age at onset) of a dominant model (FIG. 15C) and a recessive model (FIG. 15D). Both the dominant model (FIGS. 15B and 15C) and the recessive model (FIGS. 15D and 15E) show that the presence of a risk haplotype can reduce the survival of FTLT-DTP patients. Dash lines mark the median survival for each genotype. Log rank p-values were calculated using Score test. Rows colored in green indicate factors within one variable.

FIGS. 16A-16F. The effect of *UNC13A* risk haplotype on survival is more significant in *C9ORF72* hexanucleotide repeat expansion carriers and *GRN* mutation carriers. FIGS. 16A, 16C and 16E: Survival curves of FTLT-DTP patients carrying *C9ORF72* or *GRN* mutations (n= 80, Mayo Clinic Brain bank), according to an additive model (FIG. 16A), a dominant model (FIG. 16C) and a recessive model (FIG.

16E), and their corresponding risk tables. Summary results of Cox multivariable analysis (adjusted for genetic mutations, sex and age at onset) of an additive model (FIG. 16B), a dominant model (FIG. 16D) and a recessive model (FIG. 16F). When we only include FTL-ALS patients who have mutations that are associated with TDP-43 pathology, both the additive model (FIGS. 16A and 16B) and the dominant model (FIGS. 16C and 16D) indicate that the effect of the risk haplotype on survival time becomes more significant. While the survival distributions of the two groups do not differ significantly (log rank p-value = 0.3), the number of risk haplotype is still a strong prognostic factor (p-value = 0.03800). Dash lines mark the median survival for each genotype. Log rank p-values were calculated using Score test.

FIG. 17 shows the *UNC13A* genomic region comprising exon 20, the cryptic exon #1 (128 bp), and exon 21.

FIG. 18 shows the *STMN2* exon structure for the reference transcript and a splice variant containing cryptic exon 2a (top) and the exon 2a sequence (bottom).

FIGS. 19A-19D show *UNC13A* mRNA levels in motor neurons following treatment with *UNC13A* specific 2'MOE antisense oligonucleotides as measured by qPCR. FIGS. 19A-19B show qPCR results using primers/probes specific for *UNC13A* cryptic exon inclusion. FIGS. 19C-19D show qPCR results using primer/probes specific for reference *UNC13A*.

DETAILED DESCRIPTION

Prior to setting forth this disclosure in more detail, it may be helpful to an understanding thereof to provide definitions of certain terms used herein. Additional definitions are set forth throughout this disclosure.

In the present description, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer) or subranges, unless otherwise indicated.

As used herein, the term "about" means $\pm 20\%$ of the indicated range, value, or structure, unless otherwise indicated.

It should be understood that the terms "a" and "an" as used herein refer to "one or more" of the enumerated components. The use of the alternative (*e.g.*, "or") should be understood to mean either one, both, or any combination thereof of the alternatives.

As used herein, the terms "include," "have," and "comprise" are used
5 synonymously, which terms and variants thereof are intended to be construed as non-limiting.

"Optional" or "optionally" means that the subsequently described element, component, event, or circumstance may or may not occur, and that the description includes instances in which the element, component, event, or circumstance occurs and
10 instances in which they do not.

As used herein, "nucleic acid" or "nucleic acid molecule" or "polynucleotide" refers to any of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), oligonucleotide, molecules generated, for example, by the polymerase chain reaction (PCR) or by *in vitro* translation, and molecules generated by any of ligation, scission, endonuclease
15 action, exonuclease action or mechanical action (*e.g.*, shearing). Nucleic acids may be composed of a plurality of monomers that are naturally occurring nucleotides (such as deoxyribonucleotides and ribonucleotides), analogs of naturally occurring nucleotides (*e.g.*, α -enantiomeric forms of naturally-occurring nucleotides), or a combination of both. Modified nucleotides can have modifications in or replacement of sugar moieties,
20 or pyrimidine or purine base moieties (*e.g.*, morpholino nucleotides). Nucleic acid monomers of the polynucleotides can be linked by phosphodiester bonds or analogs of such linkages. Analogs of phosphodiester linkages include phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoranilidate, phosphoramidate, or the like. Nucleic acid molecules can be either
25 single stranded or double stranded.

As used herein, "protein" or "polypeptide" as used herein refers to a compound made up of amino acid residues that are covalently linked by peptide bonds. The term "protein" may be synonymous with the term "polypeptide" or may refer, in addition, to a complex of two or more polypeptides. In certain embodiments, a polypeptide may be
30 a fragment. As used herein, a "fragment" means a polypeptide that is lacking one or more amino acids that are found in a reference sequence. A fragment can comprise a

binding domain, antigen, or epitope found in a reference sequence. A fragment of a reference 5 polypeptide can have at least about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more of amino acids of the amino acid sequence of the reference

5 sequence.

The term "isolated" means that a material, complex, compound, or molecule is removed from its original environment (*e.g.*, the natural environment if it is naturally occurring). For example, a naturally occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or polypeptide, separated
10 from some or all of the co-existing materials in the natural system, is isolated. Such nucleic acid could be part of a vector and/or such nucleic acid or polypeptide could be part of a composition (*e.g.*, a cell lysate), and still be isolated in that such vector or composition is not part of the natural environment for the nucleic acid or polypeptide. The term "gene" means the segment of DNA involved in producing a polypeptide
15 chain; it includes regions preceding and following the coding region "leader and trailer" as well as intervening sequences (introns), if present, between individual coding segments (exons).

As used herein, the term "recombinant" or "genetically engineered" refers to a cell, microorganism, nucleic acid molecule, polypeptide or vector that has been
20 genetically modified by human intervention. For example, a recombinant polynucleotide is modified by human or machine introduction of an exogenous or heterologous nucleic acid molecule, or refers to a cell or microorganism that has been altered by human or machine intervention such that expression of an endogenous nucleic acid molecule or gene is controlled, deregulated or constitutive. Human
25 generated genetic alterations may include, for example, modifications that introduce nucleic acid molecules (which may include an expression control element, such as a promoter) that encode one or more proteins or enzymes, or other nucleic acid molecule additions, deletions, substitutions, or other functional disruption of or addition to a cell's genetic material or encoded products. Exemplary human or machine introduced
30 modifications include those in coding regions or functional fragments thereof of heterologous or homologous polypeptides from a reference or parent molecule.

A “wild-type” gene or gene product is that which is most frequently observed in a population and is thus arbitrarily designed the “normal” or “reference” or “wild-type” form of the gene.

As used herein, "mutation" refers to a change in the sequence of a nucleic acid molecule or polypeptide molecule as compared to a reference or wild-type nucleic acid molecule or polypeptide molecule, respectively. A mutation can result in several different types of change in sequence, including substitution, insertion or deletion of nucleotide(s) or amino acid(s).

A "conservative substitution" refers to amino acid substitutions that do not significantly affect or alter binding characteristics of a particular protein. Generally, conservative substitutions are ones in which a substituted amino acid residue is replaced with an amino acid residue having a similar side chain. Conservative substitutions include a substitution found in one of the following groups: Group 1: Alanine (Ala or A), Glycine (Gly or G), Serine (Ser or S), Threonine (Thr or T); Group 2: Aspartic acid (Asp or D), Glutamic acid (Glu or Z); Group 3: Asparagine (Asn or N), Glutamine (Gln or Q); Group 4: Arginine (Arg or R), Lysine (Lys or K), Histidine (His or H); Group 5: Isoleucine (Ile or I), Leucine (Leu or L), Methionine (Met or M), Valine (Val or V); and Group 6: Phenylalanine (Phe or F), Tyrosine (Tyr or Y), Tryptophan (Trp or W). Additionally or alternatively, amino acids can be grouped into conservative substitution groups by similar function, chemical structure, or composition (*e.g.*, acidic, basic, aliphatic, aromatic, or sulfur-containing). For example, an aliphatic grouping may include, for purposes of substitution, Gly, Ala, Val, Leu, and Ile. Other conservative substitutions groups include: sulfur-containing: Met and Cysteine (Cys or C); acidic: Asp, Glu, Asn, and Gln; small aliphatic, nonpolar or slightly polar residues: Ala, Ser, Thr, Pro, and Gly; polar, negatively charged residues and their amides: Asp, Asn, Glu, and Gln; polar, positively charged residues: His, Arg, and Lys; large aliphatic, nonpolar residues: Met, Leu, Ile, Val, and Cys; and large aromatic residues: Phe, Tyr, and Trp. Additional information can be found in Creighton (1984) *Proteins*, W.H. Freeman and Company.

The term "expression", as used herein, refers to the process by which a polypeptide is produced based on the encoding sequence of a nucleic acid molecule,

such as a gene. The process may include transcription, post-transcriptional control, post-transcriptional modification, translation, post-translational control, post-translational modification, or any combination thereof.

"Sequence identity," as used herein, refers to the percentage of nucleotides (amino acid residues) in one sequence that are identical with the nucleotides (amino acid residues) in another reference polynucleotide (polypeptide) sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. The percentage sequence identity values can be generated using the NCBI BLAST2.0 software as defined by Altschul *et al.* (1997) "Gapped BLAST and PSI-BLAST: a new generation of protein database search programs", Nucleic Acids Res. 25:3389-3402, with the parameters set to default values.

As used herein, "UNC13A" refers to a presynaptic protein found in central and neuromuscular synapses that regulates the release of neurotransmitters, peptides, and hormones. *UNC13A* reference or wildtype mRNA transcript contains 44 exons encoding a 1,703 amino acid protein. In embodiments, NCBI Reference Sequence: NP_001073890.2 (SEQ ID NO:11) is an example of a wildtype or reference UNC13A protein. In embodiments, NCBI Reference Sequence NM_001080421.3 (SEQ ID NO:1) is an example of a wild-type or reference *UNC13A* mRNA transcript. In embodiments, UNC13A includes all forms of UNC13A including wildtype, splice isoforms, variants, mutants, native conformation, misfolded, and post-translationally modified. In embodiments, UNC13A does not include UNC13A cryptic exon splice variant.

As used herein, the term "pre-processed mRNA" or "pre-mRNA" or "precursor mRNA" refers to a primary transcript synthesized from transcription of a DNA template and that has not undergone processing, e.g., splicing, addition of 5' cap, and addition of a 3' polyA tail, in order to become a mature mRNA. The mature mRNA is capable of being translated into protein by the ribosome.

As used herein, the term "cryptic exon" or "pseudoexon" refers to an exon that is absent or not detectably used in wild-type pre-mRNA but are selected in a variant isoform, Cryptic exons may arise as a result of mutations that create new splice sites or

remove the existing binding sites for splicing repressors. Cryptic exons can also emerge from transposable elements (e.g., Alu elements).

As used herein, “UNC13A cryptic exon splice variant” refers to a mRNA, or protein encoded by said mRNA, that comprises a cryptic exon between exon 20 and
5 exon 21. The cryptic exon is obtained from intron 20-21 of the *UNC13A* gene. In embodiments, the cryptic exon has the nucleotide sequence of SEQ ID NO:5 or SEQ ID NO:6. In embodiments, the UNC13A cryptic exon splice variant may have the nucleotide sequence of SEQ ID NO:7, encoding a protein sequence of SEQ ID NO:8, or the nucleotide sequence of SEQ ID NO:9, encoding a protein sequence of SEQ ID
10 NO:10.

As used herein, “transactivation response element DNA-binding protein 43” or “TAR-DNA binding protein-43” or “TDP-43” refers to a protein of typically 414 amino acid residues encoded by *TARDBP*. In embodiments, wildtype TDP43 amino acid sequence is provided by Uniprot Accession number Q13148 (SEQ ID NO:378). In
15 embodiments, TDP43 includes all forms of TDP-43 including wildtype, splice isoforms, variants, mutants, native conformation, misfolded, and post-translationally modified (e.g., ubiquitinated, phosphorylated, acetylated, sumoylated, or cleaved into C-terminal fragments) proteins.

As used herein, the “TAR-DNA binding protein-43 proteinopathy” or “TDP-43
20 proteinopathy” refers to a neurodegenerative disease that is characterized by the deposition of TDP-43 positive protein inclusions in the brain and/or spinal cord of subjects. Cytoplasmic inclusions of hyperphosphorylated, ubiquitinated, cleaved form of TDP-43 are a pathological feature of diseases including but not limited to amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD),
25 primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), facial onset sensory and motor neuronopathy (FOSMN), hippocampal sclerosis (HS), limbic-predominant age-related TDP-43 encephalopathy (LATE), cerebral age-related TDP-43 with sclerosis (CARTS), Guam Parkinson-dementia complex (G-PDC), Guam ALS (G-ALS), Multisystem proteinopathy (MSP), Perry disease, Alzheimer’s disease (AD), and
30 chronic traumatic encephalopathy (CTE).

The terms “complementary” and “complementarity” refer to polynucleotides (*i.e.*, a sequence of nucleotides) related by the base-pairing rules. For example, the sequence “A-G-T,” is complementary to the sequence “T-C-A.” Complementarity may be “partial,” in which only some of the nucleic acids’ bases are matched according to the base pairing rules, or there may be “complete” or “total” complementarity between the nucleic acids. The degree of complementarity between nucleic acid strands has significant effects on the efficiency and strength of hybridization between nucleic acid strands. While perfect complementarity is often desired, some embodiments can include one or more but preferably 6, 5, 4, 3, 2, or 1 mismatches with respect to the target nucleic acid (e.g., RNA). Variations at any location within the oligomer are included. In certain embodiments, variations in sequence near the termini of an oligomer are generally preferable to variations in the interior, and if present are typically within about 6, 5, 4, 3, 2, or 1 nucleotides of the 5’ and/or 3’ terminus.

The terms “antisense oligomer” or “antisense compound” or “antisense oligonucleotide” or “oligonucleotide” are used interchangeably and refer to a short, single-stranded polynucleotide (*e.g.*, 10-50 subunits) made up of DNA, RNA or both, that hybridizes to a target sequence in a nucleic acid (typically an RNA) by Watson-Crick base pairing, to form a nucleic acid:oligomer heteroduplex within the target sequence. An antisense oligonucleotide may comprise unmodified nucleotides or may contain modified nucleotides, non-natural nucleotides, or analog nucleotides, such as morpholino, phosphorothioate, peptide nucleic acid, LNA, 2'-O-Me RNA, 2'F-RNA, 2'-O-MOE-RNA, 2'F-ANA, or any combination thereof.

Such an antisense oligomer can be designed to block or inhibit translation of mRNA or to inhibit natural pre-mRNA splice processing, or induce degradation of targeted mRNAs, and may be said to be “directed to” or “targeted against” a target sequence with which it hybridizes. In embodiments, the target sequence is a region surrounding or including an AUG start codon of an mRNA, a 3’ or 5’ splice site of a pre-processed mRNA, or a branch point. The target sequence may be within an exon or within an intron or a combination thereof. The target sequence for a splice site may include an mRNA sequence having its 5’ end at 1 to about 25 base pairs downstream of a normal splice acceptor junction in a preprocessed mRNA. An exemplary target

sequence for a splice site is any region of a preprocessed mRNA that includes a splice site or is contained entirely within an exon coding sequence or spans a splice acceptor or donor site. An oligomer is more generally said to be “targeted against” a biologically relevant target such as, in the present disclosure, a human *UNC13A* gene pre-mRNA
 5 encoding the UNC13A protein, when it is targeted against the nucleic acid of the target in the manner described above. Exemplary targeting sequences include those listed in Tables 2-5.

The term “oligonucleotide analog” refers to an oligonucleotide having (i) a modified backbone structure, *e.g.*, a backbone other than the standard phosphodiester
 10 linkage found in natural oligo- and polynucleotides, and (ii) optionally, modified sugar moieties, *e.g.*, morpholino moieties rather than ribose or deoxyribose moieties. Oligonucleotide analogs support bases capable of hydrogen bonding by Watson-Crick base pairing to standard polynucleotide bases, where the analog backbone presents the bases in a manner to permit such hydrogen bonding in a sequence-specific fashion
 15 between the oligonucleotide analog molecule and bases in a standard polynucleotide (*e.g.*, single-stranded RNA or single-stranded DNA). Exemplary analogs are those having a substantially uncharged, phosphorus containing backbone.

A “subunit” of an oligonucleotide refers to one nucleotide (or nucleotide analog) unit comprising a purine or pyrimidine base pairing moiety. The term may refer to the
 20 nucleotide unit with or without the attached intersubunit linkage, although, when referring to a “charged subunit”, the charge typically resides within the intersubunit linkage (*e.g.*, a phosphate or phosphorothioate linkage or a cationic linkage).

The purine or pyrimidine base pairing moiety, also referred to herein simply as a “nucleobases,” “base,” or “bases,” may be adenine, cytosine, guanine, uracil, thymine
 25 or inosine. Also included are bases such as pyridin-4-one, pyridin-2-one, phenyl, pseudouracil, 2,4,6-trimethylthoxy benzene, 3-methyl uracil, dihydrouridine, naphthyl, aminophenyl, 5-alkylcytidines (*e.g.*, 5-methylcytidine), 5-alkyluridines (*e.g.*, ribothymidine), 5-halouridine (*e.g.*, 5-bromouridine) or 6-azapyrimidines or 6-alkylpyrimidines (*e.g.* 6-methyluridine), propyne, quesosine, 2-thiouridine, 4-
 30 thiouridine, wybutosine, wybutoxosine, 4-acetyltidine, 5-(carboxyhydroxymethyl)uridine, 5'-carboxymethylaminomethyl-2-thiouridine, 5-

carboxymethylaminomethyluridine, β -D-galactosylqueosine, 1-methyladenosine, 1-methylinosine, 2,2-dimethylguanosine, 3-methylcytidine, 2-methyladenosine, 2-methylguanosine, N6-methyladenosine, 7-methylguanosine, 5-methoxyaminomethyl-2-thiouridine, 5-methylaminomethyluridine, 5-methylcarbonylmethyluridine, 5-methoxyuridine, 5-methyl-2-thiouridine, 2-methylthio-N6-isopentenyladenosine, β -D-mannosylqueosine, uridine-5-oxyacetic acid, 2-thiocytidine, threonine derivatives and others (Burgin *et al.*, 1996, Biochemistry, 35:14090; Uhlman & Peyman, *supra*). By “modified bases” in this aspect is meant nucleotide bases other than adenine (A), guanine (G), cytosine (C), thymine (T), and uracil (U), as illustrated above; such bases can be used at any position in the antisense molecule. Persons skilled in the art will appreciate that depending on the uses of the oligomers, Ts and Us are interchangeable. For instance, with other antisense chemistries such as 2'-O-methyl antisense oligonucleotides that are more RNA-like, the T bases may be shown as U.

The term “targeting sequence” is the sequence in the oligomer or oligomer analog that is complementary (meaning, in addition, substantially complementary) to the “target sequence” in the RNA genome. The entire sequence, or only a portion, of the antisense oligomer may be complementary to the target sequence. For example, in an oligomer having 20-30 bases, about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29 may be targeting sequences that are complementary to the target region. Typically, the targeting sequence is formed of contiguous bases in the oligomer, but may alternatively be formed of non-contiguous sequences that when placed together, *e.g.*, from opposite ends of the oligomer, constitute sequence that spans the target sequence.

A “targeting sequence” may have “near” or “substantial” complementarity to the target sequence and still function for the purpose of the present disclosure, that is, still be “complementary.” Preferably, the oligomer analog compounds employed in the present disclosure have at most one mismatch with the target sequence out of 10 nucleotides, and preferably at most one mismatch out of 20. Alternatively, the antisense oligomers employed have at least 90% sequence identity, and preferably at least 95% sequence identity, with the exemplary targeting sequences as designated herein.

An “amino acid subunit” or “amino acid residue” can refer to an α -amino acid residue ($-\text{CO}-\text{CHR}-\text{NH}-$) or a β - or other amino acid residue (*e.g.*, $-\text{CO}-(\text{CH}_2)_n\text{CHR}-\text{NH}-$), where R is a side chain (which may include hydrogen) and n is 1 to 7, preferably 1 to 4.

- 5 The term “naturally occurring amino acid” refers to an amino acid present in proteins found in nature, such as the 20 (L)-amino acids utilized during protein biosynthesis as well as others such as 4-hydroxyproline, hydroxylysine, desmosine, isodesmosine, homocysteine, citrulline and ornithine. The term “non-natural amino acids” refers to those amino acids not present in proteins found in nature, examples include beta-alanine
10 (β -Ala), 6-aminohexanoic acid (Ahx) and 6-aminopentanoic acid. Additional examples of “non-natural amino acids” include, without limitation, (D)-amino acids, norleucine, norvaline, p-fluorophenylalanine, ethionine and the like, which are known to a person skilled in the art.

- The term “target sequence” refers to a portion of the target RNA against which
15 the oligonucleotide or antisense agent is directed, that is, the sequence to which the oligonucleotide will hybridize by Watson-Crick base pairing of a complementary sequence. In embodiments, the target sequence may be a contiguous region of a pre-mRNA that includes both intron and exon target sequence. In embodiments, the target sequence will consist exclusively of either intron or exon sequences.

- 20 Target and targeting sequences are described as “complementary” to one another when hybridization occurs in an antiparallel configuration. A targeting sequence may have “near” or “substantial” complementarity to the target sequence and still function for the purpose of the present disclosure, that is, it may still be functionally “complementary.” In certain embodiments, an oligonucleotide may have
25 at most one mismatch with the target sequence out of 10 nucleotides, and preferably at most one mismatch out of 20. Alternatively, an oligonucleotide may have at least 90% sequence identity, and preferably at least 95% sequence identity, with the exemplary antisense targeting sequences described herein.

- An oligonucleotide “specifically hybridizes” to a target polynucleotide if the
30 oligomer hybridizes to the target under physiological conditions, with a T_m substantially greater than 45°C , preferably at least 50°C , and typically 60°C - 80°C or

higher. Such hybridization preferably corresponds to stringent hybridization conditions. At a given ionic strength and pH, the T_m is the temperature at which 50% of a target sequence hybridizes to a complementary polynucleotide. Again, such hybridization may occur with “near” or “substantial” complementarity of the antisense oligomer to the target sequence, as well as with exact complementarity.

A “nuclease-resistant” oligomeric molecule (oligomer) refers to one whose backbone is substantially resistant to nuclease cleavage, in non-hybridized or hybridized form; by common extracellular and intracellular nucleases in the body; that is, the oligomer shows little or no nuclease cleavage under normal nuclease conditions in the body to which the oligomer is exposed.

An “effective amount” or “therapeutically effective amount” refers to an amount of therapeutic agent, such as an UNC13A cryptic splice variant inhibitor, administered to a mammalian subject, either as a single dose or as part of a series of doses, which is effective to produce a desired therapeutic effect. For an antisense oligonucleotide, this effect is typically brought about by inhibiting translation or natural splice-processing of a selected target sequence. An “effective amount,” targeted against *UNC13A* cryptic exon splice variant mRNA, also relates to an amount effective to modulate expression of UNC13A cryptic exon splice variant protein.

The term “inhibit” or “inhibitor” refers to an alteration, interference, reduction, down regulation, blocking, suppression, abrogation or degradation, directly or indirectly, in the expression, amount or activity of a target gene, target protein, or signaling pathway relative to (1) a control, endogenous or reference target or pathway, or (2) the absence of a target or pathway, wherein the alteration, interference, reduction, down regulation, blocking, suppression, abrogation or degradation is statistically, biologically, or clinically significant. The term “inhibit” or “inhibitor” includes gene “knock out” and gene “knock down” methods, such as by chromosomal editing.

For example, a “UNC13A cryptic exon splice variant inhibitor” may block, inactivate, reduce or minimize UNC13A cryptic exon splice variant activity or reduce activity by reducing expression of or promoting degradation of UNC13A cryptic exon splice variant, by about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%,

75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more as compared to untreated UNC13A cryptic exon splice variant.

“Treatment” of an individual or a cell is any type of intervention provided as a means to alter the natural course of a disease or pathology in the individual or cell.

5 Treatment includes, but is not limited to, administration of, *e.g.*, a pharmaceutical composition, and may be performed either prophylactically, or subsequent to the initiation of a pathologic event or contact with an etiologic agent. Treatment includes any desirable effect on the symptoms or pathology of a disease or condition associated with inflammation, among others described herein.

10 Also included are “prophylactic” treatments, which can be directed to reducing the rate of progression of the disease or condition being treated, delaying the onset of that disease or condition, or reducing the severity of its onset. “Treatment” or “prophylaxis” does not necessarily indicate complete eradication, cure, or prevention of the disease or condition, or associated symptoms thereof.

15 Additional definitions are provided in the sections below.

UNC13A Cryptic Exon Splice Variants

In one aspect, the present disclosure provides novel *UNC13A* cryptic splice variants that includes a cryptic exon between exons 20 and 21. These cryptic exons are
 20 absent from wildtype *UNC13A* from neuronal nuclei and not present in any of the known isoforms of *UNC13A*. The cryptic exons are obtained from intron 20-21 of the *UNC13A* gene (SEQ ID NO:4). Depletion of TDP-43 introduces two alternative 3’ splicing acceptors in intron 20-21, one at chr19:17642591 ($\Delta\Psi=0.05184$) and the other one is at chr19:17642541 ($\Delta\Psi=0.48865$). An alternative 5’ splicing donor is also
 25 introduced at chr19:17642414 ($\Delta\Psi=0.772$). The chr19:17642541 3’ splicing acceptor, which is more frequently used than the chr19:17642591 3’ splicing acceptor, and alternative 5’ splicing donor results in a 128 bp cryptic exon having a nucleotide sequence as set forth in SEQ ID NO:5 (“cryptic exon #1”). The *UNC13A* cryptic exon #1 variant comprises a nucleotide sequence as set forth in SEQ ID NO:7, encoding a
 30 protein comprising an amino acid sequence as set forth in SEQ ID NO:8. The chr19:17642591 3’ splicing acceptor and alternative 5’ splicing donor results in a 179

bp cryptic exon having a nucleotide sequence as set forth in SEQ ID NO:6 ("cryptic exon #2"). The *UNC13A* cryptic exon #2 variant comprises a nucleotide sequence as set forth in SEQ ID NO:9, encoding a protein comprising an amino acid sequence as set forth in SEQ ID NO:10.

5 *UNC13A* cryptic exon #1 splice variant expression level is significantly increased in frontal cortexes of frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP) patients compared to normal controls. *UNC13A* cryptic exon #1 splice variant has also been detected in disease relevant tissues of ALS patients. In embodiments, expression of *UNC13A* cryptic splice variant #1 or *UNC13A* cryptic
10 splice variant #2 may be used as a biomarker for identifying a subject with a TDP-43 proteinopathy, e.g., FTLD or ALS.

Once TDP-43 becomes depleted from the nucleus and accumulates in the cytoplasm, it becomes phosphorylated. Hyperphosphorylated TDP43 (pTDP-43) is a key feature of pathology of TDP-43 proteinopathies. *UNC13A* cryptic exon #1 splice
15 variant is strongly associated with phosphorylated TDP-43 levels in FTD/ALS patients. In embodiments, expression of *UNC13A* cryptic splice variant #1 or *UNC13A* cryptic splice variant #2 may be used as a biomarker for phosphorylated TDP-43 level in a subject.

Several genetic mutations in intron 20-21 of *UNC13A* have been identified as
20 promoting *UNC13A* cryptic exon inclusion upon TDP-43 depletion. Examples of such genetic mutations include 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 CATC 0-2 repeats → 3-5 CATC repeats), and rs62121687 (hg38 chr19:17,642,351 C→
A). Moreover, *UNC13A* genetic mutations that increase cryptic exon inclusion are
25 associated with decreased survival in FTD-ALS patients. In embodiments, identification of a genetic mutation in intron 20-21 of *UNC13A* in a subject may be used as a biomarker for *UNC13A* cryptic exon inclusion. In embodiments, identification of a genetic mutation in intron 20-21 of *UNC13A* in a subject with a TDP-43 proteinopathy (e.g., FTD, ALS) may be used as a biomarker for decreased survival.

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Table 1: *UNC13A* Sequences

Name	Sequence	SEQ ID NO:
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UNC13A reference mRNA NM_001080421.3	GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGGCCCCG GCGTGAGCCAAGCGCGGGCTGCAGCC GGGAGATGCCCCAGCCCAGCGGCCGCTGAGCCCGACCCGACAGA GCCGGCCCGGCCGCTCCGGCCACC TGCGAGCTCGGAGACATGTCTGTCTTTCGCTTGAGTCAAAAA AGCCAAGTTTGATGGTGCCCAAGAGA AATTCAACACGTACGTGACCCTGAAAGTGCAGAATGTCAAGAGC ACGACCATCGCGGTGCGGGGCAGCCA GCCAGCTGGGAGCAGGATTTTCATGTTTCGAGATTAACCGTCTGG ATTTGGGACTGACGGTGGAGGTGTGG AATAAGGGTCTCATCTGGGACACAATGGTGGGCACTGTGTGGAT CCCACTGAGGACCATCCGCCAGTCCA ATGAGGAGGGCCCTGGAGAGTGGCTGACGCTGGACTCCCAGGTC ATCATGGCAGACAGTGAGATCTGTGG CACCAAGGACCCACCTTCCACCGCATCCTCCTGGACACGCGCT TTGAGCTACCCTTAGACATTCCTGAA GAGGAGGCTCGCTACTGGGCCAAGAAGCTGGAGCAGCTCAATGC TATGCGGGACCAAGGATGAATATTCGT TCCAAGATGAGCAAGACAAGCCTCTGCCTGTCCCCAGCAACCAG TGCTGCAACTGGAATTATTTGGCTG GGGTGAGCAGCACAACGATGACCCCGACAGTGCAGTGGATGATC GTGACAGTGACTACCGCAGTGAAACG AGCAACAGCATCCCGCCGCCCTATTATACTACGTCACAACCCAA CGCCTCAGTCCACCAATATTCCTGTT GCCCACCACCCCTGGGCTCCCGGGAGTCCCTACAGTGAATCCATG CACAGTTACGAGGAGTTCTCTGAGCC ACAAGCCCTCAGCCCCACGGGTAGCAGCCGCTATGCCTCTTCCG GGGAGCTGAGCCAGGGAAGCTCTCAG CTGAGCGAGGACTTCGACCCTGACGAGCACAGCCTGCAGGGCTC CGACATGGAGGATGAGCGGGACCGG ACTCTACCACTCCTGCCACAGCTCGGTACGCTACCACAAAGAC TCGCCTCGCTGGGACCAGGATGAGGA AGAGCTGGAGGAGGACCTGGAGGACTTCCTGGAGGAGGAGGAGC TGCTTGAAGATGAGGAGGAGCTGGAG GAGGAGGAGGAGGAGGTGCCTGACGATTTGGGCAGCTATGCCCA GCGTGAAGACGTAGCTGTGGCTGAGC CCAAAGACTTCAAACGCATCAGCCTCCCGCCAGCTGCCCCAGGG AAGGAGGACAAGGCCCCAGTGGCACC CACCGAGGCCCCGACATGGCCAAGGTGGCCCCCAAGCCAGCCA CGCCCGACAAGGTGCCTGCAGCTGAG CAGATCCCTGAGGCTGAGCCACCCAAGGACGAGGAGAGTTTCAG GCCGAGAGAGGATGAGGAAGGCCAGG AGGGGCAGGACTCCATGTCCAGGGCCAAGGCCAAGTGGCTGCGT GCCTTCAACAAGGTGCGGATGCAGCT GCAGGAGGCCCCGGGAGAAGGAGAGATGTCTAAATCCCTATGGT TCAAAGGCGGCCAGGGGCGGTCTC ATCATCATCGACAGCATGCCAGACATCCGCAAGAGGAAACCTAT CCCACTCGTGAGCGACTTGGCCATGT CCCTGGTCCAGTCCAGGAAAGCGGGCATCACCTCGGCCTTGGCC TCCAGCACGTTGAACAACGAGGAGCT GAAAAACACGTTTACAAGAAGACCCTGCAAGCCTTAATCTACC CCATCTCGTGACGACGCCACACAAC TTCGAAGTGTGGACGGCCACCACGCCCACCTACTGTACGAGTG CGAGGGGCTGCTGTGGGGCATCGCGA GGCAGGGCATGCGCTGCACCGAGTGCAGTGTCAAGTGCCACGAG AAGTGCCAGGACCTGCTCAACGCCGA CTGCCTGCAGCGGGCTGCGGAGAAGAGCTCCAAGCACGGGGCGG AGGACCGGACACAGAACATCATCATG	1
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	GTGCTCAAGGACCGCATGAAGATCCGGGAGCGCAACAAGCCCCGA GATCTTCGAGCTCATCCAGGAGATCT TCGCGGTGACCAAGACGGCGCACACGCAGCAGATGAAGGCGGTC AAGCAGAGCGTGCTGGACGGCACGTC CAAGTGGTCCGCCAAGATCAGCATCACCGTGGTCTGCGCCCAGG GCTTGCAGGCAAAGGACAAGACAGGA TCCAGTGACCCCTATGTACCGTCCAGGTCGGGAAGACCAAGAA ACGGACAAAAACCATCTATGGGAACC TCAACCCGGTGTGGGAGGAGAATTTCCACTTTGAATGTCACAAT TCCTCCGACCGCATCAAGGTGCGCGT CTGGGACGAGGATGACGACATCAAATCCCGCGTGAAACAGAGGT TCAAGAGGGAATCTGACGATTTCTG GGGCAGACGATCATTGAGGTGCGGACGCTCAGCGGCGAGATGGA CGTGTGGTACAACCTGGACAAGCGAA CTGACAAATCTGCCGTGTGCGGTGCCATCCGGCTCCACATCAGT GTGGAGATCAAAGGCGAGGAGAAGGT GGCCCCGTACCATGTCCAGTACACCTGTCTGCATGAGAACCTGT TCCACTTCGTGACCGACGTGCAGAAC AATGGGGTCGTGAAGATCCCAGATGCCAAGGGTGACGATGCCTG GAAGGTTTACTACGATGAGACAGCCC AGGAGATTGTGGACGAGTTTGCCATGCGCTACGGCGTCGAGTCC ATCTACCAAGCCATGACCCACTTTGC CTGCCTCTCCTCCAAGTATATGTGCCAGGGGTGCCTGCCGTCA TGAGCACCTTGCTCGCCACATCAAT GCCTACTACGCACACACCACCGCCTCCACCAACGTGTCTGCCTC CGACCGCTTCGCCGCTCCAACTTTG GGAAAGAGCGCTTCGTGAAACTCCTGGACCAGCTGCATAACTCC CTGCGGATTGACCTCTCCATGTACCG GAATAACTTCCCAGCCAGCAGCCCGGAGAGACTCCAGGACCTCA AATCCACTGTGGACCTTCTCACCAGC ATCACCTTCTTTCGATGAAGGTACAAGAACTCCAGAGCCCGCC CCGAGCCAGCCAGGTGGTAAAGGACT GTGTGAAAGCCTGCCTTAATTCTACCTACGAGTACATCTTCAAT AACTGCCATGAACTGTACAGCCGGGA GTACCAGACAGACCCGGCCAAGAAGGGGGAAGTTCTCCCAGAGG AACAGGGGGCCAGCATCAAGAACCTC GACTTCTGGTCCAAGCTGATTACCCTCATAGTGTCCATCATTGA GGAAGACAAGAATTCTTACACTCCCT GCCTCAACCAGTTTCCCCAGGAGCTGAATGTGGGTAAAATCAGC GCTGAAGTGATGTGGAATCTGTTTGC CCAAGACATGAAGTACGCCATGGAGGAGCACGACAAGCATCGTC TATGCAAGAGTGCCGACTACATGAAC CTCCACTTCAAGGTGAAATGGCTCTACAATGAGTATGTGACGGA ACTTCCCGCCTTCAAGGACCGCGTGC CTGAGTACCCTGCATGGTTTGAACCCTTCGTCATCCAGTGGCTG GATGAGAATGAGGAGGTGTCCCGGA TTTCTTGCACGGTGCCCTGGAGCGAGACAAGAAGGATGGGTTC AGCAGACCTCAGAGCATGCCCTATTCT TCCTGCTCCGTGGTGGATGTTTTCTCCCACTCAACCAGAGCTT TGAAATCATCAAGAACTCGAGTGTC CCGACCTCAGATCGTGGGGCACTACATGAGGCGCTTTGCCAAG ACCATCAGTAATGTGCTCCTCCAGTA TGCAGACATCATCTCAAGGACTTTGCCTCCTACTGCTCCAAGG AGAAGGAGAAAGTGCCCTGCATTCTC ATGAATAACACTCAACAGCTACGAGTTCAGCTGGAGAAGATGTT CGAAGCCATGGGAGGAAAGGAGCTGG ATGCTGAAGCCAGTGACATCCTGAAGGAGCTTCAGGTGAAACTC AATAACGTCTTGGATGAGCTCAGCCG	
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	GGTGTTTGCTACCAGCTTCCAGCCGCACATTGAAGAGTGTGTCA AACAGATGGGTGACATCCTTAGCCAG GTTAAGGGCACAGGCAATGTGCCAGCCAGTGCCTGCAGCAGCGT GGCCCAGGACGCGGACAATGTGTTGC AGCCCATCATGGACCTGCTGGACAGCAACCTGACCCTCTTTGCC AAAATCTGTGAGAAGACTGTGCTGAA GCGAGTGTGAAGGAGCTGTGGAAGCTGGTTATGAACACCATGG AGAAAACCATCGTCCTGCCGCCCTC ACTGACCAGACGATGATCGGGAACCTCTTGAGAAAACATGGCAA GGGATTAGAAAAGGGCAGGGTGAAAT TGCCAAGCCACTCAGACGGAACCCAGATGATCTTCAATGCAGCC AAGGAGCTGGGTGAGCTGTCCAAACT CAAGGATCACATGGTACGAGAAGAAGCCAAGAGCTTGACCCCAA AGCAGTGCGCGGTTGTTGAGTTGGCC CTGGACACCATCAAGCAATATTTCCACGCGGGTGGCGTGGGCCT CAAGAAGACCTTCTGGAGAAGAGCC CGGACCTGCAATCCTTGCGCTATGCCCTGTGCTCTACACGCAG GCCACCGACCTGCTAATCAAGACCTT TGTACAGACGCAATCGGCCCAGGGCTTGGGTGTAGAAGACCCTG TGGGTGAAGTCTCTGTCCATGTTGAG CTGTTCACTCATCCAGGAAGTGGGGAACACAAGGTACAGTGAA AGTGGTGGCTGCCAATGACCTCAAGT GGCAGACTTCTGGCATCTTCCGGCCGTTTCATCGAGGTCAACATC ATTGGGCCCCAGCTCAGCGACAAGAA ACGCAAGTTTGCACCAATCCAAGAACAATAGCTGGGCTCCCA AGTACAATGAGAGCTTCCAGTTCACG CTGAGCGCCGACGCGGGTCCCGAGTGTATGAGCTGCAGGTGTG CGTCAAGGACTACTGCTTCGCGCGCG AGGACCGCACGGTGGGGCTGGCCGTGCTGCAGCTGCGTGAGCTG GCCCAGCGCGGGAGCGCCGCTGCTG GCTGCCGCTCGGCCGCGCATCCACATGGACGACACGGGCCTCA CGGTGCTGCGAATCCTCTCGCAGCGC AGCAACGACGAGGTGGCCAAGGAGTTCGTGAAGCTCAAGTCGGA CACGCGCTCCGCCGAGGAGGCGGTG CCGCGCCTGCGCCTTAGCGCGGGCGGTGCGCCGAGCGGCACTGC GCCTGCGCGGAGGGCGCTGGGCGGGG AGGGACGGGGCTTGCGCCTTGGTGGGACCTCCCCAGGGGCGGGG CTCGGGGGGCTCCACGCCAAGGGTGG GCTGCGCCTACGCCCTTGACTCAGCTTTCCCTTTTGGGGAATTA GGAATGGAGGATGCCCCGCCCTCTCG GGAGGCCACGCCAAGGGCGCGACGAAGGAAGGAGCCACATCCC CAACTTGAGGCCACGCCCCCAGCACC TAGGGGGCATTTTGAGCTGGGATGGGGAAACCTCGTCCCTATG GAGGAGGCCACATCCCGGGGCTCTGG TACCGGGAGGCACCACTCATGTCCCCTGGAAAAGCCATAAGAT GGGACCCAGACCCCTGGGACCCAGA CCAATTGCCAAGTATGGAATCTCAGCTCCCTCGAGGGGGGGCC CTGGGCAAGGGGTAGGGCTCTCTGGA GCGCCCTCTAGGTGGCTGGGGACTGGAGGGACCAGGATGCTG GTTGGAGGGCCCCGAATACCGGAGT CCCTTTAGATATTTGTGCAAAAAATAAATGGGGGAGGGGGGAG GATGGGATTTCAAAGCACATGCGCC CTTGGGCGCCCAAACCTTGGGGGCGAGGGGACGGCTCTGGTTC CCCACGCTGCCCTACTTCCCTTTGG GAGTTTGCTCTCCCTCTCCCCAACAAACCCAGTCTCATATC ATAGAGTTCAACACACCCATTTGACA GATGGCAAACTGAGGCTTAAAGAGCTGCTTGAGACTTGGCCAA GGTTCCAGGTGCCATACCTCTGTGC	
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	CCCTCCCTTAGGCCTGTGTGCCCCATGGAAGGGTGGGCTGAGAT CGGGATGACCTGACACAGCTCCCTAT TGCTGCTAATTCCCCCTCGGCCTCCTCCAAGGGTGGGAATTCC AGGCCAAGACCCCTACTTCGCCTTTC CTTCTCCGGCTGCCAAGCAGGACCTTTGCCCTCAGCCCTTTCTC CTGGGATCTCCATGGGGGATGCCATG AGGGCCTCCCACCACAAAAGAGAATTTGGGATCCCCTGGTCCCA GGTTTCTCCATCCCTTCTCCTTTTC CAGAATTTTCCAAATAGGAAAGAACAGAAGGAGACCAGAAACTC TAGGGGGGAGAAAGAGAATGAGAGAA AGAGAATGAGAGAGAGAGAAACACAAACACAGTGACACAGTGAG AGCTTAGTCTCCAAGAGCCTATTAT TGATTCAAACACCCAAGCCACAGGATACCTCAGATGGCCCTCTT GCCAGCTGGAAGCTCTTTCTCCAATG AGCAAAGTTACAGTGACCTGGCTGGAGTTACCTGGTGACATAG GACCTTAGGGGAAAGTTCAGCGTGGA CTACACTTGCTCTGGGATCTGCTTTTCCACATGTGTGTATGGCA CGCCTTTTTCTGCTGGATTGGGAAGG ACAAGATTTTGCTGTGCTAGGGAGAAATGAAAACGGGGTGAGCT GAGTAGCTGGGTTTCTGGAGGATAGA ACATCAGATGGGGAGGCTTCCGAGGTGAAGAATGAGAGGGAAC CACTTACTAGAGAGAAAAGAGCTCCA GGCCTGGGGAACAGCACGTGCGAAGGCCAGGAGAGAAGAACTGT TGAAACAACGAGAAGGGTGGCACGGC TGGAGCTGAGCCAGCAAGGGGGATCGTGAGGAGCCTTGGGGTTG GGGAGATCTGCAGAAGCATCAGACCA GGCAGGGCCTCGTACGCAGTCCTGAGGAGTTTACTTTTATTCT AAGACAGTTGGGGAGCTCCAGGAGCT GTTTTAAGTTGGGGAGAGACTGGATTCCAGCCTGCAAAAGCTGT TTTGTGAAGACTAAAACCACTGAGGA GAGGTGGAGTGCTTTGGGGACACTGAAATGGATTCTTGAAAG ATTCTGAAGGCTGTGTTGAAAAGACA CCTATAGCTGTGGGGACATGACTATAATCCCAGCATTGTTGGGGAG ACCGAGGCTGGCAGATCACTTAAGGT CAGGAGTTTGAGACCAGCCTGGCCAACATGGCGAAACCCCATCT CTGCTAAAAATACAAAATTAGCTGG GTGCAGTGGTGATGCCTGTAGTCCCAGCTACTCAGGAGACTGA GGCGGGAGAAATTGTTTGAACCTGGA GGCAGAGGTTGTAGTGAGTCGTGATCACACAACTGCACTCCAGC CTGGGCAACAGAACAATACTCCATTCT CCTCCCCTCTACCCACCAAAAAAAAAAAAAAAAAATCCTGCCCTTA GATGAGCTCTAGGGCTGCTGAGTACA GTTGTCCCAGTTGCACAGTGCCCAAGGGTTTGGCATTGCTAAGA AGGCCACGTGCAAATCCTAGATATTG AGTGTTGTATGTTTGTGACGTTGGTTTCCCGACATGTGAATGGC CCAAGTGTCTGGAAGAAGTGGCGCCA CTTTCTAATTGCTTGGAGATGTTGCATGTCCCTTAAATTCAGA CAGGTGCAGGTAACCTGGAGGTTCTGA ACCAAAGGTTAAAATGCAAATCTCATACAGGGTTGGGAAGTTG TAGCCAGGGATAAGCTTATGTGACTG TTATATGGACTGAGGAGCAGATGTGAATTTGAACCATGACATG GCTGAGGGTAGGGGTCGGGTGGATGG ATGATTACAGGTTGTAACCCATAGAGCCCAAAGGGGAAGTGATC TGTGACCTGGGGTGAGGGTGATCTGG AAGATTTTTGGATGGCTGGAAAGAAATGGGGAAGTCGAGCTGCC TGAGAGAGCCAAGTTATTTCCCAAAA GATTCTTAGGAGTCTTTCTGTTCAAGACCTCCGTGTGTGTGTG TGTGTGTTTAGGGTCCCCAGCAATG	
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	GCCCAGGCATGTGAAGGAAACAAGCTTCTTCAGGGAATATTTGT TGAATGAGTTTCTGACTCCCAGGC TAGAACTGTTTTGCAATTCCACCCTCTTTCTTTCCCCCAGA GAACTCCTATTCGTCCTTCAAAACCC ATCACGGAAACCCCTCTTGAGAAAACCTCCTTCCTTCCCCTC AGGACTTTCCAGCCACCGTCTCTCC TCCAGTCCAGCCTGATGCCATGGGACTGGGGGTTTCTCTGTCCA GCTCTGTTTCTCCAGACTGGGGTCT GAGGACTCTCAGGACCCCAACTTTACCTAGCACAGGCTGGGCA CAAGTGGGTGACAGGGAGTCTACGCC TAGTGGAATTATGTATTGGGGCAGGGTCAGTGTGAGAATACACA TCCGCATGCATGTCTGTCCATGTCTG TCCGTACCAACCTTCCCCTTCCACACGGACCTGGGCACATAGGA GGTGTCTGAGCCTGACACATGGGACA GAGAGTGGACATGGCTGAGACACGGACAGAGAAAAGACAAGGAG TCCAGGGGGCTGAAAGCCTTTTGAAA TCAGGAAGTTCCTGTATTGGCAGAACAAGCCCAGAGAGGAGCA GGGCTTTCCCTCAACGCCACCCAGCAA GTGGACACAGAGCCCGGCCTTGATGACACCTCCAGGGTTCTGA ACCCTGGACCTCGCTTTATGCAAGGA GCTGGCCCCACATTTCCATGAATCGGGGAAACAGCACAAGAAGG TTGGCCTGTGGCAGGGCAAGGGTTAA AGGGGTGACATTGAGGGATGCCTCAGAGTCAAAGTCCCCTGACC AAGAGGAATAGAGTAGAAAAACAGA GACAGAGGGTGAGATCACGCCCCGATGAGGACGGAGAGAGACAG AGATGGAGAGAGACATAGAGGTGGAA ATATACAGAGAAAGATAAATGCAGAGACCAAGGCAGGGAGTGTG GGGGAAGTAAAGAGGGTGTCTGAA GAAAGAAGGATCTGTCACTCTTACCAGTCTGTCTCGAATGAT TTGCATAAAATGAGGAGGTGCCTGTG CACACCCCAATTCTCTCTCAGGCCCCAGAGCCTGAGACCTCA CCATGCCCCCATCAGAGATGCAAAAA ACTAAACACCCAAGTAGAAATCCTTGGGACCTCTCTCGGCTGGG ATCTCAGAGCCTTTCTGTCCCTACC CCTACCCCATGTGCTGTCTGATTTTGCAGATGGGGACAACCTGGG GCCTCCCGGAACCTCTGCCACCCTGGG GAAGTTGGGGGAGGGCCTTAGTCCCGGATCACAACCCCGTCTGC TCCCCAGAATCCTTTCTAAGAATCG TTGAGGACCAAAGTTGTCTTTGCTGACACGTGTTGCTTTTCTCT TTGCCTTTTATGTTTCAGAGAAAAA TCAAGTTGACTGTGTCAAGTAACACCCCAACCCCTTACCCCGTC CAGCCATAGTGGCTCTCTGGAGACAC AGGTACAGGCGGAGGGTCCCCTGATCATCCCCAACACACAGC CAGGGGGACTTGACCCCTGTCCACCC CTGTCTCGTGCTCCCTCAGACCCCCACAAACCGGCCAAGCAGTC CGGGGAGGCTTCCCCTCCACACAACT CTAGCATGTGATTGCAGATGTGAAATCAAAACGTTGTTGTTT TTTGTTTTGTTTGATTCTACCCCGT CGGTCCAGTGTCTGCACAGACGCCTTCATTTCTCTGTAAATATG TGACTTGGAACAAATGTTTAACACAA ACGAGAAGTGGTCATGAATGCATGGTGTGAGATGTTTGCAC ATTCTGACTTTTGGTCTCTGTAAAAA ATATTTTATTAACAGCAGACATTAAAAAAGAAAAACACACAC A	
UNC13A reference protein NP_001073890.2	MSLLCVGVKKAKFDGAQEKENTYVTLKVQNVKSTTIAVRGSQPS WEQDFMFEINRLDLGLTVEVWNKGLI WDTMVGTVWIPLRTIRQSNEEGPGEWLTLDSQVIMADSEICGTK DPTFHRILLDRFELPLDIPEEEAR	11

	WAKKLEQLNAMRDQDEYSFQDEQDKPLVPFSNQCCNWNFYFGWGE QHNDPDSAVDDRSDYRSETSNSIP PPYYTTSQPNASVHQYSVRPPPLGSRESYSDSMHSYEEFSEPQA LSPTGSSRYASSGELSQGSSQLSEDF DPDEHSLQGSMDERDRDSYHSHCSSVSYHKDSPRWDQDEEEL EEDLEDLEEEELPEDEEELEEEEEE VPDDLGSYAQREDVAVAEPKDFKRISLPPAAPGKEDKAPVAPTE APDMAKVAPKPATPKVPAAEQIPEA EPPKDEESFRPREDEEGQEGQDSMSRAKANWLRafNKVRMQLQE ARGEEMSKSLWFKGGPGGLIIIDS MPDIRKRKPIPLVSDLAMSLVQSRKAGITSALASSTLNNEELKN HVKKTLQALIYIPISCTTPHNFEVWT ATTPTYCYECEGLLWGIARQGMRCETCGVKCHEKCQDLLNADCL QRAAEKSSKHGAEDRTQNIIMVLKDR MKIRERNKPEIFELIQEIFAVTKTAHTQQMKAVKQSVLDGTSKW SAKISITVCAQGLQAKDKTGSSDPY VTVQVGKTKKRTKTIYGNLNPVWEENFHFECHNSSDRIKVRVWD EDDDIKSRVKQRFKRESDDFLGQTII EVRTLSEMDVWYNLDKRTDKSAVSGAIRLHISVEIKGEEKVAP YHVQYTCLENLHFHFTDVQNNGVVK IPDAKGDDAWKVYYDETAQEIVDEFAMRYGVESIYQAMTHFACL SSKYMCPGVPVAVMSTLLANINAYYAH TTASTNVSASDRFAASNFGKERFVKLLDQLHNSLRIDL SMYRNN FPASSPERLQDLKSTVDLLTSITFFR MKVQELQSPPRASQVVKDCVKACLNSTYEI FNNCHELYSREYQ TDPAKKGEVLPEEQGPSIKNLDFWSK LITLIVSII EEDKNSYTPCLNQFPQELNVGKISAEVMWNLFQD MKYAMEEHDKHRLCKSADYMNLFKV KWLYNEYVTELPFAFKDRVPEYPAWFEPFVIQWLDENEEVSRDFL HGALEKDDKDGFOQTSEHALFSCSVV DVFSQLNQSFELIKKLECPDPQIVGHYMRRAKTI SNVLLQYAD IISKDFASYCSKEKEKVPCLMNNTQ QLRVQLEKMFEAMGGKELDAEASDILKELQVKLNNVLDELSRVF ATSFPQPHIEECVKQMGDILSQVKGTG NVPASACSSVAQDADNVLPIMDLLDSNLTLFAKICEKTVLKRV LKELWKLVMNTMEKTIVLPPLTDQTM IGNLLRKHGKLEKGRVKLP SHSDGTQMI FNAAKELGQLSKLKD HVMREEAKSLTPKQCAVVELALDTIK QYFHAGGVGLKKTFLKSPDLQSLRYALSlytQATDLLIKTFVQ TQSAQGLGVEDPVGEVSVHVELFTHP GTGEHKVTVKVVAANDLKWQTSGIFRPFIEVNIIGPQLSDKKRK FATKSKNNSWAPKYNESFQFTLSADA GPECYELQVCVKDYCFAREDRTVGLAVLQLRELAQRGSAACWLP LGRRIHMDDTGLTVLRILSQRSDNEV AKEFVKLKS DTRS AEEGGAAPAP	
Exon 20	ACAAGCGAACTGACAAATCTGCCGTGTCCGGTGCCATCCGGCTC CACATCAGTGTGGAGATCAAAGCGAGGAGAAGGTGCCCCGTA CCATGTCCAGTACACCTGTCTGCATGAG	2
Exon 21	AACCTGTTCCACTTCGTGACCGACGTGCAGAACAAATGGGGTCGT GAAGATCCCAGATGCCAAGGGTGACGATGCCTGGAAGGTTTACT ACGATGAGACAGCCAGGAGATTGTGGACGAGTTTGCCATGCGC TACGGCGTCGAGTCCATCTACCAAGCCATGAC	3
Intron 20-21	GTGAGGGTCATTGCTCGGCCCCCTCCCATGCCACTTCCACTCACC ATTCTGCTGCCAGCTCTTCTCTTTCTGGCCACACCATCCA CACTCTCTGCCCCCTCTGAGACTGCCGCCATGCCATTCCTTT ACCTGGAAGAACTCCTCCCTATCCATCAAAGTCCAGATTGAGGGT CACCTCCTCTGGGAAGCCACCTTGGCCTCCAGGTTGACTCTCA CTACTCATCATCAGGTTCTTCTTCTATTCAGCCCTAACCACCT	4

	CAGGATTGGGCCGTTTGTGTCTGGGTATGTCTCTTCCAGCTGCC TGGGTTTCCTGGAAAGAACTCTTATCCCCAGGAAGTAGTTTGT GAATAAATGCTGGTGAATGAATGAATGATTGAACAGATGAATGA GTGATGAGTAGATAAAAGGATGGATGGAGAGATGGGTGAGTACA TGGATGGATAGATGGATGAGTTGGTGGGTAGATTCTGGCTAGA TGGATGATGGATGGATGGACAGATGGATGGATATATGATTGAAC TATTGAAAGTATAGATGTATGGATGGGTGAATTTGGGGTAATT GTTAGATGATGGATGAGTATAGATGAATGATGGATGGATAAATT GATGAGTGGATAGATAGATTGCTGGATAGATGATTGACTGGGTG GATAGATGAAATGTTGGATGAGCAGATTAAGTTGTATTGGATGG GATGGATGGAAGTGTGGTTGAGTTATTAGAAGGAAGATTGAGTA GATAGGTGAATTTGTTGATAGTCAGATGGGTAGATAGGTAGATG GATGGATGGATGGATGGATGTATAGGCAGATGGACAAATGGATG AATGGGTGGTGGATGAATGGAAGGATGTGTGGTTGAACATATTG CAAGTATTGATAATTGGGTTTATAATTTCTGAATATTTAGATGG ATGGTTGTGAGTGGCTGGTGGACAGACGAAAAATGGATGGTTGG ATAAATTGATGGGTGGATGGATGGTTGGTTGTATGAAAGAATGA ATGATTGGGTAGGTGGATTAAGTTGCGGATCAATGTATGGGATG GATGAATGGATGGATGGATGGATGTGTGGTTGAATTACTGAAAG GTTGGAAGAGTGGATGGGTGAAATTTGGGGTAGTTAGATGGGTG GGTGTGTGGATGGATAAAAGAGTAGATGAATGAATTAATGAATA AACAGGCAGATGGATGATGTAAGCTGCCCCAGACCTGGGACCT CTGACCCCCGCGACCCCTTGCACTCTCCATGACACTTTCTCTC CCATGGTGGCAG	
Cryptic Exon 1	CTGCCTGGGTTTCCTGGAAAGAACTCTTATCCCCAGGAAGTAGT TTGTTGAATAAATGCTGGTGAATGAATGAATGATTGAACAGATG AATGAGTGATGAGTAGATAAAAGGATGGATGGAGAGATGG	5
Cryptic Exon 2	CCCTAACCACTCAGGATTGGGCCGTTTGTGTCTGGGTATGTCTC TTCCAGCTGCCTGGGTTTCCTGGAAAGAACTCTTATCCCCAGGA ACTAGTTTGTGAATAAATGCTGGTGAATGAATGAATGATTGAA CAGATGAATGAGTGATGAGTAGATAAAAGGATGGATGGAGAGAT GGG	6
Cryptic Exon Splice Variant 1	GCCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGCCCCG GCGTGAGCCAAGCGCGGGCTGCAGCCGGGAGATGCCCCAGCCCA GCGGCCGCTGAGCCCGACCCGACAGAGCCGGCCCGCCGCTCC GGCCACCTGCGAGCTCGGAGACATGTCTCTGCTTTGCGTTGGA GTCAAAAAGCCAAGTTTGATGGTGCCCAAGAGAAATCAACAC GTACGTGACCCTGAAAGTGCAGAATGTCAAGAGCACGACCATCG CGGTGCGGGGCAGCCAGCCAGCTGGGAGCAGGATTCATGTTT GAGATTAACCGTCTGGATTGGGACTGACGGTGGAGGTGTGGAA TAAGGGTCTCATCTGGGACACAATGGTGGGCACTGTGTGGATCC CACTGAGGACCATCCGCCAGTCCAATGAGGAGGGCCCTGGAGAG TGGCTGACGCTGGACTCCAGGTCATCATGGCAGACAGTGAGAT CTGTGGCACCAGGACCCACCTTCCACCGCATCCTCCTGGACA CGCGCTTTGAGCTACCCCTAGACATTCCTGAAGAGGAGGCTCGC TACTGGGCCAAGAAGCTGGAGCAGCTCAATGCTATGCGGGACCA GGATGAATATTCGTTCCAAGATGAGCAAGACAAGCCCTGCGCTG TCCCCAGCAACCAAGTGTGCAACTGGAATTATTTGGCTGGGGT GAGCAGCACAAACGATGACCCGACAGTGACGTGGATGATCGGTGA CAGTGACTACCGCAGTGAAACGAGCAACAGCATCCCGCCGCCCT ATTATACTACGTCAACAACCAACGCCTCAGTCCACCAATATTCT GTTGCGCCACCACCCCTGGGCTCCCGGGAGTCTACAGTGACTC CATGCACAGTTACGAGGAGTTCTCTGAGCCACAAGCCCTCAGCC CCACGGGTAGCAGCCGCTATGCCTCTTCCGGGGAGCTGAGCCAG GGAAGCTCTCAGCTGAGCGAGGACTTCGACCCTGACGAGCACAG CCTGCAGGGCTCCGACATGGAGGATGAGCGGGACCGGGACTCCT ACCACTCCTGCCACAGCTCGGTGAGTACCACAAAGACTCGCCT CGCTGGGACCAGGATGAGGAAGAGCTGGAGGAGGACCTGGAGGA CTTCCTGGAGGAGGAGGAGCTGCCTGAAGATGAGGAGGAGCTGG	7

	AGGAGGAGGAGGAGGAGGTGCCTGACGATTTGGGCAGCTATGCC CAGCGTGAAGACGTAGCTGTGGCTGAGCCCAAAGACTTCAAACG CATCAGCCTCCCGCCAGCTGCCCCAGGGAAGGAGGACAAGGCC CAGTGGCACCACCGAGGCCCCGACATGGCCAAGGTGGCCCC AAGCCAGCCACGCCCCGACAAGGTGCCTGCAGCTGAGCAGATCCC TGAGGCTGAGCCACCCAAGGACGAGGAGAGTTTCAGGCCGAGAG AGGATGAGGAAGGCCAGGAGGGGAGGACTCCATGTCCAGGGCC AAGGCCAACTGGCTGCGTGCCCTTCAACAAGGTGCGGATGCAGCT GCAGGAGGCCCCGGGAGAAGGAGAGATGTCTAAATCCCTATGGT TCAAAGGCGGCCAGGGGGCGGTCTCATCATCATCGACAGCATG CCAGACATCCGCAAGAGGAAACCTATCCCACTCGTGAGCGACTT GGCCATGTCCCTGGTCCAGTCCAGGAAAGCGGGCATCACCTCGG CCTTGGCCTCCAGCACGTTGAACAACGAGGAGCTGAAAAACCA GTTTACAAGAAGACCCTGCAAGCCTTAATCTACCCCATCTCGTG CACGACGCCACACAACCTCGAAGTGTGGACGGCCACCACGCCCA CCTACTGCTACGAGTGCAGGGGCTGCTGTGGGGCATCGCGAGG CAGGGCATGCGCTGCACCGAGTGCAGGTGTCAAGTGCCACGAGAA GTGCCAGGACCTGCTCAACGCCGACTGCCTGCAGCGGGCTGCGG AGAAGAGCTCCAAGCACGGGGCGGAGGACCGGACACAGAATC ATCATGGTGCTCAAGGACCGCATGAAGATCCGGGAGCGCAACAA GCCCCAGATCTTCGAGCTCATCCAGGAGATCTTCGCGGTGACCA AGACGGCGCACACGCAGCAGATGAAGGCGGTCAAGCAGAGCGTG CTGGACGGCACGTCCAAGTGGTCCGCCAAGATCAGCATCACCGT GGTCTGCGCCAGGGCTTGCAGGCAAAGGACAAGACAGGATCCA GTGACCCCTATGTACCGTCCAGGTCCGGAAGACCAAGAAACGG ACAAAAACCATCTATGGGAACCTCAACCCGGTGTGGGAGGAGAA TTTCCACTTTGAATGTCACAATTCTCCGACCGCATCAAGGTGC GCGTCTGGGACGAGGATGACGACATCAAATCCCGCGTGAAACAG AGGTTCAAGAGGGAATCTGACGATTTCTGGGGCAGACGATCAT TGAGGTGCGGACGCTCAGCGGCGAGATGGACGTGTGGTACAAC TGGACAAGCGAACTGACAAATCTGCCGTGTGCGGTGCCATCCGG CTCCACATCAGTGTGGAGATCAAAGGCGAGGAGAAGGTGGCCCC GTACCATGTCCAGTACACCTGTCTGCATGAGCTGCCTGGGTTTC CTGGAAAGAACTTTATCCCAGGAAGTAGTTTGTGAATAAAT GCTGGTGAATGAATGAATGATTGAACAGATGAATGAGTGATGAG TAGATAAAAGGATGGATGGAGAGATGGAACCTGTTCCACTTCGT GACCGACGTGCAGAACAAATGGGGTCTGTAAGATCCAGATGCCA AGGGTGACGATGCCTGGAAGGTTTACTACGATGAGACAGCCCAG GAGATTGTGGACGAGTTTGCCATGCGCTACGGCGTCGAGTCCAT CTACCAAGCCATGACCCACTTTGCCTGCCTCTCCTCCAAGTATA TGTGCCCAGGGGTGCCTGCCGTGATGAGCACCTGCTCGCCAAC ATCAATGCCTACTACGCACACACCACCGCTCCACCAACGTGTC TGCTCCGACCGCTTCGCCGCTCCAACCTTGGGAAAGAGCGCT TCGTGAAACTCCTGGACCAGCTGCATAACTCCCTGCGGATTGAC CTCTCCATGTACCGGAATAACTTCCCAGCCAGCAGCCCGGAGAG ACTCCAGGACCTCAAATCCACTGTGGACCTTCTCACCAGCATCA CCTTCTTTCGGATGAAGGTACAAGAACTCCAGAGCCCGCCCCGA GCCAGCCAGGTGGTAAAGGACTGTGTGAAAGCCTGCCTTAATTC TACCTACGAGTACATCTTCAATAACTGCCATGAAGTGTACAGCC GGGAGTACCAGACAGACCCGGCCAAGAAGGGGGAAGTTCTCCCA GAGGAACAGGGGCCAGCATCAAGAACCTCGACTTCTGGTCCAA GCTGATTACCCTCATAGTGTCCATCATGAGGAAGACAAGAATT CCTACACTCCCTGCCTCAACCAGTTTCCCCAGGAGCTGAATGTG GGTAAAATCAGCGCTGAAGTGATGTGGAATCTGTTTGCCCAAGA CATGAAGTACGCCATGGAGGAGCACGACAAGCATCGTCTATGCA AGAGTGCCGACTACATGAACCTCCACTTCAAGGTGAAATGGCTC TACAATGAGTATGTGACGGAACCTCCCGCCTTCAAGGACCGCGT GCCTGAGTACCCTGCATGGTTTGAACCTTCGTATCCAGTGGC TGGATGAGAATGAGGAGGTGTCGCGGATTTCTGCACGGTGCC	
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	CCTTTGCCCTCAGCCCTTTCTCCTGGGATCTCCATGGGGGATGC CATGAGGGCTCCACCACAAAAGAGAATTTGGGATCCCCTGGT CCCAGGTTTCTCCATCCCTTCTTCTTTTCCAGAATTTCCAAA TAGGAAAGAACAGAAGGAGACCAGAACTCTAGGGGGGAGAAAG AGAATGAGAGAAAGAGAATGAGAGAGAGAGAAACACAAACACAG TGACACAGTGAGAGCTTAGTCTCCAAGAGCCTATTCATTGATTC AAACACCCAAGCCACAGGATACCTCAGATGGCCCTCTTGCCAGC TGGAAGCTCTTCTCCAATGAGCAAAGTTACAGTGACCTGGCTG GAGTTACCTGGTGACATAGGACCTTAGGGGAAAGTTCAGCGTG GACTACACTTGCTCTGGGATCTGCTTTTCCACATGTGTGTATGG CACGCCTTTTCTGCTGGATTGGGAAGGACAAGATTTGCTGTG CTAGGGAGAAATGAAAACGGGGTGAGCTGAGTAGCTGGGTTTCT GGAGGATAGAACATCAGATGGGGAGGCTTTCGAGGTGAAGAAT GAGAGGGAACCACTTACTAGAGAGAAAAGAGCTCCAGGCCTGGG GAACAGCACGTGCGAAGGCCAGGAGAGAAGAACTGTTGAAACAA CGAGAAGGGTGGCACGGCTGGAGCTGAGCCAGCAAGGGGGATCG TGAGGAGCCTTGGGGTTGGGGAGATCTGCAGAAGCATCAGACCA GGCAGGGCCTCGTACGCAGCTCCTGAGGAGTTTACTTTTATTCT AAGACAGTTGGGGAGCTCCAGGAGCTGTTTAAAGTTGGGGAGAG ACTGGATTCCAGCCTGCAAAAGCTGTTTGTGAAGACTAAAACC AGTGAGGAGAGGTGGAGGTGCTTTGGGGACACTGAAATGGATTC TTGGAAGATTCTGAAGGCTGTGTTGAAAAGACACCTATAGCTG TGGGGACATGACTATAATCCAGCATTGGGGAGACCGAGGCTG GCAGATCACTTAAGGTCAGGAGTTTGAGACCAGCCTGGCCAACA TGGCGAAACCCCATCTCTGCTAAAAATACAAAATTAGCTGGGT GCAGTGGTGATGCCTGTAGTCCAGCTACTCAGGAGACTGAGG CGGGAGAATTGTTTGAACCCTGGAGGCAGAGGTTGTAGTGAGTC GTGATCACACAACCTGCACTCCAGCCTGGGCAACAGAACTACT CCATTCCCTCCCCTCTACCCACCAAAAAAAAAAAAAAAAAATCCTG CCCTTAGATGAGCTCTAGGGCTGCTGAGTACAGTTGTCCCAGTT GCACAGTGCCCAAGGGTTTGGCATTGCTAAGAAGGCCACGTGCA AATCCTAGATATTGAGTGTGTATGTTTGTGACGTTGGTTTCCC GACATGTGAATGGCCCAAGTGTCTGGAAGAAGTGGCGCCACTTT CTAATTTGCTTGGAGATGTTGCATGTCCCTTAAATTGAGACAGG TGCAGGTAACCTGGAGGTTCTGAACCAAGGTTAAAAATGCAATT CTCATACAGGGTTGGGAAGTTGTAGCCAGGGATAAGCTTATGTG ACTGTTATATGGAAGTGGAGCAGATGTGAATTTGCAACCATGA CATGGCTGAGGGTAGGGGTCGGGTGGATGGATGATTGAGGGTTG TAACCCATAGAGCCCAAGGGGAAGTGATCTGTGACCTGGGGTG AGGGTGATCTGGAAGATTTTGGATGGCTGGAAAGAAATGGGGA AGTCGAGCTGCCTGAGAGAGCCAAGTTATTTCCCAAAGATTCC TTAGGAGTCTTCTGTTCAAGACCTCCGTGTGTGTGTGTGTGTG TTTAGGGTTCCCAGCAATGGCCAGGCATGTGAAGGAAACAAG CTTCTTCAGGGAATATTTGTTGAATGAGTTTCTGACTCCCAG GCTAGAACTGTTTTTGCAATTTCCACCCTCTTTTCTTCCCCCA GAGAACTCCTATTTCGTCTTCAAACCCATCACGGAACCCCTC TTGGAGAAAACCTCCTTCTTCCCCTCAGGACTTTCCAGCCA CCGTCTCTCCTCCAGTCCAGCCTGATGCCATGGGACTGGGGGTT TCTCTGTCCAGCTCTGTTTCTCCAGACTGGGGTCTGAGGAATC TCAGGACCCCCAACTTTACCTAGCACAGGCTGGGCACAAGTGGG TGACAGGGAGTCTACGCCTAGTGGAATTATGTATTGGGGCAGGG TCAGTGTGAGAATACACATCCGCATGCATGTCTGTCCATGTCTG TCCGTACCAACCTTCCCCTTCCACACGGACCTGGGCACATAGGA GGTGTCTGAGCCTGACACATGGGACAGAGGTGGACATGGCTGA GACACGGACAGAGAAAAGACAAGGAGTCCAGGGGGCTGAAAGCC TTTTGAAATCAGGAAGTTCCTGTATTGGCAGAACAAAGCCCAGA GAGGAGCAGGGCTTTCCTCAACGCCACCCAGCAAGTGGACACAG AGCCCGGCCCTGGATGACACCTCCAGGGTCTGAACCCTGGACC TCGCTTTATGCAAGGAGCTGGCCCCACATTTCCATGAATCGGGG	
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	AAACAGCACAGAAGGTTGGCCTGTGGCAGGGCAAGGGTTAAAG GGGTGACATTGAGGGATGCCTCAGAGTCAAAGTCCCCTGACCAA GAGGAATAGAGTAGAAAACACAGAGACAGAGGGTGAGATCACGC CCCGATGAGGACGGAGAGAGACAGAGATGGAGAGAGACATAGAG GTGGAATATACAGAGAAAGATAAATGCAGAGACCAAGGCAGGG AGTGTGGGGGAAGTAAAGAGGGGTGTCTGAAGAAAGAAGGATC TGTTCACTCTTACCAGTCTGTCTCGAATGATTTGCATAAAATG AGGAGGTGCCTGTCCACACCCCCAATTCTCTCTCAGGCCCCAG AGCCTGAGACCTCACCATGCCCCATCAGAGATGCAAAAACTA AACACCCAACTAGAAATCCTTGGGACCTCTCTCGGCTGGGATCT CAGAGCCTTCTGTCCCCTACCCCTACCCCATGTGCTGTCGATT TTGCAGATGGGGACAACCTGGGGCCTCCCGGAACCTGCCCACCC TGGGGAAGTTGGGGGAGGGCCTTAGTCCCGGATCACAACCCCGT CTGCTCCCCAGAATCCTTTCCTAAGAATCGTTGAGGACCAAGT TGTCTTTGCTGACACGTGTGCTTTTCTCTTTGCCTTTTATTGT TTCAGAGAAAATCAAGTTGACTGTGTCAAGTAACACCCACCC CTTACCCCGTCCAGCCATAGTGGCTCTCTGGAGACACAGGTCA CAGGCGGAGGGTCCCCTGATCATCCCCAACACACAGCCAGGGG GACTTGACCCCTGTCCACCCCTGTCTCGTGTCTCCCTCAGACCCC CACAAACCGGCCAAGCAGTCCGGGGAGGCTTCCCCTCCACACAA CTCTTAGCATGTGATTGCAGATGTGAATCAAACGTTGTTTGT TTTTTGTGTTTGTGTTTGTGTTTCTACCCCGTGGTCCAGTGTCTGCA CAGACGCCTTCATTTCTCTGTAAATATGTGACTTGGAAACAAATG TTTAACACAAACGAGAAGTGGTCATGAATGCATGGTGTGAGAT GTTTTGCACTATTCTGACTTTTTTGGTCTCTGTAAAAATATTTTA TTAACAGCAGACATTAAAAAAGAAAAACACACACA	
Cryptic Exon Splice Variant 1	MSLLCVGVKKAKFDGAQEKFNITYVTLKVQNVKSTTIAVRGSQPS WEQDFMFEINRLDLGLTVEVWNKGLIWDTMVGTWVWIPLRTIRQS NEEGPGEWLTLDQVIMADSEICGTDPTFHRIILLDRFELPLD IPEEEARYWAKKLEQLNAMRDQDEYSFQDEQDKPLPVPSNQCCN WNYFGWGEQHNDPDSAVDDRSDYRSETSNSIPPPYTTSQPN ASVHQYSVRPPPLGSRESYSDSMHSYEEFSEPQALSPTGSSRYA SSGELSQQSSQLSEDFDPDEHSLQGSDEDERDRDSYHSCHSSV SYHKDSPRWQDEEELEEDLEDFLEEEELPEDEEELEEEEEEV DDLGSYAQREDVAEAPKDFKRI SLPPAAPGKEDKAPVAPTEAP DMAKVAPKATPDKVPAAEQIPEAEPPKDEESFRPREDEEGQEG QDSMSRAKANWLRANFKVRMLQLEARGEEMSKSLWFKGGPGGG LIIDSMPDIRKRKPIPLVSDLAMSLVQSRKAGITSALASSTLN NEELKNHVYKKTLLQALIYPISCTTPHNFEVWTATTPTYCYECEG LLWGIARQGMRICTEGVKCHEKCQDLLNADCLQRAAEKSSKHGA EDRTQNIIMVLKDRMKIRERNKPEIFELIQEI FAVTKTAHTQQM KAVKQSVLDGTSKWSAKISITVVCAQGLQAKDKTGSSDPYVTVQ VGKTKKRTKTIYGNLNPVWEENFHFECNSSDRIKVRVWDEDDD IKSRVKQRFRKRESDDFLGQTIIEVRTLSEMDVWYNLDKRTDKS AVSGAIRLHISVEIKGEEKVAPYHVQYTCHELPGFPGKNSYPQ ELVC*	8
Cryptic Exon Splice Variant 2	GCCCCGGTGCTGAACCAAGATGGCCGGTGGCGGCCGGCCCCCG GCGTGAGCCAAGCGCGGGCTGCAGCCGGGAGATGCCCAAGCCCA GCGGCCGCTGAGCCCGACCCGACAGAGCCGGCCCGCCGCTCC GGCCACCTGCGAGCTCGGAGACATGTCTCTGCTTTGCGTTGGA GTCAAAAAGCCAAGTTTGATGGTGCCAAGAGAAATCAACAC GTACGTGACCTGAAAGTGCAGAATGTCAAGAGCACGACCATCG CGGTGCGGGGCAGCCAGCCAGCTGGGAGCAGGATTTTATGTTT GAGATTAACCGTCTGGATTGGGACTGACGGTGGAGGTGTGGAA TAAGGGTCTCATCTGGGACACAATGGTGGGCACTGTGTGGATCC CACTGAGGACCATCCGCCAGTCCAATGAGGAGGGCCCTGGAGAG TGGCTGACGCTGGACTCCAGGTCATCATGGCAGACAGTGAGAT CTGTGGCACCAGGACCCACCTTCCACCGCATCCTCTGGACA	9

	CGCGCTTTGAGCTACCCTTAGACATTCTGAAGAGGAGGCTCGC TACTGGGCCAAGAAGCTGGAGCAGCTCAATGCTATGCGGGACCA GGATGAATATTCGTTCCAAGATGAGCAAGACAAGCCTCTGCCTG TCCCCAGCAACCAGTGCTGCAACTGGAATTATTTTGGCTGGGGT GAGCAGCACACGATGACCCCGACAGTGCAAGTGATGATCGTGA CAGTGACTACCGCAGTGAAACGAGCAACAGCATCCCGCCGCCCT ATTATACTACGTCAACAACCAACGCCTCAGTCCACCAATATTCT GTTCGCCCCACCACCCCTGGGCTCCCGGGAGTCTACAGTGACTC CATGCACAGTTACGAGGAGTTCTCTGAGCCACAAGCCCTCAGCC CCACGGGTAGCAGCCGCTATGCCTCTTCCGGGGAGCTGAGCCAG GGAAGCTCTCAGCTGAGCGAGGACTTCGACCCTGACGAGCACAG CCTGCAGGGCTCCGACATGGAGGATGAGCGGGACCGGGACTCCT ACCACTCCTGCCACAGCTCGGTGAGTACCACAAAGACTCGCCT CGCTGGGACCAGGATGAGGAAGAGCTGGAGGAGGACCTGGAGGA CTTCTGAGGAGGAGGAGGAGTGCCTGAAGATGAGGAGGAGCTGG AGGAGGAGGAGGAGGAGGAGTGCCTGACGATTTGGGCAGCTATGCC CAGCGTGAAGACGTAGCTGTGGCTGAGCCCAAAGACTTCAAACG CATCAGCCTCCCGCCAGCTGCCCCAGGGAAGGAGGACAAGGCC CAGTGGCACCCACCGAGGCCCCGACATGGCCAAGGTGGCCCCC AAGCCAGCCACGCCCCGACAAGGTGCCTGCAGCTGAGCAGATCCC TGAGGCTGAGCCACCCAAGGACGAGGAGAGTTTCAGGCCGAGAG AGGATGAGGAAGGCCAGGAGGGGAGGACTCCATGTCCAGGGCC AAGGCCAAGTGGCTGCGTGCCTTCAACAAGGTGCGGATGCAGCT GCAGGAGGCCCCGGGAGAGGAGAGATGTCTAAATCCCTATGGT TCAAAGGCGGCCAGGGGGCGGTCTCATCATCATCGACAGCATG CCAGACATCCGCAAGAGGAAACCTATCCCACTCGTGAGCGACTT GGCCATGTCCCTGGTCCAGTCCAGGAAAGCGGGCATCACCTCGG CCTTGGCCTCCAGCACGTTGAACAACGAGGAGCTGAAAAACCAC GTTTACAAGAAGACCCTGCAAGCCTTAATCTACCCCATCTCGTG CACGACGCCACACAACCTCGAAGTGTGGACGGCCACCACGCCCCA CCTACTGCTACGAGTGCGAGGGGCTGCTGTGGGGCATCGCGAGG CAGGGCATGCGCTGCACCGAGTGCGGTGTCAAGTGCCACGAGAA GTGCCAGGACCTGCTCAACGCCGACTGCCTGCAGCGGGCTGCGG AGAAGAGCTCCAAGCACGGGGCGGAGGACCGGACACAGAACATC ATCATGGTGCTCAAGGACCGCATGAAGATCCGGGAGCGCAACAA GCCCCGAGATCTTCGAGCTCATCCAGGAGATCTTCGCGGTGACCA AGACGGCGCACACGACGAGATGAAGGCGGTCAAGCAGAGCGTG CTGGACGGCACGTCCAAGTGGTCCGCCAAGATCAGCATCACCGT GGTCTGCGCCAGGGCTTGCAGGCAAGGACAAGACAGGATCCA GTGACCCCTATGTACCGTCCAGGTGCGGAAGACCAAGAAACGG ACAAAAACCATCTATGGGAACCTCAACCCGGTGTGGGAGGAGAA TTTCCACTTTGAATGTACAATTCTCCGACCGCATCAAGGTGC GCGTCTGGGACGAGGATGACGACATCAAATCCCGCGTGAAACAG AGGTTCAGAGGGAATCTGACGATTTCTGGGGCAGACGATCAT TGAGGTGCGGACGCTCAGCGGCGAGATGGACGTGTGGTACAACC TGGACAAGCGAAGTACAAATCTGCCGTGTGCGGTGCCATCCGG CTCCACATCAGTGTGAGATCAAAGGCGAGGAGAAGGTGGCCCC GTACCATGTCCAGTACACCTGTCTGCATGAGCCCTAACCACTCA GGATTGGGCCGTTTGTGTCTGGGTATGTCTCTCCAGCTGCCTG GGTTTCTGGAAGAAGTCTTATCCCCAGGAAGTAGTTTGTGTA ATAAATGCTGGTGAATGAATGAATGATTGAACAGATGAATGAGT GATGAGTAGATAAAAGGATGGATGGAGAGATGGGAACCTGTTCC ACTTCGTGACCGACGTGCAGAACAAATGGGGTTCGTGAAGATCCCA GATGCCAAGGGTGACGATGCCTGGAAGGTTTACTACGATGAGAC AGCCCAGGAGATTGTGGACGAGTTTGCCATGCGCTACGGCGTCG AGTCCATCTACCAAGCCATGACCCACTTTGCCTGCCTCTCCTCC AAGTATATGTGCCAGGGGTGCCTGCCGTGATGAGCACCCCTGCT CGCCAACATCAATGCCTACTACGCACACACCACCGCTCCACCA ACGTGTCTGCCTCCGACCGCTTCGCCGCTCCAACCTTTGGGAAA	
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	GAGCGCTTCGTGAAACTCCTGGACCAGCTGCATAACTCCCTGCG GATTGACCTCTCCATGTACCGGAATAACTTCCCAGCCAGCAGCC CGGAGAGACTCCAGGACCTCAAATCCACTGTGGACCTTCTCACC AGCATCACCTTCTTTCCGATGAAGGTACAAGAACTCCAGAGCCC GCCCCGAGCCAGCCAGGTGGTAAAGGACTGTGTGAAAGCCTGCC TTAATTCTACCTACGAGTACATCTTCAATAACTGCCATGAACTG TACAGCCGGGAGTACCAGACAGACCCGGCCAAGAAGGGGAAGT TCTCCCAGAGGAACAGGGGCCAGCATCAAGAACCCTCGACTTCT GGTCCAAGCTGATTACCCTCATAGTGTCCATCATTGAGGAAGAC AAGAATTCTTACACTCCCTGCCTCAACCAGTTTCCCAGGAGCT GAATGTGGGTAAAATCAGCGCTGAAGTGATGTGGAATCTGTTTG CCCAAGACATGAAGTACGCCATGGAGGAGCACGACAAGCATCGT CTATGCAAGAGTGCCGACTACATGAACCTCCACTTCAAGGTGAA ATGGCTCTACAATGAGTATGTGACGGAACCTCCCGCCTTCAAGG ACCGCGTGCCTGAGTACCCTGCATGGTTTGAACCCCTTCGTATC CAGTGGCTGGATGAGAATGAGGAGGTGTCCGGGATTCTCTGCA CGGTGCCCTGGAGCGAGACAAGAAGGATGGGTTCACGACAGCCT CAGAGCATGCCCTATTCTCTGCTCCGTGGTGGATGTTTTCTCC CAACTCAACCAGAGCTTTGAAATCATCAAGAACTCGAGTGTCC CGACCTCAGATCGTGGGGCACTACATGAGGCGCTTGGCCAAGA CCATCAGTAATGTGCTCCTCCAGTATGCAGACATCATCTCCAAG GACTTTGCCTCCTACTGCTCCAAGGAGAAGGAGAAAGTGCCCTG CATTCTCATGAATAACACTCAACAGCTACGAGTTCACTGGAGA AGATGTTTGAAGCCATGGGAGGAAAGGAGCTGGATGCTGAAGCC AGTGACATCCTGAAGGAGCTTCAGGTGAACTCAATAACGTCTT GGATGAGCTCAGCCGGGTGTTTGCTACCAGCTTCCAGCCGCACA TTGAAGAGTGTGTCAAACAGATGGGTGACATCCTTAGCCAGGTT AAGGGCACAGGCAATGTGCCAGCCAGTGCCTGCAGCAGCGTGGC CCAGGACGCGACAATGTGTTGCAGCCCATCATGGACCTGCTGG ACAGCAACCTGACCCTCTTGGCCAAATCTGTGAGAAGACTGTG CTGAAGCGAGTGCTGAAGGAGCTGTGGAAGCTGGTTATGAACAC CATGGAGAAAACCATCGTCTGCGCCCTCACTGACCAGACGA TGATCGGGAACCTCTTGAGAAAACATGGCAAGGGATTAGAAAAG GGCAGGGTGAAATTGCCAAGCCACTCAGACGGAACCCAGATGAT CTTCAATGCAGCCAAGGAGCTGGGTCACTGTCCAACTCAAGG ATCACATGGTACGAGAAGAAGCCAAGAGCTTGACCCCAAAGCAG TGCGCGGTTGTTGAGTTGGCCCTGGACACCATCAAGCAATATTT CCACGCGGGTGGCGTGGGCTCAAGAAGACCTTCTTGAGAGAAGA GCCCCGACCTGCAATCCTTGCGCTATGCCCTGTGCTCTACACG CAGGCCACCGACCTGCTAATCAAGACCTTGTACAGACGCAATC GGCCAGGGCTTGGGTGTAGAAGACCCTGTGGGTGAAGTCTCTG TCCATGTTGAGCTGTTCACTCATCCAGAACTGGGGAACACAAG GTCACAGTGAAAGTGGTGGCTGCCAATGACCTCAAGTGGCAGAC TTCTGGCATCTTCCGGCCGTTTCATCGAGGTCAACATCATTGGGC CCCAGCTCAGCGACAAGAAACGCAAGTTTGGGACCAAATCCAAG AACAATAGCTGGGCTCCCAAGTACAATGAGAGCTTCCAGTTTAC GCTGAGCGCCGACGCGGGTCCCGAGTGTATGAGCTGCAGGTGT GCGTCAAGGACTACTGCTTGCAGCGGAGGACCGCAGGTTGGG CTGGCCGTGCTGCAGCTGCGTGAGCTGGCCAGCGCGGGAGCGC CGCCTGCTGGCTGCCGCTCGGCCGCGCATCCACATGGACGACA CGGGCCTCACGGTGTGCGAATCCTCTCGCAGCGCAGCAACGAC GAGGTGGCCAAGGAGTTCGTGAAGCTCAAGTCGGACACGCGCTC CGCCGAGGAGGGCGGTGCCGCGCTGCGCCTTAGCGCGGGCGGT CGGCCGAGCGGCACTGCGCCTGCGCGGAGGGCGCTGGGCGGGGA GGGACGGGGCTTGCGCCCTGGTGGGACCTCCCAGGGGCGGGGC TCGGGGGGCTCCACGCCAAGGGTGGGCTGCGCCTACGCCCTTGA CTCAGCTTTCCCTTTTGGGGAATTAGGAATGGAGGATGCCCCGC CCTCTCGGGAGGCCACGCCCAAGGGCGGACGAAGGAAGGAGCC ACATCCCCAACTTGAGGCCACGCCCCAGCACCTAGGGGGCATT	
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	TTGAGCTGGGATGGGGGAAACCTCGTCCCTATGGAGGAGGCCAC ATCCCGGGGCTCTGGTACGGGAGGCACCACCTCATGTCCCCTG GAAAAGCCATAAGATGGGACCCAGACCCCTGGGACCCAGACCA ATTGCCAAGTATGGAAATCTCAGCTCCCTCGAGGGGGGGCCCTG GGCAAGGGGTAGGGCTCTCTGGAGCGCCCTCTAGGTGGCCTGG GGACTGGAGGGACAGGATGCTGGTGGAGGGCCCCGGAATACC GGAGTCCCTTTAGATATTTGTGCAAAAAATAATGGGGGGAGGG GGGAGGATGGGATTTCAAAGCACATGCGCCCTTGGGCGCCCAA ACCCTGGGGGCCGAGGGGACGGCTCTGGTTCCCCACGCTGCCCC TACTTCCCTTTGGGAGTTTGCCTCTCCCTCTCCCCAACAAACC CAGTCCCTCATATCATAGAGTTCAACACACCCATTTGACAGATGG CAAAAGTGGAGCTTAAAGAGCTGCTTGAGACTTGGCCAAGGTTT CAGGTGCCATACCCCTCTGTGCCCCCTCCCTTAGGCCTGTGTGCC CATGGAAGGTGGGCTGAGATCGGGATGACCTGACACAGCTCCC TATTGCTGCTAATTCCCCCTCGGCCTCCTCCAAGGGGTGGGAAT TCCAGGCCAAGACCCCTACTTCGCCTTTCCTTCTCCGGCTGCCA AGCAGGACCTTTGCCCTCAGCCCTTTCTCCTGGGATCTCCATGG GGGATGCCATGAGGGCCTCCCAACACAAAAGAGAATTTGGGATC CCCTGGTCCCAGGTTTCTCCATCCCTTCTTCTTTTCCAGAATT TTCCAAATAGGAAAGAACAAGAGAGACCAGAACTCTAGGGGG GAGAAAGAGAATGAGAGAAAGAGAATGAGAGAGAGAGAAACACA AACACAGTGACACAGTGAGAGCTTAGTCTCCAAGAGCCTATTCA TTGATTCAAACACCCCAAGCCACAGGATACCTCAGATGGCCCTCT TGCCAGCTGGAAGCTCTTTCTCCAATGAGCAAAGTTACAGTGAC CTGGCTGGAGTTACCTGGTGCACATAGGACCTTAGGGGAAAGTT CAGCGTGGACTACACTTGCTCTGGGATCTGCTTTTCCACATGTG TGTATGGCACGCCTTTTTCTGCTGGATTGGGAAGGACAAGATTT TGCTGTGCTAGGGAGAAATGAAAACGGGGTGAGCTGAGTAGCTG GGTCTTCTGGAGGATAGAACATCAGATGGGGAGGCTTCCGAGGT GAAGAATGAGAGGGAACCACTTACTAGAGAGAAAAGAGCTCCAG GCCTGGGGAACAGCACGTGCGAAGGCCAGGAGAGAAGAACTGTT GAAACAACGAGAAGGGTGGCACGGCTGGAGCTGAGCCAGCAAGG GGGATCGTGAGGAGCCTTGGGGTTGGGGAGATCTGCAGAAGCAT CAGACCAGGCAGGGCCTCGTACGCAGTCTGAGGAGTTTACTTT TTATTCTAAGACAGTTGGGGAGCTCCAGGAGCTGTTTAAAGTTG GGGAGAGACTGGATTCCAGCCTGCAAAAGCTGTTTTGTGAAGAC TAAAACCACTGAGGAGAGGTGGAGGTGCTTTGGGGACACTGAAA TGGATTCTTGAAAGATTCTGAAGGCTGTGTTGAAAGACACCT ATAGCTGTGGGGACATGACTATAATCCCAGCATTGTTGGGGAGACC GAGGCTGGCAGATCACTTAAGGTGAGGAGTTTGAGACCAGCCTG GCCAACATGGCGAAACCCCATCTCTGCTAAAAATACAAAAATTA GCTGGGTGCAGTGGTGCATGCCTGTAGTCCCAGCTACTCAGGAG ACTGAGGCGGGAGAATTGTTGAACCTGGAGGCAGAGGTTGTA GTGAGTCGTGATCACACAACCTGCACTCCAGCCTGGGCAACAGAA CAATACTCCATTCCCTCCCCTCTACCCACCAAAAAAAAAAAAAA AATCCTGCCCTTAGATGAGCTCTAGGGCTGCTGAGTACAGTTGT CCCAGTTGCACAGTGCCCAAGGGTTTGGCATTGCTAAGAAGGCC ACGTGCAAATCCTAGATATTGAGTGTTGTATGTTTGTGACGTTG GTTCCCGACATGTGAATGGCCCAAGTGTCTGGAAGAAGTGGCG CCACTTTCTAATTTGCTTGGAGATGTTGCATGTCCCTTAAATTC AGACAGGTGCAGGTAACCTGGAGGTTCTGAACCAAGGTTAAAAT GCAAATTTCTATACAGGGTTGGGAAGTTGTAGCCAGGGATAAGC TTATGTGACTGTTATATGGACTGAGGAGCAGATGTGAATTTCTGA ACCATGACATGGCTGAGGGTAGGGTGGGTGGATGGATGATTC AGGGTTGTAACCCATAGAGCCCAAAGGGGAAGTGATCTGTGACC TGGGGTGAGGGTGATCTGGAAGATTTTGGATGGCTGGAAAGAA ATGGGGAAAGTCGAGCTGCCTGAGAGAGCCAAGTTATTTCCCAA AGATTCTTAGGAGTCTTCTGTTCAAGACCTCCGTGTGTGTGT GTGTGTGTTTAGGGTTCCCCAGCAATGGCCAGGCATGTGAAGG	
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	AAACAAGCTTCTTCAGGGAATATTTGTTGAATGAGTTTTCCTGA CTCCCAGGCTAGAACTGTTTTTGAATTTCCACCCTCTTTCTT TCCCCAGAGAACTCCTATTTCGTCTTCAAAACCCATCACGGAA ACCCCTCTTGGAGAAAACCTCCTTCCTTCCCCTCAGGACTTTC CCAGCCACCGTCTCTCCTCCAGTCCAGCCTGATGCCATGGGACT GGGGGTTTTCTGTCCAGCTCTGTTTCTCCAGACTGGGGTCTG AGGACTCTCAGGACCCCCAACTTTACCTAGCACAGGCTGGGCAC AAGTGGGTGACAGGGAGTCTACGCCTAGTGGAATTATGTATTGG GGCAGGGTCAGTGTGAGAATACACATCCGCATGCATGTCTGTCC ATGTCTGTCCGTACCAACCTTCCCCTTCCACACGGACCTGGGCA CATAGGAGGTGTCTGAGCCTGACACATGGGACAGAGAGTGGACA TGGCTGAGACACGGACAGAGAAAAGACAAGGAGTCCAGGGGGCT GAAAGCCTTTTGAAATCAGGAAGTTCTGTATTGGCAGAACAAA GCCCAGAGAGGAGCAGGGCTTTCCTCAACGCCACCCAGCAAGTG GACACAGAGCCCGGCCTTGGATGACACCTCCAGGGTTCTGAACC CTGGACCTCGCTTTATGCAAGGAGCTGGCCCCACATTTCCATGA ATCGGGGAAACAGCACAAAGAGTTGGCCTGTGGCAGGGCAAGG GTTAAAGGGGTGACATTGAGGGATGCCTCAGAGTCAAAGTCCCC TGACCAAGAGGAATAGAGTAGAAAACACAGAGACAGAGGGTGAG ATCACGCCCCGATGAGGACGGAGAGAGACAGAGATGGAGAGAGA CATAGAGGTGGAAATATACAGAGAAAGATAAATGCAGAGACCAA GGCAGGGAGTGTCTGGGGGAAGTAAAGAGGGTGTCTGAAGAAAG AAGGATCTGTCACTCTTACCAGTCTGTCTCGAATGATTTGCA TAAAATGAGGAGGTGCCTGTCCACACCCCCAATTCCTCTCTCAG GCCCCAGAGCCTGAGACCTCACCATGCCCCCATCAGAGATGCAA AAAATAAACACCCCACTAGAAATCCTTGGGACCTCTCTCGGCT GGGATCTCAGAGCCTTCTGTCCCCTACCCCTACCCCATGTGCT GTCGATTTTGCAGATGGGGACAACCTGGGGCTCCCGGAATCT GCCACCCTGGGGAAGTTGGGGGAGGGCCTTAGTCCCGGATCACA ACCCCGTCTGCTCCCCAGAATCCTTTCCTAAGAATCGTTGAGGA CCAAAGTTGTCTTTGCTGACACGTGTTGCTTTTCTCTTTCCTT TTATTGTTTCAGAGAAAAATCAAGTTGACTGTGTCAAGTAACAC CCCCCCCCCTTACCCCGTCCAGCCATAGTGGCTCTCTGGAGACA CAGGTCACAGCGGAGGGTCCCCTGATCATCCCCAACCACACAG CCAGGGGGACTTGACCCCTGTCCACCCCTGTCTCGTCTCCCTC AGACCCCCACAAACCGGCCAAGCAGTCCGGGGAGGCTTCCCCTC CACACAACCTTAGCATGTGATTGCAGATGTGAAATCAAACAGT TGTTTGTGTTTTGTTTTGTTTTGATTCTACCCCGTCCGTCCAGT GTCTGCACAGACGCCTTCATTTCTCTGTAAATATGTGACTTGGGA ACAAATGTTTAACACAAACGAGAAGTGGTCATGAATGCATGGTG TTGAGATGTTTTGCACTATTCTGACTTTTTTGGTCTCTGTAAAAA TATTTTATTAACAGCAGACATTAAAAAAGAAAAACCACACACA	
Cryptic Exon Splice Variant 2	MSLLCVGVKKAKFDGAQEKFNITYVTLKVQNVKSTTIAVRGSQPS WEQDFMFEINRLDLGLTVEVWNKGLIWDTMVGTWVWIPLRTIRQS NEEGPGEWLTLDQVIMADSEICGTDPTFHRILLDTRFELPLD IPEEEARYWAKKLEQLNAMRDQDEYSFQDEQDKPLPVPSNQCCN WNYFGWGEQHNDPDSAVDDRSDYRSETSNSIPPPYTTSSQPN ASVHQYSVRPPPLGSRESYSMSHSEYEFSEPPQALSPTGSSRYA SSGELSQQSSQLSEDFDPDEHSLQGSMDERDRDSYHSCSSV SYHKDSPRWQDEEELEEDLEDFLEEEELPEDEEELEEEEEEV DDLGSYAQREDVAVAEPKDFKRISLPPAAPGKEDKAPVAPTEAP DMAKVAPKPATPDKVPAAEQIPEAEPPKDEESFRPREDEEGQEG QDSMSRAKANWLRFAFNKVRMLQEQEARGESEMSKSLWFKGGPGGG LIIIDSMPDIRKRKPIPLVSDLAMSLVQSRKAGITSALASSTLN NEELKNHVYKKTLLQALIYPISTTPHNFEVWTATTPTYCECEG LLWGIARQGMRCTECGVKCHEKCQDLLNADCLQRAAEKSSKHGA EDRTQNIIMVLKDRMKIRERNKPEIFELIQEIFAVTKTAHTQQM KAVKQSVLDGTSKWSAKISITVCAQGLQAKDKTGSSDPYVTVQ VGKTKKRTKTIYGNLNPVWEENFHFECNSSDRIKVRVWDEDDDD	10

	IKSRVKQRFKRESDDFLGQTII EVRTL SGEMDVWYNLDKRTDKS AVSGAIRLHISVEIKGEEKVAPYHVQYTCLHEP*	
TDP-43	MSEYIRVTEDENDIEPIEPSDDGTVLLSTVTAQFPGACGLRYR NPVSQCMRGVRLVEGI LHAPDAGWGNLVVYVNYPKDNKRKMDDETASSAVKVKRAVQKTS DLIVLGLPWKTTEQDL KEYFSTFGEVLMVQVKDLKTGHSGFGFVRFTETQVKVMSQ RHMIDGRWCDCKLPNS KQSQDEPLRSRKVFVGRCTEDMTEDELREFFSQYGDVMDVFIPK PFRAFAFVTFADDQIA QSLCGEDLI IKGISVHISNAEPKHNSNRQLERSGRFGGNPGGFG NQGGFGNSRGGGAGLG NNQGSNMGGGMNFGAFSINPAMMAAQAALQSSWGMMGMLASQQ NQSGPSGNNQNGNMQ REFNQAFSGGNSYSGSNSGAAIGWGSASNAGSGSGFNGGFGSS MDSKSSGWGM	378

UNC13A Cryptic Exon Splice Variant Specific Inhibitors

The present disclosure also provides UNC13A cryptic exon splice variant specific inhibitors, which may be used for research and therapeutic methods described herein. In embodiments, an UNC13A cryptic exon splice variant specific inhibitor selectively binds to or reduces or inhibits the expression or activity of UNC13A cryptic exon splice variant over full length UNC13A or other variants thereof (i.e., variants that do not contain a cryptic exon from intron 20-21 such as SEQ ID NO:5 or SEQ ID NO:6). In embodiments, an UNC13A cryptic exon splice variant specific inhibitor selectively binds to or reduces or inhibits the activity of UNC13A cryptic exon splice variant #1, UNC13A cryptic exon splice variant #2, or both UNC13A cryptic exon splice variant #1 and UNC13A cryptic exon splice variant #2 over full length UNC13A or other variants thereof. In embodiments, an UNC13A cryptic exon splice variant specific inhibitor specifically targets the cryptic exon from intron 20-21, e.g., SEQ ID NO:5 or SEQ ID NO:6, or the peptide region encoded therefrom. In embodiments, an UNC13A cryptic exon splice variant specific inhibitor exhibits about 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, or 5% or less of the activity for full length UNC13A or variants that do not contain a cryptic exon from intron 20-21 as compared to an UNC13A cryptic exon splice variant.

UNC13A cryptic exon splice variant specific inhibitors include, but are not limited to inhibitory nucleic acids (e.g., RNA interference agents, antisense

oligonucleotides), peptides, antibodies, binding proteins, small molecules, ribozymes, and aptamers.

In embodiments, the UNC13A cryptic exon splice variant specific inhibitor comprises a small molecule. A small molecule is a compound that is less than 2000
5 Daltons in mass. The molecular mass of the small molecule is preferably less than 1000 Daltons, more preferably less than 600 Daltons, e.g., the compound is less than 500 Daltons, less than 400 Daltons, less than 300 Daltons, less than 200 Daltons, or less than 100 Daltons.

Small molecules may be organic or inorganic. Exemplary organic small
10 molecules include, but are not limited to, aliphatic hydrocarbons, alcohols, aldehydes, ketones, organic acids, esters, mono- and disaccharides, aromatic hydrocarbons, amino acids, and lipids. Exemplary inorganic small molecules comprise trace minerals, ions, free radicals, and metabolites. Alternatively, small molecules can be synthetically engineered to consist of a fragment, or small portion, or a longer amino acid chain to fill
15 a binding pocket of an enzyme. Typically small molecules are less than one kilodalton.

In embodiments, the UNC13A cryptic exon splice variant specific inhibitor comprises an antibody or binding fragment thereof. The term "antibody" refers to an intact antibody comprising at least two heavy (H) chains and two light (L) chains interconnected by disulfide bonds, as well as any antigen-binding portion or fragment of an
20 intact antibody that has or retains the ability to bind to the antigen target molecule recognized by the intact antibody, such as an scFv, Fab, or Fab'2 fragment. Thus, the term "antibody" herein is used in the broadest sense and includes polyclonal and monoclonal antibodies, including intact antibodies and functional (antigen-binding) antibody fragments thereof, including fragment antigen binding (Fab) fragments,
25 F(ab')2 fragments, Fab' fragments, Fv fragments, recombinant IgG (rIgG) fragments, single chain antibody fragments, including single chain variable fragments (scFv), and single domain antibodies (e.g., sdAb, sdFv, nanobody). The term encompasses genetically engineered and/or otherwise modified forms of immunoglobulins, such as intrabodies, peptibodies, chimeric antibodies, fully human antibodies, humanized
30 antibodies, and heteroconjugate antibodies, multispecific, e.g., bispecific antibodies, diabodies, triabodies, tetrabodies, tandem di-scFv, and tandem tri-scFv. Unless

otherwise stated, the term "antibody" should be understood to encompass functional antibody fragments thereof. The term also encompasses intact or full-length antibodies, including antibodies of any class or sub-class, including IgG and sub-classes thereof (IgG1, IgG2, IgG3, IgG4), IgM, IgE, IgA, and IgD.

5 A monoclonal antibody or antigen-binding portion thereof may be non-human, chimeric, humanized, or human. Immunoglobulin structure and function are reviewed, for example, in Harlow *et al.*, Eds., *Antibodies: A Laboratory Manual*, Chapter 14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, 1988).

 The terms "VL" and "VH" refer to the variable binding region from an antibody
10 light chain and an antibody heavy chain, respectively. The variable binding regions comprise discrete, well-defined sub-regions known as "complementarity determining regions" (CDRs) and "framework regions" (FRs). The terms "complementarity determining region," and "CDR," are synonymous with "hypervariable region" or "HVR," and refer to sequences of amino acids within antibody variable regions, which,
15 in general, together confer the antigen specificity and/or binding affinity of the antibody, wherein consecutive CDRs (*i.e.*, CDR1 and CDR2, CDR2 and CDR3) are separated from one another in primary amino acid sequence by a framework region. There are three CDRs in each variable region (HCDR1, HCDR2, HCDR3; LCDR1, LCDR2, LCDR3; also referred to as CDRHs and CDRLs, respectively). In
20 embodiments, an antibody VH comprises four FRs and three CDRs as follows: FR1-HCDR1-FR2-HCDR2-FR3-HCDR3-FR4; and an antibody VL comprises four FRs and three CDRs as follows: FR1-LCDR1-FR2-LCDR2-FR3-LCDR3-FR4. In general, the VH and the VL together form the antigen-binding site through their respective CDRs.

 Numbering of CDR and framework regions may be determined according to any
25 known method or scheme, such as the Kabat, Chothia, EU, IMGT, and AHO numbering schemes (*see, e.g.*, Kabat *et al.*, "Sequences of Proteins of Immunological Interest, US Dept. Health and Human Services, Public Health Service National Institutes of Health, 1991, 5th ed.; Chothia and Lesk, *J. Mol. Biol.* 196:901-917 (1987)); Lefranc *et al.*, *Dev. Comp. Immunol.* 27:55, 2003; Honegger and Plückthun, *J. Mol. Bio.* 309:657-670
30 (2001)). Equivalent residue positions can be annotated and for different molecules to

be compared using Antigen receptor Numbering And Receptor Classification (ANARCI) software tool (2016, Bioinformatics 15:298-300).

In embodiments, the UNC13A cryptic exon splice variant specific antibody or antigen binding fragment thereof binds to a peptide encoded by SEQ ID NO:5 or SEQ ID NO:6.

In embodiments, the UNC13A cryptic exon splice variant specific inhibitor comprises an inhibitory nucleic acid. An "inhibitory nucleic acid" refers to a short, single stranded or double stranded nucleic acid molecule that has sequence complementary to a target gene or mRNA transcript and is capable of reducing expression of the target gene or mRNA transcript. Reduced expression may be accomplished via a variety of processes, including blocking of transcription or translation (*e.g.*, steric hindrance), degradation of the target mRNA transcript, blocking of pre-mRNA splicing sites, blocking mRNA processing (*e.g.*, capping, polyadenylation). Inhibitory nucleic acids may be single stranded or double stranded. Inhibitory nucleic acids may be composed of DNA, RNA, or both. Inhibitory nucleic acids may contain unmodified nucleotides or may contain modified nucleotides, non-natural nucleotides, or analog nucleotides. Inhibitory nucleic acids include but are not limited to antisense oligonucleotides, siRNAs, shRNAs, miRNAs, double-stranded RNAs (dsRNAs), and endoribonuclease-prepared siRNAs (esiRNAs).

As used herein, the terms "siRNA" or "short interfering RNA" refer to a short, double-stranded polynucleotide sequence (*e.g.*, 17-30 subunits) that mediates a process of sequence-specific post-transcriptional gene silencing, translational inhibition, transcriptional inhibition, or epigenetic RNAi in animals (Zamore *et al.*, *Cell* 101:25-33, 2000; Fire *et al.*, *Nature* 391:806, 1998; Hamilton *et al.*, *Science* 286:950-951, 1999; Lin *et al.*, *Nature* 402:128-129, 1999; Sharp, *Genes Dev.* 13:139-141, 1999; and Strauss, *Science* 286:886, 1999).

In embodiments, a siRNA comprises a first strand and a second strand that have the same number of nucleosides; however, the first and second strands are offset such that the two terminal nucleosides on the first and second strands are left overhanging. In embodiments, the two overhanging nucleosides are thymidine residues. The antisense (or guide) strand of the siRNA includes a region which is at least partially

complementary to the target RNA. In embodiments, there is 100% complementarity between the antisense strand of the siRNA and the target RNA. In embodiments where there is partial complementarity of the antisense strand of the siRNA, the complementarity must be sufficient to enable the siRNA, or a cleavage product thereof, to direct sequence specific silencing, such as by RNAi cleavage of the target RNA. In some embodiments, an antisense strand of a siRNA comprises one or more, such as 10, 8, 6, 5, 4, 3, 2 or fewer, mismatches with respect to the target RNA. The mismatches are most tolerated in the terminal regions, and if present are preferably in a terminal region or regions, *e.g.*, within 6, 5, 4, or 3 nucleotides of the 5' or 3' terminus. The sense (or passenger) strand of the siRNA need only be sufficiently complementary to the antisense strand to maintain the overall double-strand character of the molecule RNA-induced silencing complex (RISC).

In embodiments, a siRNA may be modified or include nucleoside analogs. Single stranded regions of a siRNA may be modified or include nucleoside analogs, *e.g.*, the unpaired region or regions of a hairpin structure or a region that links two complementary regions. In embodiments, a siRNA may be modified to stabilize the 3'-terminus, the 5'-terminus, or both, of the siRNA. For example, modifications can stabilize the siRNA against degradation by exonucleases, or to favor the antisense strand to enter into a RNA-induced silencing complex (RISC). In embodiments, each strand of a siRNA can be equal to or less than 30, 25, 24, 23, 22, 21, or 20 nucleotides in length. In further embodiments, each strand is at least 19 nucleotides in length. For example, each strand can be from 21 to 25 nucleotides in length such that the siRNA has a duplex region of at least 17, 18, 19, 20, 21, 22, 23, 24, or 25 nucleotide pairs, and one or more overhangs of 2-3 nucleotides, such as overhangs one or both 3'-ends.

Endoribonuclease-prepared siRNAs (esiRNAs) are siRNAs resulting from cleavage of long double stranded RNA with an endoribonuclease such as RNase III or dicer. The esiRNA product is a heterogeneous mixture of siRNAs that target the same mRNA sequence.

As used herein, the terms "miRNA" or "microRNA" refer to small non-coding RNAs of about 20-22 nucleotides, which is generated from longer RNA hairpin loop precursor structures known as pri-miRNAs. The pri-miRNA undergoes a two-step

cleavage process into a microRNA duplex, which is incorporated into RISC. The level of complementarity between the miRNA guide strand and the target RNA determines which silencing mechanism is employed. miRNAs that bind with perfect or extensive complementarity to RNA target sequences, typically in the 3'-UTR, induce cleavage of the target via RNA-mediated interference (RNAi) pathway. miRNAs with limited complementarity to the target RNA, repress target gene expression at the level of translation.

As used herein, the terms "shRNA" or "short hairpin RNA" refer to double-stranded structure formed two complementary (19–22 bp) RNA sequences linked by a short loop (4–11 nt). shRNAs are usually encoded by a vector that is introduced into cells, and the shRNA is processed in the cytosol by Dicer into siRNA duplexes, which are incorporated into the RISC complex, where complementarity between the guide strand and RNA target mediates RNA target specific cleavage and degradation.

As used herein, the term "ribozyme" refers to a catalytically active RNA molecule capable of site-specific cleavage of target mRNA. In certain embodiments, a ribozyme is a Varkud satellite ribozyme, a hairpin ribozyme, a hammerhead ribozyme, or a hepatitis delta ribozyme.

In embodiments, antisense oligonucleotides of the present disclosure target intron 20-21 and/or adjacent sequence in exon 20 or exon 21. Aberrant splicing can be corrected using splice-switching antisense oligonucleotides. Splice-switching antisense oligonucleotides block aberrant splicing sites by hybridizing at or near the splicing sites thereby preventing recognition by the cellular splicing machinery. In embodiments, splice-switching antisense oligonucleotides are modified to be resistant to nucleases, and the resulting target nucleic acid:oligonucleotide heteroduplex is not cleaved by RNase H. Splice-switching antisense oligonucleotides may comprise nucleotides that do not form RNase H substrates when paired with RNA or a mixture of nucleotide chemistries such that runs of consecutive DNA-like bases are avoided. Thus, in embodiments, splice-switching antisense oligonucleotides may modify *UNC13A* splicing without altering the abundance of the *UNC13A* mRNA transcript.

In embodiments, the antisense oligonucleotide is complementary to: the exon 20 splice donor site region in a preprocessed mRNA encoding UNC13A; the cryptic exon

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

In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:641. In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 3'
 15 end of the cryptic exon having a sequence set forth in SEQ ID NO:642.

In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:643. In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 3'
 20 end of the cryptic exon having a sequence set forth in SEQ ID NO:644. In embodiments, the *UNC13A* cryptic exon splice variant specific antisense oligonucleotide has about 15-40 bases, e.g., about 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 bases in length. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has about 18-30 bases, 18-
 25 25 bases, 18-22 bases, or 20-30 bases.

In embodiments, the *UNC13A* cryptic exon splice variant specific antisense oligonucleotide has a base sequence that has at least 80%, 85%, 90%, 95%, or 100% identity to any one of the sequences in Tables 2-7 (e.g., SEQ ID NOS:13-90, 92-219, 221-298, 300-377, and 423-640). In embodiments, the *UNC13A* cryptic exon splice
 30 variant specific antisense oligonucleotide comprises or consists of any one of the sequences in Tables 2-5 (e.g., SEQ ID NOS: 13-90, 92-219, 221-298, 300-377, and

423-640). In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide comprises or consists of any one of the sequences set forth in SEQ ID NOS:423-432, 439-443, 491-498, 502-507, and 513-514.

In embodiments, the UNC13A cryptic exon splice variant specific antisense
5 oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:650. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO:650.

In embodiments, the UNC13A cryptic exon splice variant specific antisense
10 oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO: 651. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO: 651.

In embodiments, the UNC13A cryptic exon splice variant specific antisense
15 oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:652. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO:652.

In embodiments, the UNC13A cryptic exon splice variant specific antisense
20 oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:653. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO:653.

In embodiments, the UNC13A cryptic exon splice variant specific antisense
25 oligonucleotide has 18-21 bases that are complementary to SEQ ID NO:654. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, or 21 bases that are complementary to SEQ ID NO:654.

In embodiments, the *UNC13A* cryptic exon splice variant specific antisense oligonucleotide is a modified antisense oligonucleotide. A modified antisense
30 oligonucleotide may comprise at least one backbone modification, nucleobase modification, 2'-ribose substitution, or bridged nucleic acid, Examples of modified

oligonucleotide chemistries include, without limitation, phosphoramidate morpholino oligonucleotides and phosphorodiamidate morpholino oligonucleotides (PMO), phosphorothioate modified oligonucleotides, 2' O-methyl (2' O-Me) modified oligonucleotides, peptide nucleic acid (PNA), locked nucleic acid (LNA),
5 phosphorodithioate oligonucleotides, 2' O-Methoxyethyl (2'-MOE) modified oligonucleotides, 2'-fluoro-modified oligonucleotides, 2'O,4'C-ethylene-bridged nucleic acids (ENAs), tricyclo-DNAs, tricyclo-DNA phosphorothioate nucleotides, constrained ethyl bridged nucleic acids, 2'-O-[2-(N-methylcarbamoyl)ethyl] modified oligonucleotides, morpholino oligonucleotides, and peptide-conjugated
10 phosphoramidate morpholino oligonucleotides (PPMO). In embodiments, the *UNC13A* cryptic exon splice variant specific antisense oligonucleotide comprises 2'O-Me modified nucleotides and phosphorothioate linkages.

In some embodiments, the compositions provided herein may be assembled into pharmaceutical or research kits to facilitate their use in therapeutic or research use. A
15 kit may include one or more containers comprising: (a) *UNC13A* cryptic exon splice variant specific antisense oligonucleotide(s) described herein; and (b) instructions for use. In some embodiments, the kit component (a) may be in a pharmaceutical formulation and dosage suitable for a particular use and mode of administration. For example, the kit component (a) may be presented in unit-dose or multi-dose containers,
20 such as sealed ampoules or vials. The components of the kit may require mixing one or more components prior to use or may be prepared in a premixed state. The components of the kit may be in liquid or solid form, and may require addition of a solvent or further dilution. The components of the kit may be sterile. The instructions may be in written or electronic form and may be associated with the kit (e.g., written insert, CD,
25 DVD) or provided via internet or web-based communication. The kit may be shipped and stored at a refrigerated or frozen temperature.

Pharmaceutical Compositions

In some aspects, the disclosure provides pharmaceutical compositions
30 comprising an *UNC13A* cryptic exon splice variant specific inhibitor as described herein and a pharmaceutically acceptable carrier. As used herein, the term

“pharmaceutically acceptable” refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with cells and/or tissues without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, the term "pharmaceutically acceptable carrier" means a pharmaceutically acceptable material, composition or carrier, such as a liquid or solid filler, stabilizer, dispersing agent, suspending agent, diluent, excipient, thickening agent, solvent or encapsulating material, involved in carrying or transporting a compound useful within the invention within or to the patient such that it may perform its intended function. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the cell or tissue being contacted. Additional ingredients that may be included in the pharmaceutical compositions used in the practice of the invention are known in the art and described, for example in Remington's Pharmaceutical Sciences (Genaro, Ed., Mack Publishing Co., 1985, Easton, PA), which is incorporated herein by reference.

As is well known in the medical arts, the dosage for any one patient depends upon many factors, including the patient's size, weight, body surface area, age, the level of UNC13A cryptic exon splice variant specific inhibitor required to achieve a therapeutic effect, stability of the UNC13A cryptic exon splice variant specific inhibitor, specific disease being treated, stage of disease, sex, time and route of administration, general health, and other drugs being administered concurrently.

Pharmaceutical compositions may be administered in a manner appropriate to the disease or condition to be treated (or prevented) as determined by persons skilled in the medical art. An appropriate dose and a suitable duration and frequency of administration of the compositions will be determined by such factors as the health condition of the patient, size of the patient (*i.e.*, weight, mass, or body area), the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provide the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (such as described herein, including an improved clinical outcome,

such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity). For prophylactic use, a dose should be sufficient to prevent, delay the onset of, or diminish the severity of a disease associated with disease or disorder. Prophylactic benefit of the compositions

- 5 administered according to the methods described herein can be determined by performing pre-clinical (including *in vitro* and *in vivo* animal studies) and clinical studies and analyzing data obtained therefrom by appropriate statistical, biological, and clinical methods and techniques, all of which can readily be practiced by a person skilled in the art.
- 10 Compositions (e.g., pharmaceutical compositions) may be administered by any route, including enteral (e.g., oral), parenteral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subpial, intraparenchymal, intrastriatal, intracranial, intracisternal, intra-cerebral, intracerebral ventricular, intraocular, intraventricular, intralumbar, subcutaneous, transdermal, interdermal, rectal, intravaginal,
- 15 intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. In general, the most appropriate route of administration will depend upon a variety of factors including the nature of the agent (e.g., its stability in the environment of the gastrointestinal tract),
- 20 and/or the condition of the subject. In some embodiments, compositions are directly injected into the CNS of the subject. In some embodiments, direct injection into the CNS is intracerebral injection, intraparenchymal injection, intrathecal injection, subpial injection, or any combination thereof. In some embodiments, direct injection into the CNS is direct injection into the cerebrospinal fluid (CSF) of the subject, optionally
- 25 wherein the direct injection is intracisternal injection, intraventricular injection, and/or intralumbar injection.

Methods of Using UNC13A Cryptic Splice Variant Inhibitors

- The present disclosure provides methods of using UNC13A cryptic exon splice
- 30 variant specific inhibitors disclosed herein for various research and therapeutics uses. In one aspect, 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 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. In embodiments, the UNC13A cryptic exon splice variant specific inhibitor selectively inhibits the expression or activity of the
 5 UNC13A cryptic exon splice variant over full length UNC13A (wildtype) or other variants thereof (*i.e.*, variants that do not contain a cryptic exon from intron 20-21 such as SEQ ID NO:5 or SEQ ID NO:6).

In embodiments, the cryptic exon is obtained from intron 20-21 of the *UNC13A* gene. In embodiments, the cryptic exon comprises SEQ ID NO:5 or SEQ ID NO:6. In
 10 embodiments, the *UNC13* cryptic exon splice variant comprises a polynucleotide sequence of SEQ ID NO:7 or SEQ ID NO:9. In embodiments, the UNC13 cryptic exon splice variant comprises the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:10.

In embodiments, the UNC13 cryptic splice variant specific inhibitor comprises
 15 an inhibitory nucleic acid, peptides, antibody, binding protein, small molecule, ribozyme, or aptamer.

In embodiments, the UNC13 cryptic splice variant specific inhibitor comprises an inhibitory nucleic acid. The inhibitory nucleic acid may be an antisense oligonucleotide, siRNA, shRNA, miRNA, double-stranded RNA (dsRNAs), or esiRNA.
 20 In embodiments, the inhibitory nucleic acid comprises an antisense oligonucleotide that is complementary to: the exon 20 splice donor site region in a preprocessed mRNA encoding UNC13A; the cryptic exon splice acceptor site region in a preprocessed mRNA encoding UNC13A; the cryptic exon splice donor site region in a preprocessed mRNA encoding UNC13A; or the exon 21 splice acceptor site region in a preprocessed
 25 mRNA encoding UNC13A. In embodiments, the exon 20 splice donor site region comprises or consists of SEQ ID NO:12. In embodiments, the cryptic exon splice acceptor site region comprises or consists of SEQ ID NO:91. In embodiments, the cryptic exon splice donor site region comprises or consists of SEQ ID NO:220. In
 30 embodiments, the exon 21 splice acceptor site comprises or consists of SEQ ID NO:299.

In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:641. In embodiments, the inhibitory nucleic acid,

e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:642.

In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:643. In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:644.

In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide has about 15-40 bases in length, preferably about 18-30 bases, 18-25 bases, 18-22 bases, or 20-30 bases in length.

In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide has a base sequence that is at least 80%, 85%, 90%, 95%, 97%, or 100% identical to any one of the sequences listed in Table 2 (e.g., SEQ ID NOS:13-90), Table 3 (SEQ ID NOS:92-219), Table 4 (SEQ ID NOS:221-298), Table 5 (SEQ ID NOS:300-377), Table 7B (SEQ ID NOS:423-522), and Table 8B (SEQ ID NOS:523-640). In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide has a base sequence comprising or consisting of any one of the sequences listed in Table 2 (e.g., SEQ ID NOS:13-90), Table 3 (SEQ ID NOS:92-219), Table 4 (SEQ ID NOS:221-298), Table 5 (SEQ ID NOS:300-377), Table 7B (SEQ ID NOS:423-522), and Table 8B (SEQ ID NOS:523-640).

In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:650. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO:650.

In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO: 651. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO: 651.

In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to

SEQ ID NO:652. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO:652.

In embodiments, the UNC13A cryptic exon splice variant specific antisense
 5 oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:653. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO:653.

In embodiments, the UNC13A cryptic exon splice variant specific antisense
 10 oligonucleotide has 18-21 bases that are complementary to SEQ ID NO:654. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, or 21 bases that are complementary to SEQ ID NO:654. In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide is a modified antisense oligonucleotide. In embodiments, the modified
 15 antisense oligonucleotide comprises a phosphoramidate morpholino oligonucleotide, phosphorodiamidate morpholino oligonucleotide, phosphorothioate modified oligonucleotide, 2' O-methyl (2' O-Me) modified oligonucleotide, peptide nucleic acid (PNA), locked nucleic acid (LNA), phosphorodithioate oligonucleotide, 2' O-Methoxyethyl (2'-MOE) modified oligonucleotide, 2'-fluoro-modified oligonucleotide,
 20 2'O,4'C-ethylene-bridged nucleic acid (ENAs), tricyclo-DNA, tricyclo-DNA phosphorothioate nucleotide, constrained ethyl bridged nucleic acid, 2'-O-[2-(N-methylcarbamoyl)ethyl] modified oligonucleotide, morpholino oligonucleotide, and peptide-conjugated phosphoramidate morpholino oligonucleotide (PPMO), or any combination thereof.

25 In embodiments, the cell is within a subject. As used here, a "patient" or "subject" includes an animal, such as a human, cow, horse, sheep, lamb, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit or guinea pig. The animal can be a mammal, such as a non-primate and a primate (*e.g.*, monkey and human). In embodiments, a patient is a human, such as a human infant, child, adolescent or adult.

30 In embodiments, the subject has been identified as having a *UNC13A* gene mutation in intron 20-21. In embodiments, the *UNC13* 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.

In another aspect, 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 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.

In embodiments, the UNC13A cryptic exon splice variant specific inhibitor selectively inhibits the expression or activity of the UNC13A cryptic exon splice variant over full length UNC13A (wildtype) or other variants thereof (*i.e.*, variants that do not contain a cryptic exon from intron 20-21 such as SEQ ID NO:5 or SEQ ID NO:6).

In embodiments, the cryptic exon is obtained from intron 20-21 of the *UNC13A* gene. In embodiments, the cryptic exon comprises SEQ ID NO:5 or SEQ ID NO:6. In embodiments, the *UNC13* cryptic exon splice variant comprises a polynucleotide sequence of SEQ ID NO:7 or SEQ ID NO:9. In embodiments, the UNC13 cryptic exon splice variant comprises the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:10.

In embodiments, the UNC13 cryptic splice variant specific inhibitor comprises an inhibitory nucleic acid, peptides, antibody, binding protein, small molecule, ribozyme, or aptamer.

In embodiments, the UNC13 cryptic splice variant specific inhibitor comprises an inhibitory nucleic acid. The inhibitory nucleic acid may be an antisense oligonucleotide, siRNA, shRNA, miRNA, double-stranded RNA (dsRNAs), or esiRNA. In embodiments, the inhibitory nucleic acid comprises an antisense oligonucleotide that is complementary to: the exon 20 splice donor site region in a preprocessed mRNA encoding UNC13A; the cryptic exon splice acceptor site region in a preprocessed mRNA encoding UNC13A; the cryptic exon splice donor site region in a preprocessed mRNA encoding UNC13A; or the exon 21 splice acceptor site region in a preprocessed mRNA encoding UNC13A. In embodiments, the exon 20 splice donor site region comprises or consists of SEQ ID NO:12. In embodiments, the cryptic exon splice acceptor site region comprises or consists of SEQ ID NO:91. In embodiments, the cryptic exon splice donor site region comprises or consists of SEQ ID NO:220. In

embodiments, the exon 21 splice acceptor site comprises or consists of SEQ ID NO:299.

In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:641. In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:642.

In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:643. In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:644.

In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide has about 15-40 bases in length, preferably about 18-30 bases, 18-25 bases, 18-22 bases, or 20-30 bases in length.

In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide has a base sequence that is at least 80%, 85%, 90%, 95%, 97%, or 100% identical to any one of the sequences listed in Table 2 (e.g., SEQ ID NOS:13-90), Table 3 (SEQ ID NOS:92-219), Table 4 (SEQ ID NOS:221-298), Table 5 (SEQ ID NOS:300-377), Table 7B (SEQ ID NOS:423-522), and Table 8B (SEQ ID NOS:523-640). In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide has a base sequence comprising or consisting of any one of the sequences listed in Table 2 (e.g., SEQ ID NOS:13-90), Table 3 (SEQ ID NOS:92-219), Table 4 (SEQ ID NOS:221-298), Table 5 (SEQ ID NOS:300-377), Table 7B (SEQ ID NOS:423-522), and Table 8B (SEQ ID NOS:523-640).

In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:650. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO:650.

In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to

SEQ ID NO: 651. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO: 651.

In embodiments, the UNC13A cryptic exon splice variant specific antisense
 5 oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:652. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO:652.

In embodiments, the UNC13A cryptic exon splice variant specific antisense
 10 oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:653. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO:653.

In embodiments, the UNC13A cryptic exon splice variant specific antisense
 15 oligonucleotide has 18-21 bases that are complementary to SEQ ID NO:654. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, or 21 bases that are complementary to SEQ ID NO:654.

In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide is a modified antisense oligonucleotide. In embodiments, the modified
 20 antisense oligonucleotide comprises a phosphoramidate morpholino oligonucleotide, phosphorodiamidate morpholino oligonucleotide, phosphorothioate modified oligonucleotide, 2' O-methyl (2' O-Me) modified oligonucleotide, peptide nucleic acid (PNA), locked nucleic acid (LNA), phosphorodithioate oligonucleotide, 2' O-Methoxyethyl (2'-MOE) modified oligonucleotide, 2'-fluoro-modified oligonucleotide,
 25 2'O,4'C-ethylene-bridged nucleic acid (ENAs), tricyclo-DNA, tricyclo-DNA phosphorothioate nucleotide, constrained ethyl bridged nucleic acid, 2'-O-[2-(N-methylcarbamoyl)ethyl] modified oligonucleotide, morpholino oligonucleotide, and peptide-conjugated phosphoramidate morpholino oligonucleotide (PPMO), or any combination thereof.

30 In embodiments, the cell is within a subject. In embodiments, the subject has been identified as having a *UNC13A* gene mutation in intron 20-21. In embodiments, the *UNC13* 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.

In another aspect, the present disclosure provides a method of treating TAR-
5 DNA binding protein-43 (TDP-43) proteinopathy in a subject comprising administering a UNC13A cryptic exon splice variant specific inhibitor to the subject, wherein 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.

In embodiments, the UNC13A cryptic exon splice variant specific inhibitor
10 selectively inhibits the expression or activity of the UNC13A cryptic exon splice variant over full length UNC13A (wildtype) or other variants thereof (*i.e.*, variants that do not contain a cryptic exon from intron 20-21 such as SEQ ID NO:5 or SEQ ID NO:6).

In embodiments, the cryptic exon is obtained from intron 20-21 of the *UNC13A* gene. In embodiments, the cryptic exon comprises SEQ ID NO:5 or SEQ ID NO:6. In
15 embodiments, the *UNC13* cryptic exon splice variant comprises a polynucleotide sequence of SEQ ID NO:7 or SEQ ID NO:9. In embodiments, the UNC13 cryptic exon splice variant comprises the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:10.

In embodiments, the UNC13 cryptic splice variant specific inhibitor comprises an inhibitory nucleic acid, peptides, antibody, binding protein, small molecule,
20 ribozyme, or aptamer.

In embodiments, the UNC13 cryptic splice variant specific inhibitor comprises an inhibitory nucleic acid. The inhibitory nucleic acid may be an antisense oligonucleotide, siRNA, shRNA, miRNA, double-stranded RNA (dsRNAs), or esiRNA. In embodiments, the inhibitory nucleic acid comprises an antisense oligonucleotide that
25 is complementary to: the exon 20 splice donor site region in a preprocessed mRNA encoding UNC13A; the cryptic exon splice acceptor site region in a preprocessed mRNA encoding UNC13A; the cryptic exon splice donor site region in a preprocessed mRNA encoding UNC13A; or the exon 21 splice acceptor site region in a preprocessed mRNA encoding UNC13A. In embodiments, the exon 20 splice donor site region
30 comprises or consists of SEQ ID NO:12. In embodiments, the cryptic exon splice acceptor site region comprises or consists of SEQ ID NO:91. In embodiments, the cryptic exon splice donor site region comprises or consists of SEQ ID NO:220. In

embodiments, the exon 21 splice acceptor site comprises or consists of SEQ ID NO:299.

In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:641. In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:642.

In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:643. In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:644.

In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide has about 15-40 bases in length, preferably about 18-30 bases, 18-25 bases, 18-22 bases, or 20-30 bases in length.

In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide has a base sequence that is at least 80%, 85%, 90%, 95%, 97%, or 100% identical to any one of the sequences listed in Table 2 (e.g., SEQ ID NOS:13-90), Table 3 (SEQ ID NOS:92-219), Table 4 (SEQ ID NOS:221-298), Table 5 (SEQ ID NOS:300-377), Table 7B (SEQ ID NOS:423-522), and Table 8B (SEQ ID NOS:523-640). In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide has a base sequence comprising or consisting of any one of the sequences listed in Table 2 (e.g., SEQ ID NOS:13-90), Table 3 (SEQ ID NOS:92-219), Table 4 (SEQ ID NOS:221-298), and Table 5 (SEQ ID NOS:300-377), Table 7B (SEQ ID NOS:423-522), and Table 8B (SEQ ID NOS:523-640).

In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO:650. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO:650.

In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to SEQ ID NO: 651. In embodiments, the UNC13A cryptic exon splice variant specific

antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO: 651.

In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to
5 SEQ ID NO:652. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO:652.

In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to
10 SEQ ID NO:653. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO:653.

In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18-21 bases that are complementary to SEQ ID NO:654. In
15 embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, or 21 bases that are complementary to SEQ ID NO:654.

In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide is a modified antisense oligonucleotide. In embodiments, the modified antisense oligonucleotide comprises a phosphoramidate morpholino oligonucleotide,
20 phosphordiamidate morpholino oligonucleotide, phosphorothioate modified oligonucleotide, 2' O-methyl (2' O-Me) modified oligonucleotide, peptide nucleic acid (PNA), locked nucleic acid (LNA), phosphorodithioate oligonucleotide, 2' O-Methoxyethyl (2' -MOE) modified oligonucleotide, 2'-fluoro-modified oligonucleotide, 2'O,4'C-ethylene-bridged nucleic acid (ENAs), tricyclo-DNA, tricyclo-DNA
25 phosphorothioate nucleotide, constrained ethyl bridged nucleic acid, 2'-O-[2-(N-methylcarbamoyl)ethyl] modified oligonucleotide, morpholino oligonucleotide, and peptide-conjugated phosphoramidate morpholino oligonucleotide (PPMO), or any combination thereof.

In embodiments, the cell is within a subject. In embodiments, the subject has
30 been identified as having a *UNC13A* gene mutation in intron 20-21. In embodiments, the *UNC13* 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.

In embodiments, the TDP-43 proteinopathy comprises amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), facial onset sensory and motor neuronopathy (FOSMN), hippocampal sclerosis (HS), limbic-predominant age-related TDP-43 encephalopathy (LATE), cerebral age-related TDP-43 with sclerosis (CARTS), Guam Parkinson-dementia complex (G-PDC), Guan ALS (G-ALS), Multisystem proteinopathy (MSP), Perry disease, Alzheimer's disease (AD), and chronic traumatic encephalopathy (CTE), or any combination thereof.

In another aspect, the present disclosure provides a method of treating a subject has been identified as having an *UNC13A* gene mutation in intron 20-21 comprising administering an UNC13A cryptic exon splice variant specific inhibitor to the subject, wherein 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. In embodiments, the *UNC13* 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.

In embodiments, the subject has decreased expression of TDP-43. In embodiments, the subject exhibits decreased nuclear TDP-43.

In embodiments, the UNC13A cryptic exon splice variant specific inhibitor selectively inhibits the expression or activity of the UNC13A cryptic exon splice variant over full length UNC13A (wildtype) or other variants thereof (*i.e.*, variants that do not contain a cryptic exon from intron 20-21 such as SEQ ID NO:5 or SEQ ID NO:6).

In embodiments, the cryptic exon is obtained from intron 20-21 of the *UNC13A* gene. In embodiments, the cryptic exon comprises SEQ ID NO:5 or SEQ ID NO:6. In embodiments, the *UNC13* cryptic exon splice variant comprises a polynucleotide sequence of SEQ ID NO:7 or SEQ ID NO:9. In embodiments, the UNC13 cryptic exon splice variant comprises the amino acid sequence of SEQ ID NO:8 or SEQ ID NO:10.

In embodiments, the UNC13 cryptic splice variant specific inhibitor comprises an inhibitory nucleic acid, peptides, antibody, binding protein, small molecule, ribozyme, or aptamer.

In embodiments, the UNC13 cryptic splice variant specific inhibitor comprises an inhibitory nucleic acid. The inhibitory nucleic acid may be an antisense oligonucleotide, siRNA, shRNA, miRNA, double-stranded RNA (dsRNAs), or esiRNA. In embodiments, the inhibitory nucleic acid comprises an antisense oligonucleotide that is complementary to: the exon 20 splice donor site region in a preprocessed mRNA encoding UNC13A; the cryptic exon splice acceptor site region in a preprocessed mRNA encoding UNC13A; the cryptic exon splice donor site region in a preprocessed mRNA encoding UNC13A; or the exon 21 splice acceptor site region in a preprocessed mRNA encoding UNC13A. In embodiments, the exon 20 splice donor site region comprises or consists of SEQ ID NO:12. In embodiments, the cryptic exon splice acceptor site region comprises or consists of SEQ ID NO:91. In embodiments, the cryptic exon splice donor site region comprises or consists of SEQ ID NO:220. In embodiments, the exon 21 splice acceptor site comprises or consists of SEQ ID NO:299.

In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:641. In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:642.

In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 5' end of the cryptic exon having a sequence set forth in SEQ ID NO:643. In embodiments, the inhibitory nucleic acid, e.g., an antisense oligonucleotide, comprises a sequence that is complementary to the 3' end of the cryptic exon having a sequence set forth in SEQ ID NO:644.

In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide has about 15-40 bases in length, preferably about 18-30 bases, 18-25 bases, 18-22 bases, or 20-30 bases in length.

In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide has a base sequence that is at least 80%, 85%, 90%, 95%, 97%, or 100% identical to any one of the sequences listed in Table 2 (e.g., SEQ ID NOS:13-90),

Table 3 (SEQ ID NOS:92-219), Table 4 (SEQ ID NOS:221-298), Table 5 (SEQ ID NOS:300-377), Table 7B (SEQ ID NOS:423-522), and Table 8B (SEQ ID NOS:523-640). In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide has a base sequence comprising or consisting of any one of the
5 sequences listed in Table 2 (e.g., SEQ ID NOS:13-90), Table 3 (SEQ ID NOS:92-219), Table 4 (SEQ ID NOS:221-298), Table 5 (SEQ ID NOS:300-377), Table 7B (SEQ ID NOS:423-522), and Table 8B (SEQ ID NOS:523-640).

In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to
10 SEQ ID NO:650. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO:650.

In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to
15 SEQ ID NO: 651. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO: 651.

In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are
20 complementary to SEQ ID NO:652. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO:652.

In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18-30 bases, 18-25 bases, or 18-22 bases that are complementary to
25 SEQ ID NO:653. In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 bases that are complementary to SEQ ID NO:653.

In embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18-21 bases that are complementary to SEQ ID NO:654. In
30 embodiments, the UNC13A cryptic exon splice variant specific antisense oligonucleotide has 18, 19, 20, or 21 bases that are complementary to SEQ ID NO:654.

In embodiments, the UNC13 cryptic splice variant specific antisense oligonucleotide is a modified antisense oligonucleotide. In embodiments, the modified

antisense oligonucleotide comprises a phosphoramidate morpholino oligonucleotide, phosphorodiamidate morpholino oligonucleotide, phosphorothioate modified oligonucleotide, 2' O-methyl (2' O-Me) modified oligonucleotide, peptide nucleic acid (PNA), locked nucleic acid (LNA), phosphorodithioate oligonucleotide, 2' O-Methoxyethyl (2'-MOE) modified oligonucleotide, 2'-fluoro-modified oligonucleotide, 2'O,4'C-ethylene-bridged nucleic acid (ENAs), tricyclo-DNA, tricyclo-DNA phosphorothioate nucleotide, constrained ethyl bridged nucleic acid, 2'-O-[2-(N-methylcarbamoyl)ethyl] modified oligonucleotide, morpholino oligonucleotide, and peptide-conjugated phosphoramidate morpholino oligonucleotide (PPMO), or any combination thereof.

In embodiments, the subject has a TDP-43 proteinopathy. In embodiments, the TDP-43 proteinopathy comprises amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), facial onset sensory and motor neuronopathy (FOSMN), hippocampal sclerosis (HS), limbic-predominant age-related TDP-43 encephalopathy (LATE), cerebral age-related TDP-43 with sclerosis (CARTS), Guam Parkinson-dementia complex (G-PDC), Guan ALS (G-ALS), Multisystem proteinopathy (MSP), Perry disease, Alzheimer's disease (AD), and chronic traumatic encephalopathy (CTE), or a combination thereof.

In embodiments, the methods for treatment of the present disclosure reduces, prevents, or slows development or progression of one or more symptom characteristic of a TDP-43 proteinopathy. Examples of symptoms characteristic of TDP-43 proteinopathy include motor dysfunction, cognitive dysfunction, emotional/behavioral dysfunction, paralysis, shaking, unsteadiness, rigidity, twitching, muscle weakness, muscle cramping, muscle stiffness, muscle atrophy, difficulty swallowing, difficulty breathing, speech and language difficulties (e.g., slurred speech), slowness of movement, difficulty with walking, dementia, depression, anxiety, or any combination thereof.

In embodiments, the methods for treatment of the present disclosure comprise administration of the UNC13A cryptic splice variant specific inhibitor as a monotherapy or in combination with one or more additional therapies for the treatment of the TDP-43 proteinopathy. Combination therapy may mean administration of the

compositions of the present disclosure (e.g., antisense oligonucleotide) to the subject concurrently, prior to, subsequent to one or more additional therapies. Concurrent administration of combination therapy may mean that the compositions of the present disclosure (e.g., antisense oligonucleotide) and additional therapy are formulated for
5 administration in the same dosage form or administered in separate dosage forms.

In embodiments, the one or additional therapies that may be used in combination with the UNC13A cryptic splice variant specific inhibitors of the present disclosure include: inhibitory nucleic acids or antisense oligonucleotides that target neurodegenerative disease related genes or transcripts (e.g., C9ORF72), gene editing
10 agents (e.g., CRISPR, TALEN, ZFN based systems) that target neurodegenerative related genes (e.g., C9ORF72), agents that reduce oxidative stress, such as free radical scavengers (e.g., Radicava (edaravone), bromocriptine); ant glutamate agents (e.g., Riluzole, Topiramate, Lamotrigine, Dextromethorphan, Gabapentin and AMPA receptor antagonist (e.g., Talampanel)); anti-apoptosis agents (e.g., Minocycline,
15 Sodium phenylbutyrate and Arimoclomol); anti-inflammatory agents (e.g., ganglioside, Celecoxib, Cyclosporine, Nimesulide, Azathioprine, Cyclophosphamide, Plasmapheresis, Glatiramer acetate and thalidomide); Beta-lactam antibiotics (penicillin and its derivatives, ceftriaxone, and cephalosporin); Dopamine agonists (Pramipexole, Dexamipexole); and neurotrophic factors (e.g., IGF-1, GDNF, BDNF, CTNF, VEGF,
20 Colivelin, Xaliproden, Thyrotrophin-releasing hormone and ADFN).

In embodiments, an UNC13A cryptic splice variant specific inhibitor of the present disclosure is administered in combination with an additional therapy targeting C9ORF72. In some embodiments, the additional therapy targeting C9ORF72 comprises an inhibitory nucleic acid targeting C9ORF72 transcript, a C9ORF72
25 specific antisense oligonucleotide, or a C9ORF72 specific gene editing agent. Examples of C9ORF72 specific therapies are described in US Patent No. 9,963,699 (antisense oligonucleotides); PCT Publication No. WO2019/032612 (antisense oligonucleotides); US Patent No. 10,221,414 (antisense oligonucleotides); US Patent No. 10,407,678 (antisense oligonucleotides); US Patent No. 9,963,699 (antisense
30 oligonucleotides); US Patent Publication US2019/0316126 (inhibitory nucleic acids); US Patent Publication No. 2019/0167815 (gene editing); PCT Publication No.

WO2017/109757 (gene editing), each of which is incorporated by reference in its entirety.

In embodiments, the methods for treatment of the present disclosure, including treating a TDP-43 proteinopathy such as ALS or FTD, may be used in combination with an *STMN2* cryptic splice variant specific inhibitor. *STMN2*, which encodes a regulator of microtubule stability called Stathmin-2, is the gene whose expression is most significantly reduced when TDP-43 is depleted from neurons. The stathmin-2 gene is annotated to contain 5 constitutive exons plus a proposed alternative exon between exons 4 and 5 (see Table 10). *STMN2* harbors a cryptic exon (exon 2a) contained in intron 1 that is normally excluded from the mature *STMN2* mRNA (see, FIG. 18). The first intron of *STMN2* (Table 10) contains a TDP-43 binding site. When TDP-43 is lost or its function is impaired, exon2a gets incorporated into the mature mRNA. Exon 2a harbors a stop codon and a polyadenylation signal (FIG. 18), resulting in truncated *STMN2* mRNA and 8-fold reduction of Stathmin-2. Aberrant splicing and reduced Stathmin-2 levels seem to be a major feature of sporadic and familial ALS cases (except those with *SOD1* mutations) and in FTLT-DTP.

Table 10: STMN2 transcript sequence and intron 1 sequences

STMN2 transcript (NCBI Reference NM_001199214.1 Sequence)
AGCTCCTAGGAAGCTTCAGGGCTTAAAGCTCCACTCTACTTGGACTGTACTATCA GGCCCCCAAATGGGGGGAGCCGACAGGGAAGGACTGATTTCCATTTCAAACTG CATTCTGGTACTTTGTACTCCAGCACCATTGGCCGATCAATATTTAATGCTTGGAG ATTCTGACTCTGCGGGAGTCATGTCAGGGGACCTTGGGAGCCAATCTGCTTGAGC TTCTGAGTGATAATTATTCATGGGCTCCTGCCTCTTGCTCTTTCTCTAGCACGGTC CCACTCTGCAGACTCAGTGCCTTATTCAGTCTTCTCTCTCGCTCTCTCCGCTGCTG TAGCCGGACCCTTTGCCTTCGCCACTGCTCAGCGTCTGCACATCCCTACAATGGCT AAAACAGCAATGGCCTACAAGGAAAAAATGAAGGAGCTGTCCATGCTGTCACTG ATCTGCTCTTGCTTTTACCCGGAACCTCGCAACATCAACATCTATACTTACGATGA TATGGAAGTGAAGCAAATCAACAAACGTGCCTCTGGCCAGGCTTTTGAGCTGATC TTGAAGCCACCATCTCCTATCTCAGAAGCCCCACGAACCTTTAGCTTCTCCAAAGA AGAAAGACCTGTCCCTGGAGGAGATCCAGAAGAACTGGAGGCTGCAGAGGAA AGAAGAAAGTCTCAGGAGGCCAGGTGCTGAAACAATTGGCAGAGAAGAGGGA ACACGAGCGAGAAGTCCTTCAGAAGGCTTTGGAGGAGAACAACAACCTCAGCAA GATGGCGGAGGAAAAGCTGATCCTGAAAATGGAACAAATTAAGGAAAACCGTG AGGCTAATCTAGCTGCTATTATTGAACGTCTGCAGGAAAAGCTGGTCAAGTTTAT TTCTTCTGAACATAAAGAATCTATAGAGTCTCAATTTCTGGAGCTTCAGAGGGAA

GGAGAGAAGCAATGAGAGGCATGCTGCGGAGGTGCGCAGGAACAAGGAACTCC
 AGGTTGAACTGTCTGGCTGAAGCAAGGGAGGGTCTGGCACGCCCCACCAATAGT
 AAATCCCCCTGCCTATATTATAATGGATCATGCGATATCAGGATGGGGAATGTAT
 GACATGGTTTAAAAAGAACTCATTATAAAAAAAAAAAAAACAAAAAAATCAAA
 AATTAAAAAAATCAATGCGGTCTCTTTGCAGAATGTTTTGCTTGATGTTTAAAA
 AATACCTTGGATCTTATTTTGTAATACTTACATTTTTGTAAAAAATACAAGTAT
 TGCATTATGCAAGTTATTTTCATAATCTTACATGTCCTGTAACAGGCTTTTGATGTT
 GTGTCTTTCCACTCAAATGAATTTGCTAGGTCTGTTCTTTTTGAAGCTCCCCATGT
 CTAATCCATTCCAAAAGAAAAATGAGGTCAGTAGACAGTCTATGGTGCTAGAA
 ACCCACCATTGCCTAATGACCTAGAAGGCTTTGTTGTCTCTGAGCTTGACTAAGA
 CCATACCTAGATCACAGGTATTATGACTCCACATGAACCTTCACATTTGTTTCGCTC
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 ATAGCATTTACTTCTGCTTCTCCTGGATTATGTGCTACAAATGTGCTTTGGCTTTA
 GAAAGGGATGGATGAGAAGACAGACCTGAGACCAATCTGGGTAGAAGCAAAAA
 GTTGAACCTTTTAAAGTGCTGAACACAAATCCAAATTCGAATGGTTCAAGCAGCC
 GTGAAATCGCTCTTCATAAAGTGGGCTTAATTCTCTAGTTTAAAGTCTTTTGATGG
 AATGAATTAATTAATGTGTCAGGTGGCTTATTTGTGGATGCCATGATTGATGATG
 TTCATTTTAAAGCTCTTACCTATAGTACAAGTACATGATGCTACTGAATATTTTCC
 ACTTGAAACTGTGAGCTGGTTGTTGCATTAAACACACATACAAACAAAATCA
 AAAACACTGCGGACTTTCACTCAAGCTGGTCTTTCTTCCCCAGTGTAAGGCAATC
 CTGCCTACTAACAACACCAACAACAAAACACTCCATCTGTGAAGCTGACGCAGTT
 AAGGGGGCTAGGCAGGGCATTGTGCCAACTAAGAATCACCAGATACCCACCAT
 AAGTACCTATCGCAGTTTTGAAGTCGTTTCTCCCCAACTCCCAACTCCTGAAGGTT
 GCTGCCTGCATATTTACTCTTCATTAGTGCTATTTTCCTGTATGTCATTGTGAGCA
 AGCTGTGATTAATAAAGAATTGGAGTTCTGTGAACTAATAAAGGTTTGGTCTGTT
 AAAAAAAAA (SEQ ID NO:390)

STMN2 Intron 1 Sequence

gtaaggcactgcgcctcggttccgtcggtctacctggagccacctcctcctcttgagctctagaagcattcagagatatattta
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 gacataaatatgagaacaataaacactgtggactactagaggggggaaggagagagggttgaaaaactacctacaggtgctatgctca
 atacctgggtgatgggatttacccccaaacatcagcatcatttaataatccccatgtaaaaagactgcacatatacccttctatctaaata
 aaacttgaattaaaaaaaagaaagaaagagggtggaaatagagggtcacacctgtaatcccagcactttgggtggccaag

```
gtgggtgattgcttgagcccggaattcaagaccagcctgagaaacctggtgaaactctgtctgtacaaaaatacaaaaattatcca
ggcatggtggagcgcacctgtagtcccagctaattggggaggctgaggggggaacatcacttgagcccaggaggtggaggtgcagt
gagctgggatcacaccactgcactacagcctgggtaacagagcaactctgtctcaagagagagaggaaagaaaaagaaaagatg
gacagataagaaaatgcacttgagattaagagaaagcagcaacataggaccctggataatgtgtttgcttaataactatcctgatgagt
tatctgactattcccaatgagtacgtggcaattcaggctgaaccatcagagttagccctccggaatcttactatgtacaatagacctgcat
gcacatttactagaatgagcctctctctggaatcatgtctgcttccactaattccatctgtttcctctctcctcctatcctgctagatctt
aattccttcgaccttctttgttttctaactccctttcttctgttatttaacctgctatactatgcaattgatctcctctgcactaagggaacat
gcacttcagaattctgttgacatcttgcaatcctttatatttagtgaagaatgcaaaggagtctacctggcaatattcactctgcaggaggc
aataattatttcaaattaaggaagcagtaagagaaattcagaaaaaatgaaatataactaattcttcagcttttcatttcag (SEQ ID
NO:393)
```

In embodiments, the *STMN2* cryptic exon splice variant specific inhibitor selectively inhibits the expression or activity of the *STMN2* cryptic exon splice variant over full length *STMN2* (wildtype) or other variants thereof (*i.e.*, variants that do not contain a cryptic exon 2a contained in intron 1.

In embodiments, the *STMN2* cryptic exon is obtained from intron 1 of the *STMN2* gene. In embodiments, the cryptic exon 2a comprises the red sequence shown in FIG. 19.

In embodiments, the *STMN2* cryptic splice variant specific inhibitor comprises an inhibitory nucleic acid, peptides, antibody, binding protein, small molecule, ribozyme, or aptamer.

In embodiments, the *STMN2* cryptic splice variant specific inhibitor targets the cryptic exon 2a.

In embodiments, the *STMN2* cryptic splice variant specific inhibitor comprises an inhibitory nucleic acid. The inhibitory nucleic acid may be an antisense oligonucleotide, siRNA, shRNA, miRNA, double-stranded RNA (dsRNAs), or esiRNA. In embodiments, the inhibitory nucleic acid comprises an antisense oligonucleotide that is complementary to: the exon 1 splice donor site region in a preprocessed mRNA encoding *STMN2*; the cryptic exon 2a splice acceptor site region in a preprocessed mRNA encoding *STMN2*.

In embodiments, the *STMN2* cryptic splice variant specific antisense oligonucleotide has about 15-40 bases in length, preferably about 18-30 bases, 18-25 bases, 18-22 bases, or 20-30 bases in length.

In embodiments, the *STMN2* cryptic splice variant specific antisense oligonucleotide is a modified antisense oligonucleotide. In embodiments, the modified antisense oligonucleotide comprises a phosphoramidate morpholino oligonucleotide, phosphorodiamidate morpholino oligonucleotide, phosphorothioate modified
5 oligonucleotide, 2' O-methyl (2' O-Me) modified oligonucleotide, peptide nucleic acid (PNA), locked nucleic acid (LNA), phosphorodithioate oligonucleotide, 2' O-Methoxyethyl (2'-MOE) modified oligonucleotide, 2'-fluoro-modified oligonucleotide, 2'O,4'C-ethylene-bridged nucleic acid (ENAs), tricyclo-DNA, tricyclo-DNA phosphorothioate nucleotide, constrained ethyl bridged nucleic acid, 2'-O-[2-(N-
10 methylcarbamoyl)ethyl] modified oligonucleotide, morpholino oligonucleotide, and peptide-conjugated phosphoramidate morpholino oligonucleotide (PPMO), or any combination thereof.

UNC13A cryptic splice variant specific inhibitors of the present disclosure may be administered to a subject by any route, including enteral (e.g., oral), parenteral,
15 intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subpial, intraparenchymal, intrastriatal, intracranial, intracisternal, intra-cerebral, intracerebral ventricular, intraocular, intraventricular, intralumbar, subcutaneous, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation,
20 bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Preferably, UNC13A cryptic splice variant specific inhibitors of the present disclosure (e.g., antisense oligonucleotide) are administered directly to the CNS of the subject, e.g., by intrathecal, subpial, intraparenchymal, intrastriatal, intracranial, intracisternal, intra-cerebral, intracerebral ventricular, intraocular, intraventricular,
25 intralumbar administration, or any combination thereof.

In embodiments, the methods of the present disclosure reduces *UNC13A* cryptic splice variant expression or activity in a cell by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% at least 95% or more in a cell compared to
30 the expression level of *UNC13A* cryptic splice variant in a cell that has not been contacted with the UNC13A cryptic splice variant specific inhibitor. In some embodiments, the methods of the present disclosure reduces *UNC13A* cryptic splice

variant expression or activity in a cell by 10-20%, 10-30%, 10-40%, 10-50%, 10-60%, 10-70%, 10-80%, 10-90%, 10-95%, 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% compared to the expression level of *UNC13A* cryptic splice variant in a cell that has not been contacted with the inhibitory nucleic acid.

In embodiments, the methods of the present disclosure reduces *UNC13A* cryptic splice variant expression or activity in the CNS of a subject by at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 35%, at least 40%, at least 45%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% at least 95% or more in the CNS compared to the expression level of *UNC13A* cryptic splice variant in the CNS of an untreated subject. In embodiments, the methods of the present disclosure reduces *UNC13A* cryptic splice variant expression or activity in the CNS of a subject by 10-20%, 10-30%, 10-40%, 10-50%, 10-60%, 10-70%, 10-80%, 10-90%, 10-95%, 20-30%, 20-40%, 20-50%, 20-60%, 20-70%, 20-80%, 20-90%, 20-95%, 20-100%, 30-40%, 30-50%, 30-60%, 30-70%, 30-80%, 30-90%, 30-95%, 30-100%, 40-50%, 40-60%, 40-70%, 40-80%, 40-90%, 40-95%, 40-100%, 50-60%, 50-70%, 50-80%, 50-90%, 50-95%, 50-100%, 60-70%, 60-80%, 60-90%, 60-95%, 60-100%, 70-80%, 70-90%, 70-95%, 70-100%, 80-90%, 80-95%, 80-100%, 90-95%, 90-100% compared to the expression level of *UNC13A* cryptic splice variant in the CNS of an untreated subject.

25

EXAMPLES

EXAMPLE 1: TDP-43 REPRESSES CRYPTIC EXON INCLUSION IN FTD/ALS GENE *UNC13A*

Materials and Methods

RNA-Seq alignment and splicing analysis

Detailed pipeline v2.0.1 for RNA-Seq alignment and splicing analysis is available on https://github.com/emc2cube/Bioinformatics/sh_RNAseq.sh. FASTQ files were downloaded from the Gene Expression Omnibus (GEO) database as GSE126543. Adaptors in FASTQ files were removed using trimmomatic (0.39) (ILLUMINACLIP:TruSeq3-PE.fa:2:30:10 LEADING:3 TRAILING:3 SLIDINGWINDOW:4:15 MINLEN:36). The quality of the resulting files was then evaluated using FastQC (v0.11.9). RNA-Seq reads were then mapped to the human (hg38) using STAR v2.7.3a.

Splicing analysis

MAJIQ: Alternative splicing events were analyzed using MAJIQ (2.2) and VOILA (12). Briefly, uniquely mapped, junction-spanning reads were used by MAJIQ with the following parameters “maji build -c config --min-intronic-cov 1 --simplify” to construct splice graphs for transcripts by using the UCSC transcriptome annotation (release 82) supplemented with *de novo* detected junctions. Here, *de novo* refers to junctions that were not in the UCSC transcriptome annotation, but had sufficient evidence in the RNA-Seq data (--min-intronic-cov 1). Distinct local splice variations (LSVs) were identified in gene splice graphs and the MAJIQ quantifier (maji psi) estimated the fraction of each junction in each LSV, denoted as percent spliced in (PSI or Ψ), in each RNA-Seq samples. The changes in each junction’s PSI (Δ PSI or $\Delta\Psi$) between the two conditions (TDP-43-positive neuronal nuclei vs. TDP-43-negative neuronal nuclei) were calculated by using the command “maji deltapsi”. The gene splice graphs, the posterior distribution of PSI and Δ PSI were visualized using VOILA.

LeafCutter (commit 249fc26 on <https://github.com/davidaknowles/leafcutter>): Using the already aligned RNA-Seq reads as previously described, reads that span exon-exon junction and map with a minimum of 6 bp into each exon were extracted from the alignment (bam) files using filter_cs.py with the default settings. Intron clustering was performed using the default settings in leafcutter_cluster.py. Differential excision of the introns between the two conditions (TDP-43- positive neuronal nuclei vs. TDP-43-negative neuronal nuclei) were calculated using leafcutter_ds.R

Cell culture

SH-SY5Y (ATCC) cells were grown in DMEM/F12 media supplemented with Glutamax (Thermo Scientific), 10% Fetal Bovine Serum and 10% penicillin–streptomycin at 37°C, 5% CO₂. For shRNA treatments, cells were plated on Day 0, transduced with shRNA on Day 2 followed by media refresh on Day 3, and harvested for readout (RT-qPCR, immunoblotting) on Day 6. HEK293T TDP-43 knock-out cells and parent HEK-293T cells were generated as described in (37). The cells were cultured in DMEM medium (Gibco 10564011) supplemented with 10% Fetal Bovine Serum (Invitrogen 16000-044), 1% penicillin–streptomycin, 2 mM L-glutamine (Gemini Biosciences), 1x MEM non-essential amino acids solution (Gibco) at 37°C, 5% CO₂.

10 Immunoblotting

SH-SY5Y cells and iPSC derived motor neurons (iPSCs-MNs) were transfected and treated as above before lysis. Cells were lysed in ice-cold RIPA buffer (Sigma-Aldrich R0278) supplemented with a protease inhibitor cocktail (Thermo Fisher 78429) and phosphatase inhibitor (Thermo Fisher 78426). After pelleting lysates at maximum speed on a table-top centrifuge for 15 min at 4 °C, bicinchoninic acid (Invitrogen 23225) assays were conducted to determine protein concentrations. 60 µg (SH-SY5Y) and 30 µg (iPSCs-MNs) protein of each sample was denatured for 10 min at 70 °C in LDS sample buffer (Invitrogen NP0008) containing 2.5% 2- mercaptoethanol (Sigma-Aldrich). These samples were loaded onto 4–12% Bis–Tris gels (Thermo Fisher NP0335BOX) for gel electrophoresis, then transferred onto 0.45-µm nitrocellulose membranes (Bio-Rad 162-0115) at 100 V for 2 h using the wet transfer method (Bio-Rad Mini Trans-Blot Electrophoretic Cell 170-3930). Membranes were blocked in Odyssey Blocking Buffer (LiCO₂ 927-40010) for 1h then incubated overnight at room temperature in blocking buffer containing antibodies against UNC13A (1:500, Proteintech 55053-1-AP), TDP-43 (1:1,000, Abnova H00023435-M01), or GAPDH (Cell Signaling Technologies 5174S). Membranes were subsequently incubated in blocking buffer containing HRP-conjugated anti-mouse IgG (H+L) (1:2000, Fisher 62-6520) or HRP-conjugated anti-rabbit IgG (H+L) (1:2000, Life Technologies 31462) for one hour. ECL Prime kit (Invitrogen) was used for development of blots, which were imaged using ChemiDox XRS+ System (BIO-RAD). The intensity of bands was quantified using Fiji, and then normalized to the corresponding controls.

RNA Extraction, cDNA Synthesis, and RT-qPCR/RT-PCR for detecting the UNC13A splice variant

- Total RNA was extracted using RNeasy Micro kit (Qiagen) per manufacturer's instructions, with lysate passed through a QIAshredder column (Qiagen) to maximize yield. RNA was quantified by Nanodrop (Thermo Scientific), with 75ng used for cDNA synthesis with SuperScript IV VILO Master Mix (Thermo Scientific). qPCR was run with 6ng cDNA input in a 20ul reaction using PowerTrack SYBR Green Master Mix (Thermo Scientific) with readout on a QuantStudio 6 Flex using standard cycling parameters (95°C for 2 minutes, 40 cycles of 95°C for 15s/60°C for 60s), followed by standard dissociation (95°C for 15s at 1.6°C/second, 60°C for 60s at 1.6°C/second, 95°C for 15s at 0.075°C/second). $\Delta\Delta C_t$ was calculated with *RPLP0* as housekeeper and relevant shScramble as reference; measured C_t values greater than 40 were set to 40 for visualizations. The following primer pairs were used:

Primer Name	Sequence	SEQ ID NO:
UNC13A_CE FWD 5'-3'	TGGATGGAGAGATGGAACCT	379
UNC13A_CE RVS 5'-3'	GGGCTGTCTCATCGTAGTAAAC	380
UNC13A FWD 5'-3'	GGACGTGTGGTACAACCTGG	381
UNC13A RVS 5'-3'	GTGTACTGGACATGGTACGGG	382
TARDBP_1 FWD 5'-3'	AATTCTGCATGCCCCAGA	383
TARDBP_1 RVS 5'-3'	GAAGCATCTGTCTCATCCATTTT	384
RPLP0_1 FWD 5'-3'	TCTACAACCCTGAAGTGCTTGAT	385
RPLP0_1 RVS 5'-3'	CAATCTGCAGACAGACACTGG	386

- RT-PCR was conducted with 15ng cDNA input in a 100ul reaction using NEBNext Ultra II Q5 Master Mix (New England Biolabs), with resulting products visualized on a 1.5% TAE gel. The following primer pairs were used:

Primer Name	Sequence	SEQ ID NO:
UNC13A_19_21 FWD 5'-3'	CAACCTGGACAAGCGAACTG	387
UNC13A_19_21 RVS 5'-3'	GGGCTGTCTCATCGTAGTAAAC	388
UNC13A_CE FWD 5'-3'	TGGATGGAGAGATGGAACCT	379
UNC13A_CE RVS 5'-3'	GGGCTGTCTCATCGTAGTAAAC	380

shRNA cloning, lentiviral packaging, and cellular transduction

shRNA sequences originated from the Broad GPP Portal (TDP-43: AGATCTTAAGACTGGTCATTC (SEQ ID NO:391), scramble: GATATCGCTTCTACTAGTAAG (SEQ ID NO:392)). To clone, complementary oligos were synthesized to generate 4 nt overhangs, annealed, and ligated into pRSITCH (Tet inducible U6) or pRSI16 (constitutive U6) (Cellecta). Ligations were transformed into Stbl3 chemically competent cells (Thermo Scientific) and grown at 30 °C. Large scale plasmid generation was performed using Maxiprep columns (Promega), with purified plasmid used as input for lentiviral packaging with second generation packaging plasmids psPAX2 and pMD2.G (Cellecta), transduced with Lipofectamine 2000 (Invitrogen) in Lenti-X 293T cells (Takara). Viral supernatant was collected at 48 and 72 hours post transfection and concentrated using Lenti-X Concentrator (Takara). Viral titer was established by serial dilution in relevant cell lines and readout of %BFP+ by flow cytometry, with a dilution achieving a minimum of 80% BFP+ cells selected for experiments.

15 Variant validation

Variants in iPSC-derived motor neuron cells were established by PCR amplification from UNC13A exon 19 to exon 21 (UNC13A_19_21 FWD 5'-3'=
CAACCTGGACAAGCGAACTG (SEQ ID NO:387), UNC13A_19_21 RVS 5'-3'=
GGGCTGTCTCATCGTAGTAAAC (SEQ ID NO:388)). Resulting products were
20 purified using Wizard SV Gel and PCR Clean-Up columns (Promega) and submitted for Sanger and NGS (Amplicon EZ) (Genewiz).

iPSC maintenance and differentiation into motor neurons (iPSC-MNs)

iPSC lines were obtained from public biobanks (GM25256-Corriell Institute; NDS00262, NDS00209-NINDS) and maintained in mTeSR1 media (StemCell Technologies) on matrigel (Corning). iPSCs were fed daily and split every 4-7 days using ReLeSR (StemCell Technologies) according to manufacturer's instructions. Differentiation of iPSCs into motor neurons was carried out as previously described (41). Briefly, iPSCs were dissociated and placed in ultra-low adhesion flasks (Corning) to form 3D spheroids in media containing DMEMF12/Neurobasal (Thermo Fisher), N2 supplement (Thermo Fisher), and B-27 supplement-Xeno free (Thermo Fisher). Small
30 molecules were added to induce neuronal progenitor patterning of the spheroids, (LDN193189, SB-431542, Chir99021), followed by motor neuron induction (RA, SAG,

- DAPT). After 14 days, neuronal spheroids were dissociated with Papain and DNase (Worthington Biochemical) and plated on Poly-D-Lysine/Laminin coated plates in Neurobasal medium (Thermo Fisher) containing neurotrophic factors (BDNF, GDNF, CNTF; R&D Systems). For viral transductions, neuronal cultures were incubated for 18 hr with media containing lentivirus particles for shScramble, or shTDP-43. Infection efficiency of over 90% was assessed by RFP expression. Neuronal cultures were analyzed for RNA and protein 7 days post transduction.

Cell line name	Sex	Age	Disease Mutation	Source
GM25256	M	30	N/A	Coriell Institute
NDS00209	M	64	TDP43 G298S	NINDS
NDS00262	M	N/A	N/A	NINDS

Human iPSC-neurons for detecting UNC13A splice variant

- Complementary cDNA was available from CRISPRi-i³Neuron iPSCs (i³N) generated from our previous publication (10), in which TDP-43 is downregulated to about 50%. Quantitative real-time PCR (RT-qPCR) was performed using SYBR GreenER qPCR SuperMix (Invitrogen). Samples were run in triplicate, and RT-qPCRs were run on a QuantStudio™ 7 Flex Real-Time PCR System (Applied Biosystems).
- The following primer pairs were used: UNC13A_CE FWD 5'-3' = TGGATGGAGAGATGGAACCT (SEQ ID NO:379), UNC13A_CE RVS 5'-3' = GGGCTGTCTCATCGTAGTAAAC (SEQ ID NO:380). Relative quantification was determined using the $\Delta\Delta C_t$ method and normalized to the endogenous controls RPLP0 and GAPDH (GAPDH FWD 5'-3' = GTTCGACAGTCAGCCGCATC (SEQ ID NO:397), GAPDH RVS 5'-3' = GGAATTTGCCATGGGTGGA (SEQ ID NO:398); RPLP0_2 FWD 5'-3' = TCTACAACCCTGAAGTGCTTGAT (SEQ ID NO:399), RPLP0_2 RVS 5'-3' = CAATCTGCAGACAGACACTGG (SEQ ID NO:400)). Relative transcript levels for wild-type *UNC13A* were normalized to that of the healthy controls (mean set to 1).

Post-mortem brain tissues for detecting UNC13A splice variant

Post-mortem brain tissues from patients with FTLD-TDP and cognitively normal control individuals were obtained from the Mayo Clinic Florida Brain Bank. Diagnosis was independently ascertained by trained neurologists and neuropathologists

upon neurological and pathological examinations, respectively. Written informed consent was given by all participants or authorized family members and all protocols were approved by the Mayo Clinic Institution Review Board and Ethics Committee. Complementary DNA (cDNA) obtained from 500 ng of RNA ($RIN \geq 7.0$) from medial frontal cortex was available from a previous study, as well as matching pTDP-43 data from the same samples (42). Following standard protocols, quantitative real-time PCRs (RT-qPCR) were conducted using SYBR GreenER qPCR SuperMix (Invitrogen, Carlsbad, CA, USA) for all samples in triplicates. Primer pair used for detecting UNC13A splice variant were UNC13A_CE FWD 5'-3'=
 10 TGGATGGAGAGATGGAACCT (SEQ ID NO:379), UNC13A_CE RVS 5'-3'=
 GGGCTGTCTCATCGTAGTAAAC (SEQ ID NO:380). RT-qPCRs were run in a QuantStudio™ 7 Flex Real-Time PCR System (Applied Biosystems). Relative quantification was determined using the $\Delta\Delta C_t$ method and normalized to the endogenous controls *RPLP0* and *GAPDH* (*GAPDH* FWD 5'-3'=
 15 GTTCGACAGTCAGCCGCATC (SEQ ID NO:397), *GAPDH* RVS 5'-3'=
 GGAATTTGCCATGGGTGGA (SEQ ID NO:398); *RPLP0_2* FWD 5'-3'=
 TCTACAACCCTGAAGTGCTTGAT (SEQ ID NO:399), *RPLP0_2* RVS 5'-3'=
 CAATCTGCAGACAGACACTGG (SEQ ID NO:400)). Relative transcript levels were normalized to that of the healthy controls (mean set to 1).

20

Quantification of UNC13A splice variants

RNA-Seq data generated by NYGC ALS Consortium cohort were downloaded from the NCBF's Gene Expression Omnibus (GEO) database (GSE137810, GSE124439, GSE116622, and GSE153960). The 1658 available and quality-controlled
 25 samples classified as described in (10) was used. After pre-processing and aligning the reads to human (hg38) as described previously, the expression of the full-length *UNC13A* was estimated using RSEM (v1.3.2). The average TPM of UNC13A across all the tissue samples from all the individuals was 10.5 on average. PCR duplicates were removed using MarkDuplicates from Picard Tools (2.23.0) using the
 30 command "MarkDuplicates REMOVE_DUPLICATES=true CREATE_INDEX=true". Reads that span either "Exon 19-Exon 20" junction, "Exon 20-CE" junction, "CE- Exon 21" junction, or "Exon 20-exon 21" junction were quantified using bedtools (2.27.1) using the command "bedtools intersect -split". Because of the relatively low level of

expression of *UNC13A* in post-mortem tissues and the heterogeneity of the tissues, it is possible that not all tissues have enough detectable *UNC13A* for us to detect the splice variants. Since *UNC13A* contains more than 40 exons and RNA-Seq coverages of mRNA transcripts are often not uniformly distributed (43), reads spanning “Exon 19-
 5 Exon 20” junction, which is included in both the canonical isoform and the splice variant, were examined and there is a strong correlation (Pearson’s $r = 0.99$) between the numbers of reads mapped to “Exon 19- Exon 20” junction and “Exon 20-Exon 21” junction. Samples that have at least 2 reads spanning either “Exon 20-CE” junction or “CE-Exon 21” junction were observed to have at least either *UNC13A* TPM = 1.55 or
 10 20 reads spanning “Exon 19- Exon 20” junction. Therefore, the 1151 samples that had a TPM ≥ 1.55 , or at least 20 reads mapped to the “Exon 19-Exon 20” junction were selected as samples suitable for *UNC13A* splice variant analysis.

15 Determination of rs12608932 and rs12973192 SNP genotype in human postmortem brain

Genomic DNA (gDNA) was extracted from human frontal cortex using Wizard Genomic DNA Purification Kit (Promega), according to the manufacturer’s instructions. TaqMan SNP genotyping assays were performed on 20 ng of gDNA per assay, using a commercial pre-mixture consisted of a primer pair and VIC/FAM labeled
 20 probes specific for each SNP (Cat#4351379, assay ID “43881386_10” for rs12608932 and “11514504_10” for rs12973192, Thermo Fisher Scientific), and run on a QuantStudio™ 7 Flex Real-Time PCR system (Applied Biosystems), according to the manufacturer’s instructions. The PCR-programs were 60°C for 30 s, 95°C for 10min, 40 cycles of 95°C for 15s and, 60°C (rs12973192) or 62.5°C for 1min (rs12608932),
 25 and 60°C for 30s.

Splicing Reporter Assay

Minigene constructs were designed in silico, synthesized by GeneScript and sub-cloned into a vector with the GFP splicing control. HEK293T TDP-43 knock-out cells and the parent HEK- 293T cells were seeded into standard P12 tissue culture
 30 plates (at 1.6×10^5 cells/well), allowed to adhere overnight and transfected with the indicated splicing reporter constructs (400 ng/well) using Lipofectamine 3000 Transfection Reagent (Invitrogen). Each reporter comprised one of the splicing modules

(shown in Fig. 4E), which is expressed from a bidirectional promoter. Twenty- four hours after transfection, RNA was extracted from these cells using PureLink RNA Mini Kit (Life Technologies) according to the manufacturer's protocol, with on-column PureLink DNase treatment. The RNA was reverse transcribed into cDNA using the

5 High Capacity cDNA Reverse Transcription Kit (Invitrogen) according to the manufacturers' instructions. PCRs were performed using OneTaq 2X Master Mix with Standard Buffer (NEB) using the following primers: mCherry FWD 5'-3'=
 GTTCATGCGCTTCAAGGTG (SEQ ID NO:407), mCherry RVS 5'-
 3'=TTGGTCACCTTCAGCTTGG (SEQ ID NO:408); EGFP FWD 5'-
 10 3'=ACAGGTAAGTGTGCCTATCAAAG (SEQ ID NO:409); EGFP RVS 5'-3'=
 TGTGGCGGATCTTGAAGTTAG (SEQ ID NO:410) on a Mastercycler Pro (Eppendorf) thermocycler PCR machine. PCR products were separated by electrophoresis on a 1.5% TAE gel and imaged ChemiDox XRS+ System (BIO-RAD).

15 Generation of pTB *UNC13A* minigene construct

The pTB *UNC13A* minigene construct containing the human *UNC13A* cryptic exon sequence and the nucleotide flanking sequences upstream (50 bp at the of end of intron 19, the entire exon 20, the entire intron 20 sequence upstream of the cryptic exon) and downstream (~300 bp intron 20) of the cryptic exon were amplified from

20 human genomic DNA using the following primers: FWD 5'-
 3'=AGGTCATATGCACTGCTATAGTGGGAAGTTC (SEQ ID NO:411) and RVS
 5'-3'=CTTACATATGTAATAACTCAACCACACTTCCATC SEQ ID NO:412); and subcloned into the NdeI site of the pTB vector. Note a similar approach to study TDP-43 splicing regulation of other TDP-43 targets was previously used (44).

25

Rescue of *UNC13A* splicing using the pTB minigene and TDP-43 overexpression constructs

HeLa cells were grown in Opti-MEM I Reduced Serum Medium, GlutaMAX Supplement (Gibco) plus 10% fetal bovine serum (Sigma) and 1%
 30 penicillin/streptomycin (Gibco). For double- transfection and knockdown experiments, cells were first transfected with 1.0 µg of pTB *UNC13A* minigene construct and 1.0 µg of one of the following plasmids: GFP, GFP-TDP-43 or GFP-TDP- 43 5FL (constructs to express GFP-tagged TDP-43 proteins have been previously described (40, 44), in

- serum-free media and using Lipofectamine 2000 following manufacturer's instructions (Invitrogen). Four hours following transfection, media was replaced with complete media containing siLentfect (Bio-Rad) and siRNA complexes (AllStars Neg. Control siRNA or siRNA against *TARDBP* 3'UTR, a region not included in the TDP-43 overexpression constructs) (Qiagen) following the manufacturer's protocol.
- Cycloheximide (Sigma) was added at a final concentration of 100 µg/ml at six hours prior harvesting the cells. Then cells were harvested and RNA extracted using TRIzol Reagent (Zymo Research), following manufacturer's instructions. Approximately 1 µg of RNA was converted into cDNA using the High Capacity cDNA Reverse
- 10 Transcription Kit with RNA inhibitor (Applied Biosystems). The RT-qPCR assay was performed on cDNA (diluted 1:40) with SYBR GreenER qPCR SuperMix (Invitrogen) using QuantStudio7™ Flex Real-Time PCR System (Applied Biosystems). All samples were analyzed in triplicates. The RT-qPCR program was as follows: 50°C for 2 min, 95°C for 10 min, and 40 cycles of 95 °C for 15 s and 60°C for 1 min. For dissociation
- 15 curves, a dissociation stage of 95°C for 15 s, 60°C for 1 min and 95°C for 15 s was added at the end of the program. Relative quantification was determined using the $\Delta\Delta C_t$ method and normalized to the endogenous controls *RPLP0* and *GAPDH*. Relative transcript levels for wild-type *UNC13A* and GFP were normalized to that of the control siRNA condition (mean set to 1).
- 20 The following primer pairs were used:

Primer Name	Sequence	SEQ ID NO:
UNC13A_CE_minigene FWD 5'-3'	GATTGAACAGATGAATGAGTGATGA	413
UNC13A_CE_minigene RVS 5'-3'	TGTCTGGACCAATGTTGGTG	414
GFP_OE FWD 5'-3'	GAAGCGCGATCACATGGT	415
GFP_OE RVS 5'-3'	CCATGCCGAGAGTGATCC	416
<i>GAPDH</i> FWD 5'-3'	GTTGACAGTCAGCCGCATC	397
<i>GAPDH</i> RVS 5'-3'	GGAATTTGCCATGGGTGGA	398
<i>RPLP0_2</i> FWD 5'-3'	TCTACAACCCTGAAGTGCTTGAT	399
<i>RPLP0_2</i> RVS 5'-3'	CAATCTGCAGACAGACACTGG	400
<i>TARDBP_2</i> FWD 5'-3'	TGGACGATGGTGTGACTGCAA	421
<i>TARDBP_2</i> RVS 5'-3'	AGAGAAGAACTCCCGCAGCTCA	422

*In situ hybridization UNC13A cryptic exon analysis in postmortem brain samples**Patients and diagnostic neuropathological assessment*

Postmortem brain tissue samples used for this study were obtained from the

5 University of California San Francisco (UCSF) Neurodegenerative Disease Brain Bank. Table 6 provides demographic, clinical, and neuropathological information. Consent for brain donation was obtained from subjects or their surrogate decision makers in accordance to the Declaration of Helsinki, and following a procedure approved by the UCSF Committee on Human Research. Brains were cut fresh into 1 cm thick coronal

10 slabs and alternate slices were fixed in 10% neutral buffered formalin for 72 h. Blocks from medial frontal pole were dissected from the fixed coronal slabs, cryoprotected in graded sucrose solutions, frozen, and cut into 50 μ m thick sections as described previously (45). Clinical and neuropathological diagnosis were performed as described previously (44). Subjects were selected based on clinical and neuropathological

15 assessment. Patients selected had a primary clinical diagnosis of behavioral variant frontotemporal dementia (bvFTD) with or without amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND) and 2) a neuropathological diagnosis of frontotemporal lobar degeneration (FTLD)-TDP, Type B. We excluded subjects if they had a known disease-causing mutation, post-mortem interval $\geq$ 24 h, Alzheimer's

20 disease neuropathologic change $>$ low, Thal amyloid phase $>$ 2, Braak neurofibrillary tangle stage $>$ 4, CERAD neuritic plaque density $>$ sparse, and Lewy body disease $>$ brainstem predominant (45).

Table 6: Post-mortem brain tissue samples

Case Number	Age (years)	Sex	PMI (hrs)	Clinical diagnosis	Primary neuropathological diagnosis	ADNC
FTD-MND 1	72	M	6.7	bvFTD-MND	FTLD-TDP-B	Not
FTD-MND 2	57	M	7.6	bvFTD-ALS	FTLD-TDP-B, MND	Not
FTD-MND 3	66	M	12.1	bvFTD/nfvPPA, MND	FTLD-TDP-B, ALS	Low
FTD-MND 4	65	F	8.5	bvFTD	FTLD-TDP-B, MND	Low
Control 1	76	M	8.2	N/A	None	Low
Control 2	67	F	19.4	N/A	None	Not

Control 3	60	F	20.5	N/A	None	Low
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In situ hybridization (ISH) and immunofluorescence

To detect single RNA molecules, a BaseScope Red Assay kit (ACDBIO, USA) was used. One 50 μ m thick fixed frozen tissue section from each subject was used for staining. Experiments were performed under RNase free conditions as appropriate. Probes that target the transcript of interest, UNC13A, specific to either the mRNA (exon20/21 junction) or the cryptic exon containing spliced target (exon20/cryptic exon junction) were used. Positive (*Homo sapiens* PPIB) and negative (*Escherichia coli* DapB) control probes were also included. *In situ* hybridization was performed based on vendor specifications for the BaseScope Red Assay kit. Briefly, frozen tissue sections were washed in PBS and placed under an LED grow light (HTG Supply, LED-6B240) chamber for 48 h at 4 °C to quench tissue autofluorescence. Sections were quickly rinsed in PBS and blocked for endogenous peroxidase activity. Sections were transferred on to slides and dried overnight. Slides were subjected to target retrieval and protease treatment and advanced to ISH. Probes were detected with TSA Plus-Cy3 (Akoya Biosciences) and subjected to immunofluorescence staining with antibodies to TDP-43 (rabbit polyclonal, Proteintech, RRID: AB_615042) and NeuN (Guinea pig polyclonal, Synaptic systems) and counterstained with DAPI (Life Technologies) for nuclei.

Image acquisition and analysis

Z-stack images were captured using a Leica SP8 confocal microscope with an 63x oil immersion objective (1.4 NA). For RNA probes, image capture settings were established during initial acquisition based on PPIB and DAPB signal and remained constant across *UNC13A* probes and subjects. TDP-43 and NeuN image capture settings were modified based on staining intensity differences between cases. For each case, 6 non-overlapping Z-stack images were captured across cortical layers 2-3. RNA puncta for the UNC13A cryptic exon were quantified using the “analyze particle” plugin in ImageJ. Briefly, all images were adjusted for brightness using similar parameters and converted to maximum intensity Z-projections, images were adjusted for auto-threshold (intermodes), and puncta were counted (size: 6-infinity, circularity – 0-1).

Linkage Disequilibrium analysis

Recalibrated VCF files generated by GATK HaplotypeCallers were downloaded from Answer ALS in July 2020. VCFtools (0.1.16) were used to filter for sites that are in intron 20-21. The filtered VCF files were merged using BCFtools (1.8). Since there are sites that contain more than 2 alleles, we tested for genotype independence using the chi-squared statistics by using the command “vcftools --geno-chisq --min-alleles 2 --max-alleles 8” (4.0.0).

Statistical methods

Survival curves were compared using the coxph function in the survival (3.1.12) R package, which fits a multivariable Cox proportional hazards model that contains sex, reported genetic mutations and age at onset, and performs a Score (log-rank) test. Effect sizes are reported as the hazard ratios. Proportional Hazards assumptions were tested using cox.zph() function. The survival curves were plotted using ggsurvplot() in survminer (v.0.4.8) R package.

Correlations between the cryptic exon signal and phosphorylation levels of TDP-43 or number of risk haplotypes were done after filtering out all the samples that do not have the cryptic exon signal (n = 4). Linear mixed effects models were analyzed using lmerTest R package (3.1.3).

Statistical analyses were performed using R (version 4.0.0), or Prism 8 (GraphPad), which were also used to generate graphs.

Results

To discover cryptic splicing targets that are regulated by TDP-43 that may also play a role in disease pathogenesis, a recently generated RNA sequencing (RNA-seq) dataset was utilized (11). To identify changes associated with loss of TDP-43 from the nucleus, Liu et al. cleverly realized that they could use fluorescence-activated cell sorting (FACS) to enrich neuronal nuclei that either contained TDP-43 or did not and then perform RNA-seq to compare the transcriptomes between TDP-43-positive and TDP-43-negative neuronal nuclei from 7 frozen neocortices of postmortem brains from FTD/ALS patients. They identified a multitude of interesting differentially expressed genes (11). The present study re-analyzed the data in a different way – not looking for differentially expressed genes like Liu et al. did but instead searching for novel alternative splicing events impacted by the loss of TDP-43. Splicing analyses using two pipelines, MAJIQ

(12) and LeafCutter (13) was performed, designed to detect novel splicing events (**FIG. 1A**). Each RNA-seq library contains approximately 50M paired-end reads with a length of 125 bp, greater read length and coverage facilitating discovery of splicing changes caused by the loss of TDP-43. 197 alternative splicing events ($P(\Delta\Psi > 0.1) > 0.95$) ($\Delta\Psi$, changes of local splicing variations between two conditions; P: probability) were identified with MAJIQ and 152 with LeafCutter ($P < 0.05$). There were 65 alternatively spliced genes in common between both analyses (**FIG. 1B**), likely because each tool uses different definitions for transcript variations and different criteria to control for false positives. Notably, among the alternatively spliced genes identified by both tools were *STMN2* and *POLDIP3*, both of which have been extensively validated as *bona fide* TDP-43 splicing targets (8–10, 14).

Unexpectedly, *UNC13A* was found to be one of the most significantly alternatively spliced genes in neurons with TDP-43 depleted from the nucleus (**FIG. 1B** and **FIGS. 5A–5D**). Depletion of TDP-43 resulted in the inclusion of a 128 bp cryptic exon #1 between the canonical exons 20 and 21 (hg38; chr19: 17642414–17642541) (**FIG. 1C and 1D**) or a ### bp cryptic exon #2 between exons 20 and 21 (hg38; chr19: 17642414–17642591). Since higher usage of the chr19:17642541 3' splicing acceptor was observed, the focus of the study is on the 128 bp cryptic exon #1. Hereinafter, in this example, if not specified, reference to cryptic exon refers to the 128 bp cryptic exon #1. This new exon, referred to as CE #1 (for cryptic exon), was absent in wild type neuronal nuclei (**FIG. 1C**) and is not present in any of the known human isoforms of *UNC13A* (15). Furthermore, analysis of ultraviolet cross-linking and immunoprecipitation (iCLIP) data for TDP-43 in SH-SY5Y cells (3) provides evidence that TDP-43 directly binds to the intron harboring this cryptic exon (**FIG. 1D**). Insertion of the 128 bp cryptic exon sequence into the mature transcript was confirmed by direct sequencing. Intron 20–21 of *UNC13A* and the CE sequence are conserved among most primates (**FIGS. 6A and 6B**) but not conserved in mouse, similar to *STMN2* and other cryptic splicing targets of TDP-43 (4, 8, 9). Together, these results suggest that TDP-43 functions to repress the inclusion of a cryptic exon in the *UNC13A* mRNA transcript.

To test if TDP-43 directly regulates this *UNC13A* cryptic splicing event, doxycycline-inducible shRNA was used to reduce TDP-43 levels in SH-SY5Y cells. Quantitative reverse transcription PCR (qRT-PCR) was used to detect cryptic exon inclusion, which was present in cells with TDP-43 depleted (by treatment with

shTARDBP) but not in control shRNA treated cells (**FIG. 1E**). Along with the increase in cryptic exon levels, there was a corresponding decrease in levels of the canonical *UNC13A* transcript upon TDP-43 depletion (**FIG. 1E**). By immunoblotting, a marked reduction in UNC13A protein in TDP-43-depleted cells was also observed (**FIGS. 1F, 1G**). TDP-43 levels were reduced in induced motor neurons (iMNs) (**FIGS. 1H, 1I; FIGS. 7A and 7B**) and excitatory neurons (i³Ns) derived from human iPS cells (**FIG. 1J**). TDP-43 depletion resulted in cryptic exon inclusion in *UNC13A* and a reduction in *UNC13A* mRNA and protein. Thus, lowering levels of TDP-43 in human cells and neurons causes inclusion of a cryptic exon in the *UNC13A* transcript, resulting in decreased UNC13A protein.

UNC13A belongs to a family of genes originally discovered in *C. elegans* based on the uncoordinated (*unc*) movements exhibited by animals with mutations in these genes (*16*), owing to deficits in neurotransmitter release. UNC13A encodes a large multidomain protein expressed in the nervous system, where it localizes to neuromuscular junctions and plays an essential role in the vesicle priming step, prior to synaptic vesicle fusion (*17–20*). *In vitro* studies demonstrate that the cryptic exon splicing event upon TDP-43 depletion causes marked reduction in UNC13A expression (**FIG. 1F**). Mice lacking *Unc13a* (also called *Munc13-1*) show morphological defects in spinal cord motor neurons and functional deficits at the neuromuscular junction. These data suggest that depletion of TDP-43 leads to a loss of UNC13A function (*21*).

To extend this analysis of *UNC13A* cryptic exon inclusion to a larger collection of patient samples, a series of 115 frontal cortex brain samples from the Mayo Clinic brain bank were first analyzed and a significant increase in *UNC13A* cryptic exon (CE) levels was found in FTLT-TDP patients compared to healthy controls (**FIG. 2A**). A decrease in total *UNC13A* transcripts in frontal cortex of some subtypes of FTD patients was also observed (**FIG. 8**). Next, brain samples from the New York Genome Center (NYGC) were analyzed. After filtering for relatively high-quality data (Methods), this data set includes RNA-seq data from 1151 samples from 413 individuals (more than one tissue per individual), 330 of which are ALS or FTD patients. Because FACS analysis by Liu et al. (*11*) indicates that pathological neuronal nuclei with loss of TDP-43 represent only ~7% of all neuronal nuclei and less than 2% of all cortical cells (*11*) it was expected that splicing analysis algorithms would struggle to detect differentially spliced genes in RNA-seq data generated from bulk RNA sequencing. To overcome this problem, reads

that spanned the exon 20-CE and CE-exon 21 junctions were specifically looked for. Owing to noise generated from bulk sequencing, the *UNC13A* splice variant was scored as present if there were more than two reads spanning at least one of the exon-exon junctions. 63 samples, from 49 patients, were identified which met the above criteria.

5 Notably, *UNC13A* splice variant was detected in close to 50% of the frontal cortical and temporal cortical tissues donated by neuropathologically confirmed FTLD-TDP patients. The splice variants were also detected in some of the ALS patients whose pathology has not been confirmed (**FIG. 9**). Notably, *UNC13A* CE was not observed in any of the samples from FTLD-FUS (n=9), FTLD-TAU (n=18) and ALS-SOD1 (n=22) patients,

10 nor in any of the control samples (n=197). Thus, *UNC13A* cryptic exon inclusion is a robust and specific facet of pathology in TDP-43 proteinopathies (**FIG. 2B**).

Once TDP-43 becomes depleted from the nucleus and accumulates in the cytoplasm, it becomes phosphorylated. Hyperphosphorylated TDP-43 (pTDP-43) is a key feature of pathology (22). To determine the relationship between pTDP-43 levels and

15 *UNC13A* cryptic exon inclusion, a set of 86 FTD patients from the Mayo Clinic brain bank, for which RNA-seq and pTDP-43 levels from frontal cortices was obtained, was analyzed. A striking association between higher pTDP-43 levels and higher levels of *UNC13A* cryptic exon inclusion was found in patients from all disease subtypes (Spearman's $\rho = 0.564$, $P < 0.0001$) (**FIGS. 3C and 3D**, and **FIG. 10A**; figures using

20 untransformed data: **FIGS. 10E and 10F**). The levels of total *UNC13A* transcripts were also negatively correlatedly with pTDP-43 levels (**FIGS. 10B, 10C, 10G and 10H**). Thus, *UNC13A* cryptic exon inclusion and decreased full-length transcript level seem to be a common feature of multiple TDP-43 proteinopathies and to strongly correlate with the burden of TDP-43 pathology.

25 To visualize the *UNC13A* CE at single cell sensitivity with spatial resolution, custom BaseScope™ *in situ* hybridization probes were designed that specifically bind to the exon 20-exon 21 (**FIG. 11A**) or the exon 21-CE junction (**FIG. 11B**). The probes were designed to span exon-exon junctions in order to minimize the possibility of binding to pre-mRNA. These probes were used for *in situ* hybridization along with

30 immunofluorescence for NeuN (to detect neurons) and TDP-43 (to detect nuclear or cytoplasmic TDP-43). Sections from the medial frontal pole of 4 FTLD-TDP patients and 3 controls were stained. Using the exon21-CE probe robust *UNC13A* CE inclusion was detected in nearly every neuron with TDP-43 depleted from the nucleus but not in ones

with nuclear TDP-43 (**FIG. 3A, FIGS. 11C and 11E**). *UNC13A* mRNA was detected using the exon20/21 probe in neurons of both cases and controls (**FIG. 3B, FIG. 11D**). *UNC13A* cryptic exon inclusion now seems to be a robust facet of FTLD-TDP pathology.

UNC13A is one of the top GWAS hits for ALS and FTD-ALS, replicated across multiple studies (23–28). SNPs in *UNC13A* are associated with increased risk of sporadic ALS (24) and sporadic FTD with TDP-43 pathology (23). In addition to increasing susceptibility to ALS, SNPs in *UNC13A* are also associated with shorter survival in ALS patients (29–32). But the mechanism by which genetic variation in *UNC13A* increase risk for ALS and FTD is unknown. Remarkably, the two most significantly associated SNPs, rs12608932 (A>C) and rs12973192 (C>G), are both located in the same intron that we found harbors the cryptic exon, with rs12973192 located right in the cryptic exon itself (**FIG. 4A**). This immediately suggested the hypothesis that these SNPs (or other genetic variation nearby tagged by these SNPs) might make *UNC13A* more vulnerable to cryptic exon inclusion upon TDP-43 depletion. To test this hypothesis, the percentage of RNA-seq reads (**FIGS. 12A and 12B**) that span intron 20-21 that support the inclusion of the cryptic exon was analyzed. Among the 7 RNA-Seq libraries from TDP-43 depleted neuronal nuclei that were included in the initial splicing analysis, 2 out of 3 patients that were homozygous (G/G) and the one patient that was heterozygous (C/G) for the risk allele at rs12973192 showed inclusion of the cryptic exon in almost every *UNC13A* mRNA that was mapped to intron 20-21. In contrast, the patients who were homozygous for the reference allele (C/C) showed much less inclusion of the cryptic exon. Another way to directly assess the impact of the *UNC13A* risk alleles on cryptic exon inclusion is to measure potential allele imbalance in RNAs from individuals who happen to be heterozygous for the risk allele. In other words, is there an equal number of RNAs with cryptic exon inclusion produced from the risk allele as the protective allele? Or are there more from the risk allele? Two of the iMN lines that were used to detect cryptic exon inclusion upon TDP-43 knockdown (**FIG. 1G**, iMN1 and iMN2) are heterozygous (C/G) at rs12973192. The RT-PCR product that spans the cryptic exon was sequenced and the allele distribution from these two samples was analyzed as well as the one patient sample from the original RNA-seq dataset (**FIG. 1A**) that is heterozygous (C/G) at rs12973192 (**FIG. 12B**). A significant difference between the percentage of C and G alleles was found in the spliced variant, with higher inclusion of the risk allele (p-value = 0.01, two-tailed paired t-test; **FIG. 4B and FIG. 12C**). Given this evidence for an effect of the risk allele

on cryptic exon inclusion, analysis was extended by genotyping FTD-TDP patients (n = 86) in the Mayo Clinic brain bank dataset for the *UNC13A* risk alleles at rs12973192 and rs12608932. One patient who is homozygous for the reference allele (C/C) at the rs12973192 but heterozygous (A/C) at rs12608932 was excluded. The rest of the patients (n=85) have exactly the same number of risk alleles at both loci. The correlation between the level of cryptic exon inclusion (from RNA-seq of frontal cortex) and the number of risk alleles at rs12973192 was first modeled as a simple linear regression –a strong correlation (P=0.0136) between the number of risk alleles and the abundance of *UNC13A* cryptic exon inclusion was found (**FIG. 4C**). After including other known variables such as TDP-43 phosphorylation levels, sex, genetic mutations and disease types as predictors of the abundance of *UNC13A* cryptic exon in a multiple linear regression model (adjusted R²=0.3616, figure and statistics from untransformed data **FIG. 13A**), it was found that the number of risk alleles is one of the strongest predictors of cryptic exon inclusion (p-value=0.00792, figure from untransformed data **FIG. 13B**), but not of overall *UNC13A* expression level (**FIGS. 13C and 13D**, untransformed data **FIGS. 13E and 13F**). Taken together, these data suggest that genetic variation in *UNC13A* that increases risk for ALS and FTD in humans promote cryptic exon inclusion upon TDP-43 nuclear depletion.

GWAS SNPs typically do not cause the trait but rather “tag” other neighboring genetic variation (33). Thus, a major challenge in human genetics is to go from GWAS hit to identifying the causative genetic variation that increases risk for disease (34). A LocusZoom (35) plot (**FIG. 4A**) generated using a linear mixed model analysis of ALS GWAS results (36) suggests that the strongest association signal on *UNC13A* is indeed in the region surrounding the two lead SNPs (rs12973192 and rs12608932). To look for other genetic variants in intron 20-21 that might also cause risk for disease by influencing cryptic exon inclusion but were not included in the original GWASs, genetic variants identified in whole genome sequencing data of ALS patients (Answer ALS) were analyzed. This dataset includes 297 ALS patients of European descent. Novel genetic variants that could be tagged by the two SNPs were searched for by looking for other loci in intron 20-21 that are in linkage disequilibrium with both rs12608932 and rs12973192. One was found that fit these criteria – rs56041637 (FDR-corrected P-value <0.0001 with rs12608932, P-value <0.0001 with rs12973192) (**FIG. 14**). rs56041637 is a CATC-repeat insertion. In the patient dataset, it was observed that patients who are homozygous for the risk alleles at both rs12608932 and rs12973192 tend to have 3 to 5 CATC-repeats at

rs56041637; patients who are homozygous for reference alleles at both rs12608932 and rs12973192 tend to have shorter (0 to 2) repeats at rs56041637. Thus, in addition to the two lead GWAS SNPs (rs12608932 and rs12973192), now another one, rs56041637, is nominated as potentially contributing to risk for disease by making *UNC13A* more vulnerable to cryptic exon inclusion when TDP-43 is depleted from the nucleus.

To directly test if these three variants in *UNC13A*, which are part of the FTD/ALS risk haplotype, increase cryptic exon inclusion upon TDP-43 depletion, we synthesized minigene reporter constructs, containing either the risk haplotype or the protective haplotype (**FIG. 4F**). The reporter uses a bidirectional reporter to co-express full-length EGFP and an mCherry construct interrupted by *UNC13A* intron 20-21 with either the reference sequence (control) or the ALS/FTD risk alleles at rs12608932 (C), rs56041637 ((CATC)₄) and rs12973192 (G). WT and TDP-43-deficient HEK-293T cells (37), which do not express *UNC13A* endogenously, were transfected with each minigene reporter construct. Using RT-PCR, both versions of intron 20-21 were found to be efficiently spliced out in WT cells (**FIG. 4G**, lane 1-4). However, in TDP43^{-/-} cells there was a decrease in splicing products that completely excise intron 20-21. Instead, splicing products that contain the cryptic exon, the longer variant of the cryptic exon (cryptic exon #2) (**FIG. 5A**) or both CE and intron 20-CE (**FIG. 4G**, lane 5-6). Strikingly, in TDP-43^{-/-} cells transfected with the minigene construct harboring the risk haplotype in the intron, there was an even greater decrease in complete intron 20-21 splicing, and a concomitant increase in cryptic splicing products (**FIG. 4G**, lane 7-8). The expression of the splicing reporter and the efficiency of the splicing machinery independent of TDP-43 is shown by the expression level of EGFP, which is not TDP-43-dependent. A different minigene reporter construct, this one with the *UNC13A* intron embedded in the context of the *CFTR* gene, was also tested. Knockdown of TDP-43 in HeLa cells transfected with this construct resulted in mis-splicing defects. Demonstrating a direct role of TDP-43 in regulating this splicing event, expressing WT TDP-43 (but not an RNA-binding deficient mutant version with five phenylalanine residues mutated to leucine (5FL)) rescued mis-splicing (**FIG. 4H**). Together, these two assays provide direct functional evidence that 1) TDP-43 regulates splicing of *UNC13A* intron 20-21 and 2) genetic variants associated with ALS and FTD susceptibility potentiate cryptic exon inclusion when TDP-43 is dysfunctional.

To define if these SNPs affect survival of the FTD-ALS patients (n=205) in the Mayo Clinic Brain bank, the association of the risk haplotype with survival time after disease onset was evaluated. Using Cox multivariable analysis adjusting for other factors (genetic mutations, sex, age at onset) known to influence survival, the risk haplotype was associated with survival time under an additive model (log-rank p-value=0.01) ((**FIG. 4I**). The number of risk haplotypes an individual carries was a strong prognostic factor (hazard ratio (HR) = 1.733, p-value = 0.00717) (**FIG. 15A**). The association remained significant under a dominant model (log-rank p-value = 0.05, **FIGS. 15B and 15C**) and a recessive model (log-rank p-value=0.02 **FIGS. 15D and 15E**), indicating that carrying the risk haplotype reduces patient survival time after disease onset. The effect was more significant when only including patients carrying either the *C9ORF72* hexanucleotide repeat expansion or *GRN* mutations (**FIGS. 16A-16F**). Thus, genetic variants in *UNC13A* that increase cryptic exon inclusion are associated with decreased survival in patients.

Here, it was found that TDP-43 regulates a cryptic splicing event in the FTD/ALS gene *UNC13A*. The most significant genetic variants associated with disease risk, including a new one that we have nominated here, are located right in the intron harboring the cryptic exon itself. Brain samples from FTLD-TDP patients carrying these SNPs exhibited more *UNC13A* cryptic exon inclusion than did samples from FTLD-TDP patients that did not contain the risk alleles. It does not seem that these risk alleles are sufficient to cause cryptic exon inclusion because we do not detect them in RNA-seq data from healthy control samples (e.g., GTEx). Instead, the risk alleles in *UNC13A* are genuine genetic risk factors or modifiers and that the cryptic splicing event is TDP-43-loss dependent. In that way, the *UNC13A* risk alleles is proposed to act as a kind of Achilles' heel – lurking under the surface, not causing problems up until TDP-43 starts becoming dysfunctional (**FIG. 4J**). Severe loss of function mutations in the *UNC13A* coding region is not expected to be observed because these would result in early lethality, like in mouse. The SNPs that promote cryptic exon inclusion seem to be innocuous on their own and only become deleterious when TDP-43 function is compromised (e.g., by mutation or nuclear depletion). The discovery of a novel TDP-43-dependent cryptic splicing event in a *bona fide* FTD-ALS risk gene opens up a multitude of new directions for validating *UNC13A* as a biomarker and therapeutic target in ALS and FTD. It still remains a mystery why TDP-43 pathology is associated with ALS or FTD or FTD/ALS, or even other aging-related neuropathological changes (38). TDP-43 dysfunction-related

cryptic splicing plays out across the diverse regional and neuronal landscape of the human brain. It is tempting to speculate that in addition to *STMN2*, and now *UNC13A*, there could be disease subtype specific portfolios of other important cryptic exon splicing events (and genetic variations that increase or decrease susceptibility to some of these events) that contribute to heterogeneity in clinical manifestation of TDP-43 dysfunction.

EXAMPLE 2: INHIBITION OF UNC13A CRYPTIC EXON SPLICE VARIANT USING ANTISENSE OLIGONUCLEOTIDES

Antisense oligonucleotides (ASOs) targeting the *UNC13A* transcript are synthesized (Tables 2-5) and delivered to cultured iPSC-derived motor neurons (MNs) either by lipid transfection or gymnotic (free) uptake. iMNs are cultured in the presence of ASOs for 2-3 days followed by introduction of lentivirus delivering either a scrambled or TDP-43 targeting shRNA. The cells are cultured for an additional 4-5 days post-lentiviral infection, followed by mRNA and protein isolation. mRNA are reverse transcribed into cDNA and subjected to qPCR with primers/probes specific for *UNC13A* cryptic exon inclusion, in addition to primers/probes targeting properly spliced (WT) *UNC13A* and housekeeping genes. Protein lysates are processed for *UNC13A* detection by Western blot.

Table 2: Antisense Oligonucleotides Targeting Exon 20 Splice Donor Region of *UNC13A*

Name	Position	Nucleotide Sequence	SEQ ID NO:
Exon 20 splice donor	chr19:17,642,794-17,642,894	GCGAGGAGAAGGTGGCCCCGTACCATGTC CAGTACACCTGTCTGCATGAGGTGAGGGT CATTGCTCGGCCCCCTCCCATGCCACTTCC ACTCACCATTCTCTG	12
Exon 20 splice donor	Reverse complement	CAGGAATGGTGAGTGGAAGTGGCATGGGA GGGGCCGAGCAATGACCCTCACCTCATGC AGACAGGTGTACTGGACATGGTACGGGGC CACCTTCTCCTCGC	13
MTx_ASO_0001	1	CAGGAATGGTGAGTGGAAGTGGCAT	14
MTx_ASO_0002	2	AGGAATGGTGAGTGGAAGTGGCATG	15
MTx_ASO_0003	3	GGAATGGTGAGTGGAAGTGGCATGG	16
MTx_ASO_0004	4	GAATGGTGAGTGGAAGTGGCATGGG	17
MTx_ASO_0005	5	AATGGTGAGTGGAAGTGGCATGGGA	18

MTx_ASO_0006	6	ATGGTGAGTGGAAGTGGCATGGGAG	19
MTx_ASO_0007	7	TGGTGAGTGGAAGTGGCATGGGAGG	20
MTx_ASO_0008	8	GGTGAGTGGAAGTGGCATGGGAGGG	21
MTx_ASO_0009	9	GTGAGTGGAAGTGGCATGGGAGGGG	22
MTx_ASO_0010	10	TGAGTGGAAGTGGCATGGGAGGGGC	23
MTx_ASO_0011	11	GAGTGGAAGTGGCATGGGAGGGGCC	24
MTx_ASO_0012	12	AGTGGAAGTGGCATGGGAGGGGCCG	25
MTx_ASO_0013	13	GTGGAAGTGGCATGGGAGGGGCCGA	26
MTx_ASO_0014	14	TGGAAGTGGCATGGGAGGGGCCGAG	27
MTx_ASO_0015	15	GGAAGTGGCATGGGAGGGGCCGAGC	28
MTx_ASO_0016	16	GAAGTGGCATGGGAGGGGCCGAGCA	29
MTx_ASO_0017	17	AAGTGGCATGGGAGGGGCCGAGCAA	30
MTx_ASO_0018	18	AGTGGCATGGGAGGGGCCGAGCAAT	31
MTx_ASO_0019	19	GTGGCATGGGAGGGGCCGAGCAATG	32
MTx_ASO_0020	20	TGGCATGGGAGGGGCCGAGCAATGA	33
MTx_ASO_0021	21	GGCATGGGAGGGGCCGAGCAATGAC	34
MTx_ASO_0022	22	GCATGGGAGGGGCCGAGCAATGACC	35
MTx_ASO_0023	23	CATGGGAGGGGCCGAGCAATGACCC	36
MTx_ASO_0024	24	ATGGGAGGGGCCGAGCAATGACCCT	37
MTx_ASO_0025	25	TGGGAGGGGCCGAGCAATGACCCTC	38
MTx_ASO_0026	26	GGGAGGGGCCGAGCAATGACCCTCA	39
MTx_ASO_0027	27	GGAGGGGCCGAGCAATGACCCTCAC	40
MTx_ASO_0028	28	GAGGGGCCGAGCAATGACCCTCACC	41
MTx_ASO_0029	29	AGGGGCCGAGCAATGACCCTCACCT	42
MTx_ASO_0030	30	GGGGCCGAGCAATGACCCTCACCTC	43
MTx_ASO_0031	31	GGGCCGAGCAATGACCCTCACCTCA	44
MTx_ASO_0032	32	GGCCGAGCAATGACCCTCACCTCAT	45
MTx_ASO_0033	33	GCCGAGCAATGACCCTCACCTCATG	46
MTx_ASO_0034	34	CCGAGCAATGACCCTCACCTCATGC	47
MTx_ASO_0035	35	CGAGCAATGACCCTCACCTCATGCA	48
MTx_ASO_0036	36	GAGCAATGACCCTCACCTCATGCAG	49
MTx_ASO_0037	37	AGCAATGACCCTCACCTCATGCAGA	50
MTx_ASO_0038	38	GCAATGACCCTCACCTCATGCAGAC	51
MTx_ASO_0039	39	CAATGACCCTCACCTCATGCAGACA	52
MTx_ASO_0040	40	AATGACCCTCACCTCATGCAGACAG	53
MTx_ASO_0041	41	ATGACCCTCACCTCATGCAGACAGG	54
MTx_ASO_0042	42	TGACCCTCACCTCATGCAGACAGGT	55
MTx_ASO_0043	43	GACCCTCACCTCATGCAGACAGGTG	56
MTx_ASO_0044	44	ACCCTCACCTCATGCAGACAGGTGT	57
MTx_ASO_0045	45	CCCTCACCTCATGCAGACAGGTGTA	58
MTx_ASO_0046	46	CCTCACCTCATGCAGACAGGTGTAC	59
MTx_ASO_0047	47	CTCACCTCATGCAGACAGGTGTACT	60
MTx_ASO_0048	48	TCACCTCATGCAGACAGGTGTACTG	61

MTx_ASO_0049	49	CACCTCATGCAGACAGGTGTACTGG	62
MTx_ASO_0050	50	ACCTCATGCAGACAGGTGTACTGGA	63
MTx_ASO_0051	51	CCTCATGCAGACAGGTGTACTGGAC	64
MTx_ASO_0052	52	CTCATGCAGACAGGTGTACTGGACA	65
MTx_ASO_0053	53	TCATGCAGACAGGTGTACTGGACAT	66
MTx_ASO_0054	54	CATGCAGACAGGTGTACTGGACATG	67
MTx_ASO_0055	55	ATGCAGACAGGTGTACTGGACATGG	68
MTx_ASO_0056	56	TGCAGACAGGTGTACTGGACATGGT	69
MTx_ASO_0057	57	GCAGACAGGTGTACTGGACATGGTA	70
MTx_ASO_0058	58	CAGACAGGTGTACTGGACATGGTAC	71
MTx_ASO_0059	59	AGACAGGTGTACTGGACATGGTACG	72
MTx_ASO_0060	60	GACAGGTGTACTGGACATGGTACGG	73
MTx_ASO_0061	61	ACAGGTGTACTGGACATGGTACGGG	74
MTx_ASO_0062	62	CAGGTGTACTGGACATGGTACGGGG	75
MTx_ASO_0063	63	AGGTGTACTGGACATGGTACGGGGC	76
MTx_ASO_0064	64	GGTGTACTGGACATGGTACGGGGCC	77
MTx_ASO_0065	65	GTGTACTGGACATGGTACGGGGCCA	78
MTx_ASO_0066	66	TGTACTGGACATGGTACGGGGCCAC	79
MTx_ASO_0067	67	GTACTGGACATGGTACGGGGCCACC	80
MTx_ASO_0068	68	TACTGGACATGGTACGGGGCCACCT	81
MTx_ASO_0069	69	ACTGGACATGGTACGGGGCCACCTT	82
MTx_ASO_0070	70	CTGGACATGGTACGGGGCCACCTTC	83
MTx_ASO_0071	71	TGGACATGGTACGGGGCCACCTTCT	84
MTx_ASO_0072	72	GGACATGGTACGGGGCCACCTTCTC	85
MTx_ASO_0073	73	GACATGGTACGGGGCCACCTTCTCC	86
MTx_ASO_0074	74	ACATGGTACGGGGCCACCTTCTCCT	87
MTx_ASO_0075	75	CATGGTACGGGGCCACCTTCTCCTC	88
MTx_ASO_0076	76	ATGGTACGGGGCCACCTTCTCCTCG	89
MTx_ASO_0077	77	TGGTACGGGGCCACCTTCTCCTCGC	90

Table 3: Antisense Oligonucleotides Targeting Cryptic Exon Splice Acceptor**Region of *UNC13A***

Name	Position	Nucleotide Sequence	SEQ ID NO:
Cryptic exon splice acceptor	chr19:17,642,491-17,642,641	CTCCAGGTTGACTCTCACTACTCATCATC AGGTTCTTCTTCTATTCCAGCCCTAACC ACTCAGGATTGGGCCGTTTGTGTCTGGGT ATGTCTCTTCCAGCTGCCTGGGTTTCTCTG GAAAGAACTCTTATCCCCAGGAAC TAGTT TGT TGA	91
Cryptic exon splice acceptor	Reverse complement	TCAACAAACTAGTTCCTGGGGATAAGAGT TCTTTCCAGGAAACCCAGGCAGCTGGAAG AGACATACCCAGACACAAACGGCCCAATC CTGAGTGGTTAGGGCTGGAATAGAAGGAA	92

		GAACCTGATGATGAGTAGTGAGAGTCAAC CTGGAG	
MTx_ASO_0078	1	TCAACAACTAGTTCCTGGGGATAA	93
MTx_ASO_0079	2	CAACAACTAGTTCCTGGGGATAAG	94
MTx_ASO_0080	3	AACAACTAGTTCCTGGGGATAAGA	95
MTx_ASO_0081	4	ACAACTAGTTCCTGGGGATAAGAG	96
MTx_ASO_0082	5	CAAACCTAGTTCCTGGGGATAAGAGT	97
MTx_ASO_0083	6	AAACTAGTTCCTGGGGATAAGAGTT	98
MTx_ASO_0084	7	AACTAGTTCCTGGGGATAAGAGTTC	99
MTx_ASO_0085	8	ACTAGTTCCTGGGGATAAGAGTTCT	100
MTx_ASO_0086	9	CTAGTTCCTGGGGATAAGAGTTCTT	101
MTx_ASO_0087	10	TAGTTCCTGGGGATAAGAGTTCTTT	102
MTx_ASO_0088	11	AGTTCCTGGGGATAAGAGTTCTTTC	103
MTx_ASO_0089	12	GTTCTTCCTGGGGATAAGAGTTCTTTCC	104
MTx_ASO_0090	13	TTCTTCCTGGGGATAAGAGTTCTTTCCA	105
MTx_ASO_0091	14	TCCTGGGGATAAGAGTTCTTTCCAG	106
MTx_ASO_0092	15	CCTGGGGATAAGAGTTCTTTCCAGG	107
MTx_ASO_0093	16	CTGGGGATAAGAGTTCTTTCCAGGA	108
MTx_ASO_0094	17	TGGGGATAAGAGTTCTTTCCAGGAA	109
MTx_ASO_0095	18	GGGGATAAGAGTTCTTTCCAGGAAA	110
MTx_ASO_0096	19	GGGATAAGAGTTCTTTCCAGGAAAC	111
MTx_ASO_0097	20	GGATAAGAGTTCTTTCCAGGAAACC	112
MTx_ASO_0098	21	GATAAGAGTTCTTTCCAGGAAACCC	113
MTx_ASO_0099	22	ATAAGAGTTCTTTCCAGGAAACCCA	114
MTx_ASO_0100	23	TAAGAGTTCTTTCCAGGAAACCCAG	115
MTx_ASO_0101	24	AAGAGTTCTTTCCAGGAAACCCAGG	116
MTx_ASO_0102	25	AGAGTTCTTTCCAGGAAACCCAGGC	117
MTx_ASO_0103	26	GAGTTCTTTCCAGGAAACCCAGGCA	118
MTx_ASO_0104	27	AGTTCTTTCCAGGAAACCCAGGCAG	119
MTx_ASO_0105	28	GTTCTTTCCAGGAAACCCAGGCAGC	120
MTx_ASO_0106	29	TTCTTTCCAGGAAACCCAGGCAGCT	121
MTx_ASO_0107	30	TCTTTCCAGGAAACCCAGGCAGCTG	122
MTx_ASO_0108	31	CTTTCCAGGAAACCCAGGCAGCTGG	123
MTx_ASO_0109	32	TTTCCAGGAAACCCAGGCAGCTGGA	124
MTx_ASO_0110	33	TTCCAGGAAACCCAGGCAGCTGGAA	125
MTx_ASO_0111	34	TCCAGGAAACCCAGGCAGCTGGAAG	126
MTx_ASO_0112	35	CCAGGAAACCCAGGCAGCTGGAAGA	127
MTx_ASO_0113	36	CAGGAAACCCAGGCAGCTGGAAGAG	128
MTx_ASO_0114	37	AGGAAACCCAGGCAGCTGGAAGAGA	129
MTx_ASO_0115	38	GGAAACCCAGGCAGCTGGAAGAGAC	130
MTx_ASO_0116	39	GAAACCCAGGCAGCTGGAAGAGACA	131
MTx_ASO_0117	40	AAACCCAGGCAGCTGGAAGAGACAT	132
MTx_ASO_0118	41	AACCCAGGCAGCTGGAAGAGACATA	133
MTx_ASO_0119	42	ACCCAGGCAGCTGGAAGAGACATAC	134

MTx_ASO_0120	43	CCCAGGCAGCTGGAAGAGACATACC	135
MTx_ASO_0121	44	CCAGGCAGCTGGAAGAGACATACCC	136
MTx_ASO_0122	45	CAGGCAGCTGGAAGAGACATACCCA	137
MTx_ASO_0123	46	AGGCAGCTGGAAGAGACATACCCAG	138
MTx_ASO_0124	47	GGCAGCTGGAAGAGACATACCCAGA	139
MTx_ASO_0125	48	GCAGCTGGAAGAGACATACCCAGAC	140
MTx_ASO_0126	49	CAGCTGGAAGAGACATACCCAGACA	141
MTx_ASO_0127	50	AGCTGGAAGAGACATACCCAGACAC	142
MTx_ASO_0128	51	GCTGGAAGAGACATACCCAGACACA	143
MTx_ASO_0129	52	CTGGAAGAGACATACCCAGACACAA	144
MTx_ASO_0130	53	TGGAAGAGACATACCCAGACACAAA	145
MTx_ASO_0131	54	GGAAGAGACATACCCAGACACAAAC	146
MTx_ASO_0132	55	GAAGAGACATACCCAGACACAAACG	147
MTx_ASO_0133	56	AAGAGACATACCCAGACACAAACGG	148
MTx_ASO_0134	57	AGAGACATACCCAGACACAAACGGC	149
MTx_ASO_0135	58	GAGACATACCCAGACACAAACGGCC	150
MTx_ASO_0136	59	AGACATACCCAGACACAAACGGCCC	151
MTx_ASO_0137	60	GACATACCCAGACACAAACGGCCCA	152
MTx_ASO_0138	61	ACATACCCAGACACAAACGGCCCAA	153
MTx_ASO_0139	62	CATACCCAGACACAAACGGCCCAAT	154
MTx_ASO_0140	63	ATACCCAGACACAAACGGCCCAATC	155
MTx_ASO_0141	64	TACCCAGACACAAACGGCCCAATCC	156
MTx_ASO_0142	65	ACCCAGACACAAACGGCCCAATCCT	157
MTx_ASO_0143	66	CCCAGACACAAACGGCCCAATCCTG	158
MTx_ASO_0144	67	CCAGACACAAACGGCCCAATCCTGA	159
MTx_ASO_0145	68	CAGACACAAACGGCCCAATCCTGAG	160
MTx_ASO_0146	69	AGACACAAACGGCCCAATCCTGAGT	161
MTx_ASO_0147	70	GACACAAACGGCCCAATCCTGAGTG	162
MTx_ASO_0148	71	ACACAAACGGCCCAATCCTGAGTGG	163
MTx_ASO_0149	72	CACAAACGGCCCAATCCTGAGTGGT	164
MTx_ASO_0150	73	ACAAACGGCCCAATCCTGAGTGGTT	165
MTx_ASO_0151	74	CAAACGGCCCAATCCTGAGTGGTTA	166
MTx_ASO_0152	75	AAACGGCCCAATCCTGAGTGGTTAG	167
MTx_ASO_0153	76	AACGGCCCAATCCTGAGTGGTTAGG	168
MTx_ASO_0154	77	ACGGCCCAATCCTGAGTGGTTAGGG	169
MTx_ASO_0155	78	CGGCCCAATCCTGAGTGGTTAGGGC	170
MTx_ASO_0156	79	GGGCCAATCCTGAGTGGTTAGGGCT	171
MTx_ASO_0157	80	GCCCAATCCTGAGTGGTTAGGGCTG	172
MTx_ASO_0158	81	CCCAATCCTGAGTGGTTAGGGCTGG	173
MTx_ASO_0159	82	CCAATCCTGAGTGGTTAGGGCTGGA	174
MTx_ASO_0160	83	CAATCCTGAGTGGTTAGGGCTGGAA	175
MTx_ASO_0161	84	AATCCTGAGTGGTTAGGGCTGGAAT	176
MTx_ASO_0162	85	ATCCTGAGTGGTTAGGGCTGGAATA	177

MTx_ASO_0163	86	TCCTGAGTGGTTAGGGCTGGAATAG	178
MTx_ASO_0164	87	CCTGAGTGGTTAGGGCTGGAATAGA	179
MTx_ASO_0165	88	CTGAGTGGTTAGGGCTGGAATAGAA	180
MTx_ASO_0166	89	TGAGTGGTTAGGGCTGGAATAGAAG	181
MTx_ASO_0167	90	GAGTGGTTAGGGCTGGAATAGAAGG	182
MTx_ASO_0168	91	AGTGGTTAGGGCTGGAATAGAAGGA	183
MTx_ASO_0169	92	GTGGTTAGGGCTGGAATAGAAGGAA	184
MTx_ASO_0170	93	TGGTTAGGGCTGGAATAGAAGGAAG	185
MTx_ASO_0171	94	GGTTAGGGCTGGAATAGAAGGAAGA	186
MTx_ASO_0172	95	GTTAGGGCTGGAATAGAAGGAAGAA	187
MTx_ASO_0173	96	TTAGGGCTGGAATAGAAGGAAGAAC	188
MTx_ASO_0174	97	TAGGGCTGGAATAGAAGGAAGAACC	189
MTx_ASO_0175	98	AGGGCTGGAATAGAAGGAAGAACCT	190
MTx_ASO_0176	99	GGGCTGGAATAGAAGGAAGAACCTG	191
MTx_ASO_0177	100	GGCTGGAATAGAAGGAAGAACCTGA	192
MTx_ASO_0178	101	GCTGGAATAGAAGGAAGAACCTGAT	193
MTx_ASO_0179	102	CTGGAATAGAAGGAAGAACCTGATG	194
MTx_ASO_0180	103	TGGAATAGAAGGAAGAACCTGATGA	195
MTx_ASO_0181	104	GGAATAGAAGGAAGAACCTGATGAT	196
MTx_ASO_0182	105	GAATAGAAGGAAGAACCTGATGATG	197
MTx_ASO_0183	106	AATAGAAGGAAGAACCTGATGATGA	198
MTx_ASO_0184	107	ATAGAAGGAAGAACCTGATGATGAG	199
MTx_ASO_0185	108	TAGAAGGAAGAACCTGATGATGAGT	200
MTx_ASO_0186	109	AGAAGGAAGAACCTGATGATGAGTA	201
MTx_ASO_0187	110	GAAGGAAGAACCTGATGATGAGTAG	202
MTx_ASO_0188	111	AAGGAAGAACCTGATGATGAGTAGT	203
MTx_ASO_0189	112	AGGAAGAACCTGATGATGAGTAGTG	204
MTx_ASO_0190	113	GGAAGAACCTGATGATGAGTAGTGA	205
MTx_ASO_0191	114	GAAGAACCTGATGATGAGTAGTGAG	206
MTx_ASO_0192	115	AAGAACCTGATGATGAGTAGTGAGA	207
MTx_ASO_0193	116	AGAACCTGATGATGAGTAGTGAGAG	208
MTx_ASO_0194	117	GAACCTGATGATGAGTAGTGAGAGT	209
MTx_ASO_0195	118	AACCTGATGATGAGTAGTGAGAGTC	210
MTx_ASO_0196	119	ACCTGATGATGAGTAGTGAGAGTCA	211
MTx_ASO_0197	120	CCTGATGATGAGTAGTGAGAGTCAA	212
MTx_ASO_0198	121	CTGATGATGAGTAGTGAGAGTCAAC	213
MTx_ASO_0199	122	TGATGATGAGTAGTGAGAGTCAACC	214
MTx_ASO_0200	123	GATGATGAGTAGTGAGAGTCAACCT	215
MTx_ASO_0201	124	ATGATGAGTAGTGAGAGTCAACCTG	216
MTx_ASO_0202	125	TGATGAGTAGTGAGAGTCAACCTGG	217
MTx_ASO_0203	126	GATGAGTAGTGAGAGTCAACCTGGA	218
MTx_ASO_0204	127	ATGAGTAGTGAGAGTCAACCTGGAG	219

Table 4: Antisense Oligonucleotides Targeting Cryptic Exon Splice Donor Region of *UNC13A*

Name	Position	Nucleotide Sequence	SEQ ID NO:
Cryptic exon splice donor	chr19:17,642,363-17,642,463	TGAACAGATGAATGAGTGATGAGTAGATA AAAGGATGGATGGAGAGATGGGTGAGTAC ATGGATGGATAGATGGATGAGTTGGTGGG TAGATTTCGTGGCTA	220
Cryptic exon splice donor	Reverse Complement	TAGCCACGAATCTACCCACCAACTCATCC ATCTATCCATCCATGTACTCACCCATCTC TCCATCCATCCCTTTTATCTACTCATCACT CATTTCATCTGTTCA	221
MTx_ASO_0205	1	TAGCCACGAATCTACCCACCAACTC	222
MTx_ASO_0206	2	AGCCACGAATCTACCCACCAACTCA	223
MTx_ASO_0207	3	GCCACGAATCTACCCACCAACTCAT	224
MTx_ASO_0208	4	CCACGAATCTACCCACCAACTCATC	225
MTx_ASO_0209	5	CACGAATCTACCCACCAACTCATCC	226
MTx_ASO_0210	6	ACGAATCTACCCACCAACTCATCCA	227
MTx_ASO_0211	7	CGAATCTACCCACCAACTCATCCAT	228
MTx_ASO_0212	8	GAATCTACCCACCAACTCATCCATC	229
MTx_ASO_0213	9	AATCTACCCACCAACTCATCCATCT	230
MTx_ASO_0214	10	ATCTACCCACCAACTCATCCATCTA	231
MTx_ASO_0215	11	TCTACCCACCAACTCATCCATCTAT	232
MTx_ASO_0216	12	CTACCCACCAACTCATCCATCTATC	233
MTx_ASO_0217	13	TACCCACCAACTCATCCATCTATCC	234
MTx_ASO_0218	14	ACCCACCAACTCATCCATCTATCCA	235
MTx_ASO_0219	15	CCCACCAACTCATCCATCTATCCAT	236
MTx_ASO_0220	16	CCACCAACTCATCCATCTATCCATC	237
MTx_ASO_0221	17	CACCAACTCATCCATCTATCCATCC	238
MTx_ASO_0222	18	ACCAACTCATCCATCTATCCATCCA	239
MTx_ASO_0223	19	CCAACTCATCCATCTATCCATCCAT	240
MTx_ASO_0224	20	CAACTCATCCATCTATCCATCCATG	241
MTx_ASO_0225	21	AACTCATCCATCTATCCATCCATGT	242
MTx_ASO_0226	22	ACTCATCCATCTATCCATCCATGTA	243
MTx_ASO_0227	23	CTCATCCATCTATCCATCCATGTAC	244
MTx_ASO_0228	24	TCATCCATCTATCCATCCATGTACT	245
MTx_ASO_0229	25	CATCCATCTATCCATCCATGTACTC	246
MTx_ASO_0230	26	ATCCATCTATCCATCCATGTACTCA	247
MTx_ASO_0231	27	TCCATCTATCCATCCATGTACTCAC	248
MTx_ASO_0232	28	CCATCTATCCATCCATGTACTCACC	249
MTx_ASO_0233	29	CATCTATCCATCCATGTACTCACCC	250
MTx_ASO_0234	30	ATCTATCCATCCATGTACTCACCCA	251
MTx_ASO_0235	31	TCTATCCATCCATGTACTCACCCAT	252
MTx_ASO_0236	32	CTATCCATCCATGTACTCACCCATC	253
MTx_ASO_0237	33	TATCCATCCATGTACTCACCCATCT	254

MTx_ASO_0238	34	ATCCATCCATGTACTCACCCATCTC	255
MTx_ASO_0239	35	TCCATCCATGTACTCACCCATCTCT	256
MTx_ASO_0240	36	CCATCCATGTACTCACCCATCTCTC	257
MTx_ASO_0241	37	CATCCATGTACTCACCCATCTCTCC	258
MTx_ASO_0242	38	ATCCATGTACTCACCCATCTCTCCA	259
MTx_ASO_0243	39	TCCATGTACTCACCCATCTCTCCAT	260
MTx_ASO_0244	40	CCATGTACTCACCCATCTCTCCATC	261
MTx_ASO_0245	41	CATGTACTCACCCATCTCTCCATCC	262
MTx_ASO_0246	42	ATGTACTCACCCATCTCTCCATCCA	263
MTx_ASO_0247	43	TGTACTCACCCATCTCTCCATCCAT	264
MTx_ASO_0248	44	GTACTCACCCATCTCTCCATCCATC	265
MTx_ASO_0249	45	TACTCACCCATCTCTCCATCCATCC	266
MTx_ASO_0250	46	ACTCACCCATCTCTCCATCCATCCT	267
MTx_ASO_0251	47	CTCACCCATCTCTCCATCCATCCTT	268
MTx_ASO_0252	48	TCACCCATCTCTCCATCCATCCTTT	269
MTx_ASO_0253	49	CACCCATCTCTCCATCCATCCTTTT	270
MTx_ASO_0254	50	ACCCATCTCTCCATCCATCCTTTTA	271
MTx_ASO_0255	51	CCCATCTCTCCATCCATCCTTTTAT	272
MTx_ASO_0256	52	CCATCTCTCCATCCATCCTTTTATC	273
MTx_ASO_0257	53	CATCTCTCCATCCATCCTTTTATCT	274
MTx_ASO_0258	54	ATCTCTCCATCCATCCTTTTATCTA	275
MTx_ASO_0259	55	TCTCTCCATCCATCCTTTTATCTAC	276
MTx_ASO_0260	56	CTCTCCATCCATCCTTTTATCTACT	277
MTx_ASO_0261	57	TCTCCATCCATCCTTTTATCTACTC	278
MTx_ASO_0262	58	CTCCATCCATCCTTTTATCTACTCA	279
MTx_ASO_0263	59	TCCATCCATCCTTTTATCTACTCAT	280
MTx_ASO_0264	60	CCATCCATCCTTTTATCTACTCATC	281
MTx_ASO_0265	61	CATCCATCCTTTTATCTACTCATCA	282
MTx_ASO_0266	62	ATCCATCCTTTTATCTACTCATCAC	283
MTx_ASO_0267	63	TCCATCCTTTTATCTACTCATCACT	284
MTx_ASO_0268	64	CCATCCTTTTATCTACTCATCACTC	285
MTx_ASO_0269	65	CATCCTTTTATCTACTCATCACTCA	286
MTx_ASO_0270	66	ATCCTTTTATCTACTCATCACTCAT	287
MTx_ASO_0271	67	TCCTTTTATCTACTCATCACTCATT	288
MTx_ASO_0272	68	CCTTTTATCTACTCATCACTCATTC	289
MTx_ASO_0273	69	CTTTTATCTACTCATCACTCATTC	290
MTx_ASO_0274	70	TTTTATCTACTCATCACTCATTCAT	291
MTx_ASO_0275	71	TTTATCTACTCATCACTCATTCATC	292
MTx_ASO_0276	72	TTATCTACTCATCACTCATTCATCT	293
MTx_ASO_0277	73	TATCTACTCATCACTCATTCATCTG	294
MTx_ASO_0278	74	ATCTACTCATCACTCATTCATCTGT	295
MTx_ASO_0279	75	TCTACTCATCACTCATTCATCTGTT	296
MTx_ASO_0280	76	CTACTCATCACTCATTCATCTGTTC	297

MTx_ASO_0281	77	TACTCATCACTCATTCATCTGTTCA	298
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Table 5: Antisense Oligonucleotides Targeting Exon 21 Splice Acceptor Region of *UNC13A*

Name	Position	Nucleotide Sequence	SEQ ID NO:
Exon 21 splice acceptor	chr19:17,641,506-17,641,606	CCCGGCGACCCCTTGCACCTCTCCATGACA CTTTCTCTCCCATGGTGGCAGAACCCTGTT CCACTTCGTGACCGACGTGCAGAACAAATG GGGTCGTGAAGATC	299
Exon 21 splice acceptor	Reverse complement	GATCTTCACGACCCCATTTGTTCTGCACGT CGGTACAGAAAGTGAACAGGTTCTGCCAC CATGGGAGAGAAAGTGTCTATGGAGAGTGC AAGGGGTCGCCGGG	300
MTx_ASO_0282	1	GATCTTCACGACCCCATTTGTTCTGC	301
MTx_ASO_0283	2	ATCTTCACGACCCCATTTGTTCTGCA	302
MTx_ASO_0284	3	TCTTCACGACCCCATTTGTTCTGCAC	303
MTx_ASO_0285	4	CTTCACGACCCCATTTGTTCTGCACG	304
MTx_ASO_0286	5	TTCACGACCCCATTTGTTCTGCACGT	305
MTx_ASO_0287	6	TCACGACCCCATTTGTTCTGCACGTC	306
MTx_ASO_0288	7	CACGACCCCATTTGTTCTGCACGTCG	307
MTx_ASO_0289	8	ACGACCCCATTTGTTCTGCACGTCGG	308
MTx_ASO_0290	9	CGACCCCATTTGTTCTGCACGTCGGT	309
MTx_ASO_0291	10	GACCCCATTTGTTCTGCACGTCGGTC	310
MTx_ASO_0292	11	ACCCCATTTGTTCTGCACGTCGGTCA	311
MTx_ASO_0293	12	CCCCATTGTTCTGCACGTCGGTCAC	312
MTx_ASO_0294	13	CCCATTGTTCTGCACGTCGGTCACG	313
MTx_ASO_0295	14	CCATTGTTCTGCACGTCGGTCACGA	314
MTx_ASO_0296	15	CATTGTTCTGCACGTCGGTCACGAA	315
MTx_ASO_0297	16	ATTGTTCTGCACGTCGGTCACGAAG	316
MTx_ASO_0298	17	TTGTTCTGCACGTCGGTCACGAAGT	317
MTx_ASO_0299	18	TGTTCTGCACGTCGGTCACGAAGTG	318
MTx_ASO_0300	19	GTTCTGCACGTCGGTCACGAAGTGG	319
MTx_ASO_0301	20	TTCTGCACGTCGGTCACGAAGTGGA	320
MTx_ASO_0302	21	TCTGCACGTCGGTCACGAAGTGGA	321
MTx_ASO_0303	22	CTGCACGTCGGTCACGAAGTGGAAC	322
MTx_ASO_0304	23	TGCACGTCGGTCACGAAGTGGAACA	323
MTx_ASO_0305	24	GCACGTCGGTCACGAAGTGGAACAG	324
MTx_ASO_0306	25	CACGTCGGTCACGAAGTGGAACAGG	325
MTx_ASO_0307	26	ACGTCGGTCACGAAGTGGAACAGGT	326
MTx_ASO_0308	27	CGTCGGTCACGAAGTGGAACAGGTT	327
MTx_ASO_0309	28	GTCGGTCACGAAGTGGAACAGGTTCT	328
MTx_ASO_0310	29	TCGGTCACGAAGTGGAACAGGTTCT	329
MTx_ASO_0311	30	CGGTACGAAGTGGAACAGGTTCTG	330
MTx_ASO_0312	31	GGTCACGAAGTGGAACAGGTTCTGC	331

MTx_ASO_0313	32	GTCACGAAGTGGAACAGGTTCTGCC	332
MTx_ASO_0314	33	TCACGAAGTGGAACAGGTTCTGCCA	333
MTx_ASO_0315	34	CACGAAGTGGAACAGGTTCTGCCAC	334
MTx_ASO_0316	35	ACGAAGTGGAACAGGTTCTGCCACC	335
MTx_ASO_0317	36	CGAAGTGGAACAGGTTCTGCCACCA	336
MTx_ASO_0318	37	GAAGTGGAACAGGTTCTGCCACCAT	337
MTx_ASO_0319	38	AAGTGGAACAGGTTCTGCCACCATG	338
MTx_ASO_0320	39	AGTGGAACAGGTTCTGCCACCATGG	339
MTx_ASO_0321	40	GTGGAACAGGTTCTGCCACCATGGG	340
MTx_ASO_0322	41	TGGAACAGGTTCTGCCACCATGGGA	341
MTx_ASO_0323	42	GGAACAGGTTCTGCCACCATGGGAG	342
MTx_ASO_0324	43	GAACAGGTTCTGCCACCATGGGAGA	343
MTx_ASO_0325	44	AACAGGTTCTGCCACCATGGGAGAG	344
MTx_ASO_0326	45	ACAGGTTCTGCCACCATGGGAGAGA	345
MTx_ASO_0327	46	CAGGTTCTGCCACCATGGGAGAGAA	346
MTx_ASO_0328	47	AGGTTCTGCCACCATGGGAGAGAAA	347
MTx_ASO_0329	48	GGTTCTGCCACCATGGGAGAGAAAG	348
MTx_ASO_0330	49	GTTCTGCCACCATGGGAGAGAAAGT	349
MTx_ASO_0331	50	TTCTGCCACCATGGGAGAGAAAGTG	350
MTx_ASO_0332	51	TCTGCCACCATGGGAGAGAAAGTGT	351
MTx_ASO_0333	52	CTGCCACCATGGGAGAGAAAGTGTC	352
MTx_ASO_0334	53	TGCCACCATGGGAGAGAAAGTGTC	353
MTx_ASO_0335	54	GCCACCATGGGAGAGAAAGTGTCAT	354
MTx_ASO_0336	55	CCACCATGGGAGAGAAAGTGTCATG	355
MTx_ASO_0337	56	CACCATGGGAGAGAAAGTGTCATGG	356
MTx_ASO_0338	57	ACCATGGGAGAGAAAGTGTCATGGA	357
MTx_ASO_0339	58	CCATGGGAGAGAAAGTGTCATGGAG	358
MTx_ASO_0340	59	CATGGGAGAGAAAGTGTCATGGAGA	359
MTx_ASO_0341	60	ATGGGAGAGAAAGTGTCATGGAGAG	360
MTx_ASO_0342	61	TGGGAGAGAAAGTGTCATGGAGAGT	361
MTx_ASO_0343	62	GGGAGAGAAAGTGTCATGGAGAGTG	362
MTx_ASO_0344	63	GGAGAGAAAGTGTCATGGAGAGTGC	363
MTx_ASO_0345	64	GAGAGAAAGTGTCATGGAGAGTGCA	364
MTx_ASO_0346	65	AGAGAAAGTGTCATGGAGAGTGCAA	365
MTx_ASO_0347	66	GAGAAAGTGTCATGGAGAGTGCAAG	366
MTx_ASO_0348	67	AGAAAGTGTCATGGAGAGTGCAAGG	367
MTx_ASO_0349	68	GAAAGTGTCATGGAGAGTGCAAGGG	368
MTx_ASO_0350	69	AAAGTGTCATGGAGAGTGCAAGGGG	369
MTx_ASO_0351	70	AAGTGTCATGGAGAGTGCAAGGGGT	370
MTx_ASO_0352	71	AGTGTCATGGAGAGTGCAAGGGGTC	371
MTx_ASO_0353	72	GTGTCATGGAGAGTGCAAGGGGTCG	372
MTx_ASO_0354	73	TGTCATGGAGAGTGCAAGGGGTCGC	373
MTx_ASO_0355	74	GTCATGGAGAGTGCAAGGGGTCGCC	374

MTx_ASO_0356	75	TCATGGAGAGTGCAAGGGGTCGCCG	375
MTx_ASO_0357	76	CATGGAGAGTGCAAGGGGTCGCCG	376
MTx_ASO_0358	77	ATGGAGAGTGCAAGGGGTCGCCGG	377

EXAMPLE 3: ANTISENSE OLIGONUCLEOTIDE SCREENING

Antisense oligonucleotides (ASOs) were designed to target the cryptic exon of *UNC13A* transcript (Table 7A). ASOs 1-45 (SEQ ID NOS:423-467) of Table 7B are 18mers tiling the 5' end of the cryptic exon containing the splice acceptor region (SEQ ID NO:641) with 3 nucleotide spacing. ASOs 121-142 (SEQ ID NOS:468-489) of Table 7B are 18mers tiling the 5' end of the cryptic exon with 1 nucleotide spacing. ASOs 248-280 (SEQ ID NOS:490-522) of Table 7B are 18mers tiling the 3' end of the cryptic exon containing the splice donor region (SEQ ID NO:642) with 3 nucleotide spacing. The genomic coordinates of the ASOs are set forth as follows: 5' end of cryptic exon: chr19:17,642,491-17,642,641; 3' end of cryptic exon: chr19:17,642,363-17,642,470. ASOs with 2'MOE modifications targeting the cryptic exon of *UNC13A* transcript were synthesized (Table 7B) and delivered to cultured iPSC-derived motor neurons (MNs) at a concentration of 3mM by free uptake. Motor neurons were cultured in the presence of *UNC13A*-specific ASOs as well as three non-targeting ASOs for two days followed by introduction of lentivirus delivering either a scrambled or TDP-43 targeting shRNA. The cells were cultured for an additional seven days post-lentiviral infection, followed by mRNA isolation. mRNA were reverse transcribed into cDNA and subjected to qPCR with primers/probes specific for *UNC13A* cryptic exon inclusion (FIGS. 19A-19B), in addition to primers/probes targeting properly spliced *UNC13A* (FIGS. 19C-19D). Regions where active ASOs reduced cryptic exon inclusion while increasing total *UNC13A* RNA levels were identified (ASOs in 5' splice acceptor region: ASOs 1-10 and 17-21 corresponding to SEQ ID NOS:423-432 and 439-443; ASOs in 3' splice donor region: ASOs 249-256, 260-265, and 271-272 corresponding to SEQ ID NOS: 491-498, 502-507, and 513-514, respectively. 21mer ASOs were designed to further tile these regions (Table 8B). ASOs 306-354 (SEQ ID NOS:523-571) of Table 8B are 21mers tiling the 5' end of the cryptic exon (SEQ ID NO:643) with 1 nucleotide spacing. ASOs 355-423 (SEQ ID NOS:572-640) of Table 8B are

21mers tiling the 3' end of the cryptic exon (SEQ ID NO:644) with 1 nucleotide spacing.

Table 7A: UNC13A Cryptic Exon Targeted Regions

Name	Tiling Coordinates	Target Sequence
Cryptic Exon Splice Acceptor	hg38 chr19:17,642,640- 17,642,491	TCCAGGTTGACTCTCACTACTCATC ATCAGGTTCTTCCTTCTATTCCAGC CCTAACCCTCAGGATTGGGCCGTT TGTGTCTGGGTATGTCTCTTCCAGC TGCCTGGGTTTCCTGGAAAGAACTC TTATCCCCAGGAACTAGTTTGTGTA [SEQ ID NO:641]
Cryptic Exon Splice Donor	hg38 chr19 17,642,504- 17,642,391	AACTAGTTTGTGTAATAAATGCTGG TGAATGAATGAATGATTGAACAGA TGAATGAGTGATGAGTAGATAAAA GGATGGATGGAGAGATGGGTGAGT ACATGGATGGATAGATG [SEQ ID NO:642]

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Table 7B: 18mer Antisense Oligonucleotides Targeting UNC13A Cryptic Exon

Name	Target	Nucleotide Sequence	SEQ ID NO:
MTx_ASO_1	UNC13A	TCAACAACTAGTTCCTG	423
MTx_ASO_2	UNC13A	ACAACTAGTTCCTGGGG	424
MTx_ASO_3	UNC13A	AACTAGTTCCTGGGGATA	425
MTx_ASO_4	UNC13A	TAGTTCCTGGGGATAAGA	426
MTx_ASO_5	UNC13A	TTCTGTTGGGATAAGAGTT	427
MTx_ASO_6	UNC13A	CTGGGGATAAGAGTTCTT	428
MTx_ASO_7	UNC13A	GGGATAAGAGTTCTTTCC	429
MTx_ASO_8	UNC13A	ATAAGAGTTCTTTCCAGG	430
MTx_ASO_9	UNC13A	AGAGTTCTTTCCAGGAAA	431
MTx_ASO_10	UNC13A	GTTCTTTCCAGGAAACCC	432
MTx_ASO_11	UNC13A	CTTTCCAGGAAACCCAGG	433
MTx_ASO_12	UNC13A	TCCAGGAAACCCAGGCAG	434
MTx_ASO_13	UNC13A	AGGAAACCCAGGCAGCTG	435
MTx_ASO_14	UNC13A	AAACCCAGGCAGCTGGAA	436
MTx_ASO_15	UNC13A	CCCAGGCAGCTGGAAGAG	437
MTx_ASO_16	UNC13A	AGGCAGCTGGAAGAGACA	438
MTx_ASO_17	UNC13A	CAGCTGGAAGAGACATAC	439
MTx_ASO_18	UNC13A	CTGGAAGAGACATACCCA	440
MTx_ASO_19	UNC13A	GAAGAGACATACCCAGAC	441
MTx_ASO_20	UNC13A	GAGACATACCCAGACACA	442

MTx_ASO_21	UNC13A	ACATACCCAGACACAAAC	443
MTx_ASO_22	UNC13A	TACCCAGACACAAACGGC	444
MTx_ASO_23	UNC13A	CCAGACACAAACGGCCCA	445
MTx_ASO_24	UNC13A	GACACAAACGGCCCAATC	446
MTx_ASO_25	UNC13A	ACAAACGGCCCAATCCTG	447
MTx_ASO_26	UNC13A	AACGGCCCAATCCTGAGT	448
MTx_ASO_27	UNC13A	GGCCCAATCCTGAGTGGT	449
MTx_ASO_28	UNC13A	CCAATCCTGAGTGGTTAG	450
MTx_ASO_29	UNC13A	ATCCTGAGTGGTTAGGGC	451
MTx_ASO_30	UNC13A	CTGAGTGGTTAGGGCTGG	452
MTx_ASO_31	UNC13A	AGTGGTTAGGGCTGGAAT	453
MTx_ASO_32	UNC13A	GGTTAGGGCTGGAATAGA	454
MTx_ASO_33	UNC13A	TAGGGCTGGAATAGAAGG	455
MTx_ASO_34	UNC13A	GGCTGGAATAGAAGGAAG	456
MTx_ASO_35	UNC13A	TGGAATAGAAGGAAGAAC	457
MTx_ASO_36	UNC13A	AATAGAAGGAAGAACCTG	458
MTx_ASO_37	UNC13A	AGAAGGAAGAACCTGATG	459
MTx_ASO_38	UNC13A	AGGAAGAACCTGATGATG	460
MTx_ASO_39	UNC13A	AAGAACCTGATGATGAGT	461
MTx_ASO_40	UNC13A	AACCTGATGATGAGTAGT	462
MTx_ASO_41	UNC13A	CTGATGATGAGTAGTGAG	463
MTx_ASO_42	UNC13A	ATGATGAGTAGTGAGAGT	464
MTx_ASO_43	UNC13A	ATGAGTAGTGAGAGTCAA	465
MTx_ASO_44	UNC13A	AGTAGTGAGAGTCAACCT	466
MTx_ASO_45	UNC13A	AGTGAGAGTCAACCTGGA	467
MTx_ASO_121	UNC13A	GGCAGCTGGAAGAGACAT	468
MTx_ASO_122	UNC13A	GCAGCTGGAAGAGACATA	469
MTx_ASO_123	UNC13A	CAGCTGGAAGAGACATAC	470
MTx_ASO_124	UNC13A	AGCTGGAAGAGACATACC	471
MTx_ASO_125	UNC13A	GCTGGAAGAGACATACCC	472
MTx_ASO_126	UNC13A	CTGGAAGAGACATACCCA	473
MTx_ASO_127	UNC13A	TGGAAGAGACATACCCAG	474
MTx_ASO_128	UNC13A	GGAAGAGACATACCCAGA	475
MTx_ASO_129	UNC13A	GAAGAGACATACCCAGAC	476
MTx_ASO_130	UNC13A	AAGAGACATACCCAGACA	477
MTx_ASO_131	UNC13A	AGAGACATACCCAGACAC	478
MTx_ASO_132	UNC13A	GGCAGCTGGAAGAGACAT	479
MTx_ASO_133	UNC13A	GCAGCTGGAAGAGACATA	480
MTx_ASO_134	UNC13A	CAGCTGGAAGAGACATAC	481
MTx_ASO_135	UNC13A	AGCTGGAAGAGACATACC	482

MTx_ASO_136	UNC13A	GCTGGAAGAGACATACCC	483
MTx_ASO_137	UNC13A	CTGGAAGAGACATACCCA	484
MTx_ASO_138	UNC13A	TGGAAGAGACATACCCAG	485
MTx_ASO_139	UNC13A	GGAAGAGACATACCCAGA	486
MTx_ASO_140	UNC13A	GAAGAGACATACCCAGAC	487
MTx_ASO_141	UNC13A	AAGAGACATACCCAGACA	488
MTx_ASO_142	UNC13A	AGAGACATACCCAGACAC	489
MTx_ASO_248	UNC13A	CATCTATCCATCCATGTA	490
MTx_ASO_249	UNC13A	CTATCCATCCATGTACTC	491
MTx_ASO_250	UNC13A	TCCATCCATGTACTCACC	492
MTx_ASO_251	UNC13A	ATCCATGTACTCACCCAT	493
MTx_ASO_252	UNC13A	CATGTACTCACCCATCTC	494
MTx_ASO_253	UNC13A	GTACTCACCCATCTCTCC	495
MTx_ASO_254	UNC13A	CTCACCCATCTCTCCATC	496
MTx_ASO_255	UNC13A	ACCCATCTCTCCATCCAT	497
MTx_ASO_256	UNC13A	CATCTCTCCATCCATCCT	498
MTx_ASO_257	UNC13A	CTCTCCATCCATCCTTTT	499
MTx_ASO_258	UNC13A	TCCATCCATCCTTTTATC	500
MTx_ASO_259	UNC13A	ATCCATCCTTTTATCTAC	501
MTx_ASO_260	UNC13A	CATCCTTTTATCTACTCA	502
MTx_ASO_261	UNC13A	CCTTTTATCTACTCATCA	503
MTx_ASO_262	UNC13A	TTTATCTACTCATCACTC	504
MTx_ASO_263	UNC13A	ATCTACTCATCACTCATT	505
MTx_ASO_264	UNC13A	TACTCATCACTCATTCAT	506
MTx_ASO_265	UNC13A	TCATCACTCATTCATCTG	507
MTx_ASO_266	UNC13A	TCACTCATTCATCTGTTC	508
MTx_ASO_267	UNC13A	CTCATTCATCTGTTCAAT	509
MTx_ASO_268	UNC13A	ATTCATCTGTTCAATCAT	510
MTx_ASO_269	UNC13A	CATCTGTTCAATCATTCA	511
MTx_ASO_270	UNC13A	CTGTTCAATCATTCATTC	512
MTx_ASO_271	UNC13A	TTCAATCATTCAATTCATT	513
MTx_ASO_272	UNC13A	AATCATTCATTCAATCAC	514
MTx_ASO_273	UNC13A	CATTCAATTCATTACCAG	515
MTx_ASO_274	UNC13A	TCATTCAATTCACCAGCAT	516
MTx_ASO_275	UNC13A	TTCATTCAATTCACCAGTTA	517
MTx_ASO_276	UNC13A	ATTCACCAGCATTTATTC	518
MTx_ASO_277	UNC13A	CACCAGCATTTATTCAAC	519
MTx_ASO_278	UNC13A	CAGCATTTATTCAACAAA	520
MTx_ASO_279	UNC13A	CATTTATTCAACAACTA	521
MTx_ASO_280	UNC13A	TTATTCAACAACTAGTT	522

Table 8A: UNC13A Cryptic Exon Targeted Regions

Name	Tiling Coordinates	Target Sequence
Cryptic Exon Splice Acceptor	hg38 chr19 17,642,562- 17,642,494	GTCTGGGTATGTCTCTTCCAGCTGC CTGGGTTTCCTGGAAAGAAGCTCTTA TCCCAGGAAGTAGTTTGT [SEQ ID NO:643]
Cryptic Exon Splice Donor	hg38 chr19 17,642,479- 17,642,391	TGAATGAATGAATGATTGAACAGA TGAATGAGTGATGAGTAGATAAAA GGATGGATGGAGAGATGGGTGAGT ACATGGATGGATAGATG [SEQ ID NO:644]

Table 8B: 21mer Antisense Oligonucleotides Targeting UNC13A Spaced 1bp5 **Apart**

Name	Target	Nucleotide Sequence	SEQ ID NO:
MTx_ASO_306	UNC13A	ACAAACTAGTTCCTGGGGATA	523
MTx_ASO_307	UNC13A	CAAAC TAGTTCCTGGGGATAA	524
MTx_ASO_308	UNC13A	AAACTAGTTCCTGGGGATAAG	525
MTx_ASO_309	UNC13A	AACTAGTTCCTGGGGATAAGA	526
MTx_ASO_310	UNC13A	ACTAGTTCCTGGGGATAAGAG	527
MTx_ASO_311	UNC13A	CTAGTTCCTGGGGATAAGAGT	528
MTx_ASO_312	UNC13A	TAGTTCCTGGGGATAAGAGTT	529
MTx_ASO_313	UNC13A	AGTTCCTGGGGATAAGAGTTC	530
MTx_ASO_314	UNC13A	GTTTCCTGGGGATAAGAGTTCT	531
MTx_ASO_315	UNC13A	TTCCTGGGGATAAGAGTTCTT	532
MTx_ASO_316	UNC13A	TCCTGGGGATAAGAGTTCTTT	533
MTx_ASO_317	UNC13A	CCTGGGGATAAGAGTTCTTTTC	534
MTx_ASO_318	UNC13A	CTGGGGATAAGAGTTCTTTCC	535
MTx_ASO_319	UNC13A	TGGGGATAAGAGTTCTTTCCA	536
MTx_ASO_320	UNC13A	GGGGATAAGAGTTCTTTCCAG	537
MTx_ASO_321	UNC13A	GGGATAAGAGTTCTTTCCAGG	538
MTx_ASO_322	UNC13A	GGATAAGAGTTCTTTCCAGGA	539
MTx_ASO_323	UNC13A	GATAAGAGTTCTTTCCAGGAA	540
MTx_ASO_324	UNC13A	ATAAGAGTTCTTTCCAGGAAA	541
MTx_ASO_325	UNC13A	TAAGAGTTCTTTCCAGGAAAC	542
MTx_ASO_326	UNC13A	AAGAGTTCTTTCCAGGAAACC	543
MTx_ASO_327	UNC13A	AGAGTTCTTTCCAGGAAACCC	544

MTx_ASO_328	UNC13A	GAGTTCTTTCCAGGAAACCCA	545
MTx_ASO_329	UNC13A	AGTTCTTTCCAGGAAACCCAG	546
MTx_ASO_330	UNC13A	GTTCTTTCCAGGAAACCCAGG	547
MTx_ASO_331	UNC13A	TTCTTTCCAGGAAACCCAGGC	548
MTx_ASO_332	UNC13A	TCTTTCCAGGAAACCCAGGCA	549
MTx_ASO_333	UNC13A	CTTTCCAGGAAACCCAGGCAG	550
MTx_ASO_334	UNC13A	TTTCCAGGAAACCCAGGCAGC	551
MTx_ASO_335	UNC13A	TTCCAGGAAACCCAGGCAGCT	552
MTx_ASO_336	UNC13A	TCCAGGAAACCCAGGCAGCTG	553
MTx_ASO_337	UNC13A	CCAGGAAACCCAGGCAGCTGG	554
MTx_ASO_338	UNC13A	CAGGAAACCCAGGCAGCTGGA	555
MTx_ASO_339	UNC13A	AGGAAACCCAGGCAGCTGGAA	556
MTx_ASO_340	UNC13A	GGAAACCCAGGCAGCTGGAAG	557
MTx_ASO_341	UNC13A	GAAACCCAGGCAGCTGGAAGA	558
MTx_ASO_342	UNC13A	AAACCCAGGCAGCTGGAAGAG	559
MTx_ASO_343	UNC13A	AACCCAGGCAGCTGGAAGAGA	560
MTx_ASO_344	UNC13A	ACCCAGGCAGCTGGAAGAGAC	561
MTx_ASO_345	UNC13A	CCCAGGCAGCTGGAAGAGACA	562
MTx_ASO_346	UNC13A	CCAGGCAGCTGGAAGAGACAT	563
MTx_ASO_347	UNC13A	CAGGCAGCTGGAAGAGACATA	564
MTx_ASO_348	UNC13A	AGGCAGCTGGAAGAGACATAC	565
MTx_ASO_349	UNC13A	GGCAGCTGGAAGAGACATACC	566
MTx_ASO_350	UNC13A	GCAGCTGGAAGAGACATACCC	567
MTx_ASO_351	UNC13A	CAGCTGGAAGAGACATACCCA	568
MTx_ASO_352	UNC13A	AGCTGGAAGAGACATACCCAG	569
MTx_ASO_353	UNC13A	GCTGGAAGAGACATACCCAGA	570
MTx_ASO_354	UNC13A	CTGGAAGAGACATACCCAGAC	571
MTx_ASO_355	UNC13A	CATCTATCCATCCATGTACTC	572
MTx_ASO_356	UNC13A	ATCTATCCATCCATGTACTCA	573
MTx_ASO_357	UNC13A	TCTATCCATCCATGTACTCAC	574
MTx_ASO_358	UNC13A	CTATCCATCCATGTACTCACC	575
MTx_ASO_359	UNC13A	TATCCATCCATGTACTCACCC	576
MTx_ASO_360	UNC13A	ATCCATCCATGTACTCACCCA	577
MTx_ASO_361	UNC13A	TCCATCCATGTACTCACCCAT	578
MTx_ASO_362	UNC13A	CCATCCATGTACTCACCCATC	579
MTx_ASO_363	UNC13A	CATCCATGTACTCACCCATCT	580
MTx_ASO_364	UNC13A	ATCCATGTACTCACCCATCTC	581
MTx_ASO_365	UNC13A	TCCATGTACTCACCCATCTCT	582
MTx_ASO_366	UNC13A	CCATGTACTCACCCATCTCTC	583
MTx_ASO_367	UNC13A	CATGTACTCACCCATCTCTCC	584
MTx_ASO_368	UNC13A	ATGTACTCACCCATCTCTCCA	585

MTx_ASO_369	UNC13A	TGTACTCACCCTCTCTCCAT	586
MTx_ASO_370	UNC13A	GTACTCACCCTCTCTCCATC	587
MTx_ASO_371	UNC13A	TACTCACCCTCTCTCCATCC	588
MTx_ASO_372	UNC13A	ACTCACCCTCTCTCCATCCA	589
MTx_ASO_373	UNC13A	CTCACCCTCTCTCCATCCAT	590
MTx_ASO_374	UNC13A	TCACCCTCTCTCCATCCATC	591
MTx_ASO_375	UNC13A	CACCCTCTCTCCATCCATCC	592
MTx_ASO_376	UNC13A	ACCCTCTCTCCATCCATCCT	593
MTx_ASO_377	UNC13A	CCCCTCTCTCCATCCATCCTT	594
MTx_ASO_378	UNC13A	CCCTCTCTCCATCCATCCTTT	595
MTx_ASO_379	UNC13A	CATCTCTCCATCCATCCTTTT	596
MTx_ASO_380	UNC13A	ATCTCTCCATCCATCCTTTTA	597
MTx_ASO_381	UNC13A	TCTCTCCATCCATCCTTTTAT	598
MTx_ASO_382	UNC13A	CTCTCCATCCATCCTTTTATC	599
MTx_ASO_383	UNC13A	TCTCCATCCATCCTTTTATCT	600
MTx_ASO_384	UNC13A	CTCCATCCATCCTTTTATCTA	601
MTx_ASO_385	UNC13A	TCCATCCATCCTTTTATCTAC	602
MTx_ASO_386	UNC13A	CCATCCATCCTTTTATCTACT	603
MTx_ASO_387	UNC13A	CATCCATCCTTTTATCTACTC	604
MTx_ASO_388	UNC13A	ATCCATCCTTTTATCTACTCA	605
MTx_ASO_389	UNC13A	TCCATCCTTTTATCTACTCAT	606
MTx_ASO_390	UNC13A	CCATCCTTTTATCTACTCATC	607
MTx_ASO_391	UNC13A	CATCCTTTTATCTACTCATCA	608
MTx_ASO_392	UNC13A	ATCCTTTTATCTACTCATCAC	609
MTx_ASO_393	UNC13A	TCCTTTTATCTACTCATCACT	610
MTx_ASO_394	UNC13A	CCTTTTATCTACTCATCACTC	611
MTx_ASO_395	UNC13A	CTTTTATCTACTCATCACTCA	612
MTx_ASO_396	UNC13A	TTTTATCTACTCATCACTCAT	613
MTx_ASO_397	UNC13A	TTTATCTACTCATCACTCATT	614
MTx_ASO_398	UNC13A	TTATCTACTCATCACTCATTC	615
MTx_ASO_399	UNC13A	TATCTACTCATCACTCATTTCA	616
MTx_ASO_400	UNC13A	ATCTACTCATCACTCATTCAT	617
MTx_ASO_401	UNC13A	TCTACTCATCACTCATTCATC	618
MTx_ASO_402	UNC13A	CTACTCATCACTCATTCATCT	619
MTx_ASO_403	UNC13A	TACTCATCACTCATTCATCTG	620
MTx_ASO_404	UNC13A	ACTCATCACTCATTCATCTGT	621
MTx_ASO_405	UNC13A	CTCATCACTCATTCATCTGTT	622
MTx_ASO_406	UNC13A	TCATCACTCATTCATCTGTTC	623
MTx_ASO_407	UNC13A	CATCACTCATTCATCTGTTC	624
MTx_ASO_408	UNC13A	ATCACTCATTCATCTGTTC	625
MTx_ASO_409	UNC13A	TCACTCATTCATCTGTTC	626

MTx_ASO_410	UNC13A	CACTCATTCATCTGTTCAATC	627
MTx_ASO_411	UNC13A	ACTCATTCATCTGTTCAATCA	628
MTx_ASO_412	UNC13A	CTCATTCATCTGTTCAATCAT	629
MTx_ASO_413	UNC13A	TCATTCATCTGTTCAATCATT	630
MTx_ASO_414	UNC13A	CATTCATCTGTTCAATCATT	631
MTx_ASO_415	UNC13A	ATTCATCTGTTCAATCATTCA	632
MTx_ASO_416	UNC13A	TTCATCTGTTCAATCATTCA	633
MTx_ASO_417	UNC13A	TCATCTGTTCAATCATTCA	634
MTx_ASO_418	UNC13A	CATCTGTTCAATCATTCA	635
MTx_ASO_419	UNC13A	ATCTGTTCAATCATTCA	636
MTx_ASO_420	UNC13A	TCTGTTCAATCATTCA	637
MTx_ASO_421	UNC13A	CTGTTCAATCATTCA	638
MTx_ASO_422	UNC13A	TGTTCAATCATTCA	639
MTx_ASO_423	UNC13A	GTTCAATCATTCA	640

Table 9: Subregions of cryptic exon targeted by active 18mer ASOs that reduced cryptic exon inclusion while increasing total UNC13A RNA levels

Sequence Description	Nucleotide Sequence	SEQ ID NO:#
ASOs 1-10 compiled sequence	TCAACAACTAGTTCCTGGGGATAAGAGTTC TTTCCAGGAAACCC	645
ASOs 1-10 compiled sequence reverse complement	GGGTTTCCTGGAAGAAGTCTTATCCCCAGG AACTAGTTTGTGA	650
ASOs 17-21 compiled sequence	CAGCTGGAAGAGACATACCCAGACACAAAC	646
ASOs 17-21 compiled sequence reverse complement	GTTTGTGTCTGGGTATGTCTCTTCCAGCTG	651
ASOs 249-256 compiled sequence	CTATCCATCCATGTACTCACCCTCTCTCCA TCCATCCT	647
ASOs 249-256 compiled sequence reverse complement	AGGATGGATGGAGAGATGGGTGAGTACATGG ATGGATAG	652
ASOs 260-265 compiled sequence	CATCCTTTTATCTACTCATCACTCATTCATC TG	648
ASOs 260-265 compiled sequence reverse complement	CAGATGAATGAGTGATGAGTAGATAAAAGGA TG	653
ASOs 271-272 compiled sequence	TTCAATCATTCAATTCAC	649
ASOs 271-272 compiled sequence reverse complement	GTGAATGAATGAATGATTGAA	654

5

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The various embodiments described above and in Appendix A can be combined to provide further embodiments. All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application

Data Sheet, including but not limited to U.S. Provisional Patent Application No. 63/171,522, filed on April 6, 2021, and U.S. Provisional Patent Application No. 63/312,808, filed on February 22, 2022, are incorporated herein by reference, in their entirety. Aspects of the embodiments can be modified, if necessary to employ concepts
5 of the various patents, applications and publications to provide yet further embodiments.

These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification
10 and the claims, but should be construed to include all possible embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

CLAIMS

1. 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.

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

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

4. The method 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 method 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 method 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 method 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 method of any one of claims 1-7, wherein the antisense oligonucleotide has 15-40 bases.
9. The method of claim 8, wherein the antisense oligonucleotide has 20-30 bases.
10. The method of claim 8, wherein the antisense oligonucleotide has 18-25 bases.
11. The method of claim 8, wherein the antisense oligonucleotide has 18-22 bases.

12. The method 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 method 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 method 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 method 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 method of any one of claims 1-15, wherein the antisense oligonucleotide is a modified antisense oligonucleotide.
17. The method 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 method of any one of claims 1-17, wherein the cell is within a subject.

19. The method of any one of claims 1-18, wherein the subject is identified is 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. 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.

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

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

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

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

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

30. The method of claim 27, wherein the antisense oligonucleotide has 18-22 bases.
31. The method 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 method 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 method 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 method 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 method of any one of claims 16-34, wherein the antisense oligonucleotide is a modified antisense oligonucleotide.
36. The method 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 method of any one of claims 16-36, wherein the cell is within a subject.

38. 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.

39. The method of claim 38 wherein the cryptic exon comprises SEQ ID NO:5 or SEQ ID NO:6.

40. The method of claim 38 or 39, wherein the UNC13A cryptic exon splice variant comprises SEQ ID NO:7 or SEQ ID NO:8.

41. The method of any one of claims 38-40, 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.

42. The method of any one of claims 38-41, 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.

43. The method of any one of claims 38-42, 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.

44. The method of claim 43, 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.

45. The method of any one of claims 38-44, wherein the antisense oligonucleotide has 15-40 bases.

46. The method of claim 45, wherein the antisense oligonucleotide has 20-30 bases.

47. The method of claim 45, wherein the antisense oligonucleotide has 18-25 bases.

48. The method of claim 45, wherein the antisense oligonucleotide has 18-22 bases.

49. The method of any one of claims 38-48, 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.

50. The method 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 method 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 method of any one of claims 38-51, 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.

53. The method of any one of claims 38-52, wherein the antisense oligonucleotide is a modified antisense oligonucleotide.

54. The method of claim 53, wherein the modified antisense oligonucleotide comprises a 2'OMe antisense oligonucleotide, 2' O-Methoxyethyl antisense oligonucleotide, phosphorothioate antisense oligonucleotide, or LNA antisense oligonucleotide.

55. The method of any one of claims 38-54, wherein the TDP-43 proteinopathy comprises amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), Alzheimer's Disease, hippocampal sclerosis, Parkinson's disease, Perry Syndrome, Huntington disease, chronic traumatic encephalopathy, or a combination thereof.

56. 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.

57. The method of claim 55, 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

58. The method of claim 56 or 57, wherein the subject has decreased expression of TDP-43.

59. The method of any one of claims 56-58 wherein the cryptic exon comprises the base sequence of SEQ ID NO:5 or SEQ ID NO:6.

60. The method of any one of claims 56-59, wherein the UNC13A cryptic exon splice variant comprises SEQ ID NO:7 or SEQ ID NO:8.

61. The method of any one of claims 56-60, 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.

62. The method of any one of claims 56-61, 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.

63. The method of any one of claims 56-62, 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.

64. The method of claim 63, 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.

65. The method of any one of claims 56-64, wherein the antisense oligonucleotide has 15-40 bases.

66. The method of claim 65, wherein the antisense oligonucleotide has 20-30 bases.

67. The method of claim 65, wherein the antisense oligonucleotide has 18-25 bases.
68. The method of claim 65, wherein the antisense oligonucleotide has 18-22 bases.
69. The method of any one of claims 56-68, 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.
70. The method of claim 69, 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.
71. The method of claim 70, 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.
72. The method of any one of claims 56-71, 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.
73. The method of any one of claims 56-72, wherein the antisense oligonucleotide is a modified antisense oligonucleotide.
74. The method of claim 73, wherein the modified antisense oligonucleotide comprises a 2'OMe antisense oligonucleotide, 2' O-Methoxyethyl antisense

oligonucleotide, phosphorothioate antisense oligonucleotide, or LNA antisense oligonucleotide.

75. The method of any one of claims 56-74, wherein the subject has a TDP-43 proteinopathy, optionally wherein the TDP-43 proteinopathy comprises amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), facial onset sensory and motor neuronopathy (FOSMN), hippocampal sclerosis (HS), limbic-predominant age-related TDP-43 encephalopathy (LATE), cerebral age-related TDP-43 with sclerosis (CARTS), Guam Parkinson-dementia complex (G-PDC), Guan ALS (G-ALS), Multisystem proteinopathy (MSP), Perry disease, Alzheimer's disease (AD), and chronic traumatic encephalopathy (CTE), or a combination thereof.

76. The method of any one of claims 38-75, further comprising administering to the subject a *STMN2* cryptic splice variant specific inhibitor.

77. The method of claim 76, wherein the *STMN2* cryptic splice variant comprises cryptic exon 2a.

78. The method of claim 76 or 77, wherein the *STMN2* cryptic splice variant specific inhibitor comprises an inhibitory nucleic acid, peptide, antibody, binding protein, small molecule, ribozyme, or aptamer.

79. The method of any one of claims 76-78, wherein the *STMN2* cryptic splice variant specific inhibitor targets cryptic exon 2a.

80. The method of any one of claims 76-79, wherein the *STMN2* cryptic splice variant specific inhibitor is an antisense oligonucleotide, optionally wherein the antisense oligonucleotide is a modified antisense oligonucleotide.

81. The method of claim 80, wherein the antisense oligonucleotide is complementary to: the exon 1 splice donor site region in a preprocessed mRNA

encoding *STMN2* or the cryptic exon 2a splice acceptor site region in a preprocessed mRNA encoding *STMN2*.

82. 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.

83. The pharmaceutical composition of claim 82, 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.

84. The pharmaceutical composition of claim 83, 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.

85. 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.

86. The pharmaceutical composition of any one of claims 82-85, wherein the antisense oligonucleotide has 18-25 bases.

87. The pharmaceutical composition of claim 86, wherein the antisense oligonucleotide has 18-22 bases.

88. The pharmaceutical composition of claim 82-85, wherein the antisense oligonucleotide has 20-30 bases.

89. The pharmaceutical composition of any one of claims 82-88, wherein the antisense oligonucleotide is a modified antisense oligonucleotide.

90. The pharmaceutical composition of claim 89, wherein the modified antisense oligonucleotide comprises a 2'OMe antisense oligonucleotide, 2' O-Methoxyethyl antisense oligonucleotide, phosphorothioate antisense oligonucleotide, or LNA antisense oligonucleotide.

91. The pharmaceutical composition of any one of claims 82-90, 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.

92. The pharmaceutical composition of any one of claims 82-91, 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.

93. 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.

94. The modified antisense oligonucleotide of claim 93, 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.

95. The modified antisense oligonucleotide of claim 94, 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.

96. The modified antisense oligonucleotide of any one of claims 93-95, wherein the modified antisense oligonucleotide comprises a 2'OMe antisense oligonucleotide, 2' O-Methoxyethyl antisense oligonucleotide, phosphorothioate antisense oligonucleotide, or LNA antisense oligonucleotide.

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

98. The modified antisense oligonucleotide of claim 97, 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.

99. The modified antisense oligonucleotide of claim 97 or 98, 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.

100. The modified antisense oligonucleotide of any one of claims 97-99, 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.

101. The modified antisense oligonucleotide of any one of claims 93-100, wherein the antisense oligonucleotide has 18-25 bases.

102. The modified antisense oligonucleotide of claim 101, wherein the antisense oligonucleotide has 18-22 bases.

103. The modified antisense oligonucleotide of any one of claims 93-100, wherein the antisense oligonucleotide has 20-30 bases.

104. 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.

105. The kit of claim 104, 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.

106. The kit of claim 105, 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.

107. The kit of any one of claims 104-106, wherein the antisense oligonucleotide has 18-25 bases.

108. The kit of claim 107, wherein the antisense oligonucleotide has 18-22 bases.

109. The kit of any one of claims 104-108, wherein the antisense oligonucleotide has 20-30 bases.

110. The kit of any one of claims 104-109, wherein the antisense oligonucleotide is a modified antisense oligonucleotide.

111. The kit of any one of claims 104-110, wherein the modified antisense oligonucleotide comprises a 2'OMe antisense oligonucleotide, 2' O-Methoxyethyl antisense oligonucleotide, phosphorothioate antisense oligonucleotide, or LNA antisense oligonucleotide.