

COMPOSITIONS FOR TREATMENT OF CONDITIONS AND DISEASES ASSOCIATED WITH POLYCYSTIN EXPRESSION

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 63/145,288, filed February 3, 2021, which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Alternative splicing events in genes can lead to non-productive mRNA transcripts which in turn can lead to aberrant protein expression, and therapeutic agents which can target the alternative splicing events in genes can modulate the expression level of functional proteins in patients and/or inhibit aberrant protein expression. Such therapeutic agents can be used to treat a condition or disease caused by protein deficiency.

SUMMARY

[0002a] Described herein, in certain embodiments, is an in-vitro method of modulating expression of polycystin in a cell, the method comprising contacting the cell a composition that comprises an agent or a vector encoding the agent, wherein the agent comprises a sequence that is the reverse complement sequence of a target sequence of a pre-mRNA, whereby binding of the agent to the target sequence modulates splicing of the NMD exon from the pre-mRNA, thereby modulating the level of a processed mRNA that is processed from the pre-mRNA, and modulating the expression of polycystin in the cell, wherein the polycystin is encoded by a PKD2 gene.

[0002b] Described herein, in certain embodiments, is a composition comprising an agent or a vector encoding the agent, wherein the agent comprises a sequence that is the reverse complement sequence of a target sequence of a pre-mRNA, wherein the agent (a) binds to a target sequence of the pre-mRNA that is transcribed from a target gene and that comprises a non-sense mediated RNA decay-inducing exon (NMD exon), and (b) modulates splicing of the NMD exon from the pre-mRNA, thereby modulating the level of a processed mRNA that is processed from the pre-mRNA, and modulating expression of a target protein in a cell having the pre-mRNA, wherein the pre-mRNA is encoded by a PKD2 gene.

[0002c] Described herein, in certain embodiments, is the composition as described herein for use in therapy.

[0002d] Described herein, in certain embodiments, is a use of the composition as described herein, in manufacturing a medicament for treating a disease or condition in a subject in need thereof.

[0003] Described herein, in certain embodiments, is a method of modulating expression of a target protein in a cell having a pre-mRNA that is transcribed from a target gene and that comprises a non-sense mediated RNA decay-inducing exon (NMD exon), the method comprising: contacting an agent or a vector encoding the agent to the cell, whereby the agent modulates splicing of the NMD exon from the pre-mRNA, thereby modulating the level of a processed mRNA that is processed from the pre-mRNA,

and modulating the expression of the target protein in the cell, wherein the target protein is encoded by a *PKD2* gene.

[0004] Described herein, in certain embodiments, is a method of treating or reducing the likelihood of developing a disease or condition in a subject in need thereof by modulating expression of a target protein in a cell of the subject, comprising: contacting an agent or a vector encoding the agent to the cell of the subject, whereby the agent modulates splicing of a non-sense mediated mRNA decay-inducing exon (NMD exon) from a pre-mRNA that is transcribed from a target gene and that comprises the NMD exon, thereby modulating the level of a processed mRNA that is processed from the pre-mRNA, and modulating the expression of the target protein in the cell of the subject, wherein the target protein encoded by a *PKD2* gene.

[0005] In some embodiments, the target protein is polycystin 2.

[0006] In some embodiments, the disease or condition is a disease or condition associated with a deficiency in amount or activity of polycystin 2. In some embodiments, the disease or condition is a disease or condition associated with a deficiency in amount or activity of polycystin 1.

the main start codon of the processed mRNA. In some embodiments, the mRNA secondary structure comprises a stem, a stem loop, a Guanine quadruplex, or any combination thereof. In some embodiments, the agent does not bind to the main start codon. In some embodiments, the agent binds to at least one nucleotide of the main start codon. In some embodiments, the agent inhibits or reduces formation of a secondary mRNA structure comprising the at least one nucleotide of the main start codon of the processed mRNA. In some embodiments, the agent inhibits or reduces base-pairing of the at least one nucleotide of the main start codon of the processed mRNA with another nucleotide of the processed mRNA, optionally wherein the another nucleotide is another nucleotide of the 5' UTR of the processed mRNA. In some embodiments, the translation regulatory element comprises at least part of an upstream open reading frame (uORF). In some embodiments, the agent promotes formation of a secondary mRNA structure that involves the at least part of the uORF. In some embodiments, the translation regulatory element comprises an upstream start codon. In some embodiments, the agent promotes formation of a secondary mRNA structure that involves base-pairing with at least one nucleotide of the upstream start codon. In some embodiments, the agent does not bind to the upstream start codon. In some embodiments, the agent binds to the upstream start codon. In some embodiments, the agent promotes or increases formation of a secondary mRNA structure comprising the at least one nucleotide of the upstream start codon. In some embodiments, the agent promotes or increases base-pairing of the at least one nucleotide of the upstream start codon with another nucleotide of the processed mRNA, optionally wherein the another nucleotide is another nucleotide of the 5' UTR of the processed mRNA. In some embodiments, the translation regulatory element comprises a Guanine quadruplex formed by a G-rich sequence of the processed mRNA. In some embodiments, the agent inhibits formation of the Guanine quadruplex. In some embodiments, the G-rich sequence comprises at least a portion of 5' untranslated region (5' UTR) of the processed mRNA. In some embodiments, the G-rich sequence is present in 5' untranslated region (5' UTR) of the processed mRNA. In some embodiments, the G-rich sequence comprises a sequence according to the formula $Gx-N1-7-Gx-N1-7-Gx-N1-7-Gx$ (SEQ ID NO: 227), where $x \geq 3$ and N is A, C, G or U. In some embodiments, the G-rich sequence comprises a sequence GGGAGCCGGGCUGGGGCUCACACGGGGG (SEQ ID NO: 228). In some embodiments, at least one, two, three or all four of the Gx sequences are structured, present in a secondary structure, or base-paired with another nucleotide, optionally wherein the another nucleotide is a C or a U. In some embodiments, the agent relaxes, promotes deformation of, or inhibits or reduces formation of the Guanine quadruplex. In some embodiments, the agent relaxes, promotes deformation, or inhibits or reduces base-pairing or a structure of at least one,

exon 3 (black bar), and thus, is longer than the corresponding canonical exon 3 (black bar). Consistently, the intron resulting from the splicing at the alternative 5' splice-site (alt 5' ss) is shorter than the corresponding canonical intron 3. **FIG. 4C** shows RT-PCR using RNA from human kidney mixed epithelial cells and human kidney cortical epithelial cells treated with either DMSO (-) or cycloheximide (CHX) (+). Primers were positioned in exon 2 and 4.

[00189] FIG. 5 depicts ASO walk design for the NMD exon inclusion event. The shaded nucleotides correspond to the NMD-inducing exon 2X. FIG. 5 discloses SEQ ID NOS 263-265, respectively, in order of appearance.

[00190] FIGs. 6A-B depict the ASO walk design for the Alt 5'ss event. The shaded nucleotides correspond to portion of the extended exon 3 that results from the selection of the indicated Alt 5'ss. *alt_5 ss refers to an alternative 5' splice site. FIG. 6 discloses SEQ ID NOS 266-270, respectively, in order of appearance.

[00191] FIG. 7A depicts the changes in productive *PKD2* mRNA using primary renal mixed epithelial cells transfected for 24 hours with the indicated ASOs (see macrowalk of **FIGs. 6A-B**) at 80nM.

[00192] FIG. 7B depicts the changes in nonproductive *PKD2* mRNA using primary renal mixed epithelial cells transfected for 24 hours with the indicated ASOs (see macrowalk of **FIGs. 6A-B**) at 80nM.

[00193] FIG. 8A depicts the changes in productive *PKD2* mRNA using primary renal mixed epithelial cells transfected for 24 hours with the indicated ASOs (see macrowalk of **FIG. 5**) at 80nM.

[00194] FIG. 8B depicts the changes in nonproductive *PKD2* mRNA using primary renal mixed epithelial cells transfected for 24 hours with the indicated ASOs (see macrowalk of **FIG. 5**) at 80nM.

[00195] FIG. 9A - FIG. 9E illustrate ASOs targeting two events to increase productive mRNA and protein production. **FIG. 9A** depicts the effect of combination of ASOs on non-productive exon inclusion NMD event utilization. **FIG. 9B** depicts the expression of EX2-EX3 productive mRNA with ASO combinations. **FIG. 9C** depicts the effect of combination of ASOs on non-productive alternative 5'ss NMD event utilization. **FIG. 9D** depicts the expression of EX3-EX4 productive mRNA with ASO combinations. **FIG. 9E** depicts the quantification of Polycystin 2 (PKD2) protein western blots after treatment with ASO combinations.

[00196] FIG. 10 illustrated an upstream open reading frame macrowalk of PKD2. Shaded nucleotides correspond to the upstream open reading frame and the canonical start codon, respectively. FIG. 10 discloses SEQ ID NO: 271.

[00331] In some embodiments, an ASO of the disclosure is coupled to a dopamine reuptake inhibitor (DRI), a selective serotonin reuptake inhibitor (SSRI), a noradrenaline reuptake inhibitor (NRI), a norepinephrine-dopamine reuptake inhibitor (NDRI), and a serotonin-norepinephrine-dopamine reuptake inhibitor (SNDRI), using methods described in, *e.g.*, U.S. Pat. No. 9,193,969, incorporated herein by reference.

[00332] In some embodiments, subjects treated using the methods and compositions are evaluated for improvement in condition using any methods known and described in the art.

[00333] In some cases, a therapeutic agent comprises a modified snRNA, such as a modified human snRNA. In some cases, a therapeutic agent comprises a vector, such as a viral vector, that encodes a modified snRNA. In some embodiments, the modified snRNA is a modified U1 snRNA (see, *e.g.*, Alanis et al., Human Molecular Genetics, 2012, Vol. 21, No. 11 2389–2398). In some embodiments, the modified snRNA is a modified U7 snRNA (see, *e.g.*, Gadgil et al., J Gene Med. 2021;23:e3321). Modified U7 snRNAs can be made by any method known in the art including the methods described in Meyer, K.; Schümperli, Daniel (2012), Antisense Derivatives of U7 Small Nuclear RNA as Modulators of Pre-mRNA Splicing. In: Stamm, Stefan; Smith, Christopher W. J.; Lührmann, Reinhard (eds.) Alternative pre-mRNA Splicing: Theory and Protocols (pp. 481-494), Chichester: John Wiley & Sons 10.1002/9783527636778.ch45, incorporated by reference herein in its entirety. In some embodiments, a modified U7 (smOPT) does not compete with WT U7 (Stefanovic et al., 1995).

[00334] In some embodiments, the modified snRNA comprises an smOPT modification. For example, the modified snRNA can comprise a sequence AAUUUUUGGAG (SEQ ID NO: 229). For example, the sequence AAUUUUUGGAG (SEQ ID NO: 229) can replace a sequence AAUUUGUCUAG (SEQ ID NO: 230) in a wild-type U7 snRNA to generate the modified U7 snRNA (smOPT). In some embodiments, a smOPT modification of a U7 snRNA renders the particle functionally inactive in histone pre-mRNA processing (Stefanovic et al., 1995). In some embodiments, a modified U7 (smOPT) is expressed stably in the nucleus and at higher levels than WT U7 (Stefanovic et al., 1995). In some embodiments, the snRNA comprises a U1 snRNP-targeted sequence. In some embodiments, the snRNA comprises a U7 snRNP-targeted sequence. In some embodiments, the snRNA comprises a modified U7 snRNP-targeted sequence and wherein the modified U7 snRNP-targeted sequence comprises smOPT. In some embodiments, the modified snRNA has been modified to comprise a single-stranded nucleotide sequence that hybridizes to a *PKD2* pre-mRNA. In some embodiments, the modified snRNA has been modified to comprise a single-stranded nucleotide sequence that hybridizes to a *PKD2* mRNA.

[00335] In some embodiments, the modified snRNA has been modified to comprise a single-stranded nucleotide sequence that hybridizes to a target region of a *PKD2* pre-mRNA or a

	TACTCAAGCTTCCTGAGGGCAGGGATTCTATTTTGTAACTGCTGTATTCTCA AAGCCTTGAACAATGCCTCATATGTAAAGATACTAATA (SEQ ID NO: 231)
Alternative splice site event	
Canonical exon chr4 88036220 88036353	TGACCTACGGCATGATGAGCTCCAATGTGTACTACTACACCCGGATGATGTC ACAGCTCTTCCTAGACACCCCCGTGTCCAAAACGGAGAAAATACTTTAAA ACTCTGTCTTCCATGGAAGACTTCTGGAAG (SEQ ID NO: 232)
Canonical intron chr4 88036354 88038250	gtatttgcaaataactttgaaagtacctctcatcacagaaaattgttcatttggcttcatttcaatgcatgagtatcgacaggacc tgctttgcatthaacactgtgtgagacgtaagttatggtagttgttagaagtactgttctactctcaaagggggtaaactaacatt gagaactttgcctgtgccttgactgtgctgagtggttcatacttacctatttaatttctatagtctaactctataaggttaagtaag actatgccctagtttgtaatgaggaatgagattcaggatgtttaaagcgtatggcagtgtagggaacaagaaaaattg atTTTTttagcctgacagctacttcatcctagtttgtaattcattccatgagtcagattcaataaatatttattgagaatctcctagaat gtaaggccaatgaagggcagtggtgtcttctgtcttgccttttgtgtttgtctctttgttgatgatggcatgtatccccagctc ttagaacagtgttgattcaaagtaagcacattcttcaaaggctgctgttgggtggggcgttgggtggctcacgcctgtaatcccagc actttgggaggccaaggcaggaggattgcttagcccaggatttgaaccagctgggcacaacatagtagtactttgtctctca aaaaagttaaagaattagcaggggtgtgtgtgtacacacctgcagtcacagctactcaggaggctgaggtgggagaatcacttg agcgtattgcttgaggctcaaggctgcagtgagccatggccatgctactgcattccagctggggcaacagagttagacccttttc aaaaaaaaatcccccaaaaaaaaaacccaaaaacaaaaaaaggctgctgtgtgaagtcaaccaatccagccccttc caagttgtcacaattccaacgtagttaacagtataccaatgagtgataccacaggaataattaaactgactctgagggatattgg ggcttggaaatctaagaaaattggaagggaattgaaaaggaaattattttctccttggggagatagtttctaaaattcttactaca ccctgggggtcagagctgttgatttaaggatagagacaactgagtcacaggaactattcatatataaaagtacctggcatccaaa accacactgtataatgaatcttccatctgagtagggcaaatcagtcctatctgttgatcatctgacaaggatagcacactg agaaatagatctgtcttccctacaggcatagctagttgtacaaactaacagagactttgtatacacattccatgatgataatgcc aatcactaaaggacgaggagggttgagagttcaccatacagcaaaatagtcagacaggtgaaaggctctcaaatgcca ggctgtgaatcaaaactgtagccttttctaaacaaagtttagaacatgattgtgtgggacattatttaataagggaaggtgcag ttaatcatgacccaccttagtccaagaacaaaaatcagagctgccacgtattaagtacccactctgtgccaggtgcagtaacta tgcaaaagatgggtttccagatgcaagaacctgggtcagaggacctgtcaaggcctcatagctaacaatgatggggcaa gatgctatcccaatctctgacaacaaaactcattcttactctactatttcatagagttgccaatgcttggtatgcaaacga tgaggcaggggcaagacagcggtgagcttggaaacttttcagagatgttcccttgccttttag (SEQ ID NO: 233)
Exon resulting from splicing at the alt 5' ss chr4 88036220 88036480	TGACCTACGGCATGATGAGCTCCAATGTGTACTACTACACCCGGATGATGTC ACAGCTCTTCCTAGACACCCCCGTGTCCAAAACGGAGAAAATACTTTAAA ACTCTGTCTTCCATGGAAGACTTCTGGAAGGTATTTGCAAATACTTTGAAA GTACCTCTCTATCACAGAAAATTGTTCAATTGGCTTCATCTTCAATGCATG AGTATCGACAGGACCTGCTTTGCATTTAACACTGTGTGAGACGTAAGTTATG (SEQ ID NO: 234)
Intron resulting from splicing at the alt 5' ss chr4 88036481 88038250	gtgagttgtagaagtactgttctactctcaaagggggtaaactaacattgagaactttgcctgtgccttgactgtgctgagtggt tcatatcttacctatttaatttctatagtctaactctataaggtaagactatgccctagtttgtaatgaggaatgagattc aggatgtttaaagcgtatggtcacatggctagggacaagaaaaattgatttttctagcctgacagctacttcatcctagtttgta attcattccatgagtcagattcaataaataattattttagaactctctagaatgtaaggccaatgaagggcagtggtgtcttctgtctt gcttcgccttttgtgtttgtcttcttggatgatggcatgtatcccagctcttagaacagtgttgattcaaagtaagcacattcttc aaaggctgctgtgtgtggggccttgggtgctcacgcctgtaatcccagcactttgggaggccaaggcaggaggattgcttagc ccaggattttgaaaccagctgggcacaacatagtagtattgtctctcaaaaaagttaaagaattagcaggggtgtgtgtgata cacctgcagtcacagctactcaggaggctgaggtgggagaatcacttgagcgattgcttgaggtcaaggctgcagtgagccat ggccatgctactgcattccagctggggcaacagagttagacccttttcaaaaaaatcccccaaaaaaaacccaaaaaac aaacaaaaaaggctgctgtgtgaagtcaaccaatccagcccctcccaagttgtcaaaattccaacgtagttaacagtata ccaatgagtgataccacaggaataatataaactgatctgagggatattggggccttgaatctaagaaaattggaagggaattg aaaagggaattattttctccttggggagatagtttctaaaattcttactacaccctgggggtcagagctgttgatttaaggatagag acaactgagtcacaggaactattcatatataaagtacctggcatccaaaccacactgtataatgatatttccatctga gtagggcaaatcagtcctatctgttgatcatctgacaaggatagcacactgagaaatagatctgtcttccctacaggcatagcta gtgtacaaactaacaagagactttgtatacacattccatgatgataaatgccaatcactaaaggacgaggagggttgagga gttcaccatacagcaaatagtcagacaggtgaaaggcttatcaaatgccaggctggtaatacaaaactgtagccttttctctaaa caaagtttagaacatgattgtgtgggacattatttaataagggaaggtgcagttaatcatgacccacctttagtccaagaacaa aatcagagctgccacgtattaagtacccactctgtgccaggtgcagtaactatgcaaaagatgggttttcagatgcaagaacc ttggttcagaggaccctgctcaaggcctcatagctaacaatgatggggcaagatgctatcccaatctctctgacaacaaaact

	cctggggacactatgaactcctctcttgagtgcagagatcacgtcttgtcatcttcatgcccaatacctgtccataaatatgaat ggattagaattctaactcttaactctgccccaaagacagttctgagaggttagtaagtcataaacacctgaagaggactgttctgt cctaattacattaggtataagatgacaggtgagggagccaaaccaggggctggaaattatcatacatcttagatacagtat acaagttgtgtattatgtgtattactctgtaattgattgcttgagatgaacccccaaacacactcgtgttgatcattattatctac ccttctcctaaataatctaatttctatgatgcttgaagggaagaggggccaggtgtggtgtgtcacacctgtaatcccagca cttggggaggctgaggtgggagcatcacctgaggtctggagtcaagaccaacctgaccaacatggtgaaacctgtcttact aaaaataaaaaatcagctgggcatggttagcacatgcctgtaatcccagctacttgggagggtgaagtgggagaatcgttgaac ctgggagggggaggttgacgtgagccgagatcactccattgactccagactgggcaacaacagtgaacctccgtctcaaaa aaaaaaaaaaaaaaaaaggcagagtggggaagagagctgcataaggagagattactaaatagacttaataccaaaaataatt ctataggttgaaatgatccctgaaatttattataggttcaggtaagtataatcacgggtattcagaactgtggttaaaaaatgtat agaacatgttctcccttgaactttttatcagctaattataggaattatatactgcaatcattaaagtcagaatgagacag tacttggtaaagtgtgaaattataataatgcattatagcaatccagttaaggaggaagaccattattgaacatttgttaagt gtcagccattgtactagataaattttagttatttttttaggcacaaaaaatccatgggatatgtggttatcccatcttactgaa gaggaaactgaagctcagaaagttaagcaactgcacaggtcacatagcaagtaaggagcatggccaggaatcagacctg atctccttgggtactaagcttcaaggatcttcccgctccttccaagaccattcaatattatcagtaaattgcatggcaaggat gtagttcaggttatagggtccattcaagatatgattggtaggtgggaagcagatatgtctgtgtcaatcagtatcctggaagaagg agatgatgaactcaagtgtgattaagggaagttaatgaagggactatttacagagatgtggtgggttaagagaaccaacaa gggggaagtgtgactcaaaaagttactacctccaggcttaggggattgggggagggagtggcacagtgtgaaccaggtgtg gttgtgagaaaagggttcctcagcagccatggccaaggttagagctccactgccaactgcacccaggtggtgaggggaat ggagaataggggtgggtaacaaactctgacctggtatcccaaaagggaaggttcaggtggtacagttcgtaaagatt agcctcagggcacagaacagggcagagaagaatggagaattgatctggaggaaacaaacatggcttgccatgttattgca gggagagtaggctggtgtgcacagcaggaggggtggggagcccagcatatagctgttggggcctgtgcagatcagcctcac tggcagggaggatctgagccgagaggtggtggaagatgaaatcagtaggcatgttggtagtctaaatatcaagtaaagcttc ctgatcttaccattgatactcaatagtaagccaattttttcccataagccaatattaattacgtatttctttataagccagagata gagagataccctagaagaatgatagggaaggaaggcaagggtgagagaagacctgtgtgaattgtccaaaatgtttatcc acaggaacaatcccttgtgaaggctgctggtatgtgaatgtgtgccgggtcccttggggcggttcatttgatcttctgtgtccag (SEQ ID NO: 237)
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Table 3. Sequences of exemplary *PKD2* pre-mRNA transcripts and mRNA transcript sequences

<i>PKD2</i>		
pre-mRNA transcript	premrna ENST0000 0237596.7	AGGCGGCGGCGGGCGCCGGGAAGAAAGGAACATGGCTCCTGAG GCGCACAGCGCCGAGCGCGGCGCCGCGCACCCGCGCGCCGGAC GCCAGTGACCGCGATGGTGAAGTCCAGTTCGCGTGCAGCCTCAGC AGCCCCGGGGACGCCAAGCGGCCGCCCCGCGCCCCGCGCGCCGGA CCCGGGCCGGCTGATGGCTGGCTGCGCGGCCGTGGGCGCCAGCC TCGCCGCCCCGGGCGGCCTCTGCGAGCAGCGGGGCCTGGAGATC GAGATGCAGCGCATCCGGCAGGCGGCCGCGCGGGACCCCCCGG CCGGAGCCGCGGCCTCCCCTTCTCCTCCGCTCTCGTCGTGCTCCC GGCAGGCGTGGAGCCGCGATAACCCCGGCTTCGAGGCCGAGGA GGAGGAGGAGGAGGTGGAAGGGGAAGAAGGCGGAATGGTGGT GGAGATGGACGTAGAGTGGCGCCCGGGCAGCCGGAGGTTCGGCC GCCTCCTCGGCCGTGAGCTCCGTGGGCGCGCGGAGCCGGGGGCT TGGGGGCTACCACGGCGCGGGCCACCCGAGCGGGAGGCGGCGC CGGCGAGAGGACCAGGGCCCGCGGTGCCCCAGCCCAGTCGGCG GCGGGGACCCGCTGCATCGCCACCTCCCCCTGGAAGGGCAGCCG CCCCGAGTGGCCTGGGCGGAGAGGCTGGTTCGCGGGCTGCGAGgt aagagcgcgacccgcagcggcagatgcacgaaccagaacggccggcgccggccggccatgc ccgtgcggcagctccccgggtccatctcgcacccctctcggtccgctccttgaagcgattcccc acctccgctagtgtccctatttccggtaccagcgcggaattccactgctcttttgggtgcatattattgg atacctccttctcagatatgtcacatagcttttttactgaaaattagtgaagcctaattagagtgaagag tacatctgggttttgttttttttcttagaggaaaaatgaacattactgtgtaactgatgtagtgcactg catatttgcaatgtcacaataatctaaaggaaaatgttatagtcacccgtggttcttcttgctggacactcc attgtccggggtgaaaagggtagcagtcacagtgcataatgtcaagttgtgggaggaggtgtggcagattg tcattggtgcattttttggtgatgtgtgtggtgttttaggagtgaggagctgttaagaacaccacaaatagaat aaaataatcgtgaagttatttggcgtttctaattctagacatttttcaaaaacagttgcaaaggaaagatta cattgttttaaaaaatttgaagtatttttaataactaaattaatgttcttgaattccacaaaatgatgaagt

		<p>CCCTTTGGGCCCCGAAATGGAACCGCgtaagtgtctgtgactcattgccactcggtg atattcattcatttattctgaactcccaccattcattcattccctgacaccttcaccaaggcaaaaaaag ttcagtgtactctcagtgcttatatttaaacttggccaacttgacctttagacttctaaagtttactacttcttagc cttcttttagtttcatgcatattttcagaagactaaatcggtgacatataaacctcaaaaattaattatctga gcgtttgaaaatttcatttaagatgccctgggacctgttttacaggtgcagtaacatcatccactaagttattaa cacaagtttctgggtcaggaactcttttataggtcttgcaaacagggttttggtcagaatggagtatttaagt taagcttgtagggcaatttttggtaggttaaagcccattttgtcaaatgttgagatttaggtatatattgtaca cgtgcataattacaggggctttttagacttgggtactcctacttcaaacatctgtgtattaaggagggtcactt actattttagaagtattgtattataaagaacaagaagacctcaaggccgttcagggtgggaccttgc gggtgctgtccctgggtacgtcactgggtcggagtcatttctaagcttctcagctaattctgtcgggtcatcta gggtctttcttgaaactgagttgccagaatccacattgttactatacaatgggcaatcacctttcaattagt atattcttctgtacctccagtatacactctatttaataaccagaaccataagaaacaatttagtaaaaatcca ggttgggcacagtttctcatgctgtaatcccagcacttggaaagccaaggcggacagatcacttgaggtc aggagtcaagaccagcctagccaacatgggtgaaacctgacttactaaaaatacaaaaattagctgggtg tggtagcatgtgcttatagtcacagctattcgggaggctgaggcaggagaattgcttgagcccagtggtg gggggtgtagtgagctgaggtctcatcattgactccagcctgggcaacagagcaagactccccctcaaaa aaaaaaaaaaaaaatttagtgaaaatccagagctttagaacaagggaactaaatagtctcaaggacattat catccaagttagtagtgattcgcttcttataaaaaaaattattacagatagagtttcttgatgtgccagg ctggcctcaaacctcctgggtcaagcagtcctccagcctcagcctccaagtagctgggactatgagaatat gccaccatgccagcttattttgcttctaattgtcctttttagtctcgaagcataagcatgcctcatct gtggtacccttccaatattttatctcacatcactaataagataaattatacagccactgctctgtgccaga cattatttaagaagtatttcacgcattatctcatctgccttcacaaaacaactctaaaataggatcacctcatt tatagatgaaaaaactgaggctcacttgccaaaagtgtcacagctaacaattggactgaaccaagatttaa gcagcctgactccaaaacctatgttgcctactaaaacctcttccatataattcctcctccatataattgcgtc gttaggggtgctgtgcagcctcagctcccatcagctcaagctcctgagggcagggtattttgtt aactgctgtatttcaaaagccttgaaacaatgcctcatatgtaaagatactaata (SEQ ID NO: 231)</p>
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		<p> tgagggtcaggagtttgagaccagcctggccaacgtggtgaaaccccatcttactaaaaaatagaaaaatta tctgggcatggtggtgcacacgttagtcccagctactcgggaggctgaggcaggagaatcacttgaacct acgaggcagaagttgcagtaagccaagatcacgccactgcactccagcctgggacagagcaagactc tgtctaaaaaaaaaaaaagagtggaatgtaggatgagaaatgctggcagcctgccccctctgggaga tactgtagccctagactggaagttggggaggaggagccctgtgctcttagctgcacccatgtgaagttgt gcttctatcacatgagctggggacaggagagaaggctcagattatggcttcagtgccacagaatcttctata ctaaaatttagtagattttctgaataaatgcttttcatttgctgtacaccctaaaagttttagaaattttaatt tgagtttaaaaaataattttcaacagttacagttatttactaaagagagagtgctacagaacctcttgcacca ttgcagagggtgtcttggcttacgagttttaagatttgtatacatttttaagttcaaaataatagaattgtaag tgaacatgctgtttcactactgttttcaagctttattaatatattgtaaactaatctattttattaatatgtctgcca cagtataatgtctgatgtctccttagaattttattgtatggatgaacaatgattatattaatttctaccaattgtggg tgtttttgtttgtttgtttttgagactgggtctcactctgtcaccaggctggagtgaggagtgccgtggga atgatcacggctcactgcagcctcaacatccaaggctcaggtgatcctccacctcagcctcgcaagtagc tgggagtacaggcacatgccaccatgccacctatttttagagatgaagttttgccatcctgccaggctgg ctgaaactcctggcctcaagcgatctgcacactccgctcccaaatgccaggattacaggcgtgagccat catgccctaccccccatcaattgtttgatgtagccattttcaatgatccgcgattaagaagcagcactctttta tagcaaaaattacacatatataaaattttcttttagaaaatgttcaaaaatggaatgtctaactaaagggttag gcatacattcttaagacttctgatacgcgctgacttgcaggaaagttgttcagttaacactcctaccagcggc atccgagagttaatctgtaaagcttgagacaacttagaaagtgttcaaatgattgtgttcttaagaaaaaat cttagcacttctttgaaaagccagtggggctgaaaagacaatgacaagcactttgtccctctgtactgtgtt tccttgagCCTGGTGAGACGAGTGGACCGGATGGAGCATTCCATCGG CAGCATAGTGTCCAAGATTGACGCCGTGATCGTGAAGCTAGAGA TTATGGAGCGAGCCAACTGAAGAGGAGGGAGGTGCTGGGAAG GCTGTTGGATGGGGTGGCCGAGGtcagtagtcatgagctgaaaacaccgctgctgag catggtgttattaatgaaaatatatgttgctgacagttgtatttgaagtattgaagaagagtaaaaaaatctacg ttatagaaattcacaatgatgtttccatttactctcattttcagattttttctctgaaacagaacactcttctataa aatctcttgctataaaacatcaatgtagtcattgttctaaccttaggctgagatgtttatcttctccataactac agataaaattataatctggaggtgttactttctaatactccatagtcaatggctcctgccttactgcagggtag aattaagtgaaaattactccagcaactctgagatttgcattatagtctgtaaatctccagccttacaaaactac agattatttggtccctggacttctaaggcatttcttactgcccccaacaccagtttcttttcccttttagG ATGAAAGGCTGGGTCGTGACAGTGAAATCCATAGGGAACAGAT GGAACGGCTAGTACGTGAAGAGTTGGAACGCTGGGAATCCGATG ATGCAGCTTCCCAGATCAGTCATGGTTTAGGCACGCCAGTGGGA CTAAATGGTCAACCTCGCCCCAGAAGCTCCCCGCCATCTTCCTCC CAATCTACAGAAGGCATGGAAGGTGCAGGTGGAAATGGGAGTT CTAATGTCCACGTATGATATGTGTGTTTCAGTATGTGTGTTTCTA ATAAGTGAGGAAGTGGCTGTCCTGAATTGCTGTAACAAGCACAC TATTTATATGCCCTGACCACCATAGGATGCTAGTCTTTGTGACCG ATTGCTAATCTTCTGCACTTTAATTTATTTTATATAAACTTTACCC ATGGTT (SEQ ID NO: 243) </p>
transcript	transcript ENST0000 0237596.7	<p> AGGCGGCGGCGGGCGCCGGGAAGAAAGGAACATGGCTCCTGAG GCGCACAGCGCCGAGCGCGGCGCCGCGCACCCGCGCGCCGGAC GCCAGTGACCGCGATGGTGAACCTCCAGTCGCGTGCAGCCTCAGC AGCCCGGGGACGCCAAGCGGCCGCGCCCGCGCCCCGCGCGCCGGA CCCGGGCGGGCTGATGGCTGGCTGCGCGGCCGTGGGCGCCAGCC TCGCCGCCCCGGGCGGCCTCTGCGAGCAGCGGGGCCTGGAGATC GAGATGCAGCGCATCCGGCAGGCGGCCGCGCGGGACCCCCCGG CCGGAGCCGCGGCCTCCCCTTCTCCTCCGCTCTCGTCTGCTCCC GGCAGGCGTGAGCCGCGATAACCCCGGCTTCGAGGCCGAGGA GGAGGAGGAGGAGGTGGAAGGGGAAGAAGGCGGAATGGTGGT GGAGATGGACGTAGAGTGGCGCCCGGGCAGCCGAGGTCGGCC GCCTCCTCGGCCGTGAGCTCCGTGGGCGCGCGGAGCCGGGGGCT TGGGGGCTACCACGGCGCGGGCCACCCGAGCGGGAGGCGGCGC CGGCGAGAGGACCAGGGCCCCGCGGTGCCCCAGCCAGTCGGCG GCGGGGACCCGCTGCATCGCCACCTCCCCCTGGAAGGGCAGCCG CCCCAGTGGCCTGGGCGGAGAGGCTGGTTTCGCGGGCTGCGAGG TCTCTGGGGAACAAGACTCATGGAGGAAAGCAGCACTAACCGA </p>

		<p>TGCCACCATGACTGAGTCTTCTCAGTTGACAATGAAGTAGCCTTT TAAAGCTAGAAAACGTCAAAGGGCTTCTGAGTTTCATTTCCAGT CACAAAAATCAGTATTGTTATTTTTTTTCCAAGAGTGTGAAGGAA AATGGGGCATTCTTTTCCACTCTGGCATAAGTTTCATGAGCTTAATA CATAGCTTTCTTTTAAGAAAGGAGCCTTTTTTTTTCAACTAGCTTC CTGGGGTAAACTTTTTCTAAAAAGATAAAATGGAAAGGAACTCCAA ACTATGATAGAATCTGTGTGAATGGTTAAGATGAATGTTAAATA CTATGCTTTTTTTGTAAGTTGATCGTATCTGATGTCTGTGGGACTA ACTGTATCACTTAATTTTTTACCTTATTTTTGGCTCTAATTTGAATAA GCTGAGTAAAACCACCAAAGATCAGTTATAGGATAAAAATGGCAT CTCTAACCATAACACAGGAGAATTGGAAGGAGCCCTAAGTTGTC ACTCAGTTTAATTTCTTTTAATGGTTAGTTTAGCCTAAAGATTTAT CTGCATATTCTTTTTCCCATGTGGCTCTACTCATTTGCAACTGAAT TTAATGTTATAACTCATCTAGTGAGACCAACTTACTAAATTTTTA GTATGCACTGAAAGTTTTTATCCAACAATTATGTTTATTTTAAGC AAAATTTTAAGAAAGTTTTGAAATTCATAAAGCATTTGGTTTTAA ACTATTTTAAGAATATAGTACTCGGTCAGGTATGACGGCTCACG CCTGTAATCCCAGCACTTTGGGAGGCCGAAACAGGCCGAATCACT TGAGCCCAGGAGTTCAAGACCAACATGGGCAATGTGGCGAAACT CCATCTCTACAAAAAATGCAAAAATAAAAAATATAGTACTCAAG TATTCTTGATCCTGTGTTTTCAAAACTAGAATTTGTAATGCAATG GAGCTCAGTCTAATAAAAAAAGAGGTTTTGGTATTAAAAGTTCAT ACATTAGACAGTATCAGCCAAAATTTGAGTTAGCAACACTGTTTT CTTTACGAGAGGGTCTCACCCAAATTTATGGGGAGAAATCTATTT CTCAAAAAAATAATCTTCTTTTACAGAAATGTTGAGTAAGGTG ACATTTTGAGCGCTAATAAGCAAAAGAGCATGCAGTGCTGTTGA ATAACCCTCACTTGGAGAACCAAGAGAATCCTGTCGTTTAATGC TATATTTTAATTTCAACAAGTTGTTTCAATTTAACTGGTAGAATGTCA GTCCAATCTCCAATGAGAACATGAGCAAATAGACCTTTCCAGGT TGAAAGTGAAACATACTGGGTTTTCTGTAAGTTTTTCTCATGGCT TCATCTCTATCTTTACTTTCTCTTGAATATGCTACACAAAGTTCTT TATTACTACATACTAAAGTTTGCATTCCAGGGATATTGACTGTAC ATATTTATGTATATGTACCATGTTGTTACATGTAAACAAACTTCA ATTTGAAGTGACGCTATTATGTGGTATCCATGTGTATCGACCATG TGCCATATATCAATTATGGTCACTAGAAAGTCTCTTTATGATACT TTTTATTGTACTGTTTTTCAATTTCACTTGCAAAATTTTGCAGAATT CCTCCTTTCTACCCATAAATTACATATATTTTTCTTCTTTAGTCAT GGAGAACTCCCCCCTCATCTCTTCCCTATTATCTTTCCCTGTGTA CTGGTATTATTAAAAAGACATTACATACGCAAGTCTTTCTCGACA ATCAAGAATGTTATTAATGTGTAATACTGAGCACTTTACTTCTTA ATAAAAACTTGATATAGTAGCA (SEQ ID NO: 244)</p>
	transcript ENST0000 0502363.1	<p>ATGTCTTCTCTCTCTTACAGCTCTTCAAATTCATCAATTTTAACAG GACCATGAGCCAGCTCTCGACAACCATGTCTCGATGTGCCAAAG ACCTGTTTGGCTTTGCTATTATGTTCTTCATTATTTTCTAGCGTA TGCTCAGTTGGCATACTTGTCTTTGGCACTCAGGTCGATGACTT CAGTACTTTCCAAGAGTGTATCTTCACTCAATTCGGTATCATTTT GGCGATATCAACTTTGCAGAGATTGAGGAAGCTAATCGAGTTT TGGGACCAATTTATTTCACTACATTTGTGTTCTTTATGTTCTTCAT TCTTTTGAATATGTTTTTGGCTATCATCAATGATACTTACTCTGAA GTGAAATCTGACTTGGCACAGCAGAAAGCTGAAATGGAAGTCTC AGATCTTATCAGAAAGGGCTACCATAAAGCTTTGGTCAAACATAA AACTGAAAAAATAACCGTGGATGACATTTTCAAGAGAGTCTGCGG CAAGGAGGAGGCAAGTTAACTTTGACGAAGTTCGACAAGATCT CAAAGGGAAGGGCCATACTGATGCAGAGATTGAGGCAATATTCA CAAAGTACGACCAAGATGGAGACCAAGAACTGACCGAACATGA ACATCAGCAGATGAGAGACGACTTGGAGAAAGAGAGGGAGGAC CTGGATTTGGATCACAGTTCTTTACCACGTCCCATGAGCAGCCGA</p>

		AGTTTCCCTCGAAGCCTGGATGACTCTGAGGAGGATGACGATGA AGATAGCGGACATAGCTCCAGAAGGAGGGGAAGCATTCTAGTG GCGTTTCTTACGAAGAGTTTCAAGTCCTGGTGAGACGAGTGGAC CGGATGGAGCATTCCATCGGCAGCATAGTGTCCAAGATTGACGC CGTGATCGTGAAGCTAGAGATTATGGAGCGAGCCAACTGAAGA GGAGGGAGGTGCTGGGAAGGCTGTTGGATGGGGTGGCCGAGGA TGAAAGGCTGGGTCTGTGACAGTGAAATCCATAGGGAACAGATG GAACGGCTAGTACGTGAAGAGTTGGAACGCTGGGAATCCGATGA TGCAGCTTCCCAGATCAGTCATGGTTTAGGCACGCCAGTGGGAC TAAATGGTCAACCTCGCCCCAGAAGCTCCCGCCCATCTTCCTCCC AATCTACAGAAGGCATGGAAGGTGCAGGTGGAAATGGGAGTTCT AATGTCCACGTATGATATGTGTGTTT (SEQ ID NO: 245)
transcript ENST0000 0506367.1		GAATGATAGGGGAAAGGAAGGCAAGGGTGAGAGAAGACCTTGT GTGAATTTGTCCAAAATGTTTATCCACAGGAACAATCCCTTTGTG AAGGCTGCTGGTATGTGAATGTGTGCCGGTTCCTTGGGGCGTTC ATTTGGATCTTTCTGTGTTCCAGTGACCTACGGCATGATGAGCTC CAATGTGTACTACTACACCCGGATGATGTCACAGCTCTTCCTAGA CACCCCCGTGTCCAAAACGGAGAAAATACTTTAAACTCTGT CTTCCATGGAAGACTTCTGGAAGTTCACAGAAGGCTCCTTATTGG ATGGGCTGTACTGGAAGATGCAGCCCAGCAACCAGACTGAAGCT GACAACCGAAGTTTCATCTTCTATGAGAACCTGCTGTTAGGGGT CCACGAATACGGCAACTCCGAGTCAGAAATGGATCCTGCTCTAT CCCCAGGACTTGAGAGATGAAATTAAGAGTGCTATGATGTCT ACTCTGTCAGTAGTGAAGATAGGGCTCCCTTTGGGCCCCGAAAT GGAACCGCTTGGATCTACACAAGTGAAAAAGACTTGAATGGTAG TAGCCACTGGGGAATCATTGCAACTTATAGTGAGCTGGCTATT ATCTGGATTGTCAAGAACAAGAGAGGAAACAGCTGCACAAGTT GCTAGCCTCAAGAAAAATGTCTGGCTGG (SEQ ID NO: 246)
transcript ENST0000 0506727.1		CCAGTCGGCGGCGGGGACCCGCTGCATCGCCACCTCCCCCTGGA AGGGCAGCCGCCCCGAGTGGCCTGGGCGGAGAGGCTGGTTCGCG GGCTGCGAGGTCTCTGGGGAACAAGACTCATGGAGGAAAGCAG CACTAACCGAGAGAAATACCTTAAAGTGTTTTACGGGAACTGG TCACATACCTCCTTTTTCTCATAGTCTTGTGCATCTGAACAATCCC TTTGTGAAGGCTGCTGGTATGTGAATGTGTGCCGGTTCCTTGGG GCGTTCATTTGGATCTTTCTGTGTTCCAGTGACCTACGGCATGAT GAGCTCCAATGTGTACTACTACACCCGGATGATGTCACAGCTCTT CCTAGACACCCCCGTGTCCAAAACGGAGAAAATACTTTAAAA CTCTGTCTTCCATGGAAGACTTCTGGAAGTTCACAGAAGGCTCCT TATTGGATGGGCTGTACTGGAAGATGCAGCCCAGCAACCAGACT GAAGCTGACAACCGAAGTTTCATCTTCTATGAGAACCTGCTGTTA GGGTTCCACGAATAC (SEQ ID NO: 247)
transcript ENST0000 0508588.5		AATGGTAGTAGCCACTGGGGAATCATTGCAACTTATAGTGAGC TGGCTATTATCTGGATTTGTCAAGAACAAGAGAGGAAACAGCTG CACAAGTTGCTAGCCTCAAGAAAAATGTCTGGCTGGACCGAGGA ACCAGGGCAACTTTTATTGACTTCTCAGTGTACAACGCCAACATT AACCTGTTCTGTGTGGTCAGCTGTCAGTGGTAGCTATAGGAATTA ACATATACAGAACATCAAATGTGGAGGTGCTACTACAGTTTCTG GAAGATCAAAATACTTTCCCCAACTTTGAGCATCTGGCATATTGG CAGATACAGTTCAACAATATAGCTGCTGTCACAGTATTTTTTGTG TGGATTAAGCTCTTCAAATTCATCAATTTTAACAGGACCATGAGC CAGCTCTCGACAACCATGTCTCGATGTGCCAAAGACCTGTTTGGC TTTGCTATTATGTTCTTCATTATTTTCTAGCGTATGCTCAGTTGG CATACCTTGTCTTTGGCACTCAGGTCGATGACTTCAGTACTTTCC AAGAGTGTATCTTCACTCAATTCCGTATCATTTTGGGCGATATCA ACTTTGCAGAGATTGAGGAAGCTAATCGAGTTTTTGGGACCAATT TATTTCACTACATTTGTGTTCTTTATGTTCTTCATTCTTTTGAATA TGTTTTTGGCTATCATCAATGATACTTACTCTGAAGTGAAATCTG

		<p>ACTTGGCACAGCAGAAAGCTGAAATGGAACCTCTCAGATCTTATC AGAAAGGGCTACCATAAAGCTTTGGTCAAACCTAAAACCTGAAAAA AAATACCGTGGATGACATTTTCAGAGAGTCTGCGGCAAGGAGGAG GCAAGTTAAACTTTGACGAACTTCGACAAGATCTCAAAGGGGAAG GGCCATACTGATGCAGAGATTGAGGCAATATTCACAAAGTACGA CCAAGATGGAGACCAAGAAGCTGACCGAACATGAACATCAGCAG ATGAGAGACGACTTGGAGAAAGAGAGGGGAGGACCTGGATTTGG ATCACAGTTCTTTACCACGTCCCATGAGCAGCCGAAGTTTCCCTC GAAGCCTGGATGACTCTGAGGAGGATGACGATGAAGATAGCGG A CATAGCTCCAGAAGGAGGGGAAGCATTCTAGTGGCGTTTCTT A CGAAGAGTTTCAAGTCCTGGTGAGACGAGTGGACCGGATGGAG CATTCCATCGGCAGCATAGTGTCCAAGATTGACGCCGTGATCGT GAAGCTAGAGATTATGGAGCGAGCCAACTGAAGAGGAGGGAG GTGCTGGGAAGGCTGTTGGATGGGGTGGCCGAGGATGAAAGGCT GGGTCGTGACAGTGAAATCCATAGGGAACAGATGGAACGGCTA GTACGTGAAGAGTTGGAACGCTGGGAATCCGATGATGCAGCTTC CCAGATCAGTCATGGTTTAGGCACGCCAGTGGGACTAAATGGTC AACCTCGCCCCAGAAGCTCCCGCCCATCTTCTCCCAATCTACAG AAGGCATGGAAGGTGCAGGTGGAATGGGAGTTCTAATGTCCAC GTATGATATGTGTGTTTCAGTATGTGTGTTTCTAATAAGTGAGGA AGTGGCTGTCCTGAATTGCTGTAACAAGCACACTATTTATATGCC CTGACCACCATAGGATGCTAGTCTTTGTGACCGATTGCTAATCTT CTGCACTTTAATTTATTTTATATAAACTTTACCCA (SEQ ID NO: 248)</p>
transcript ENST0000 0511337.5		<p>ATACTTTCCCAACTTTGAGCATCTGGCATATTGGCAGATACAGT TCAACAATATAGCTGCTGTCACAGTATTTTTTGTCTGGATTAAAGC TCTTCAAATTCATCAATTTTAAACAGGACCATGAGCCAGCTCTCGA CAACCATGTCTCGATGTGCCAAAGACCTGTTTGGCTTTGCTATTA TGTTCTTCATTATTTTCTAGCGTATGCTCAGTTGGCATACCTTGT CTTTGGCACTCAGGTCGATGACTTCAGTACTTTCCAAGAGTGTAT AATATGTTTTTGGCTATCATCAATGATACTTACTCTGAAGTGAAA TCTGACTTGGCACAGCAGAAAGCTGAAATGGAACCTCTCAGATCT TATCAGAAAAGGGCTACCATAAAGCTTTGGTCAAACCTAAAACCTGA AAAAAAATACCGTGGATGACATTTTCAGAGAGTCTGCGGCAAGGA GGAGGCAAGTTAACTTTGACGAACTTCGACAAGATCTCAAAGG GAAGGGCCATACTGATGCAGAGATTGAGGCAATATTCACAAAGT A CGACCAAGATGGAGACCAAGAAGCTGACCGAACATGAACATCA GCAGATGAGAGACGACTTGGAGAAAAGAGAGGGGAGGACCTGGAT TTGGATCACAGTTCTTTACCACGTCCCATGAGCAGCCGAAGTTTC CCTCGAAGCCTGGATGACTCTGAGGAGGATGACGATGAAGATAG CGGACATAGCTCCAGAAGGAGGGGAAGCATTCTAGTGGCGTTT CTTACGAAGAGTTTCAAGTCCTGGTGAGACGAGTGGACCGGATG GAGCATTCCATCGGCAGCATAGTGTCCAAGATTGACGCCGTGAT CGTGAAGCTAGAGATTATGGAGCGAGCCAACTGAAGAGGAGG GAGGTGCTGGGAAGGCTGTTGGATGGGGTGGCCGAGGATGAAA GGCTGGGTCTGTGACAGTGAAATCCATAGGGAACAGATGGAACG GCTAGTACGTGAAGAGTTGGAACGCTGGGAATCCGATGATGCAG CTTCCCAGATCAGTCATGGTTTAGGCACGCCAGTGGGACTAAAT GGTCAACCTCGCCCCAGAAGCTCCCGCCCATCTTCTCCCAATCT A CAGAAGGCATGGAAGGTGCAGGTGGAATGGGAGTTCTAATG TCCACGTATGATATGTGTGTTTCAGTATGTGTGTTTCTAATAAGT GAGGAAGTGGCTGTCCTGAATTGCTGTAACAAGCACACTATTTA TATGCCCTGACCACATAGGATGCTAGTCTTTGTGACCGATTGCT AATCTTCTGCACTTTAATTTATTTTATATAAACTTTACCCATGGTT CAAAGATTTTTTTTTCTTTTCTCATATAAGAAA (SEQ ID NO: 249)</p>
transcript ENST0000 0512858.1		<p>ACAGTTCAACAATATAGCTGCTGTCACAGTATTTTTTGTCTGGAT TAAGCTCTTCAAATTCATCAATTTTAAACAGGACCATGAGCCAGCT CTCGACAACCATGTCTCGATGTGCCAAAGACCTGTTTGGCTTTGC</p>

		TATTATGTTCTTCATTATTTTCCTAGCGTATGCTCAGTTGGCATACTTGTCCTTTGGCACTCAGGTCGATGACTTCAGTACTTTCCAAGAGTGTATAATATGTTTTTGGCTATCATCAATGATACTTACTCTGAAGTGAAATCTGACTTGGCACAGCAGAAAGCTGAAATGGAAGTCTCAGATCTTATCAGAAAGGGCTACCATAAAGCTTTGGTCAAACATAAACTGAAAAAAAATACCGTGGATGACATTTTCAGAGAGTCTGCGGC AAGGAGGAGGCAAGTTAACTTTGACGAACTTCGACAAGATCTCAAAGGGTGAGAATCATGCTTCCTGAGGTTCTGAAAAATTCCTGCTTCTAAAGATAAATTCCTGGTGATAAGAGTATTTCTAGCCCAAGGGCTCATACAGATACTTTTTTTTTTTTTTTTCCAGAGGCAGGTATCTTCTGGAACATGTTATAAGAGGAAAACCTTGCCCCCATTTGGTGATTTCTCCTTTCTCCTGCATTTTGATGTCTCTGTGTTGAGGGTGAAC TGGGTACAAGGAATGATTTTTATCTGTATCCTCTCTCTAATTTCA GGAAGGGCCATACTGATGCAGAGATTGAGGCAATATTCACAAAGTACGACCAAGATGGAGACCAAGAAGTACCGAACATGAACATCAGCAGATGAGAGACGACTTGGAGAAAGAGAGGGAGGACCTGGA TTTGGATCACAGTCTTTTACCACGTCCCATGAGCAGCCGAAGTTT CCTCGAAGCCTGGATGACTCTGAGGAGGATGACGATGAAGATA GCGGACATAGCTCCAGAAGGAGGGGAAGCATTTCTAGTGGCGTT TCTTACGAAGAGTTTCAAGTCTGGTGAGACGAGTGACCGGAT GGAGCATTCCATCGGCAGCATAGTGTCCAAGATTGACGCCGTGATCGTGAAGCTAGAGATTATGGAGCGAGCCAACTGAAGAGGAG GGAGGTGCTGGGAAGGCTGTTGGATGGGGTGGCCGAGGATGAA AGGCTGGGTGCTGACAGTGAATCCATAGGGAACAGATGGAAC GGCTAGTACGTGAAGAGTTGGAACGCTGGGAATCCGATGATGCA GCTTCCCAGATCAGTCATGGTTTAGGCACGCCAGTGGGACTAAA TGGTCAACCTCGCCCCAGAAGCTCCCGCCCATCTTCCTCCCAATC TACAGAAGGCATGGAAGGTGCAGGTGGAATGGGAGTTCTAAT GTCCACGTATGATATGTGTGTTTCAGTATGTGTGTTTCTAATAAG TGAGGAAGTGGCTGTCCTGAATTGCTGTAACAAGCACACTATTT ATATGCCCTGACCACCATAGGATGCTAGTCTTTGTGACCGATTGC TAATCTTCTGCACTTTAATTTATTTTATATAAACTTTACCCATGGT T (SEQ ID NO: 250)
Translation modulation mechanism		
PKD2 5' UTR sequence (EN ST00000237596 .7	AGGCGGCGGCGGGCGCCGGGAAGAAAGGAACATGGCTCCTGAG GCGCACAGCGCCGAGCGCGGCGCCGCGCACCCGCGCGCCGGAC GCCAGTGACCGCG (SEQ ID NO: 251)	

Table 4: PKD2 ASO sequences

SEQ ID	Event	Sequence	Chr	Oligo Start (chr coordinate)	Oligo End (chr coordinate)
1	Alt 5'ss	GTACTTTCAAAGTTATTT	chr4	88036361	88036379
2	Alt 5'ss	GAGAGGTACTTTCAAAGT	chr4	88036366	88036384
3	Alt 5'ss	TGATAGAGAGGTACTTTC	chr4	88036371	88036389
4	Alt 5'ss	TTCTGTGATAGAGAGGTA	chr4	88036376	88036394
5	Alt 5'ss	CAATTTTCTGTGATAGAG	chr4	88036381	88036399
6	Alt 5'ss	ATGAACAATTTTCTGTGA	chr4	88036386	88036404
7	Alt 5'ss	GCCAAATGAACAATTTTC	chr4	88036391	88036409
8	Alt 5'ss	ATGAAGCCAAATGAACAA	chr4	88036396	88036414
9	Alt 5'ss	AAATGATGAAGCCAAATG	chr4	88036401	88036419
10	Alt 5'ss	CATTGAAATGATGAAGCC	chr4	88036406	88036424
11	Alt 5'ss	TCATGCATTGAAATGATG	chr4	88036411	88036429
12	Alt 5'ss	GATACTCATGCATTGAAA	chr4	88036416	88036434
13	Alt 5'ss	CTGTGATACTCATGCAT	chr4	88036421	88036439
14	Alt 5'ss	AGGTCCTGTCGATACTCA	chr4	88036426	88036444

223	uORF	CGCCUCAGGAGCCAUGUU	chr4	88007662	88007680
224	uORF	UGCGCCUCAGGAGCCAUG	chr4	88007664	88007682
225	uORF	UGUGCGCCUCAGGAGCCA	chr4	88007666	88007684
226	uORF	CUGUGCGCCUCAGGAGCC	chr4	88007667	88007685

Table 6: Exemplary Mouse U7 vector sequence

Region	Sequence
Promoter sequence (Mouse U7 promoter)	cccacaucgcccacacuuuaaguccgauucacuucggcuuuagcuccaagccuuuaaauucucgc gaagcucuuuuuuuuuuuuuuuaacaacauaggagcugugauuaggcuguuuucagccaauacagcacu gacucauuugcauagccuuuacaagcggucacaaacucaagaagagcgguuuuuuauagucuuu uagaauuuuuuuuauucgaaccgaauaaggaacugugcuuugugauucacauacaguggaggggu guggaaauggcaccuugaucucacccucaucgaaaguggaguugauguccuucccuggcucgcua cagacgcacuuccgc (SEQ ID NO: 252)
Wild-type U7 Antisense sequence	AAGUGUUACAGCUCUUUAG (SEQ ID NO: 253)
Wild-type U7 non- coding RNA sequence	<u>AAUUUGUCUAGCAGGUUUUCUGACUUCGGUCGGAAAACCCCU</u> (SEQ ID NO: 254)
ASO sequences replacing the Wild- type U7 Antisense sequence	GTACTTTCAAAGTTATTT (SEQ ID NO: 1) ATAAATCGAACCATCGTA (SEQ ID NO: 50) TTTCTTCCCGGCGCCCGC (SEQ ID NO: 100)
Modified U7 snRNA (smOPT) non-coding RNA sequence	<u>AAUUUUUGGAGCAGGUUUUCUGACUUCGGUCGGAAAACCCCU</u> (SEQ ID NO: 255)
smOPT sequence	<u>AAUUUUUGGAG</u> (SEQ ID NO: 229)
3' regulatory sequence	cccauuuacacuggucuaacaugaaagcaaaacaguucucuuccccgcuccccggugugugagagg ggcuuuuauccuucucugguuuuccuaggaacgcguauugcuagagccacgcucugagacuucc gccucgugcggucccgcuuccuucugccuccucugg (SEQ ID NO: 256)
Exemplary Full sequence of wild-type U7 snRNA	cccacaucgcccacacuuuaaguccgauucacuucggcuuuagcuccaagccuuuaaauucucgc gaagcucuuuuuuuuuuuuuuuaacaacauaggagcugugauuaggcuguuuucagccaauacagcacu gacucauuugcauagccuuuacaagcggucacaaacucaagaagagcgguuuuuuauagucuuu uagaauuuuuuuuauucgaaccgaauaaggaacugugcuuugugauucacauacaguggaggggu guggaaauggcaccuugaucucacccucaucgaaaguggaguugauguccuucccuggcucgcua cagacgcacuuccgc AAGUGUUACAGCUCUUUAGAAUUUGUCUAGC <u>AGGUUUUCUGACUUCGGUCGGAAAACCCCU</u> cccauuuacacuggucuaaca ugaaagcaaaacaguucucuuccccgcuccccggugugugagaggggcuuuuaguccuucucuggu uuccuaggaacgcguauugcuagagccacgcucugagacuuccgccucgugcggucccgcuuc cuuucugccuccucugg (SEQ ID NO: 257)
Exemplary Full sequence of modified U7 snRNA (smOPT)	cccacaucgcccacacuuuaaguccgauucacuucggcuuuagcuccaagccuuuaaauucucgc gaagcucuuuuuuuuuuuuuuuaacaacauaggagcugugauuaggcuguuuucagccaauacagcacu gacucauuugcauagccuuuacaagcggucacaaacucaagaagagcgguuuuuuauagucuuu uagaauuuuuuuuauucgaaccgaauaaggaacugugcuuugugauucacauacaguggaggggu guggaaauggcaccuugaucucacccucaucgaaaguggaguugauguccuucccuggcucgcua cagacgcacuuccgc AAGUGUUACAGCUCUUUAGAAUUUUUGGAGC <u>AGGUUUUCUGACUUCGGUCGGAAAACCCCU</u> cccauuuacacuggucuaaca ugaaagcaaaacaguucucuuccccgcuccccggugugugagaggggcuuuuaguccuucucuggu uuccuaggaacgcguauugcuagagccacgcucugagacuuccgccucgugcggucccgcuuc cuuucugccuccucugg (SEQ ID NO: 258)
Full sequence of modified U7 snRNA (smOPT) containing an ASO sequence	cccacaucgcccacacuuuaaguccgauucacuucggcuuuagcuccaagccuuuaaauucucgc gaagcucuuuuuuuuuuuuuuuaacaacauaggagcugugauuaggcuguuuucagccaauacagcacu gacucauuugcauagccuuuacaagcggucacaaacucaagaagagcgguuuuuuauagucuuu uagaauuuuuuuuauucgaaccgaauaaggaacugugcuuugugauucacauacaguggaggggu guggaaauggcaccuugaucucacccucaucgaaaguggaguugauguccuucccuggcucgcua cagacgcacuuccgc AS

replacing the antisense sequence of U7 snRNA (Exemplary sequences of [ASO sequence] include those in Table 4 and Table 5)	<u>O sequence</u> <u>]AAUUUUUGGAGCAGGU</u> <u>UUUCUGACUUCGGUCGGAAAACCCCU</u> cccauuuacacuggucuaacaugaaag caaaacaguucucuccccgcuccccggugugugagaggggcuuugauccuucucugguuuccua ggaaacgcguaugugcuagagccacgcucugagacuuccgccucgugcggucccgcuuccuuuc gccuccucugg (SEQ ID NOS 252 and 259, respectively)
Exemplary full sequence of modified U7 snRNA (smOPT) containing an ASO sequence replacing the antisense sequence of U7 snRNA	cccacaucgccugccacuacuaaaguccgauucacuucggcuuuagcuccaagccuuuaucucgc gaagcucuuuuuuuuuuuuuuaacaacauaggagcugugauuggcuguuuucagccaucagcacu gacucauuugcauagccuuuacaagcggucacaaacuagaagagcgguuuuauagucuuu uagaauauuguuuuaucaaccgaauaaggaacugugcuuugugauucacauacaguggaggggu guggaaauggcaccuugaucucacccuacucgaaaguggaguugauguccuucccugggcucgcu cagacgcacuuccgc <u>GUACUUUCAAGUUAUUUAAUUUUUGGAGCAGG</u> <u>UUUUCUGACUUCGGUCGGAAAACCCCU</u> cccauuuacacuggucuaacaugaa agcaaaacaguucucuccccgcuccccggugugugagaggggcuuugauccuucucugguuucc uaggaaacgcguaugugcuagagccacgcucugagacuuccgccucgugcggucccgcuuccuu cugccuccucugg (SEQ ID NO: 260)
Exemplary full sequence of modified U7 snRNA (smOPT) containing an ASO sequence replacing the antisense sequence of U7 snRNA	cccacaucgccugccacuacuaaaguccgauucacuucggcuuuagcuccaagccuuuaucucgc gaagcucuuuuuuuuuuuuuuaacaacauaggagcugugauuggcuguuuucagccaucagcacu gacucauuugcauagccuuuacaagcggucacaaacuagaagagcgguuuuauagucuuu uagaauauuguuuuaucaaccgaauaaggaacugugcuuugugauucacauacaguggaggggu guggaaauggcaccuugaucucacccuacucgaaaguggaguugauguccuucccugggcucgcu cagacgcacuuccgc <u>AUAAUUCGAACCAUCGUAAAUUUUUUGGAGCAGG</u> <u>UUUUCUGACUUCGGUCGGAAAACCCCU</u> cccauuuacacuggucuaacaugaa agcaaaacaguucucuccccgcuccccggugugugagaggggcuuugauccuucucugguuucc uaggaaacgcguaugugcuagagccacgcucugagacuuccgccucgugcggucccgcuuccuu cugccuccucugg (SEQ ID NO: 261)
Exemplary full sequence of modified U7 snRNA (smOPT) containing an ASO sequence replacing the antisense sequence of U7 snRNA	cccacaucgccugccacuacuaaaguccgauucacuucggcuuuagcuccaagccuuuaucucgc gaagcucuuuuuuuuuuuuuuaacaacauaggagcugugauuggcuguuuucagccaucagcacu gacucauuugcauagccuuuacaagcggucacaaacuagaagagcgguuuuauagucuuu uagaauauuguuuuaucaaccgaauaaggaacugugcuuugugauucacauacaguggaggggu guggaaauggcaccuugaucucacccuacucgaaaguggaguugauguccuucccugggcucgcu cagacgcacuuccgc <u>UUUCUUCGCGCGCCCGCAAUUUUUGGAGCAG</u> <u>GUUUUCUGACUUCGGUCGGAAAACCCCU</u> cccauuuacacuggucuaacauga aagcaaaacaguucucuccccgcuccccggugugugagaggggcuuugauccuucucugguuuc cuaggaaacgcguaugugcuagagccacgcucugagacuuccgccucgugcggucccgcuuccuu ucugccuccucugg (SEQ ID NO: 262)

EXAMPLES

[00348] The present disclosure will be more specifically illustrated by the following Examples.

However, it should be understood that the present disclosure is not limited by these examples in any manner.

Example 1: Identification of NMD-inducing Exon Inclusion Events in Transcripts by RNAseq using Next Generation Sequencing

[00349] Whole transcriptome shotgun sequencing was carried out using next generation sequencing to reveal a snapshot of transcripts produced by the genes described herein to identify NIE inclusion events. For this purpose, polyA⁺ RNA from nuclear and cytoplasmic fractions of human cells was isolated and cDNA libraries were constructed using Illumina's TruSeq