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(54) Title: ANTISENSE OLIGONUCLEOTIDES TARGETING ATXN3

(57) Abstract: The present invention relates to antisense LNA oligonucleotides (oligomers) complementary to *ATXN3* pre-mRNA sequences, which are capable of inhibiting the expression of ATXN3 protein. Inhibition of *ATXN3* expression is beneficial for the treatment of spinocerebellar ataxia.

ANTISENSE OLIGONUCLEOTIDES TARGETING ATXN3

FIELD OF INVENTION

The present invention relates to antisense LNA oligonucleotides (oligomers) complementary to *ATXN3* pre-mRNA sequences, which are capable of inhibiting the expression of ATXN3. Inhibition of *ATXN3* expression is beneficial for the treatment of spinocerebellar ataxia, such as spinocerebellar ataxia 3 (Machado-Joseph disease (MJD)).

BACKGROUND

Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease (MJD), is one of nine polyglutamine expansion diseases and the most common dominantly inherited ataxia in the world. While certain symptoms in SCA3 may respond to symptomatic therapy, there is still no effective treatment for this relentlessly progressive and fatal neurodegenerative disease. The disease is caused by a CAG repeat expansion in the *ATXN3* gene that encodes an abnormally long polyglutamine tract in the disease protein, ATXN3 (Ataxin 3). The toxic ataxin-3 protein is associated with aggregates which are frequently observed in the brain tissue of SCA3 patients.

Moore et al. reported that antisense oligonucleotides (ASOs) targeting *ATXN3* were capable of reducing levels of the pathogenic ATXN3 protein both in human disease fibroblasts and in a mouse model expressing the full-length human mutant *ATXN3* gene (Moore et al., Mol Ther Nucleic Acids. 2017;7:200-210). Therefore, ASO-mediated targeting of *ATXN3* was suggested as therapeutic approach for SCA3.

Swayze *et al.* (Nucleic Acids Res. 2007;35(2):687-700. Epub 2006 Dec 19), reports that antisense oligonucleotides containing locked nucleic acid have the potential to improve potency but cause significant toxicity in animals (hepatotoxicity).

Toonen et al. used antisense oligonucleotides to mask predicted exonic splicing signals of *ATXN3*, resulting in exon 10 skipping from ATXN3 pre-mRNA. The skipping of exon 10 led to formation of a truncated ataxin-3 protein lacking the toxic polyglutamine expansion, but retaining its ubiquitin binding and cleavage function (Toonen et al., Molecular Therapy - Nucleic Acids, 2017, Volume 8: 232-242).

WO2013/138353, WO2015/017675, WO2018/089805 & WO2019/217708 disclose antisense oligonucleotides targeting human ATXN3 mRNA for use in the treatment of SCA3.

OBJECTIVE OF THE INVENTION

The present invention identifies regions of the ATXN3 transcript (*ATXN3*) for antisense inhibition *in vitro* or *in vivo*, and provides for antisense oligonucleotides, including LNA gapmer oligonucleotides, which target these regions of the *ATXN3* premRNA or mature mRNA. The present invention identifies oligonucleotides which inhibit human ATXN3 which are useful in the treatment of spinocerebellar ataxia.

STATEMENT OF THE INVENTION

The invention provides for an antisense oligonucleotide, 10-30 nucleotides in length, targeting a mammalian ATXN3 (Ataxin 3) target nucleic acid, wherein the antisense oligonucleotide is capable of inhibiting the expression of mammalian ATXN3 in a cell which is expressing mammalian ATXN3.

The mammalian ATXN3 target nucleic acid may be, e.g., a human, monkey or mouse ATXN3 target nucleic acid.

The invention provides for an LNA gapmer antisense oligonucleotide, 10-30 nucleotides in length, wherein said antisense oligonucleotide comprises a contiguous nucleotide sequence 10 – 30 nucleotides in length, wherein the contiguous nucleotide sequence is at least 90% complementary, such as fully complementary, to SEQ ID NO 1, wherein the antisense oligonucleotide is capable of inhibiting the expression of human ATXN3 in a cell which is expressing human ATXN3.

The invention provides for an antisense oligonucleotide which comprises a contiguous nucleotide sequence selected from group consisting of the Oligonucleotide Base Sequences shown in tables 2, 4, 5 and 6, wherein the antisense oligonucleotide is capable of inhibiting the expression of human ATXN3 in a cell which is expressing human ATXN3; or a pharmaceutically acceptable salt thereof.

The invention provides for an LNA gapmer antisense oligonucleotide which comprises a contiguous nucleotide sequence selected from group consisting of the Oligonucleotide Base Sequences shown in tables 2, 4, 5 and 6, wherein the LNA gapmer antisense oligonucleotide is capable of inhibiting the expression of human ATXN3 in a cell which is expressing human ATXN3; or a pharmaceutically acceptable salt thereof.

The invention provides for an antisense oligonucleotide which comprises a contiguous nucleotide sequence SEQ ID NO: 1122, wherein the antisense oligonucleotide is capable of inhibiting the expression of human ATXN3 in a cell which is expressing human ATXN3; or a pharmaceutically acceptable salt thereof.

The invention provides for an antisense oligonucleotide which comprises a contiguous nucleotide sequence SEQ ID NO: 1813, wherein the antisense oligonucleotide is capable of inhibiting the expression of human ATXN3 in a cell which is expressing human ATXN3; or a pharmaceutically acceptable salt thereof.

The invention provides for an antisense oligonucleotide which comprises a contiguous nucleotide sequence SEQ ID NO: 1812, wherein the antisense oligonucleotide is capable of inhibiting the expression of human ATXN3 in a cell which is expressing human ATXN3; or a pharmaceutically acceptable salt thereof.

The invention provides for an antisense oligonucleotide which comprises a contiguous nucleotide sequence SEQ ID NO: 1809, wherein the antisense oligonucleotide is capable of inhibiting the expression of human ATXN3 in a cell which is expressing human ATXN3; or a pharmaceutically acceptable salt thereof.

The invention provides for an antisense oligonucleotide which comprises a contiguous nucleotide sequence SEQ ID NO: 1807, wherein the antisense oligonucleotide is capable of inhibiting the expression of human ATXN3 in a cell which is expressing human ATXN3; or a pharmaceutically acceptable salt thereof.

In some embodiments, the antisense oligonucleotide of the invention is an LNA gapmer antisense oligonucleotide.

The invention provides antisense oligonucleotides according to the invention, such as antisense oligonucleotides 12 – 24, such as 12 – 18 in length, nucleosides in length wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 contiguous nucleotides present in a sequence selected from the Oligonucleotide Base Sequences shown in tables 2, 4, 5 and 6.

The invention provides antisense oligonucleotides according to the invention, such as antisense oligonucleotides 12 – 24, such as 12 – 18 in length, nucleosides in length wherein

the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least 12 contiguous nucleotides present in a sequence selected from the Oligonucleotide Base Sequences shown in tables 2, 4, 5 and 6.

The invention provides antisense oligonucleotides according to the invention, such as antisense oligonucleotides 12 – 24, such as 12 – 18 in length, nucleosides in length wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least 14 contiguous nucleotides present in a sequence selected from the Oligonucleotide Base Sequences shown in tables 2, 4, 5 and 6.

The invention provides antisense oligonucleotides according to the invention, such as antisense oligonucleotides 12 – 24, such as 12 – 18 in length, nucleosides in length wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least 16 contiguous nucleotides present in a sequence selected from the Oligonucleotide Base Sequences shown in tables 2, 4, 5 and 6.

The invention provides antisense oligonucleotides according to the invention, such as antisense oligonucleotides 12 – 24, such as 12 – 18 in length, nucleosides in length wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising the contiguous nucleotides present in a sequence selected from the Oligonucleotide Base Sequences shown in tables 2, 4, 5 and 6.

The invention provides antisense oligonucleotides according to the invention, such as antisense oligonucleotides 12 – 24, such as 12 – 18 in length, nucleosides in length wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence which is 100% identical to at least 10 contiguous nucleotides present in a sequence selected from SEQ ID NO 4 to SEQ ID NO: 1089; SEQ ID Nos 1099 to 1127; and SEQ ID NO 1137 – 1988; SEQ ID Nos 1099 to 1127; and SEQ ID NO 1137 – 1988.

The invention provides antisense oligonucleotides according to the invention, such as antisense oligonucleotides 12 – 24, such as 12 – 18 in length, nucleosides in length wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence which is 100% identical to at least 12 contiguous nucleotides present in a sequence selected from SEQ ID NO 4 to SEQ ID NO: 1089; SEQ ID Nos 1099 to 1127; and SEQ ID NO 1137 – 1988.

The invention provides antisense oligonucleotides according to the invention, such as antisense oligonucleotides 12 – 24, such as 12 – 18 in length, nucleosides in length wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence which is 100% identical to at least 14 contiguous nucleotides present in a sequence selected from SEQ ID NO 4 to SEQ ID NO: 1089; SEQ ID Nos 1099 to 1127; and SEQ ID NO 1137 – 1988.

The invention provides antisense oligonucleotides according to the invention, such as antisense oligonucleotides 12 – 24, such as 12 – 18 in length, nucleosides in length wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence which is 100% identical to at least 16 contiguous nucleotides present in a sequence selected from The Oligonucleotide Base Sequences shown in tables 2, 4, 5 and 6.

The invention provides antisense oligonucleotides according to the invention, such as antisense oligonucleotides 12 – 24, such as 12 – 18 in length, nucleosides in length wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence which is 100% identical to a sequence selected from The Oligonucleotide Base Sequences shown in tables 2, 4, 5 and 6.

The invention provides for the antisense oligonucleotide disclosed herein, for example an antisense oligonucleotide selected from the group consisting of 1099_1 , 1100_1 , 1101_1 , 1102_1 , 1103_1 , 1104_1 , 1105_1 , 1106_1 , 1107_1 , 1108_1 , 1109_1 , 1110_1 , 1111_1 , 1112_1 , 1113_1 , 1114_1 , 1115_1 , 1116_1 , 1117_1 , 1118_1 , 1119_1 , 1120_1 , 1121_1 , 1122_1 , 1123_1 , 1124_1 , 1125_1 , 1126_1 , and 1127_1.

The invention provides for the antisense oligonucleotide disclosed herein, for example an antisense oligonucleotide selected from the group consisting of the compounds shown in the table in example 2.

The invention provides for the antisense oligonucleotide disclosed herein, for example an antisense oligonucleotide selected from the group consisting of the compounds shown in the table in example 3.

The invention provides for the antisense oligonucleotide disclosed herein, for example an antisense oligonucleotide selected from the group consisting of the compounds shown in the table in example 4.

The invention provides for an antisense oligonucleotide selected from the group consisting of Compound No 1122_62, 1122_67, 1122_33, 1856_1, 1813_1, 1812_1, 1809_2, and 1607_1, a pharmaceutically acceptable salt thereof.

The invention provides for an antisense oligonucleotide of formula ACCcatattttactCTT (Compound No 1856_1), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.

The invention provides for an antisense oligonucleotide of formula CTGtacacttttacaTT (Compound No 1813_1), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.

The invention provides for an antisense oligonucleotide of formula TGtacacttttacatTCC (Compound No 1812_1), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.

The invention provides for an antisense oligonucleotide of formula GtacacttttacattCCC (Compound No 1809_2), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.

The invention provides for an antisense oligonucleotide of formula TTCttcattataccatCAA (Compound No 1607_1), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.

The invention provides for an antisense oligonucleotide of formula AatCtTatttacatcTtCC (Compound No 1122_62), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.

The invention provides for an antisense oligonucleotide of formula AATCttatttacatcTtCC (Compound No 1122_67), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.

The invention provides for an antisense oligonucleotide of formula AatCtTatttacatctTCC (Compound No 1122_33), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.

The oligonucleotide of the invention as referred to or claimed herein may be in the form of a pharmaceutically acceptable salt, such as a sodium of potassium salt.

The invention provides for a conjugate comprising the oligonucleotide according to the invention, and at least one conjugate moiety covalently attached to said oligonucleotide.

The invention provides for a pharmaceutical composition comprising the oligonucleotide or conjugate of the invention and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.

The invention provides for an *in vivo* or *in vitro* method for modulating *ATXN3* expression in a target cell which is expressing *ATXN3*, said method comprising administering an oligonucleotide or conjugate or pharmaceutical composition of the invention in an effective amount to said cell.

The invention provides for a method for treating or preventing a disease comprising administering a therapeutically or prophylactically effective amount of an oligonucleotide, conjugate or the pharmaceutical composition of the invention to a subject suffering from or susceptible to the disease.

In some embodiments, the disease is spinocerebellar ataxia, such as spinocerebellar ataxia 3, such as Machado-Joseph disease (MJD).

The invention provides for the oligonucleotide, conjugate or the pharmaceutical composition of the invention for use in medicine.

The invention provides for the oligonucleotide, conjugate or the pharmaceutical composition of the invention for use in the treatment or prevention of spinocerebellar ataxia, such as spinocerebellar ataxia 3, such as Machado-Joseph disease (MJD).

The invention provides for the use of the oligonucleotide, conjugate or the pharmaceutical composition of the invention, for the preparation of a medicament for treatment or prevention of spinocerebellar ataxia, such as spinocerebellar ataxia 3 such as Machado-Joseph disease (MJD).

FIGURES

Figure 1: Drawing of compound 1122_67 (SEQ ID NO 1122).

Figure 2: Drawing of compound 1813_1 (SEQ ID NO 1813).

Figure 3: Drawing of compound 1856_1 (SEQ ID NO 1856).

Figure 4: Drawing of compound 1812_1 (SEQ ID NO 1812).

Figure 5: Drawing of compound 1809_2 (SEQ ID NO 1809).

Figure 6: Drawing of compound 1607_1 (SEQ ID NO 1607).

Figure 7: Drawing of compound 1122_62 (SEQ ID NO 1122).

Figure 8: Drawing of compound 1122_33 (SEQ ID NO 1122).

Figure 9: Stability of compound 1122_67 and 1813_1, and 5 reference compounds in a 24 hour SVPD assay.

Figure 10. A) WES analysis of GM06153 cells treated with different ASOs to obtain reduction of wild type Ataxin 3 (55 kDa) and polyQ extended Ataxin 3 (77 kDa). B) Analysis of band intensity normalized to HPRT. Wild type Ataxin 3 is represented by the band at 55 kDa, and the polyQ extended Ataxin 3 is represented by the band at 77 kDa. Cells have been treated with 10 uM of ASO for 4 days prior to protein analysis. Data represents cells treated with ASOs in triplicates as mean+-SD. SC, scrambled control oligo.

The chemical drawings are of the protonated form of the antisense oligonucleotide, and it will be understood that each hydrogen on the sulphur atom in the phosphorothioate internucleoside linkage may independently be present of absent. In a salt form, one or more more of the hydrogens may for example be replaced with a cation, such as a metal cation, such as a sodium cation or a potassium cation.

DEFINITIONS

Oligonucleotide

The term "oligonucleotide" as used herein is defined as it is generally understood by the skilled person as a molecule comprising two or more covalently linked nucleosides. Such covalently bound nucleosides may also be referred to as nucleic acid molecules or oligomers. Oligonucleotides are commonly made in the laboratory by solid-phase chemical synthesis followed by purification. When referring to a sequence of the oligonucleotide, reference is made to the sequence or order of nucleobase moieties, or modifications thereof, of the covalently linked nucleotides or nucleosides. The oligonucleotide of the invention is man-made, and is chemically synthesized, and is typically purified or isolated. The oligonucleotide of the invention may comprise one or more modified nucleosides or nucleotides.

Antisense oligonucleotides

The term "Antisense oligonucleotide" as used herein is defined as oligonucleotides capable of modulating expression of a target gene by hybridizing to a target nucleic acid, in particular to a contiguous sequence on a target nucleic acid. The antisense oligonucleotides are not essentially double stranded and are therefore not siRNAs or shRNAs. Preferably, the antisense oligonucleotides of the present invention are single stranded. It is understood that single stranded oligonucleotides of the present invention can form hairpins or intermolecular duplex structures (duplex between two molecules of the same oligonucleotide), as long as the degree of intra or inter self-complementarity is less than 50% across of the full length of the oligonucleotide

Contiguous Nucleotide Sequence

The term "contiguous nucleotide sequence" refers to the region of the oligonucleotide which is complementary to the target nucleic acid. The term is used interchangeably herein with the term "contiguous nucleobase sequence" and the term "oligonucleotide motif sequence" also refered to as "motif sequence". The "motif sequence " may also be referred to as the "Oligonucleotide Base Sequence". In some embodiments all the nucleotides of the oligonucleotide constitute the contiguous nucleotide sequence. In some embodiments the oligonucleotide comprises the contiguous nucleotide sequence, such as a F-G-F' gapmer region, and may optionally comprise further nucleotide(s), for example a nucleotide linker region which may be used to attach a functional group to the contiguous nucleotide sequence. The nucleotide linker region may or may not be complementary to the target nucleic acid. Adventurously, the contiguous nucleotide sequence is 100% complementary to the target nucleic acid.

Nucleotides

Nucleotides are the building blocks of oligonucleotides and polynucleotides, and for the purposes of the present invention include both naturally occurring and non-naturally occurring nucleotides. In nature, nucleotides, such as DNA and RNA nucleotides comprise a ribose sugar moiety, a nucleobase moiety and one or more phosphate groups (which is absent in nucleosides). Nucleosides and nucleotides may also interchangeably be referred to as "units" or "monomers".

Modified nucleoside

The term "modified nucleoside" or "nucleoside modification" as used herein refers to nucleosides modified as compared to the equivalent DNA or RNA nucleoside by the introduction of one or more modifications of the sugar moiety or the (nucleo)base moiety. In a preferred embodiment the modified nucleoside comprise a modified sugar moiety. The term modified nucleoside may also be used herein interchangeably with the term "nucleoside analogue" or modified "units" or modified "monomers". Nucleosides with an unmodified DNA or RNA sugar moiety are termed DNA or RNA nucleosides herein. Nucleosides with modifications in the base region of the DNA or RNA nucleoside are still generally termed DNA or RNA if they allow Watson Crick base pairing.

Modified internucleoside linkages

The term "modified internucleoside linkage" is defined as generally understood by the skilled person as linkages other than phosphodiester (PO) linkages, that covalently couples two nucleosides together. The oligonucleotides of the invention may therefore comprise modified internucleoside linkages. In some embodiments, the modified internucleoside linkage increases the nuclease resistance of the oligonucleotide compared to a phosphodiester linkage. For naturally occurring oligonucleotides, the internucleoside linkage includes phosphate groups creating a phosphodiester bond between adjacent nucleosides. Modified internucleoside linkages are particularly useful in stabilizing oligonucleotides for *in vivo* use, and may serve to protect against nuclease cleavage at regions of DNA or RNA nucleosides in the oligonucleotide of the invention, for example within the gap region of a gapmer oligonucleotide, as well as in regions of modified nucleosides, such as region F and F'.

In an embodiment, the oligonucleotide comprises one or more internucleoside linkages modified from the natural phosphodiester, such one or more modified internucleoside linkages that is for example more resistant to nuclease attack. Nuclease resistance may be determined by incubating the oligonucleotide in blood serum or by using a nuclease resistance assay (e.g. snake venom phosphodiesterase (SVPD)), both are well known in the art. Internucleoside linkages which are capable of enhancing the nuclease resistance of an oligonucleotide are referred to as nuclease resistant internucleoside linkages. In some

embodiments at least 50% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are modified, such as at least 60%, such as at least 70%, such as at least 80 or such as at least 90% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are nuclease resistant internucleoside linkages. In some embodiments all of the internucleoside linkages of the oligonucleotide, or contiguous nucleotide sequence thereof, are nuclease resistant internucleoside linkages. It will be recognized that, in some embodiments the nucleosides which link the oligonucleotide of the invention to a non-nucleotide functional group, such as a conjugate, may be phosphodiester.

A preferred modified internucleoside linkage is phosphorothioate.

Phosphorothioate internucleoside linkages are particularly useful due to nuclease resistance, beneficial pharmacokinetics and ease of manufacture. In some embodiments at least 50% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are phosphorothioate, such as at least 60%, such as at least 70%, such as at least 80% or such as at least 90% of the internucleoside linkages in the oligonucleotide, or contiguous nucleotide sequence thereof, are phosphorothioate. In some embodiments all of the internucleoside linkages of the oligonucleotide, or contiguous nucleotide sequence thereof, are phosphorothioate.

Nuclease resistant linkages, such as phosphorothioate linkages, are particularly useful in oligonucleotide regions capable of recruiting nuclease when forming a duplex with the target nucleic acid, such as region G for gapmers. Phosphorothioate linkages may, however, also be useful in non-nuclease recruiting regions and/or affinity enhancing regions such as regions F and F' for gapmers. Gapmer oligonucleotides may, in some embodiments comprise one or more phosphodiester linkages in region F or F', or both region F and F', which the internucleoside linkage in region G may be fully phosphorothioate. Advantageously, all the internucleoside linkages in the contiguous nucleotide sequence of the oligonucleotide are phosphorothioate linkages.

It is recognized that, as disclosed in EP2 742 135, antisense oligonucleotide may comprise other internucleoside linkages (other than phosphodiester and phosphorothioate), for example alkyl phosphonate / methyl phosphonate internucleosides, which according to EP2 742 135 may for example be tolerated in an otherwise DNA phosphorothioate gap region.

Nucleobase

The term nucleobase includes the purine (e.g. adenine and guanine) and pyrimidine (e.g. uracil, thymine and cytosine) moiety present in nucleosides and nucleotides which form hydrogen bonds in nucleic acid hybridization. In the context of the present invention the term nucleobase also encompasses modified nucleobases which may differ from naturally

occurring nucleobases, but are functional during nucleic acid hybridization. In this context "nucleobase" refers to both naturally occurring nucleobases such as adenine, guanine, cytosine, thymidine, uracil, xanthine and hypoxanthine, as well as non-naturally occurring variants. Such variants are for example described in Hirao et al (2012) Accounts of Chemical Research vol 45 page 2055 and Bergstrom (2009) Current Protocols in Nucleic Acid Chemistry Suppl. 37 1.4.1.

In a some embodiments the nucleobase moiety is modified by changing the purine or pyrimidine into a modified purine or pyrimidine, such as substituted purine or substituted pyrimidine, such as a nucleobased selected from isocytosine, pseudoisocytosine, 5-methyl cytosine, 5-thiozolo-cytosine, 5-propynyl-cytosine, 5-propynyl-uracil, 5-bromouracil 5-thiazolo-uracil, 2-thio-uracil, 2'thio-thymine, inosine, diaminopurine, 6-aminopurine, 2-aminopurine, 2,6-diaminopurine and 2-chloro-6-aminopurine.

The nucleobase moieties may be indicated by the letter code for each corresponding nucleobase, e.g. A, T, G, C or U, wherein each letter may optionally include modified nucleobases of equivalent function. For example, in the exemplified oligonucleotides, the nucleobase moieties are selected from A, T, G, C, and 5-methyl cytosine. Optionally, for LNA gapmers, 5-methyl cytosine LNA nucleosides may be used.

Modified oligonucleotide

The term modified oligonucleotide describes an oligonucleotide comprising one or more sugar-modified nucleosides and/or modified internucleoside linkages. The term chimeric" oligonucleotide is a term that has been used in the literature to describe oligonucleotides with modified nucleosides.

Complementarity

The term "complementarity" describes the capacity for Watson-Crick base-pairing of nucleosides/nucleotides. Watson-Crick base pairs are guanine (G)-cytosine (C) and adenine (A) - thymine (T)/uracil (U). It will be understood that oligonucleotides may comprise nucleosides with modified nucleobases, for example 5-methyl cytosine is often used in place of cytosine, and as such the term complementarity encompasses Watson Crick base-paring between non-modified and modified nucleobases (see for example Hirao et al (2012) Accounts of Chemical Research vol 45 page 2055 and Bergstrom (2009) Current Protocols in Nucleic Acid Chemistry Suppl. 37 1.4.1).

The term "% complementary" as used herein, refers to the number of nucleotides in percent of a contiguous nucleotide sequence in a nucleic acid molecule (e.g. oligonucleotide) which, at a given position, are complementary to (*i.e.* form Watson Crick base pairs with) a contiguous sequence of nucleotides, at a given position of a separate nucleic acid molecule (e.g. the target nucleic acid or target sequence). The percentage is calculated by counting

the number of aligned bases that form pairs between the two sequences (when aligned with the target sequence 5'-3' and the oligonucleotide sequence from 3'-5'), dividing by the total number of nucleotides in the oligonucleotide and multiplying by 100. In such a comparison a nucleobase/nucleotide which does not align (form a base pair) is termed a mismatch. Preferably, insertions and deletions are not allowed in the calculation of % complementarity of a contiguous nucleotide sequence.

The term "fully complementary", refers to 100% complementarity.

Identity

The term "Identity" as used herein, refers to the proportion of nucleotides (expressed in percent) of a contiguous nucleotide sequence in a nucleic acid molecule (e.g. oligonucleotide) which across the contiguous nucleotide sequence, are identical to a reference sequence (e.g. a sequence motif). The percentage of identity is thus calculated by counting the number of aligned bases that are identical (a match) between two sequences (e.g. in the contiguous nucleotide sequence of the compound of the invention and in the reference sequence), dividing that number by the total number of nucleotides in the aligned region and multiplying by 100. Therefore, Percentage of Identity = (Matches x 100)/Length of aligned region (e.g. the contiguous nucleotide sequence). Insertions and deletions are not allowed in the calculation the percentage of identity of a contiguous nucleotide sequence. It will be understood that in determining identity, chemical modifications of the nucleobases are disregarded as long as the functional capacity of the nucleobase to form Watson Crick base pairing is retained (e.g. 5-methyl cytosine is considered identical to a cytosine for the purpose of calculating % identity).

Hybridization

The term "hybridizing" or "hybridizes" as used herein is to be understood as two nucleic acid strands (e.g. an oligonucleotide and a target nucleic acid) forming hydrogen bonds between base pairs on opposite strands thereby forming a duplex. The affinity of the binding between two nucleic acid strands is the strength of the hybridization. It is often described in terms of the melting temperature (T_m) defined as the temperature at which half of the oligonucleotides are duplexed with the target nucleic acid. At physiological conditions T_m is not strictly proportional to the affinity (Mergny and Lacroix, 2003,*Oligonucleotides* 13:515–537). The standard state Gibbs free energy ΔG° is a more accurate representation of binding affinity and is related to the dissociation constant (K_d) of the reaction by $\Delta G^\circ = -RT\ln(K_d)$, where R is the gas constant and T is the absolute temperature. Therefore, a very low ΔG° of the reaction between an oligonucleotide and the target nucleic acid reflects a strong hybridization between the oligonucleotide and target nucleic acid. ΔG° is the energy associated with a reaction where aqueous concentrations are 1M, the pH is 7, and the

temperature is 37°C. The hybridization of oligonucleotides to a target nucleic acid is a spontaneous reaction and for spontaneous reactions ΔG° is less than zero. ΔG° can be measured experimentally, for example, by use of the isothermal titration calorimetry (ITC) method as described in Hansen et al., 1965,*Chem. Comm.* 36–38 and Holdgate et al., 2005, *Drug Discov Today*. The skilled person will know that commercial equipment is available for ΔG° measurements. ΔG° can also be estimated numerically by using the nearest neighbor model as described by SantaLucia, 1998, *Proc Natl Acad Sci USA.* 95: 1460–1465 using appropriately derived thermodynamic parameters described by Sugimoto et al., 1995, *Biochemistry* 34:11211–11216 and McTigue et al., 2004, *Biochemistry* 43:5388–5405. In order to have the possibility of modulating its intended nucleic acid target by hybridization, oligonucleotides of the present invention hybridize to a target nucleic acid with estimated ΔG° values below -10 kcal for oligonucleotides that are 10-30 nucleotides in length. In some embodiments the degree or strength of hybridization is measured by the standard state Gibbs free energy ΔG°. The oligonucleotides may hybridize to a target nucleic acid with estimated ΔG° values below the range of -10 kcal, such as below -15 kcal, such as below -20 kcal and such as below -25 kcal for oligonucleotides that are 8-30 nucleotides in length. In some embodiments the oligonucleotides hybridize to a target nucleic acid with an estimated ΔG° value of -10 to -60 kcal, such as -12 to -40, such as from -15 to -30 kcal or -16 to -27 kcal such as -18 to -25 kcal.

Target nucleic acid

According to the present invention, the target nucleic acid is a nucleic acid which encodes a mammalian ATXN3 protein and may for example be a gene, a *ATXN3* RNA, a mRNA, a pre-mRNA, a mature mRNA or a cDNA sequence. The target may therefore be referred to as an ATXN3 target nucleic acid.

In some embodiments, the target nucleic acid encodes a human ATXN3 protein, such as the human ATXN3 gene encoding the pre-mRNA sequence provided herein as SEQ ID NO 1. Thus, the target nucleic acid may be SEQ ID NO 1.

In some embodiments, the target nucleic acid encodes a mouse ATXN3 protein. Suitably, the target nucleic acid encoding a mouse ATXN3 protein comprises a sequence as shown in SEQ ID NO: 3.

In some embodiments, the target nucleic acid encodes a cynomolgus monkey ATXN3 protein. Suitably, the target nucleic acid encoding a cynomolgus monkey ATXN3 protein comprises a sequence as shown in SEQ ID NO: 2.

If employing the oligonucleotide of the invention in research or diagnostics the target nucleic acid may be a cDNA or a synthetic nucleic acid derived from DNA or RNA.

For *in vivo* or *in vitro* application, the oligonucleotide of the invention is typically capable of inhibiting the expression of the *ATXN3* target nucleic acid in a cell which is expressing the *ATXN3* target nucleic acid. The contiguous sequence of nucleobases of the oligonucleotide of the invention is typically complementary to the *ATXN3* target nucleic acid, as measured across the length of the oligonucleotide, optionally with the exception of one or two mismatches, and optionally excluding nucleotide based linker regions which may link the oligonucleotide to an optional functional group such as a conjugate, or other non-complementary terminal nucleotides (e.g. region D' or D''). The target nucleic acid is a messenger RNA, such as a mature mRNA or a pre-mRNA which encodes mammalian ATXN3 protein, such as human ATXN3, e.g. the human *ATXN3* pre-mRNA sequence, such as that disclosed as SEQ ID NO 1, or *ATXN3* mature mRNA. Further, the target nucleic acid may be a cynomolgus monkey ATXN3 pre-mRNA sequence, such as that disclosed as SEQ ID NO 1, or a cynomolgus monkey ATXN3 mature mRNA. Further, the target nucleic acid may be a mouse ATXN3 pre-mRNA sequence, such as that disclosed as SEQ ID NO 3, or mouse ATXN3 mature mRNA. SEQ ID NOs 1 – 3 are DNA sequences – it will be understood that target RNA sequences have uracil (U) bases in place of the thymidine bases (T).

Table 1

Target Nucleic Acid	Sequence ID
ATXN3 *Homo sapiens* pre-mRNA	SEQ ID NO 1
ATXN3 *Macaca fascicularis* pre-mRNA	SEQ ID NO 2
ATXN3 *Mus musculus* mRNA	SEQ ID NO 3

In some embodiments, the oligonucleotide of the invention targets SEQ ID NO 1.

In some embodiments, the oligonucleotide of the invention targets SEQ ID NO 2.

In some embodiments, the oligonucleotide of the invention targets SEQ ID NO 3.

In some embodiments, the oligonucleotide of the invention targets SEQ ID NO 1 and SEQ ID NO 2.

In some embodiments, the oligonucleotide of the invention targets SEQ ID NO 1 and SEQ ID NO 3.

In some embodiments, the oligonucleotide of the invention targets SEQ ID NO 1, SEQ ID NO 2 and SEQ ID NO 3.

Target Sequence

The term "target sequence" as used herein refers to a sequence of nucleotides present in the target nucleic acid which comprises the nucleobase sequence which is complementary to the oligonucleotide of the invention. In some embodiments, the target sequence consists

of a region on the target nucleic acid which is complementary to the contiguous nucleotide sequence of the oligonucleotide of the invention.

Herein are provided numerous target sequence regions, as defined by regions of the human ATXN3 pre-mRNA (using SEQ ID NO 1 as a reference) which may be targeted by the oligonucleotides of the invention.

In some embodiments the target sequence is longer than the complementary sequence of a single oligonucleotide, and may, for example represent a preferred region of the target nucleic acid which may be targeted by several oligonucleotides of the invention.

The oligonucleotide of the invention comprises a contiguous nucleotide sequence which is complementary to or hybridizes to the target nucleic acid, such as a sub-sequence of the target nucleic acid, such as a target sequence described herein.

The oligonucleotide comprises a contiguous nucleotide sequence which are complementary to a target sequence present in the target nucleic acid molecule. The contiguous nucleotide sequence (and therefore the target sequence) comprises of at least 10 contiguous nucleotides, such as 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29 or 30 contiguous nucleotides, such as from 12-25, such as from 14-18 contiguous nucleotides.

Target Sequence Regions

In an aspect, the invention provides for an antisense oligonucleotide, 10-30 nucleotides in length, wherein said antisense oligonucleotide comprises a contiguous nucleotide sequence 10 – 30 nucleotides in length, wherein the contiguous nucleotide sequence is at least 90% complementary, to a region of SEQ ID NO 1. The region of SEQ ID NO 1 to which the antisense oligonucleotide of the invention is complementary to is referred to as the target sequence region.

In some embodiments the target sequence region is AAGAGTAAAATATGGGT (SEQ ID NO 1093).

In some embodiments the target sequence region is GAATGTAAAAGTGTACAG (SEQ ID NO 1094).

In some embodiments the target sequence region is GGAATGTAAAAGTGTACA (SEQ ID NO 1095).

In some embodiments the target sequence region is GGGAATGTAAAAGTGTAC (SEQ ID NO 1096).

In some embodiments the target sequence region is TTGATGGTATAATGAAGAA (SEQ ID NO 1097).

In some embodiments the target sequence region is GGAAGATGTAAATAAGATT (SEQ ID NO 1098).

Target Cell

The term a "target cell" as used herein refers to a cell which is expressing the target nucleic acid. In some embodiments the target cell may be *in vivo* or *in vitro*. In some embodiments the target cell is a mammalian cell such as a rodent cell, such as a mouse cell or a rat cell, or a primate cell such as a monkey cell (e.g. a cynomolgus monkey cell) or a human cell. In preferred embodiments the target cell expresses human *ATXN3* mRNA, such as the *ATXN3* pre-mRNA, e.g. SEQ ID NO 1, or *ATXN3* mature mRNA. In some embodiments the target cell expresses monkey ATXN3 mRNA, such as the ATXN3 pre-mRNA, e.g. SEQ ID NO 2, or ATXN3 mature mRNA. In some embodiments the target cell expresses mouse ATXN3 mRNA, such as the ATXN3 pre-mRNA, e.g. SEQ ID NO 3, or ATXN3 mature mRNA. The poly A tail of *ATXN3* mRNA is typically disregarded for antisense oligonucleotide targeting.

Naturally occurring variant

The term "naturally occurring variant" refers to variants of *ATXN3* gene or transcripts which originate from the same genetic loci as the target nucleic acid, but may differ for example, by virtue of degeneracy of the genetic code causing a multiplicity of codons encoding the same amino acid, or due to alternative splicing of pre-mRNA, or the presence of polymorphisms, such as single nucleotide polymorphisms (SNPs), and allelic variants. Based on the presence of the sufficient complementary sequence to the oligonucleotide, the oligonucleotide of the invention may therefore target the target nucleic acid and naturally occurring variants thereof.

The *homo sapiens* ATXN3 gene is located at chromosome 14, 92058552..92106621, complement (NC_000014.9, Gene ID 4287).

In some embodiments, the naturally occurring variants have at least 95% such as at least 98% or at least 99% homology to a mammalian *ATXN3* target nucleic acid, such as a target nucleic acid selected form the group consisting of SEQ ID NO 1, 2 and 3. In some embodiments the naturally occurring variants have at least 99% homology to the human *ATXN3* target nucleic acid of SEQ ID NO 1.

Modulation of expression

The term "modulation of expression" as used herein is to be understood as an overall term for an oligonucleotide's ability to alter the amount of ATXN3 protein or *ATXN3* mRNA when compared to the amount of ATXN3 or *ATXN3* mRNA prior to administration of the

oligonucleotide. Alternatively modulation of expression may be determined by reference to a control experiment. It is generally understood that the control is an individual or target cell treated with a saline composition or an individual or target cell treated with a non-targeting oligonucleotide (mock).

One type of modulation is an oligonucleotide's ability to inhibit, down-regulate, reduce, suppress, remove, stop, block, prevent, lessen, lower, avoid or terminate expression of ATXN3, e.g. by degradation of *ATXN3* mRNA.

High affinity modified nucleosides

A high affinity modified nucleoside is a modified nucleotide which, when incorporated into the oligonucleotide enhances the affinity of the oligonucleotide for its complementary target, for example as measured by the melting temperature (T^m). A high affinity modified nucleoside of the present invention preferably result in an increase in melting temperature between +0.5 to +12°C, more preferably between +1.5 to +10°C and most preferably between+3 to +8°C per modified nucleoside. Numerous high affinity modified nucleosides are known in the art and include for example, many 2' substituted nucleosides as well as locked nucleic acids (LNA) (see e.g. Freier & Altmann; Nucl. Acid Res., 1997, 25, 4429-4443 and Uhlmann; Curr. Opinion in Drug Development, 2000, 3(2), 293-213).

Sugar modifications

The oligomer of the invention may comprise one or more nucleosides which have a modified sugar moiety, *i.e.* a modification of the sugar moiety when compared to the ribose sugar moiety found in DNA and RNA.

Numerous nucleosides with modification of the ribose sugar moiety have been made, primarily with the aim of improving certain properties of oligonucleotides, such as affinity and/or nuclease resistance.

Such modifications include those where the ribose ring structure is modified, *e.g.* by replacement with a hexose ring (HNA), or a bicyclic ring, which typically have a biradicle bridge between the C2 and C4 carbons on the ribose ring (LNA), or an unlinked ribose ring which typically lacks a bond between the C2 and C3 carbons (e.g. UNA). Other sugar modified nucleosides include, for example, bicyclohexose nucleic acids (WO2011/017521) or tricyclic nucleic acids (WO2013/154798). Modified nucleosides also include nucleosides where the sugar moiety is replaced with a non-sugar moiety, for example in the case of peptide nucleic acids (PNA), or morpholino nucleic acids.

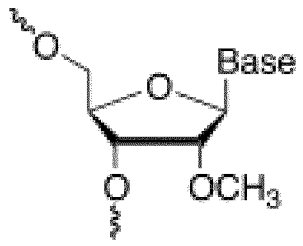
Sugar modifications also include modifications made via altering the substituent groups on the ribose ring to groups other than hydrogen, or the 2'-OH group naturally found in DNA and RNA nucleosides. Substituents may, for example be introduced at the 2', 3', 4' or 5' positions.

2' sugar modified nucleosides.

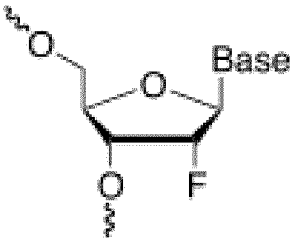
A 2' sugar modified nucleoside is a nucleoside which has a substituent other than H or –OH at the 2' position (2' substituted nucleoside) or comprises a 2' linked biradicle capable of forming a bridge between the 2' carbon and a second carbon in the ribose ring, such as LNA (2' – 4' biradicle bridged) nucleosides.

Indeed, much focus has been spent on developing 2' substituted nucleosides, and numerous 2' substituted nucleosides have been found to have beneficial properties when incorporated into oligonucleotides. For example, the 2' modified sugar may provide enhanced binding affinity and/or increased nuclease resistance to the oligonucleotide.

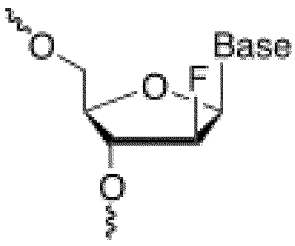
Examples of 2' substituted modified nucleosides are 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA (MOE), 2'-amino-DNA, 2'-Fluoro-RNA, and 2'-F-ANA nucleoside. For further examples, please see e.g. Freier & Altmann; Nucl. Acid Res., 1997, 25, 4429-4443 and Uhlmann; Curr. Opinion in Drug Development, 2000, 3(2), 293-213, and Deleavey and Damha, Chemistry and Biology 2012, 19, 937. Below are illustrations of some 2' substituted modified nucleosides.



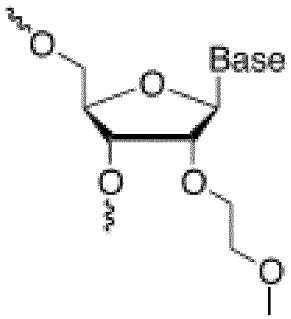
2'-O-Me



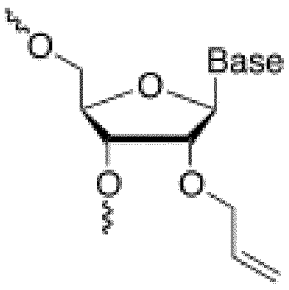
2'F-RNA



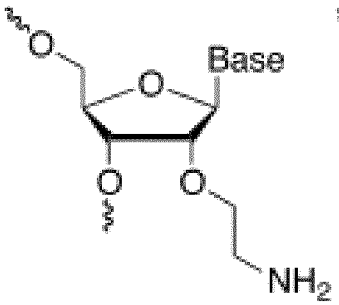
2'F-ANA



2'-O-MOE



2'-O-Allyl



2'-O-Ethylamine

In relation to the present invention 2' substituted does not include 2' bridged molecules like LNA.

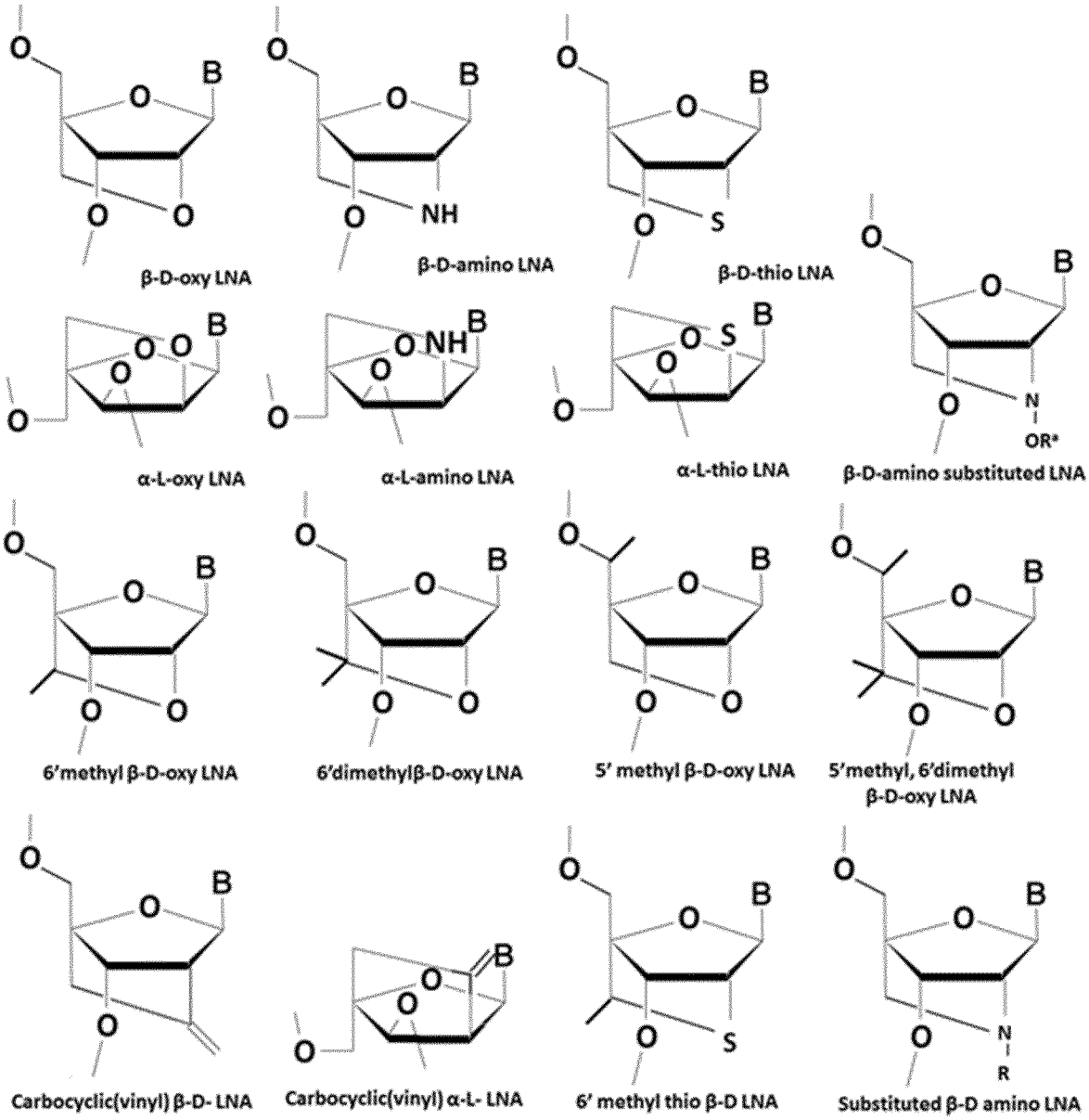
Locked Nucleic Acids (LNA)

A “LNA nucleoside” is a 2’- modified nucleoside which comprises a biradical linking the C2’ and C4’ of the ribose sugar ring of said nucleoside (also referred to as a “2’- 4’ bridge”), which restricts or locks the conformation of the ribose ring. These nucleosides are also termed bridged nucleic acid or bicyclic nucleic acid (BNA) in the literature. The locking of the conformation of the ribose is associated with an enhanced affinity of hybridization (duplex stabilization) when the LNA is incorporated into an oligonucleotide for a complementary RNA or DNA molecule. This can be routinely determined by measuring the melting temperature of the oligonucleotide/complement duplex.

Non limiting, exemplary LNA nucleosides are disclosed in WO 99/014226, WO 00/66604, WO 98/039352 , WO 2004/046160, WO 00/047599, WO 2007/134181, WO 2010/077578, WO 2010/036698, WO 2007/090071, WO 2009/006478, WO 2011/156202, WO 2008/154401, WO 2009/067647, WO 2008/150729, Morita et al., Bioorganic & Med.Chem. Lett. 12, 73-76, Seth et al. J. Org. Chem. 2010, Vol 75(5) pp. 1569-81, and Mitsuoka et al., Nucleic Acids Research 2009, 37(4), 1225-1238, and Wan and Seth, J. Medical Chemistry 2016, 59, 9645−9667.

Further non limiting, exemplary LNA nucleosides are disclosed in Scheme 1.

Scheme 1:



Particular LNA nucleosides are beta-D-oxy-LNA, 6'-methyl-beta-D-oxy LNA such as (S)-6'-methyl-beta-D-oxy-LNA (ScET) and ENA.

A particularly advantageous LNA is beta-D-oxy-LNA.

RNase H Activity and Recruitment

The RNase H activity of an antisense oligonucleotide refers to its ability to recruit RNase H when in a duplex with a complementary RNA molecule. WO01/23613 provides *in vitro* methods for determining RNaseH activity, which may be used to determine the ability to recruit RNaseH. Typically an oligonucleotide is deemed capable of recruiting RNase H if it, when provided with a complementary target nucleic acid sequence, has an initial rate, as measured in pmol/l/min, of at least 5%, such as at least 10% or more than 20% of the of the

initial rate determined when using a oligonucleotide having the same base sequence as the modified oligonucleotide being tested, but containing only DNA monomers with phosphorothioate linkages between all monomers in the oligonucleotide, and using the methodology provided by Example 91 - 95 of WO01/23613 (hereby incorporated by reference). For use in determining RHase H activity, recombinant human RNase H1 is available from Lubio Science GmbH, Lucerne, Switzerland.

Gapmer

The antisense oligonucleotide of the invention, or contiguous nucleotide sequence thereof may be a gapmer. The antisense gapmers are commonly used to inhibit a target nucleic acid via RNase H mediated degradation. A gapmer oligonucleotide comprises at least three distinct structural regions a 5'-flank, a gap and a 3'-flank, F-G-F' in the '5 -> 3' orientation. The "gap" region (G) comprises a stretch of contiguous DNA nucleotides which enable the oligonucleotide to recruit RNase H. The gap region is flanked by a 5' flanking region (F) comprising one or more sugar modified nucleosides, advantageously high affinity sugar modified nucleosides, and by a 3' flanking region (F') comprising one or more sugar modified nucleosides, advantageously high affinity sugar modified nucleosides. The one or more sugar modified nucleosides in region F and F' enhance the affinity of the oligonucleotide for the target nucleic acid (*i.e.* are affinity enhancing sugar modified nucleosides). In some embodiments, the one or more sugar modified nucleosides in region F and F' are 2' sugar modified nucleosides, such as high affinity 2' sugar modifications, such as independently selected from LNA and 2'-MOE.

In a gapmer design, the 5' and 3' most nucleosides of the gap region are DNA nucleosides, and are positioned adjacent to a sugar modified nucleoside of the 5' (F) or 3' (F') region respectively. The flanks may further defined by having at least one sugar modified nucleoside at the end most distant from the gap region, i.e. at the 5' end of the 5' flank and at the 3' end of the 3' flank.

Regions F-G-F' form a contiguous nucleotide sequence. Antisense oligonucleotides of the invention, or the contiguous nucleotide sequence thereof, may comprise a gapmer region of formula F-G-F'.

The overall length of the gapmer design F-G-F' may be, for example 12 to 32 nucleosides, such as 13 to 24, such as 14 to 22 nucleosides, Such as from 14 to17, such as 16 to18 nucleosides.

By way of example, the gapmer oligonucleotide of the present invention can be represented by the following formulae:

F_{1-8}-G_{5-16}-F'_{1-8}, such as

F_{1-8}-G_{7-16}-F'_{2-8}

with the proviso that the overall length of the gapmer regions F-G-F' is at least 12, such as at least 14 nucleotides in length.

Regions F, G and F' are further defined below and can be incorporated into the F-G-F' formula.

Gapmer - Region G

Region G (gap region) of the gapmer is a region of nucleosides which enables the oligonucleotide to recruit RNaseH, such as human RNase H1, typically DNA nucleosides. RNaseH is a cellular enzyme which recognizes the duplex between DNA and RNA, and enzymatically cleaves the RNA molecule. Suitably gapmers may have a gap region (G) of at least 5 or 6 contiguous DNA nucleosides, such as 5 – 16 contiguous DNA nucleosides, such as 6 – 15 contiguous DNA nucleosides, such as 7-14 contiguous DNA nucleosides, such as 8 – 12 contiguous DNA nucleotides, such as 8 – 12 contiguous DNA nucleotides in length. The gap region G may, in some embodiments consist of 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 contiguous DNA nucleosides. One or more cytosine (C) DNA in the gap region may in some instances be methylated (e.g. when a DNA c is followed by a DNA g) such residues are either annotated as 5-methyl-cytosine (^{me}C). In some embodiments the gap region G may consist of 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 contiguous phosphorothioate linked DNA nucleosides. In some embodiments, all internucleoside linkages in the gap are phosphorothioate linkages.

Whilst traditional gapmers have a DNA gap region, there are numerous examples of modified nucleosides which allow for RNaseH recruitment when they are used within the gap region. Modified nucleosides which have been reported as being capable of recruiting RNaseH when included within a gap region include, for example, alpha-L-LNA, C4' alkylated DNA (as described in PCT/EP2009/050349 and Vester *et al.*, Bioorg. Med. Chem. Lett. 18 (2008) 2296 – 2300, both incorporated herein by reference), arabinose derived nucleosides like ANA and 2'F-ANA (Mangos et al. 2003 J. AM. CHEM. SOC. 125, 654-661), UNA (unlocked nucleic acid) (as described in Fluiter *et al.*, Mol. Biosyst., 2009, 10, 1039 incorporated herein by reference). UNA is unlocked nucleic acid, typically where the bond between C2 and C3 of the ribose has been removed, forming an unlocked "sugar" residue. The modified nucleosides used in such gapmers may be nucleosides which adopt a 2' endo (DNA like) structure when introduced into the gap region, *i.e.* modifications which allow for RNaseH recruitment). In some embodiments the DNA Gap region (G) described herein may optionally contain 1 to 3 sugar modified nucleosides which adopt a 2' endo (DNA like) structure when introduced into the gap region.

Region G - "Gap-breaker"

Alternatively, there are numerous reports of the insertion of a modified nucleoside which confers a 3' endo conformation into the gap region of gapmers, whilst retaining some RNaseH activity. Such gapmers with a gap region comprising one or more 3'endo modified nucleosides are referred to as "gap-breaker" or "gap-disrupted" gapmers, see for example WO2013/022984. Gap-breaker oligonucleotides retain sufficient region of DNA nucleosides within the gap region to allow for RNaseH recruitment. The ability of gapbreaker oligonucleotide design to recruit RNaseH is typically sequence or even compound specific – see Rukov et al. 2015 Nucl. Acids Res. Vol. 43 pp. 8476-8487, which discloses "gapbreaker" oligonucleotides which recruit RNaseH which in some instances provide a more specific cleavage of the target RNA. Modified nucleosides used within the gap region of gap-breaker oligonucleotides may for example be modified nucleosides which confer a 3'endo confirmation, such 2' –O-methyl (OMe) or 2'-O-MOE (MOE) nucleosides, or beta-D LNA nucleosides (the bridge between C2' and C4' of the ribose sugar ring of a nucleoside is in the beta conformation), such as beta-D-oxy LNA or ScET nucleosides.

As with gapmers containing region G described above, the gap region of gap-breaker or gap-disrupted gapmers, have a DNA nucleosides at the 5' end of the gap (adjacent to the 3' nucleoside of region F), and a DNA nucleoside at the 3' end of the gap (adjacent to the 5' nucleoside of region F'). Gapmers which comprise a disrupted gap typically retain a region of at least 3 or 4 contiguous DNA nucleosides at either the 5' end or 3' end of the gap region.

Exemplary designs for gap-breaker oligonucleotides include

F_{1-8}-[D_{3-4}-E_1- D_{3-4}]-F'_{1-8}

F_{1-8}- [D_{1-4}-E_1- D_{3-4}]-F'_{1-8}

F_{1-8}- [D_{3-4}-E_1- D_{1-4}]-F'_{1-8}

wherein region G is within the brackets [D_n-E_r- D_m], D is a contiguous sequence of DNA nucleosides, E is a modified nucleoside (the gap-breaker or gap-disrupting nucleoside), and F and F' are the flanking regions as defined herein, and with the proviso that the overall length of the gapmer regions F-G-F' is at least 12, such as at least 14 nucleotides in length. In some embodiments, region G of a gap disrupted gapmer comprises at least 6 DNA nucleosides, such as 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 DNA nucleosides. As described above, the DNA nucleosides may be contiguous or may optionally be interspersed with one or more modified nucleosides, with the proviso that the gap region G is capable of mediating RNaseH recruitment.

Gapmer - flanking regions, F and F'

Region F is positioned immediately adjacent to the 5' DNA nucleoside of region G. The 3' most nucleoside of region F is a sugar modified nucleoside, such as a high affinity sugar

modified nucleoside, for example a 2' substituted nucleoside, such as a MOE nucleoside, or an LNA nucleoside.

Region F' is positioned immediately adjacent to the 3' DNA nucleoside of region G. The 5' most nucleoside of region F' is a sugar modified nucleoside, such as a high affinity sugar modified nucleoside, for example a 2' substituted nucleoside, such as a MOE nucleoside, or an LNA nucleoside.

Region F is 1 – 8 contiguous nucleotides in length, such as 2-6, such as 3-4 contiguous nucleotides in length. Advantageously the 5' most nucleoside of region F is a sugar modified nucleoside. In some embodiments the two 5' most nucleoside of region F are sugar modified nucleoside. In some embodiments the 5' most nucleoside of region F is an LNA nucleoside. In some embodiments the two 5' most nucleoside of region F are LNA nucleosides. In some embodiments the two 5' most nucleoside of region F are 2' substituted nucleoside nucleosides, such as two 3' MOE nucleosides. In some embodiments the 5' most nucleoside of region F is a 2' substituted nucleoside, such as a MOE nucleoside.

Region F' is 2 – 8 contiguous nucleotides in length, such as 3-6, such as 4-5 contiguous nucleotides in length. Advantageously, embodiments the 3' most nucleoside of region F' is a sugar modified nucleoside. In some embodiments the two 3' most nucleoside of region F' are sugar modified nucleoside. In some embodiments the two 3' most nucleoside of region F' are LNA nucleosides. In some embodiments the 3' most nucleoside of region F' is an LNA nucleoside. In some embodiments the two 3' most nucleoside of region F' are 2' substituted nucleoside nucleosides, such as two 3' MOE nucleosides. In some embodiments the 3' most nucleoside of region F' is a 2' substituted nucleoside, such as a MOE nucleoside. It should be noted that when the length of region F or F' is one, it is advantageously an LNA nucleoside.

In some embodiments, region F and F' independently consists of or comprises a contiguous sequence of sugar modified nucleosides. In some embodiments, the sugar modified nucleosides of region F may be independently selected from 2'-O-alkyl-RNA units, 2'-O-methyl-RNA, 2'-amino-DNA units, 2'-fluoro-DNA units, 2'-alkoxy-RNA, MOE units, LNA units, arabino nucleic acid (ANA) units and 2'-fluoro-ANA units.

In some embodiments, region F and F' independently comprises both LNA and a 2' substituted modified nucleosides (mixed wing design).

In some embodiments, region F and F' consists of only one type of sugar modified nucleosides, such as only MOE or only beta-D-oxy LNA or only ScET. Such designs are also termed uniform flanks or uniform gapmer design.

In some embodiments, all the nucleosides of region F or F', or F and F' are LNA nucleosides, such as independently selected from beta-D-oxy LNA, ENA or ScET nucleosides.

In some embodiments, all the nucleosides of region F or F', or F and F' are 2' substituted nucleosides, such as OMe or MOE nucleosides. In some embodiments region F consists of 1, 2, 3, 4, 5, 6, 7, or 8 contiguous OMe or MOE nucleosides. In some embodiments only one of the flanking regions can consist of 2' substituted nucleosides, such as OMe or MOE nucleosides. In some embodiments it is the 5' (F) flanking region that consists 2' substituted nucleosides, such as OMe or MOE nucleosides whereas the 3' (F') flanking region comprises at least one LNA nucleoside, such as beta-D-oxy LNA nucleosides or cET nucleosides. In some embodiments it is the 3' (F') flanking region that consists 2' substituted nucleosides, such as OMe or MOE nucleosides whereas the 5' (F) flanking region comprises at least one LNA nucleoside, such as beta-D-oxy LNA nucleosides or cET nucleosides.

In some embodiments, all the modified nucleosides of region F and F' are LNA nucleosides, such as independently selected from beta-D-oxy LNA, ENA or ScET nucleosides, wherein region F or F', or F and F' may optionally comprise DNA nucleosides (an alternating flank, see definition of these for more details). In some embodiments, all the modified nucleosides of region F and F' are beta-D-oxy LNA nucleosides, wherein region F or F', or F and F' may optionally comprise DNA nucleosides (an alternating flank, see definition of these for more details).

In some embodiments the 5' most and the 3' most nucleosides of region F and F' are LNA nucleosides, such as beta-D-oxy LNA nucleosides or ScET nucleosides.

In some embodiments, the internucleoside linkage between region F and region G is a phosphorothioate internucleoside linkage. In some embodiments, the internucleoside linkage between region F' and region G is a phosphorothioate internucleoside linkage. In some embodiments, the internucleoside linkages between the nucleosides of region F or F', F and F' are phosphorothioate internucleoside linkages.

LNA Gapmer

An LNA gapmer is a gapmer wherein either one or both of region F and F' comprises or consists of LNA nucleosides. A beta-D-oxy gapmer is a gapmer wherein either one or both of region F and F' comprises or consists of beta-D-oxy LNA nucleosides.

In some embodiments the LNA gapmer is of formula: $[LNA]_{1-5}$-[region G] -$[LNA]_{1-5}$, wherein region G is as defined in the Gapmer region G definition.

MOE Gapmers

A MOE gapmers is a gapmer wherein regions F and F' consist of MOE nucleosides. In some embodiments the MOE gapmer is of design $[MOE]_{1-8}$-[Region G]-$[MOE]_{1-8}$, such as

$[MOE]_{2-7}$-[Region G]$_{5-16}$-$[MOE]_{2-7}$, such as $[MOE]_{3-6}$-[Region G]-$[MOE]_{3-6}$, wherein region G is as defined in the Gapmer definition. MOE gapmers with a 5-10-5 design (MOE-DNA-MOE) have been widely used in the art.

Mixed Wing Gapmer

A mixed wing gapmer is an LNA gapmer wherein one or both of region F and F' comprise a 2' substituted nucleoside, such as a 2' substituted nucleoside independently selected from the group consisting of 2'-O-alkyl-RNA units, 2'-O-methyl-RNA, 2'-amino-DNA units, 2'-fluoro-DNA units, 2'-alkoxy-RNA, MOE units, arabino nucleic acid (ANA) units and 2'-fluoro-ANA units, such as a MOE nucleosides. In some embodiments wherein at least one of region F and F', or both region F and F' comprise at least one LNA nucleoside, the remaining nucleosides of region F and F' are independently selected from the group consisting of MOE and LNA. In some embodiments wherein at least one of region F and F', or both region F and F' comprise at least two LNA nucleosides, the remaining nucleosides of region F and F' are independently selected from the group consisting of MOE and LNA. In some mixed wing embodiments, one or both of region F and F' may further comprise one or more DNA nucleosides.

Mixed wing gapmer designs are disclosed in WO2008/049085 and WO2012/109395, both of which are hereby incorporated by reference.

Alternating Flank Gapmers

Oligonucleotides with alternating flanks are LNA gapmer oligonucleotides where at least one of the flanks (F or F') comprises DNA in addition to the LNA nucleoside(s). In some embodiments at least one of region F or F', or both region F and F', comprise both LNA nucleosides and DNA nucleosides. In such embodiments, the flanking region F or F', or both F and F' comprise at least three nucleosides, wherein the 5' and 3' most nucleosides of the F and/or F' region are LNA nucleosides.

In some embodiments at least one of region F or F', or both region F and F', comprise both LNA nucleosides and DNA nucleosides. In such embodiments, the flanking region F or F', or both F and F' comprise at least three nucleosides, wherein the 5' and 3' most nucleosides of the F or F' region are LNA nucleosides, and there is at least one DNA nucleoside positioned between the 5' and 3' most LNA nucleosides of region F or F' (or both region F and F').

Region D' or D'' in an oligonucleotide

The oligonucleotide of the invention may in some embodiments comprise or consist of the contiguous nucleotide sequence of the oligonucleotide which is complementary to the target nucleic acid, such as the gapmer F-G-F', and further 5' and/or 3' nucleosides. The further 5'

and/or 3' nucleosides may or may not be fully complementary to the target nucleic acid. Such further 5' and/or 3' nucleosides may be referred to as region D' and D'' herein. The addition of region D' or D'' may be used for the purpose of joining the contiguous nucleotide sequence, such as the gapmer, to a conjugate moiety or another functional group. When used for joining the contiguous nucleotide sequence with a conjugate moiety is can serve as a biocleavable linker. Alternatively it may be used to provide exonuclease protection or for ease of synthesis or manufacture.

Region D' and D'' can be attached to the 5' end of region F or the 3' end of region F', respectively to generate designs of the following formulas D'-F-G-F', F-G-F'-D'' or D'-F-G-F'-D''. In this instance the F-G-F' is the gapmer portion of the oligonucleotide and region D' or D'' constitute a separate part of the oligonucleotide.

Region D' or D'' may independently comprise or consist of 1, 2, 3, 4 or 5 additional nucleotides, which may be complementary or non-complementary to the target nucleic acid.

The nucleotide adjacent to the F or F' region is not a sugar-modified nucleotide, such as a DNA or RNA or base modified versions of these. The D' or D' region may serve as a nuclease susceptible biocleavable linker (see definition of linkers). In some embodiments the additional 5' and/or 3' end nucleotides are linked with phosphodiester linkages, and are DNA or RNA. Nucleotide based biocleavable linkers suitable for use as region D' or D'' are disclosed in WO2014/076195, which include by way of example a phosphodiester linked DNA dinucleotide. The use of biocleavable linkers in poly-oligonucleotide constructs is disclosed in WO2015/113922, where they are used to link multiple antisense constructs (e.g. gapmer regions) within a single oligonucleotide.

In one embodiment the oligonucleotide of the invention comprises a region D' and/or D'' in addition to the contiguous nucleotide sequence which constitutes the gapmer.

In some embodiments, the oligonucleotide of the present invention can be represented by the following formulae:

F-G-F'; in particular F_{1-8}-G_{5-16}-F'_{2-8}

D'-F-G-F', in particular D'_{1-3}-F_{1-8}-G_{5-16}-F'_{2-8}

F-G-F'-D'', in particular F_{1-8}-G_{5-16}-F'_{2-8}-D''_{1-3}

D'-F-G-F'-D'', in particular D'_{1-3}- F_{1-8}-G_{5-16}-F'_{2-8}-D''_{1-3}

In some embodiments the internucleoside linkage positioned between region D' and region F is a phosphodiester linkage. In some embodiments the internucleoside linkage positioned between region F' and region D'' is a phosphodiester linkage.

Conjugate

The term conjugate as used herein refers to an oligonucleotide which is covalently linked to a non-nucleotide moiety (conjugate moiety or region C or third region).

Conjugation of the oligonucleotide of the invention to one or more non-nucleotide moieties may improve the pharmacology of the oligonucleotide, *e.g.* by affecting the activity, cellular distribution, cellular uptake or stability of the oligonucleotide. In some embodiments the conjugate moiety modify or enhance the pharmacokinetic properties of the oligonucleotide by improving cellular distribution, bioavailability, metabolism, excretion, permeability, and/or cellular uptake of the oligonucleotide. In particular the conjugate may target the oligonucleotide to a specific organ, tissue or cell type and thereby enhance the effectiveness of the oligonucleotide in that organ, tissue or cell type. At the same time the conjugate may serve to reduce activity of the oligonucleotide in non-target cell types, tissues or organs, e.g. off target activity or activity in non-target cell types, tissues or organs.

In an embodiment, the non-nucleotide moiety (conjugate moiety) is selected from the group consisting of carbohydrates, cell surface receptor ligands, drug substances, hormones, lipophilic substances, polymers, proteins, peptides, toxins (e.g. bacterial toxins), vitamins, viral proteins (e.g. capsids) or combinations thereof.

Linkers

A linkage or linker is a connection between two atoms that links one chemical group or segment of interest to another chemical group or segment of interest via one or more covalent bonds. Conjugate moieties can be attached to the oligonucleotide directly or through a linking moiety (e.g. linker or tether). Linkers serve to covalently connect a third region, e.g. a conjugate moiety (Region C), to a first region, e.g. an oligonucleotide or contiguous nucleotide sequence or gapmer region F-G-F' (region A).

In some embodiments of the invention the conjugate or oligonucleotide conjugate of the invention may optionally, comprise a linker region (second region or region B and/or region Y) which is positioned between the oligonucleotide or contiguous nucleotide sequence complementary to the target nucleic acid (region A or first region) and the conjugate moiety (region C or third region).

Region B refers to biocleavable linkers comprising or consisting of a physiologically labile bond that is cleavable under conditions normally encountered or analogous to those encountered within a mammalian body. Conditions under which physiologically labile linkers undergo chemical transformation (e.g., cleavage) include chemical conditions such as pH, temperature, oxidative or reductive conditions or agents, and salt concentration found in or analogous to those encountered in mammalian cells. Mammalian intracellular conditions also include the presence of enzymatic activity normally present in a mammalian cell such as from proteolytic enzymes or hydrolytic enzymes or nucleases. In one embodiment the biocleavable linker is susceptible to S1 nuclease cleavage. DNA phosphodiester containing

biocleavable linkers are described in more detail in WO 2014/076195 (hereby incorporated by reference) – see also region D' or D'' herein.

Region Y refers to linkers that are not necessarily biocleavable but primarily serve to covalently connect a conjugate moiety (region C or third region), to an oligonucleotide (region A or first region). The region Y linkers may comprise a chain structure or an oligomer of repeating units such as ethylene glycol, amino acid units or amino alkyl groups. The oligonucleotide conjugates of the present invention can be constructed of the following regional elements A-C, A-B-C, A-B-Y-C, A-Y-B-C or A-Y-C. In some embodiments the linker (region Y) is an amino alkyl, such as a C2 – C36 amino alkyl group, including, for example C6 to C12 amino alkyl groups. In a preferred embodiment the linker (region Y) is a C6 amino alkyl group.

Treatment

The term 'treatment' as used herein refers to both treatment of an existing disease (*e.g.* a disease or disorder as herein referred to), or prevention of a disease, *i.e.* prophylaxis. It will therefore be recognized that treatment as referred to herein may, in some embodiments, be prophylactic.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to oligonucleotides, such as antisense oligonucleotides, targeting *ATXN3* expression.

The oligonucleotides of the invention targeting *ATXN3* are capable of hybridizing to and inhibiting the expression of a *ATXN3* target nucleic acid in a cell which is expressing the *ATXN3* target nucleic acid.

The ATXN3 target nucleic acid may be a mammalian *ATXN3* mRNA or premRNA, such as a human, mouse or monkey *ATXN3* mRNA or premRNA. In some embodiments, the ATXN3 target nucleic acid is *ATXN3* mRNA or premRNA for example a premRNA or mRNA originating from the *Homo sapiens* Ataxin 3 (ATXN3), RefSeqGene on chromosome 14, exemplified by NCBI Reference Sequence NM_004993.5 (SEQ ID NO 1).

The human *ATXN3* pre-mRNA is encoded on *Homo sapiens* Chromosome 14, NC_000014.9 (92058552..92106621, complement). GENE ID = 4287 (*ATXN3*).

The oligonucleotides of the invention are capable of inhibiting the expression of *ATXN3* target nucleic acid, such as the *ATXN3* mRNA, in a cell which is expressing the target nucleic acid, such as the *ATXN3* mRNA (e.g. a human, monkey or mouse cell).

In some embodiments, the oligonucleotides of the invention are capable of inhibiting the expression of *ATXN3* target nucleic acid in a cell which is expressing the target nucleic acid, so to reduce the level of *ATXN3* target nucleic acid (e.g. the mRNA) by at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% inhibition compared to the expression level of the *ATXN3* target nucleic acid (e.g. the mRNA) in the cell. Suitably the cell is selected from the group consisting of a human cell, a monkey cel and a mouse cell. In some embodiments, the cell is a SK-N-AS, A431, NCI-H23 or ARPE19 cell (for more information on these cells, see Examples). Example 1 provides a suitable assay for evaluating the ability of the oligonucleotides of the invention to inhibit the expression of the target nucleic acid. Suitably the evaluation of a compounds ability to inhibit the expression of the target nucleic acid is performed in vitro, such a gymnotic in vitro assay, for example as according to Example 1.

An aspect of the present invention relates to an antisense oligonucleotide, such as an LNA antisense oligonucleotide gapmer which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as is fully complementary to SEQ ID NO 1, 2 or 3.

In some embodiments, the oligonucleotide comprises a contiguous sequence of 10 – 30 nucleotides, which is at least 90% complementary, such as at least 91%, such as at least 92%, such as at least 93%, such as at least 94%, such as at least 95%, such as at least 96%, such as at least 97%, such as at least 98%, or 100% complementary with a region of the target nucleic acid or a target sequence. The sequences of suitable target nucleic acids are described herein above.

In some embodiments, the oligonucleotide of the invention comprises a contiguous nucleotides sequence of 12 – 24, such as 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23, contiguous nucleotides in length, wherein the contiguous nucleotide sequence is fully complementary to a target nucleic acid having a sequence as provided in the section “Taget sequence regions” above.

In some embodiments, the antisense oligonucleotide of the invention comprises a contiguous nucleotides sequence of 12 – 15, such as 13, or 14, 15 contiguous nucleotides in length, wherein the contiguous nucleotide sequence is fully complementary to a target nucleic acid having a sequence as provided in the section "Taget sequence regions" above.

Typically, the antisense oligonucleotide of the invention or the contiguous nucleotide sequence thereof is a gapmer, such as an LNA gapmer, a mixed wing gapmer, or an alternating flank gapmer.

In some embodiments, the antisense oligonucleotide according to the invention, comprises a contiguous nucleotide sequence of at least 10 contiguous nucleotides, such as at least 12 contiguous nucleotides, such as at least 13 contiguous nucleotides, such as at least 14 contiguous nucleotides, such as at least 15 contiguous nucleotides, which is fully complementary to a target nucleic acid having a sequence selected from the group consisting of SEQ ID NO 16 to SEQ ID NO 1281.

In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide according to the invention is less than 20 nucleotides in length. In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide according to the invention is 12 - 24 nucleotides in length. In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide according to the invention is 12 - 22 nucleotides in length. In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide according to the invention is 12 - 20 nucleotides in length. In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide according to the invention is 12 - 18 nucleotides in length. In some embodiments the contiguous nucleotide sequence of the antisense oligonucleotide according to the invention is 12 - 16 nucleotides in length.

Advantageously, in some embodiments all of the internucleoside linkages between the nucleosides of the contiguous nucleotide sequence are phosphorothioate internucleoside linkages.

In some embodiments, the contiguous nucleotide sequence is fully complementary to a target nucleic acid.

In some embodiments, the antisense oligonucleotide is a gapmer oligonucleotide comprising a contiguous nucleotide sequence of formula 5'-F-G-F'-3', where region F and F'

independently comprise 1 - 8 sugar modified nucleosides, and G is a region between 5 and 16 nucleosides which are capable of recruiting RNaseH.

In some embodiments, the sugar modified nucleosides of region F and F' are independently selected from the group consisting of 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA, 2'-amino-DNA, 2'-fluoro-DNA, arabino nucleic acid (ANA), 2'-fluoro-ANA and LNA nucleosides.

In some embodiments, region G comprises 5 – 16 contiguous DNA nucleosides.

In some embodiments, wherein the antisense oligonucleotide is a gapmer oligonucleotide, such as an LNA gapmer oligonucleotide.

In some embodiments, the LNA nucleosides are beta-D-oxy LNA nucleosides.

In some embodiments, the internucleoside linkages between the contiguous nucleotide sequence are phosphorothioate internucleoside linkages.

Preferred sequence motifs and antisense oligonucleotides of the present invention are shown in Table 2 and in the examples.

Table 2: Sequence Motifs and Compounds of Exemplary Compounds of the Invention

SEQ ID NO	motif sequence	start	end	design	CMP ID NO	Oligonucleotide compound
4	aagaaaccaaaccc	743	756	2-10-2	4_1	AAgaaaccaaacCC
5	aaagaaaccaaacc	744	757	2-10-2	5_1	AAagaaaccaaaCC
6	aaaagaaaccaaac	745	758	2-10-2	6_1	AAaagaaaccaaAC
7	caaaagaaaccaaa	746	759	2-10-2	7_1	CAaaagaaaccaAA
8	ccaaaagaaaccaa	747	760	2-10-2	8_1	CCaaaagaaaccAA
9	tccactcctaatac	803	816	2-10-2	9_1	TCcactcctaatAC
10	gtccactcctaata	804	817	2-10-2	10_1	GTccactcctaaTA
11	agtccactcctaat	805	818	2-10-2	11_1	AGtccactcctaAT
12	cagtccactcctaa	806	819	2-10-2	12_1	CAgtccactcctAA
13	ccagtccactccta	807	820	2-10-2	13_1	CCagtccactccTA
14	actctttccaaaca	1012	1025	2-10-2	14_1	ACtctttccaaaCA
15	aactctttccaaac	1013	1026	2-10-2	15_1	AActctttccaaAC
16	caactctttccaaa	1014	1027	2-10-2	16_1	CAactctttccaAA
17	gcaactctttccaa	1015	1028	2-10-2	17_1	GCaactctttccAA
18	agcaactctttcca	1016	1029	2-10-2	18_1	AGcaactctttcCA
19	cagcaactctttcc	1017	1030	2-10-2	19_1	CAgcaactctttCC
20	ccagcaactctttc	1018	1031	2-10-2	20_1	CCagcaactcttTC
21	accagcaactcttt	1019	1032	2-10-2	21_1	ACcagcaactctTT
22	ctcctattaaataa	1040	1053	2-10-2	22_1	CTcctattaaatAA
23	cctcctattaaata	1041	1054	2-10-2	23_1	CCtcctattaaaTA

24	tcctcctattaaat	1042	1055	2-10-2	24_1	TCctcctattaaAT
25	ctcctcctattaaa	1043	1056	2-10-2	25_1	CTcctcctattaAA
26	gctcctcctattaa	1044	1057	2-10-2	26_1	GCtcctcctattAA
27	tgctcctcctatta	1045	1058	2-10-2	27_1	TGctcctcctatTA
28	ttgctcctcctatt	1046	1059	2-10-2	28_1	TTgctcctcctaTT
29	tttgctcctcctat	1047	1060	2-10-2	29_1	TTtgctcctcctAT
30	ctttgctcctccta	1048	1061	2-10-2	30_1	CTttgctcctccTA
31	cctttgctcctcct	1049	1062	2-10-2	31_1	CCtttgctcctcCT
32	ccctttgctcctcc	1050	1063	2-10-2	32_1	CCctttgctcctCC
33	acccctttgctcctc	1051	1064	2-10-2	33_1	ACcctttgctccTC
34	aacccctttgctcct	1052	1065	2-10-2	34_1	AAcccctttgctcCT
35	aaacccctttgctcc	1053	1066	2-10-2	35_1	AAacccctttgctCC
36	aaaacccctttgctc	1054	1067	2-10-2	36_1	AAaacccctttgcTC
37	aaaaacccctttgct	1055	1068	2-10-2	37_1	AAaaacccctttgCT
38	caaaaacccctttgc	1056	1069	2-10-2	38_1	CAaaaacccctttGC
39	acaaaaacccctttg	1057	1070	2-10-2	39_1	ACaaaaacccttTG
40	aacaaaaacccttt	1058	1071	2-10-2	40_1	AAcaaaaacccctTT
41	aaacaaaaacccctt	1059	1072	2-10-2	41_1	AAacaaaaacccTT
42	aaaacaaaaaccct	1060	1073	2-10-2	42_1	AAaacaaaaaccCT
43	taaaacaaaaaccc	1061	1074	2-10-2	43_1	TAaaacaaaaacCC
44	ataaaacaaaaacc	1062	1075	2-10-2	44_1	ATaaaacaaaaaCC
45	aataaaacaaaaac	1063	1076	2-10-2	45_1	AAtaaaacaaaaAC
46	taataaaacaaaaa	1064	1077	2-10-2	46_1	TAataaaacaaaAA
47	ttaataaaacaaaa	1065	1078	2-10-2	47_1	TTaataaaacaaAA
48	tttaataaaacaaa	1066	1079	2-10-2	48_1	TTtaataaaacAA
49	atttaataaaacaa	1067	1080	2-10-2	49_1	ATttaataaaacAA
50	ttaaaataaaaatt	1194	1207	2-10-2	50_1	TTaaaataaaaTT
51	tttaaaataaaaat	1195	1208	2-10-2	51_1	TTtaaaataaaAT
52	ctttaaaataaaaa	1196	1209	2-10-2	52_1	CTttaaaataaAA
53	tctttaaaataaaa	1197	1210	2-10-2	53_1	TCtttaaaataAA
54	atctttaaaataaa	1198	1211	2-10-2	54_1	ATctttaaaataAA
55	catctttaaaataa	1199	1212	2-10-2	55_1	CAtctttaaaatAA
56	ccatctttaaaata	1200	1213	2-10-2	56_1	CCatctttaaaaTA
57	tctaacttaataaa	2886	2899	2-10-2	57_1	TCtaacttaataAA
58	ttctaacttaataa	2887	2900	2-10-2	58_1	TTctaacttaatAA
59	attctaacttaata	2888	2901	2-10-2	59_1	ATtctaacttaaTA
60	cattctaacttaat	2889	2902	2-10-2	60_1	CAttctaacttaAT
61	acattctaacttaa	2890	2903	2-10-2	61_1	ACattctaacttAA
62	tacattctaactta	2891	2904	2-10-2	62_1	TAcattctaactTA
63	ttacattctaactt	2892	2905	2-10-2	63_1	TTacattctaacTT
64	tttacattctaact	2893	2906	2-10-2	64_1	TTtacattctaaCT
65	ttttacattctaac	2894	2907	2-10-2	65_1	TTttacattctaAC

66	tttttacattctaa	2895	2908	2-10-2	66_1	TTtttacattctAA
67	gtttttacattcta	2896	2909	2-10-2	67_1	GTttttacattcTA
68	tgtttttacattct	2897	2910	2-10-2	68_1	TGtttttacattCT
69	ctgtttttacattc	2898	2911	2-10-2	69_1	CTgtttttacatTC
70	ttcaaatatttatt	2969	2982	2-10-2	70_1	TTcaaatatttaTT
71	attcaaatatttat	2970	2983	2-10-2	71_1	ATtcaaatatttAT
72	cattcaaatattta	2971	2984	2-10-2	72_1	CAttcaaatattTA
73	ccattcaaatattt	2972	2985	2-10-2	73_1	CCattcaaatatTT
74	cccattcaaatatt	2973	2986	2-10-2	74_1	CCcattcaaataTT
75	ccccattcaaatat	2974	2987	2-10-2	75_1	CCccattcaaatAT
76	gccccattcaaata	2975	2988	2-10-2	76_1	GCcccattcaaaTA
77	tatacatttttttc	3173	3186	2-10-2	77_1	TAtacatttttttC
78	atatacatttttt	3174	3187	2-10-2	78_1	ATatacatttttTT
79	tatatacatttttt	3175	3188	2-10-2	79_1	TAtatacatttttTT
80	atatatacatttt	3176	3189	2-10-2	80_1	ATatatacatttTT
81	aatatatacatttt	3177	3190	2-10-2	81_1	AAtatatacattTT
82	aaatatatacattt	3178	3191	2-10-2	82_1	AAatatatacatTT
83	caaatatatacatt	3179	3192	2-10-2	83_1	CAaatatatacaTT
84	tcaaatatatacat	3180	3193	2-10-2	84_1	TCaaatatatacAT
85	ttcaaatatataca	3181	3194	2-10-2	85_1	TTcaaatatataCA
86	attcaaatatatac	3182	3195	2-10-2	86_1	ATtcaaatatatAC
87	cattcaaatatata	3183	3196	2-10-2	87_1	CAttcaaatataTA
88	ccattcaaatatat	3184	3197	2-10-2	88_1	CCattcaaatatAT
89	tccattcaaatata	3185	3198	2-10-2	89_1	TCcattcaaataTA
90	atccattcaaatat	3186	3199	2-10-2	90_1	ATccattcaaatAT
91	tatccattcaaata	3187	3200	2-10-2	91_1	TAtccattcaaaTA
92	ttatccattcaaat	3188	3201	2-10-2	92_1	TTatccattcaaAT
93	tttatccattcaaa	3189	3202	2-10-2	93_1	TTtatccattcaAA
94	ctttatccattcaa	3190	3203	2-10-2	94_1	CTttatccattcAA
95	tctttatccattca	3191	3204	2-10-2	95_1	TCtttatccattCA
96	ctctttatccattc	3192	3205	2-10-2	96_1	CTctttatccatTC
97	tctctttatccatt	3193	3206	2-10-2	97_1	TCtctttatccaTT
98	ccatatatatctca	3221	3234	2-10-2	98_1	CCatatatatctCA
99	accatatatatctc	3222	3235	2-10-2	99_1	ACcatatatatcTC
100	caccatatatatct	3223	3236	2-10-2	100_1	CAccatatatatCT
101	gcaccatatatatc	3224	3237	2-10-2	101_1	GCaccatatataTC
102	agcaccatatatat	3225	3238	2-10-2	102_1	AGcaccatatatAT
103	cagcaccatatata	3226	3239	2-10-2	103_1	CAgcaccatataTA
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126	cttctctacactct	3914	3927	2-10-2	126_1	CTtctctacactCT
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340	gatctttcatttct	13302	13315	2-10-2	340_1	GAtctttcatttCT
341	tgatctttcatttc	13303	13316	2-10-2	341_1	TGatctttcattTC
342	atgatctttcattt	13304	13317	2-10-2	342_1	ATgatctttcatTT
343	ataaaaacccactt	13990	14003	2-10-2	343_1	ATaaaaacccacTT
344	cataaaaacccact	13991	14004	2-10-2	344_1	CAtaaaaacccaCT
345	acataaaaacccac	13992	14005	2-10-2	345_1	ACataaaaacccAC
346	cacataaaaaccca	13993	14006	2-10-2	346_1	CAcataaaaaccCA
347	tcacataaaaaccc	13994	14007	2-10-2	347_1	TCacataaaaacCC
348	atcacataaaaacc	13995	14008	2-10-2	348_1	ATcacataaaaaCC
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350	tcatcacataaaaa	13997	14010	2-10-2	350_1	TCatcacataaaAA
351	gtcatcacataaaa	13998	14011	2-10-2	351_1	GTcatcacataaAA
352	agtcatcacataaa	13999	14012	2-10-2	352_1	AGtcatcacataAA
353	tagtcatcacataa	14000	14013	2-10-2	353_1	TAgtcatcacatAA
354	atagtcatcacata	14001	14014	2-10-2	354_1	ATagtcatcacaTA
355	catagtcatcacat	14002	14015	2-10-2	355_1	CAtagtcatcacAT
356	taaatacaaatcta	14041	14054	2-10-2	356_1	TAaatacaaatcTA
357	ctaaatacaaatct	14042	14055	2-10-2	357_1	CTaaatacaaatCT
358	gctaaatacaaatc	14043	14056	2-10-2	358_1	GCtaaatacaaaTC
359	tgctaaatacaaat	14044	14057	2-10-2	359_1	TGctaaatacaaAT

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362	aatcttacactaaa	14119	14132	2-10-2	362_1	AAtcttacactaAA
363	taatcttacactaa	14120	14133	2-10-2	363_1	TAatcttacactAA
364	ataatcttacacta	14121	14134	2-10-2	364_1	ATaatcttacacTA
365	aataatcttacact	14122	14135	2-10-2	365_1	AAtaatcttacaCT
366	gaataatcttacac	14123	14136	2-10-2	366_1	GAataatcttacAC
367	tgaataatcttaca	14124	14137	2-10-2	367_1	TGaataatcttaCA
368	atgaataatcttac	14125	14138	2-10-2	368_1	ATgaataatcttAC
369	caaaattctaataa	14257	14270	2-10-2	369_1	CAaaattctaatAA
370	tcaaaattctaata	14258	14271	2-10-2	370_1	TCaaaattctaaTA
371	ttcaaaattctaat	14259	14272	2-10-2	371_1	TTcaaaattctaAT
372	attcaaaattctaa	14260	14273	2-10-2	372_1	ATtcaaaattctAA
373	gattcaaaattcta	14261	14274	2-10-2	373_1	GAttcaaaattcTA
374	agattcaaaattct	14262	14275	2-10-2	374_1	AGattcaaaattCT
375	attactacaaccaa	14570	14583	2-10-2	375_1	ATtactacaaccAA
376	cattactacaacca	14571	14584	2-10-2	376_1	CAttactacaacCA
377	ccattactacaacc	14572	14585	2-10-2	377_1	CCattactacaaCC
378	accattactacaac	14573	14586	2-10-2	378_1	ACcattactacaAC
379	aaccattactacaa	14574	14587	2-10-2	379_1	AAccattactacAA
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382	tgaaaccattacta	14577	14590	2-10-2	382_1	TGaaaccattacTA
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389	tcataatttttaaa	15783	15796	2-10-2	389_1	TCataatttttaAA
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395	cttactttatacaa	15818	15831	2-10-2	395_1	CTtactttatacAA
396	gcttactttataca	15819	15832	2-10-2	396_1	GCttactttataCA
397	tgcttactttatac	15820	15833	2-10-2	397_1	TGcttactttatAC
398	tctcaaaataataa	15877	15890	2-10-2	398_1	TCtcaaaataatAA
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405	ttaaatctctcaaa	15884	15897	2-10-2	405_1	TTaaatctctcaAA
406	tttaaatctctcaa	15885	15898	2-10-2	406_1	TTtaaatctctcAA
407	ttttaaatctctca	15886	15899	2-10-2	407_1	TTttaaatctctCA
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409	ttaatacttttcc	16081	16094	2-10-2	409_1	TTaatacttttCC
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412	atgttaatacttttt	16084	16097	2-10-2	412_1	ATgttaatacttTT
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415	atttatcactacca	16189	16202	2-10-2	415_1	ATttatcactacCA
416	catttatcactacc	16190	16203	2-10-2	416_1	CAtttatcactaCC
417	tcatttatcactac	16191	16204	2-10-2	417_1	TCatttatcactAC
418	atcatttatcacta	16192	16205	2-10-2	418_1	ATcatttatcacTA
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420	acatcatttatcac	16194	16207	2-10-2	420_1	ACatcatttatcAC
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422	taacatcatttatc	16196	16209	2-10-2	422_1	TAacatcatttaTC
423	ttaacatcatttat	16197	16210	2-10-2	423_1	TTaacatcatttAT
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427	ctaattaacatcat	16201	16214	2-10-2	427_1	CTaattaacatcAT
428	cctaattaacatca	16202	16215	2-10-2	428_1	CCtaattaacatCA
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430	gccctaattaacat	16204	16217	2-10-2	430_1	GCcctaattaacAT
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432	cggccctaattaac	16206	16219	2-10-2	432_1	CGgccctaattaAC
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437	atataaacacattt	16498	16511	2-10-2	437_1	ATataaacacatTT
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452	actatcacatataa	16513	16526	2-10-2	452_1	ACtatcacatatAA
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457	tcagtccaacataa	16837	16850	2-10-2	457_1	TCagtccaacatAA
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508	aagtaaaaccaatc	19112	19125	2-10-2	508_1	AAgtaaaaccaaTC
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575	aactaataaacttc	23624	23637	2-10-2	575_1	AActaataaactTC
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577	caatcttctatttt	24109	24122	2-10-2	577_1	CAatcttctattTT
578	ccaatcttctattt	24110	24123	2-10-2	578_1	CCaatcttctatTT
579	accaatcttctatt	24111	24124	2-10-2	579_1	ACcaatcttctaTT
580	aaccaatcttctat	24112	24125	2-10-2	580_1	AAccaatcttctAT
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583	tgcaaccaatcttc	24115	24128	2-10-2	583_1	TGcaaccaatctTC
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585	actgcaaccaatct	24117	24130	2-10-2	585_1	ACtgcaaccaatCT
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593	atgaatacaacaca	24340	24353	2-10-2	593_1	ATgaatacaacaCA
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595	tcctaataaaatat	24500	24513	2-10-2	595_1	TCctaataaaatAT
596	ctcctaataaaata	24501	24514	2-10-2	596_1	CTcctaataaaaTA
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809	ttcatcacaaaata	35318	35331	2-10-2	809_1	TTcatcacaaaaTA
810	tttcatcacaaaat	35319	35332	2-10-2	810_1	TTtcatcacaaaAT
811	ttttcatcacaaaa	35320	35333	2-10-2	811_1	TTttcatcacaaAA
812	attttcatcacaaa	35321	35334	2-10-2	812_1	ATtttcatcacaAA
813	tattttcatcacaa	35322	35335	2-10-2	813_1	TAttttcatcacAA
814	gtattttcatcaca	35323	35336	2-10-2	814_1	GTattttcatcaCA
815	atttaaatttatca	35354	35367	2-10-2	815_1	ATttaaatttatCA
816	aatttaaatttatc	35355	35368	2-10-2	816_1	AAtttaaatttaTC
817	aaatttaaatttat	35356	35369	2-10-2	817_1	AAatttaaatttAT
818	aaaatttaaattta	35357	35370	2-10-2	818_1	AAaatttaaattTA
819	taaaatttaaattt	35358	35371	2-10-2	819_1	TAaaatttaaatTT
820	ataaaatttaaatt	35359	35372	2-10-2	820_1	ATaaaatttaaaTT
821	cataaaatttaaat	35360	35373	2-10-2	821_1	CAtaaaatttaaAT

822	acataaaatttaaa	35361	35374	2-10-2	822_1	ACataaaatttaAA
823	ctactaatattcat	36332	36345	2-10-2	823_1	CTactaatattcAT
824	cctactaatattca	36333	36346	2-10-2	824_1	CCtactaatattCA
825	acctactaatattc	36334	36347	2-10-2	825_1	ACctactaatatTC
826	cacctactaatatt	36335	36348	2-10-2	826_1	CAcctactaataTT
827	tcacctactaatat	36336	36349	2-10-2	827_1	TCacctactaatAT
828	ttcacctactaata	36337	36350	2-10-2	828_1	TTcacctactaaTA
829	tttcacctactaat	36338	36351	2-10-2	829_1	TTtcacctactaAT
830	ttttcacctactaa	36339	36352	2-10-2	830_1	TTttcacctactAA
831	tttttcacctacta	36340	36353	2-10-2	831_1	TTtttcacctacTA
832	atttttcacctact	36341	36354	2-10-2	832_1	ATttttcacctaCT
833	tatttttcacctac	36342	36355	2-10-2	833_1	TAtttttcacctAC
834	ttatttttcaccta	36343	36356	2-10-2	834_1	TTatttttcaccTA
835	tttatttttcacct	36344	36357	2-10-2	835_1	TTtatttttcacCT
836	ttctactactaatt	36468	36481	2-10-2	836_1	TTctactactaaTT
837	cttctactactaat	36469	36482	2-10-2	837_1	CTtctactactaAT
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839	aacttctactacta	36471	36484	2-10-2	839_1	AActtctactacTA
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842	ctcaacttctacta	36474	36487	2-10-2	842_1	CTcaacttctacTA
843	tctcaacttctact	36475	36488	2-10-2	843_1	TCtcaacttctaCT
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854	gttacttttctct	36486	36499	2-10-2	854_1	GTtacttttctCT
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857	acattcccattaac	36789	36802	2-10-2	857_1	ACattcccattaAC
858	tacattcccattaa	36790	36803	2-10-2	858_1	TAcattcccattAA
859	ttacattcccatta	36791	36804	2-10-2	859_1	TTacattcccatTA
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862	cttttacattccca	36794	36807	2-10-2	862_1	CTtttacattccCA
863	acttttacattccc	36795	36808	2-10-2	863_1	ACttttacattcCC

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894	taattttcccttca	40076	40089	2-10-2	894_1	TAattttcccttCA
895	ttaattttcccttc	40077	40090	2-10-2	895_1	TTaattttccctTC
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898	ttttatcatttctt	40151	40164	2-10-2	898_1	TTttatcatttcTT
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902	cttcttttatcatt	40155	40168	2-10-2	902_1	CTtcttttatcaTT
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905	ttacttcttttatc	40158	40171	2-10-2	905_1	TTacttcttttaTC

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907	aattacttctttta	40160	40173	2-10-2	907_1	AAttacttctttTA
908	aaattacttctttt	40161	40174	2-10-2	908_1	AAattacttcttTT
909	aaaattacttcttt	40162	40175	2-10-2	909_1	AAaattacttctTT
910	caaaattacttctt	40163	40176	2-10-2	910_1	CAaaattacttcTT
911	ccaaaattacttct	40164	40177	2-10-2	911_1	CCaaaattacttCT
912	tccaaaattacttc	40165	40178	2-10-2	912_1	TCcaaaattactTC
913	ttccaaaattactt	40166	40179	2-10-2	913_1	TTccaaaattacTT
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915	tgttccaaaattac	40168	40181	2-10-2	915_1	TGttccaaaattAC
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924	ccatattttactct	40208	40221	2-10-2	924_1	CCatattttactCT
925	cccatattttactc	40209	40222	2-10-2	925_1	CCcatattttacTC
926	acccatattttact	40210	40223	2-10-2	926_1	ACccatattttaCT
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928	ttacccatatttta	40212	40225	2-10-2	928_1	TTacccatatttTA
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930	gtttacccatattt	40214	40227	2-10-2	930_1	GTttacccatatTT
931	tgtttacccatatt	40215	40228	2-10-2	931_1	TGtttacccataTT
932	gttacctcccttta	40368	40381	2-10-2	932_1	GTtacctcccttTA
933	ggttacctcccttt	40369	40382	2-10-2	933_1	GGttacctcccTT
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1035	ataaaaaccacctt	53263	53276	2-10-2	1035_1	ATaaaaaccaccTT
1036	aataaaaaccacct	53264	53277	2-10-2	1036_1	AAtaaaaaccacCT
1037	gaataaaaaccacc	53265	53278	2-10-2	1037_1	GAataaaaaccaCC
1038	agaataaaaaccac	53266	53279	2-10-2	1038_1	AGaataaaaaccAC
1039	cagaataaaaacca	53267	53280	2-10-2	1039_1	CAgaataaaaacCA
1040	ccagaataaaaacc	53268	53281	2-10-2	1040_1	CCagaataaaaaCC
1041	cccagaataaaaac	53269	53282	2-10-2	1041_1	CCcagaataaaaAC
1042	acccagaataaaaa	53270	53283	2-10-2	1042_1	ACccagaataaaAA
1043	tttcttactcccct	53699	53712	2-10-2	1043_1	TTtcttactcccCT
1044	ctttcttactcccc	53700	53713	2-10-2	1044_1	CTttcttactccCC
1045	actttcttactccc	53701	53714	2-10-2	1045_1	ACtttcttactcCC
1046	cactttcttactcc	53702	53715	2-10-2	1046_1	CActttcttactCC
1047	ccactttcttactc	53703	53716	2-10-2	1047_1	CCactttcttacTC
1048	cctttaccacttttt	53948	53961	2-10-2	1048_1	CCtttaccacttTT
1049	ccctttaccacttt	53949	53962	2-10-2	1049_1	CCctttaccactTT
1050	tccctttaccactt	53950	53963	2-10-2	1050_1	TCcctttaccacTT
1051	atccctttaccact	53951	53964	2-10-2	1051_1	ATccctttaccaCT
1052	catccctttaccac	53952	53965	2-10-2	1052_1	CAtccctttaccAC
1053	ctacatctaacccc	54550	54563	2-10-2	1053_1	CTacatctaaccCC
1054	tctacatctaaccc	54551	54564	2-10-2	1054_1	TCtacatctaacCC
1055	gtctacatctaacc	54552	54565	2-10-2	1055_1	GTctacatctaaCC
1056	agtctacatctaac	54553	54566	2-10-2	1056_1	AGtctacatctaAC
1057	cagtctacatctaa	54554	54567	2-10-2	1057_1	CAgtctacatctAA
1058	tcagtctacatcta	54555	54568	2-10-2	1058_1	TCagtctacatcTA
1059	ttcagtctacatct	54556	54569	2-10-2	1059_1	TTcagtctacatCT
1060	taaccacacctcct	54573	54586	2-10-2	1060_1	TAaccacacctcCT
1061	ttaaccacacctcc	54574	54587	2-10-2	1061_1	TTaaccacacctCC
1062	tttaaccacacctc	54575	54588	2-10-2	1062_1	TTtaaccacaccTC
1063	ttttaaccacacct	54576	54589	2-10-2	1063_1	TTttaaccacacCT
1064	gttttaaccacacc	54577	54590	2-10-2	1064_1	GTtttaaccacaCC
1065	agttttaaccacac	54578	54591	2-10-2	1065_1	AGttttaaccacAC
1066	caacaaaacatcaa	55228	55241	2-10-2	1066_1	CAacaaaacatcAA
1067	tcaacaaaacatca	55229	55242	2-10-2	1067_1	TCaacaaaacatCA
1068	ttcaacaaaacatc	55230	55243	2-10-2	1068_1	TTcaacaaaacaTC
1069	tttcaacaaaacat	55231	55244	2-10-2	1069_1	TTtcaacaaaacAT
1070	ttttcaacaaaaca	55232	55245	2-10-2	1070_1	TTttcaacaaaaCA
1071	gttttcaacaaaac	55233	55246	2-10-2	1071_1	GTtttcaacaaaAC
1072	tgttttcaacaaaa	55234	55247	2-10-2	1072_1	TGttttcaacaaAA
1073	ttctaaaacttacc	55269	55282	2-10-2	1073_1	TTctaaaacttaCC

1074	tttctaaaacttac	55270	55283	2-10-2	1074_1	TTtctaaaacttAC
1075	ctttctaaaactta	55271	55284	2-10-2	1075_1	CTttctaaaactTA
1076	tctttctaaaactt	55272	55285	2-10-2	1076_1	TCtttctaaaacTT
1077	atctttctaaaact	55273	55286	2-10-2	1077_1	ATctttctaaaaCT
1078	aatctttctaaaac	55274	55287	2-10-2	1078_1	AAtctttctaaaAC
1079	gaatctttctaaaa	55275	55288	2-10-2	1079_1	GAatctttctaaAA
1080	agaatctttctaaa	55276	55289	2-10-2	1080_1	AGaatctttctaAA
1081	cagaatctttctaa	55277	55290	2-10-2	1081_1	CAgaatctttctAA
1082	cctttatttccctt	55494	55507	2-10-2	1082_1	CCtttatttcccTT
1083	ccctttatttccct	55495	55508	2-10-2	1083_1	CCctttatttccCT
1084	tccctttatttccc	55496	55509	2-10-2	1084_1	TCcctttatttcCC
1085	ttccctttatttcc	55497	55510	2-10-2	1085_1	TTcctttatttCC
1086	tttccctttatttc	55498	55511	2-10-2	1086_1	TTtcctttattTC
1087	atttccctttattt	55499	55512	2-10-2	1087_1	ATttcctttatTT
1088	tatttccctttatt	55500	55513	2-10-2	1088_1	TAtttcctttaTT
1089	gtatttccctttat	55501	55514	2-10-2	1089_1	GTatttcctttAT

Oligonucleotide compound represent specific designs of a motif sequence. Typically, capital letters represent beta-D-oxy LNA nucleosides, lowercase letters represent DNA nucleosides, all LNA C are 5-methyl cytosine, and 5-methyl DNA cytosines are presented by “e” or ^{m}c, all internucleoside linkages are phosphorothioate internucleoside linkages.

Design refers to the gapmer design, F-G-F’, where each number represents the number of consecutive modified nucleosides, e.g. 2’ modified nucleosides (first number=5’ flank), followed by the number of DNA nucleosides (second number= gap region), followed by the number of modified nucleosides, e.g. 2’ modified nucleosides (third number=3’ flank), optionally preceded by or followed by further repeated regions of DNA and LNA, which are not necessarily part of the contiguous nucleotide sequence that is complementary to the target nucleic acid.

Motif sequences represent the contiguous sequence of nucleobases present in the oligonucleotide, also referred to as the Oligonucleotide Base Sequence.

The invention provides antisense oligonucleotides according to the invention, such as antisense oligonucleotides 12 – 24, such as 12 – 18 in length, nucleosides in length wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least 12, such as at least 14, such as at least 15 contiguous nucleotides present in a of sequence selected from SEQ ID NO 4 to SEQ ID NO: 1089; SEQ ID Nos 1099 to 1127; and SEQ ID NO 1137 – 1988.

The antisense oligonucleotides provided herein typically comprise or consist of a contiguous nucleotide sequence selected from SEQ ID NO 4 – 1089. For example, the antisense oligonucletodies are LNA gapmers comprising or consisting of a contiguous nucleotide sequence selected from SEQ ID NO 4 – 1089.

In some embodiments, the antisense oligonucleotide of the present invention comprises or consists of a nucleotide sequence selected from SEQ ID NO 4 – 1089. For example, the antisense oligonucleotide of the present invention is a LNA gapmer comprising or consisting of a contiguous nucleotide sequence selected from SEQ ID NO 4 – 1089. Preferred compounds are listed in Table 2 above, see columns “Oligonucleotide compounds”.

The invention provides antisense oligonucleotides according to the invention, such as antisense oligonucleotides 12 – 24, such as 12 – 18 in length, nucleosides in length wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least 12, such as at least 14, such as at least 15 contiguous nucleotides present in a sequence selected from SEQ ID NO 1190 to SEQ ID NO: 1136.

The invention provides antisense oligonucleotides according to the invention, such as antisense oligonucleotides 12 – 24, such as 12 – 18 in length, nucleosides in length wherein the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least 12, such as at least 14, such as at least 15 contiguous nucleotides present in a sequence selected from SEQ ID NO 1190 to SEQ ID NO: 1136.

The antisense oligonucleotides provided herein typically comprise or consist of a contiguous nucleotide sequence selected from SEQ ID NO 1190 – 1136. For example, the antisense oligonucletodies are LNA gapmers comprising or consisting of a contiguous nucleotide sequence selected from SEQ ID NO 1190 to SEQ ID NO: 1136.

In some embodiments, the antisense oligonucleotide of the present invention comprises or consists of a nucleotide sequence selected from SEQ ID NO 1190 – 1136. For example, the antisense oligonucleotide of the present invention is a LNA gapmer comprising or consisting of a contiguous nucleotide sequence selected from SEQ ID NO 1190 to SEQ ID NO: 1136. See the examples for exemplary oligonucleotide of the invention.

The invention provides antisense oligonucleotides according to the invention, such as antisense oligonucleotides 12 – 24, such as 12 – 18 in length, nucleosides in length wherein

the antisense oligonucleotide comprises a contiguous nucleotide sequence comprising at least 12, such as at least 14, such as at least 15 contiguous nucleotides present in a of sequence selected from SEQ ID NO 1137 to SEQ ID NO: 1988.

The antisense oligonucleotides provided herein typically comprise or consist of a contiguous nucleotide sequence selected from SEQ ID NO SEQ ID NO 1137 to SEQ ID NO: 1988. For example, the antisense oligonucletodies are LNA gapmers comprising or consisting of a contiguous nucleotide sequence selected from SEQ ID NO 1137 to SEQ ID NO: 1988.

In some embodiments, the antisense oligonucleotide of the present invention comprises or consists of a nucleotide sequence selected from SEQ ID NO 1137 to SEQ ID NO: 1988. For example, the antisense oligonucleotide of the present invention is a LNA gapmer comprising or consisting of a contiguous nucleotide sequence selected from SEQ ID NO 1137 to SEQ ID NO: 1988. See the examples for exemplary oligonucleotide of the invention.

In some embodiments, the invention refers to oligomeric compounds, capable of inhibiting the expression of ataxin3 in a cell which is expressing ataxin 3 (such as human ataxin 3), wherein the oligomeric compound comprises at least 10 contiguous nucleotides which are identical to a contiguous sequence of nucleobases present in a sequence selected from the group consisting of 4 – 1988.

In some embodiments, the invention refers to oligomeric compounds, capable of inhibiting the expression of ataxin3 in a cell which is expressing ataxin 3 (such as human ataxin 3), wherein the oligomeric compound comprises at least 12 contiguous nucleotides which are identical to a contiguous sequence of nucleobases present in a sequence selected from the group consisting of 4 – 1988.

In some embodiments, the invention refers to oligomeric compounds, capable of inhibiting the expression of ataxin3 in a cell which is expressing ataxin 3 (such as human ataxin 3), wherein the oligomeric compound comprises at least 14 contiguous nucleotides which are identical to a contiguous sequence of nucleobases present in a sequence selected from the group consisting of 4 – 1988.

In some embodiments, the invention refers to oligomeric compounds, capable of inhibiting the expression of ataxin3 in a cell which is expressing ataxin 3 (such as human ataxin 3), wherein the oligomeric compound comprises at least 16 contiguous nucleotides which are identical to a contiguous sequence of nucleobases present in a sequence selected from the group consisting of 4 – 1988.

In some embodiments, the invention refers to oligomeric compounds, capable of inhibiting the expression of ataxin3 in a cell which is expressing ataxin 3 (such as human ataxin 3), wherein the oligomeric compound comprises a contiguous nucleotides which are identical to the contiguous sequence of nucleobases shown in a sequence selected from the group consisting of 4 – 1988.

The invention provides antisense oligonucleotides selected from the group consisting of the antisense oligonucleotides listed in Table 2 in the column "Oligonucleotide compounds", wherein a capital letter is a LNA nucleoside, and a lower case letter is a DNA nucleoside. In some embodiments all internucleoside linkages in contiguous nucleoside sequence are phosphorothioate internucleoside linkages. Optionally LNA cytosine may be 5-methyl cytosine. Optionally DNA cytosine may be 5-methyl cytosine. Optionall uracil may be used in place of thymine bases.

The invention provides antisense oligonucleotides selected from the group consisting of the antisense oligonucleotides listed in Table 2 in the column "Oligonucleotide compounds", wherein a capital letter is a beta-D-oxy-LNA nucleoside, and a lower case letter is a DNA nucleoside. In some embodiments all internucleoside linkages in contiguous nucleoside sequence are phosphorothioate internucleoside linkages. Optionally LNA cytosine may be 5-methyl cytosine. Optionally DNA cytosine may be 5-methyl cytosine.

The invention provides antisense oligonucleotides selected from the group consisting of the antisense oligonucleotides listed in Table 2 in the column "Oligonucleotide compounds", wherein a capital letter is a ScET LNA nucleoside, and a lower case letter is a DNA nucleoside. In some embodiments all internucleoside linkages in contiguous nucleoside sequence are phosphorothioate internucleoside linkages. Optionally LNA cytosine may be 5-methyl cytosine. Optionally DNA cytosine may be 5-methyl cytosine.

The invention provides antisense oligonucleotides selected from the group consisting of the antisense oligonucleotides listed in Table 2 in the column "Oligonucleotide compounds", wherein a capital letter is a beta-D-oxy-LNA nucleoside, wherein all LNA cytosines are 5-methyl cytosine, and a lower case letter is a DNA nucleoside, wherein all internucleoside linkages in contiguous nucleoside sequence are phosphorothioate internucleoside linkages, and optionally DNA cytosine may be 5-methyl cytosine.

The invention provides antisense oligonucleotides selected from the group consisting of the antisense oligonucleotides listed in Table 2 in the column "Oligonucleotide compounds", wherein a capital letter is a ScET LNA nucleoside, wherein all LNA cytosines are 5-methyl cytosine, and a lower case letter is a DNA nucleoside, wherein all internucleoside linkages in contiguous nucleoside sequence are phosphorothioate internucleoside linkages, and optionally DNA cytosine may be 5-methyl cytosine.

Method of manufacture

In a further aspect, the invention provides methods for manufacturing the oligonucleotides of the invention comprising reacting nucleotide units and thereby forming covalently linked contiguous nucleotide units comprised in the oligonucleotide. Preferably, the method uses phophoramidite chemistry (see for example Caruthers et al, 1987, Methods in Enzymology vol. 154, pages 287-313). In a further embodiment the method further comprises reacting the contiguous nucleotide sequence with a conjugating moiety (ligand) to covalently attach the conjugate moiety to the oligonucleotide. In a further aspect a method is provided for manufacturing the composition of the invention, comprising mixing the oligonucleotide or conjugated oligonucleotide of the invention with a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.

Pharmaceutical Composition

In a further aspect, the invention provides pharmaceutical compositions comprising any of the aforementioned oligonucleotides and/or oligonucleotide conjugates or salts thereof and a pharmaceutically acceptable diluent, carrier, salt and/or adjuvant.

In a further aspect, the invention provides pharmaceutical compositions comprising any of the aforementioned oligonucleotides and/or oligonucleotide conjugates or salts thereof and a pharmaceutically acceptable diluent, carrier, salt or adjuvant.

A pharmaceutically acceptable diluent includes phosphate-buffered saline (PBS) and pharmaceutically acceptable salts include, but are not limited to, sodium and potassium salts. In some embodiments the pharmaceutically acceptable diluent is sterile phosphate buffered saline. In some embodiments the oligonucleotide is used in the pharmaceutically acceptable diluent at a concentration of 50 - 300μM solution.

The compounds according to the present invention may exist in the form of their pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of the present invention and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Acid-addition salts include for example those derived from inorganic acids such as hydrochloric acid, hydrobromic acid,

hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as *p*-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Base-addition salts include those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethyl ammonium hydroxide. The chemical modification of a pharmaceutical compound into a salt is a technique well known to pharmaceutical chemists in order to obtain improved physical and chemical stability, hygroscopicity, flowability and solubility of compounds. It is for example described in Bastin, Organic Process Research & Development 2000, 4, 427-435 or in Ansel, In: Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th ed. (1995), pp. 196 and 1456-1457. For example, the pharmaceutically acceptable salt of the compounds provided herein may be a sodium salt.

Suitable formulations for use in the present invention are found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Philadelphia, Pa., 17th ed., 1985. For a brief review of methods for drug delivery, see, e.g., Langer (Science 249:1527-1533, 1990). WO 2007/031091 provides further suitable and preferred examples of pharmaceutically acceptable diluents, carriers and adjuvants (hereby incorporated by reference). Suitable dosages, formulations, administration routes, compositions, dosage forms, combinations with other therapeutic agents, pro-drug formulations are also provided in WO2007/031091.

Oligonucleotides or oligonucleotide conjugates of the invention may be mixed with pharmaceutically acceptable active or inert substances for the preparation of pharmaceutical compositions or formulations. Compositions and methods for the formulation of pharmaceutical compositions are dependent upon a number of criteria, including, but not limited to, route of administration, extent of disease, or dose to be administered.

These compositions may be sterilized by conventional sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the preparations typically will be between 3 and 11, more preferably between 5 and 9 or between 6 and 8, and most preferably between 7 and 8, such as 7 to 7.5. The resulting compositions in solid form may be packaged in multiple single dose units, each containing a fixed amount of the above-mentioned agent or agents, such as in a sealed package of tablets or capsules. The composition in solid form can also be packaged in a container for a flexible quantity, such as in a squeezable tube designed for a topically applicable cream or ointment.

In some embodiments, the oligonucleotide or oligonucleotide conjugate of the invention is a prodrug. In particular with respect to oligonucleotide conjugates the conjugate moiety is cleaved of the oligonucleotide once the prodrug is delivered to the site of action, e.g. the target cell.

Applications

The oligonucleotides of the invention may be utilized as research reagents for, for example, diagnostics, therapeutics and prophylaxis.

In research, such oligonucleotides may be used to specifically modulate the synthesis of ATXN3 protein in cells (e.g. *in vitro* cell cultures) and experimental animals thereby facilitating functional analysis of the target or an appraisal of its usefulness as a target for therapeutic intervention. Typically the target modulation is achieved by degrading or inhibiting the mRNA producing the protein, thereby prevent protein formation or by degrading or inhibiting a modulator of the gene or mRNA producing the protein.

If employing the oligonucleotide of the invention in research or diagnostics the target nucleic acid may be a cDNA or a synthetic nucleic acid derived from DNA or RNA.

The present invention provides an *in vivo* or *in vitro* method for modulating *ATXN3* expression in a target cell which is expressing *ATXN3*, said method comprising administering an oligonucleotide of the invention in an effective amount to said cell.

In some embodiments, the target cell, is a mammalian cell in particular a human cell. The target cell may be an *in vitro* cell culture or an *in vivo* cell forming part of a tissue in a mammal.

In diagnostics the oligonucleotides may be used to detect and quantitate *ATXN3* expression in cell and tissues by northern blotting, *in-situ* hybridisation or similar techniques.

For therapeutics, an animal or a human, suspected of having a disease or disorder, which can be treated by modulating the expression of *ATXN3*

The invention provides methods for treating or preventing a disease, comprising administering a therapeutically or prophylactically effective amount of an oligonucleotide, an oligonucleotide conjugate or a pharmaceutical composition of the invention to a subject suffering from or susceptible to the disease.

The invention also relates to an oligonucleotide, a composition or a conjugate as defined herein for use as a medicament.

The oligonucleotide, oligonucleotide conjugate or a pharmaceutical composition according to the invention is typically administered in an effective amount.

The invention also provides for the use of the oligonucleotide or oligonucleotide conjugate of the invention as described for the manufacture of a medicament for the treatment of a

disorder as referred to herein, or for a method of the treatment of as a disorder as referred to herein.

The disease or disorder, as referred to herein, is associated with expression of *ATXN3*. In some embodiments disease or disorder may be associated with a mutation in the *ATXN3* gene. Therefore, in some embodiments, the target nucleic acid is a mutated form of the *ATXN3* sequence.

The methods of the invention are preferably employed for treatment or prophylaxis against diseases caused by abnormal levels and/or activity of *ATXN3*.

The invention further relates to use of an oligonucleotide, oligonucleotide conjugate or a pharmaceutical composition as defined herein for the manufacture of a medicament for the treatment of abnormal levels and/or activity of *ATXN3*.

In one embodiment, the invention relates to oligonucleotides, oligonucleotide conjugates or pharmaceutical compositions for use in the treatment of spinocerebellar ataxia.

Administration

In some embodiments, the oligonucleotides or pharmaceutical compositions of the present invention may be administered oral. In further embodiments, the oligonucleotides or pharmaceutical compositions of the present invention may be administered topical or enteral or parenteral (such as, intravenous, subcutaneous, intra-muscular, intracerebral, intracerebroventricular or intrathecal).

In a preferred embodiment the oligonucleotide or pharmaceutical compositions of the present invention are administered by a parenteral route including intravenous, intraarterial, subcutaneous, intraperitoneal or intramuscular injection or infusion, intrathecal or intracranial, e.g. intracerebral or intraventricular, intravitreal administration. In one embodiment the active oligonucleotide or oligonucleotide conjugate is administered intravenously. In another embodiment the active oligonucleotide or oligonucleotide conjugate is administered subcutaneously.

In some embodiments, the oligonucleotide, oligonucleotide conjugate or pharmaceutical composition of the invention is administered at a dose of 0.1 – 15 mg/kg, such as from 0.2 – 10 mg/kg, such as from 0.25 – 5 mg/kg. The administration can be once a week, every 2nd week, every third week or even once a month.

Combination therapies

In some embodiments the oligonucleotide, oligonucleotide conjugate or pharmaceutical composition of the invention is for use in a combination treatment with another therapeutic agent. The therapeutic agent can for example be the standard of care for the diseases or disorders described above.

FURTHER EMBODIMENTS

The following further emboidments may be combined with the embodiments described elsewhere in the application or claims:

1. An antisense oligonucleotide, 10-30 nucleotides in length, wherein said antisense oligonucleotide comprises a contiguous nucleotide sequence 10 – 30 nucleotides in length, wherein the contiguous nucleotide sequence is at least 90% complementary, such as fully complementary to SEQ ID NO 1, wherein the antisense oligonucleotide is capable of inhibiting the expression of human *ATXN3* in a cell which is expressing human *ATXN3*; or a pharmaceutically acceptable salt thereof.
2. The antisense oligonucleotide according to embodiment 1, wherein the contiguous nucleotide sequence is fully complementary to a region of SEQ ID NO 1, selected from the group consisting of 721 - 765; 786 - 820; 1012 - 1038; 1040 - 1080; 1186 - 1213; 2870 - 2915; 2944 - 2988; 3168 - 3206; 3210 - 3257; 3462 - 3493; 3880 - 3906; 3908 - 3977; 4094 - 4128; 4173 - 4203; 5098 - 5177; 5538 - 5560; 5690 - 5749; 6407 - 6450; 7401 - 7434; 7436 - 7521; 8609 - 8637; 8636 - 8676; 8693 - 8715; 9391 - 9414; 10943 - 11030; 11543 - 11563; 11942 - 11967; 12175 - 12204; 12206 - 12229; 12254 - 12324; 12327 - 12364; 12682 - 12708; 12739 - 12758; 13127 - 13197; 13289 - 13412; 13990 - 14031; 14041 - 14113; 14115 - 14138; 14257 - 14288; 14570 - 14612; 15778 - 15805; 15813 - 15848; 15850 - 15900; 16069 - 16115; 16187 - 16229; 16494 - 16527; 16834 - 16852; 16910 - 16956; 18012 - 18051; 18615 - 18650; 19085 - 19135; 20214 - 20241; 20554 - 20599; 22073 - 22096; 22251 - 22292; 22422 - 22447; 23196 - 23228; 23616 - 23637; 24071 - 24132; 24217 - 24383; 24486 - 24541; 24586 - 24615; 24739 - 24778; 24848 - 24888; 24975 - 24995; 25026 - 25117; 25499 - 25540; 27081 - 27233; 27771 - 27810; 27927 - 27953; 29297 - 29323; 29336 - 29445; 30705 - 30792; 31006 - 31111; 32057 - 32090; 33420 - 33470; 33792 - 33817; 33963 - 34002; 34050 - 34073; 34075 - 34103; 34523 - 34570; 35302 - 35378; 36322 - 36357; 36461 - 36500; 36786 - 36820; 36822 - 36862; 38848 - 38885; 40059 - 40091; 40149 - 40228; 40365 - 40399; 41655 - 41684; 41699 - 41720; 41773 - 41799; 42145 - 42218; 43826 - 43868; 45488 - 45508; 47371 - 47417; 48061 - 48117; 48894 - 48924; 48959 - 48996; 50076 - 50112; 51008 - 51031; 51826 - 51892; 53239 - 53301; 53688 - 53719; 53931 - 53967; 54550 - 54610; 55218 - 55258; 55269 - 55299; 55494 - 55514; or a pharmaceutically acceptable salt thereof..

3. The antisense oligonucleotide according to embodiment 1, wherein the contiguous nucleotide sequence is fully complementary to a region of SEQ ID NO 1, selected from the group consisting of 43 - 101; 721 - 736; 786 - 808; 1682 - 1698; 1682 - 1700; 1688 - 1703; 1688 - 1702; 1787 - 1801; 1832 - 1846; 2259 - 2273; 4296 - 4310; 4397 - 4411; 4402 - 4417; 4593 - 4611; 4598 - 4612; 4601 - 4615; 5031 - 5046; 5264 - 5278; 5564 - 5578; 6547 - 6567; 6676 - 6690; 7056 - 7073; 9078 - 9092; 9078 - 9093; 9079 - 9093; 9080 - 9094; 9781 - 9806; 9838 - 9854; 9857 - 9872; 9896 - 9911; 9940 - 9956; 9977 - 9992; 9977 - 9993; 9987 - 10003; 10110 - 10124; 10480 - 10510; 12330 - 12344; 12660 - 12677; 12660 - 12676; 12661 - 12677; 12787 - 12804; 12806 - 12852; 12869 - 12884; 12917 - 12931; 13317 - 13333; 13335 - 13363; 13578 - 13592; 15660 - 15676; 17803 - 17824; 17841 - 17857; 17868 - 17884; 18541 - 18556; 23358 - 23379; 23434 - 23448; 23450 - 23469; 23617 - 23632; 23843 - 23859; 23946 - 23961; 24338 - 24352; 25281 - 25296; 25634 - 25674; 27146 - 27163; 27182 - 27222; 27415 - 27434; 27415 - 27429; 27500 - 27517; 28239 - 28253; 28244 - 28258; 30158 - 30172; 32776 - 32790; 34946 - 34965; 35110 - 35124; 35331 - 35345; 35588 - 35602; 35597 - 35612; 40009 - 40023; 42239 - 42267; 43570 - 43585; 43789 - 43803; 43870 - 43884; 45381 - 45397; 47736 - 47750; 47758 - 47774; 48013 - 48035; 48037 - 48053; 49337 - 49353; 50653 - 50668; 50656 - 50670; 51424 - 51438; 56049 - 56063; and, 61333 - 61348; or a pharmaceutically acceptable salt thereof.

4. The antisense oligonucleotide according to any one of embodiments 1 - 3, wherein the contiguous nucleotide sequence comprises a region of at least 8 or at least 10 contiguous nucleotides which are fully complementary to a region of SEQ ID NO 1, selected from the group consisting of 743 - 760 ; 2969 - 2987 ; 4175 - 4191 ; 5131 - 5148 ; 7436 - 7453 ; 9395 - 9414 ; 12742 - 12758 ; 14572 - 14590 ; 16188 - 16207 ; 16924 - 16940 ; 18630 - 18647 ; 22074 - 22092 ; 23204 - 23221 ; 24509 - 24528 ; 27100 - 27119 ; 30115 - 30132 ; 32059 - 32078 ; 34075 - 34093 ; 35310 - 35329 ; 36470 - 36489 ; 38853 - 38871 ; 40158 - 40177 ; 41777 - 41794 ; 48905 - 48923 ; 51866 - 51882 ; and 53949 - 53965; or a pharmaceutically acceptable salt thereof.

5. The antisense oligonucleotide according to any one of embodiments 1 - 3, wherein the contiguous nucleotide sequence comprises a region of at least 12 or at least 14 contiguous nucleotides which are fully complementary to a region of SEQ ID NO 1, selected from the group consisting of 743 - 760 ; 2969 - 2987 ; 4175 - 4191 ; 5131 - 5148 ; 7436 - 7453 ; 9395 - 9414 ; 12742 - 12758 ; 14572 - 14590 ; 16188 - 16207 ; 16924 - 16940 ; 18630 - 18647 ; 22074 - 22092 ; 23204 -

23221 ; 24509 - 24528 ; 27100 - 27119 ; 30115 - 30132 ; 32059 - 32078 ; 34075 - 34093 ; 35310 - 35329 ; 36470 - 36489 ; 38853 - 38871 ; 40158 - 40177 ; 41777 - 41794 ; 48905 - 48923 ; 51866 - 51882 ; and 53949 - 53965; or a pharmaceutically acceptable salt thereof.

6. The antisense oligonucleotide according to any one of embodiments 1 – 5, wherein the antisense oligonucleotide is a gapmer oligonucleotide comprising a contiguous nucleotide sequence of formula 5'-F-G-F'-3', where region F and F' independently comprise 1 - 8 sugar modified nucleosides, and G is a region between 5 and 16 nucleosides which are capable of recruiting RNaseH; or a pharmaceutically acceptable salt thereof.
7. The antisense oligonucleotide according to embodiment 6, wherein the sugar modified nucleosides of region F and F' are independently selected from the group consisting of 2'-O-alkyl-RNA, 2'-O-methyl-RNA, 2'-alkoxy-RNA, 2'-O-methoxyethyl-RNA, 2'-amino-DNA, 2'-fluoro-DNA, arabino nucleic acid (ANA), 2'-fluoro-ANA and LNA nucleosides; or a pharmaceutically acceptable salt thereof.
8. The antisense oligonucleotide according to embodiment 5 or 6, wherein region G comprises 5 – 16 contiguous DNA nucleosides; or a pharmaceutically acceptable salt thereof.
9. The antisense oligonucleotide according to any one of embodiments 1 – 8, wherein the antisense oligonucleotide is a gapmer oligonucleotide such as an LNA gapmer oligonucleotide; or a pharmaceutically acceptable salt thereof.
10. The antisense oligonucleotide according to any one of embodiments 5 – 9, wherein the LNA nucleosides are beta-D-oxy LNA nucleosides; or a pharmaceutically acceptable salt thereof.
11. The antisense oligonucleotide according to any one of embodiments 1 – 10, wherein the internucleoside linkages between the contiguous nucleotide sequence are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.
12. The antisense oligonucleotide according to any one of embodiments 1 – 11, wherein the oligonucleotide comprises a contiguous nucleotide sequence selected from the group consisting of SEQ ID NO 4 to SEQ ID NO: 1089; SEQ ID Nos 1099 to 1127; and SEQ ID NO 1137 – 1988; or a pharmaceutically acceptable salt thereof.
13. The antisense oligonucleotide according to any one of embodiments 1 – 13, wherein the oligonucleotide is an oligonucleotide compound selected from the oligonucleotide compounds shown in Table 2, wherein a capital letter represents a LNA nucleoside,

a lower case letter represents a DNA nucleoside; or a pharmaceutically acceptable salt thereof.

14. The antisense oligonucleotide according to any one of embodiments 1 – 13, wherein the oligonucleotide is is an oligonucleotide compound selected from the oligonucleotide compounds shown in Table 2, wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages, or a pharmaceutically salt thereof; or a pharmaceutically acceptable salt thereof.
15. The antisense oligonucleotide according to any one of embodiments 1 – 13, wherein the compound is selected from the group consisting of compounds 1099_1, 1100_1, 1101_1, 1102_1, 1103_1, 1104_1, 1105_1, 1106_1, 1107_1, 1108_1, 1109_1, 1110_1, 1111_1, 1112_1, 1113_1, 1114_1, 1115_1, 1116_1, 1117_1, 1118_1, 1119_1, 1120_1, 1121_1, 1122_1, 1123_1, 1124_1, 1125_1, 1126_1, and 1127_1 or a oligonucleotide compound shown in the tables in Examples 2,3 or 4; or a pharmaceutically salt thereof.
16. A conjugate comprising the oligonucleotide according to any one of embodiments 1 – 15, and at least one conjugate moiety covalently attached to said oligonucleotide; or a pharmaceutically acceptable salt thereof.
17. A pharmaceutical composition comprising the oligonucleotide of embodiment 1-15 or the conjugate of embodiment 16 and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.
18. An *in vivo* or *in vitro* method for modulating *ATXN3* expression in a target cell which is expressing *ATXN3*, said method comprising administering an oligonucleotide or salt of any one of embodiments 1-15, the conjugate according to embodiment 16, or the pharmaceutical composition of embodiment 17 in an effective amount to said cell.
19. A method for treating or preventing a disease comprising administering a therapeutically or prophylactically effective amount of an oligonucleotide or salt of any one of embodiments 1 - 15 or the conjugate according to embodiment 16 or the pharmaceutical composition of embodiment 17 to a subject suffering from or susceptible to the disease.
20. The method of embodiment 19, wherein the disease is spinocerebellar ataxia, such as spinocerebellar ataxia 3, such as Machado-Joseph disease (MJD).
21. The oligonucleotide or salt of any one of embodiments 1 - 15 or the conjugate according to embodiment 16 or the pharmaceutical composition of embodiment 17 for use in medicine.

22. The oligonucleotide or salt of any one of embodiments 1 - 15 or the conjugate according to embodiment 16 or the pharmaceutical composition of embodiment 15 for use in the treatment or prevention of spinocerebellar ataxia, such as spinocerebellar ataxia 3, such as Machado-Joseph disease (MJD).
23. Use of the oligonucleotide or salt of embodiment 1 - 15 or the conjugate according to embodiment 16 or the pharmaceutical composition of embodiment 17, for the preparation of a medicament for treatment or prevention of spinocerebellar ataxia, such as spinocerebellar ataxia 3, such as Machado-Joseph disease (MJD).

EXAMPLES

Materials and methods

Oligonucleotide synthesis

Oligonucleotide synthesis is generally known in the art. Below is a protocol which may be applied. The oligonucleotides of the present invention may have been produced by slightly varying methods in terms of apparatus, support and concentrations used.

Oligonucleotides are synthesized on uridine universal supports using the phosphoramidite approach on an Oligomaker 48 at 1 µmol scale. At the end of the synthesis, the oligonucleotides are cleaved from the solid support using aqueous ammonia for 5-16hours at 60°C. The oligonucleotides are purified by reverse phase HPLC (RP-HPLC) or by solid phase extractions and characterized by UPLC, and the molecular mass is further confirmed by ESI-MS.

Elongation of the oligonucleotide:

The coupling of β-cyanoethyl- phosphoramidites (DNA-A(Bz), DNA- G(ibu), DNA- C(Bz), DNA-T, LNA-5-methyl-C(Bz), LNA-A(Bz), LNA- G(dmf), or LNA-T) is performed by using a solution of 0.1 M of the 5'-O-DMT-protected amidite in acetonitrile and DCI (4,5–dicyanoimidazole) in acetonitrile (0.25 M) as activator.

Purification by RP-HPLC:

The crude compounds are purified by preparative RP-HPLC on a Phenomenex Jupiter C18 10µ 150x10 mm column. 0.1 M ammonium acetate pH 8 and acetonitrile is used as buffers at a flow rate of 5 mL/min. The collected fractions are lyophilized to give the purified compound typically as a white solid.

Abbreviations:

DCI: 4,5-Dicyanoimidazole

DCM: Dichloromethane
DMF: Dimethylformamide
DMT: 4,4'-Dimethoxytrityl
THF: Tetrahydrofurane
Bz: Benzoyl
Ibu: Isobutyryl
RP-HPLC: Reverse phase high performance liquid chromatography

T_m Assay:

Oligonucleotide and RNA target (phosphate linked, PO) duplexes are diluted to 3 mM in 500 ml RNase-free water and mixed with 500 ml 2x T_m-buffer (200mM NaCl, 0.2mM EDTA, 20mM Naphosphate, pH 7.0). The solution is heated to 95ºC for 3 min and then allowed to anneal in room temperature for 30 min. The duplex melting temperatures (T_m) is measured on a Lambda 40 UV/VIS Spectrophotometer equipped with a Peltier temperature programmer PTP6 using PE Templab software (Perkin Elmer). The temperature is ramped up from 20ºC to 95ºC and then down to 25ºC, recording absorption at 260 nm. First derivative and the local maximums of both the melting and annealing are used to assess the duplex T_m.

Cell lines

Table 3: Details in relation to the cell lines for assaying the compounds:

Cell lines				Cells/well (96 well plate)	Hours of cell incubation prior to treatment	Days of treatment
Name	**Vendor**	**Cat.no.**	**Cell medium**			
A431	ECACC	85090402	EMEM (Cat.no. M2279), 10% FBS (Cat.no. F7524), 2mM Glutamine (Cat.no. G8541), 0.1 mM NEAA (Cat.no. M7145), 25µg/ml Gentamicin (Cat.no. G1397)	8000	24	3
NCI-H23	ATCC	CRL-5800	RPMI 1640 (Cat.no. R2405), 10% FBS (Cat.no. F7524),	10000	24	3

Cell lines				Cells/well (96 well plate)	Hours of cell incubation prior to treatment	Days of treatment
Name	Vendor	Cat.no.	Cell medium			
			10mM Hepes (Cat.no. H0887), 1mM Sodium Pyruvate (Cat.no. S8636), 25µg/ml Gentamicin (Cat.no. G1397)			
ARPE19	ATCC	CRL-2302	DMEM/F-12 HAM (Cat.no. D8437), 10% FBS (Cat.no. F7524), 25µg/ml Gentamicin (Cat.no. G1397)	2000	0	4
U251	ECACC	9063001	EMEM (Cat.no. M2279), 10% FBS (Cat.no. F7524), 2mM Glutamine (Cat.no. G8541), 0.1 mM NEAA (Cat.no. M7145), 1mM Sodium Pyruvate (Cat.no. S8636), 25µg/ml Gentamicin (Cat.no. G1397)	2000	0	4
U2-OS	ATCC	HTB-96	MCCoy 5A medium (Cat.no. M8403), 10% FBS (Cat.no. F7524), 1.5mM Glutamine (Cat.no. G8541), 25µg/ml Gentamicin	7000	24	3

Cell lines				Cells/well (96 well plate)	Hours of cell incubation prior to treatment	Days of treatment
Name	Vendor	Cat.no.	Cell medium			
			(Cat.no. G1397)			
SK-N-AS	ATCC	CRL-2137	Dulbecco's Modified Eagle's Medium, supplemented with 0.1 mM Non-Essential Amino Acids (NEAA) and fetal bovine serum to a final concentration of 10%	9300	24	4
iCell GlutaNeurons	Stemcell Technologies	R1034	BrainPhys Neuronal Medium (Cat.no. 5790) supplemented with iCell GlutaNeurons Kit (Stemcell Technoligies. no. R1034) according to vendor), N-2 (Thermo Fisher), 1µg/ml Laminin 512 (BioLamina, no. LN521)	50.000	168	4

* All medium and additives are purchased from Sigma Aldrich unless otherweise stated.

Example 1 Testing in vitro efficacy of LNA oligonucleotides in SK-N-AS, A431, NCI-H23 and ARPE19 cell lines at 25 and 5µM

An oligonucleotide screen is performed in human cell lines using the LNA oligonucleotides in table 2 (CMP ID NO: 4_1 - 1089_1, see column "oligonucleotide compounds") targeting SEQ ID NO 1. The human cell lines SK-N-AS, A341, NCI-H23 and ARPE19 are purchased from the vendors listed in table 3, and are maintained as recommended by the supplier in a humidified incubator at 37°C with 5% CO_2. For the screening assays, cells are seeded in 96

multi well plates in media recommended by the supplier (see table 3 in the Materials and Methods section). The number of cells/well is optimized for each cell line (see table 3 in the Materials and Methods section).

Cells are incubated between 0 and 24 hours before addition of the oligonucleotide in concentration of 5 or 25 µM (dissolved in PBS). 3-4 days after addition of the oligonucleotide, the cells are harvested (The incubation times for each cell line are indicated in table 3 in the Materials and Methods section).

RNA is extracted using the Qiagen RNeasy 96 kit (74182), according to the manufacturer's instructions). cDNA synthesis and qPCR is performed using qScript XLT one-step RT-qPCR ToughMix Low ROX, 95134-100 (Quanta Biosciences). Target transcript levels are quantified using FAM labeled TaqMan assays from Thermo Fisher Scientific in a multiplex reaction with a VIC labelled GUSB control. TaqMan primer assays for the target transcript of interest ATXN3 (see below) and a house keeping gene GUSB (4326320E VIC-MGB probe).

ATXN3 primer assay (Assay ID: N/A Item Name Hs.PT.58.39355049):
Forward primer: GTTTCTAAAGACATGGTCACAGC (SEQ ID NO 1128)
Reverse: CTATCAGGACAGAGTTCACATCC (SEQ ID NO 1129)
Probe: 56-FAM/AAAGGCCAG/ZEN/CCACCAGTTCAGG/3IABkFQ/ (SEQ ID NO 1130)

The relative ATXN3 mRNA expression levels are determined as % of control (PBS-treated cells) i.e. the lower the value the larger the inhibition.

Example 2: *In vitro* reduction of ATXN3 in SK-N-AS human cell line using further LNA gapmer oligonucleotides targeting ATNX3.

LNA modified oligonucleotides targeting human ATXN3 were tested for their ability to reduce ATXN3 mRNA expression in human SK-N-AS neuroblastoma cells acquired from ECACC Cat: 94092302. The cells were cultured according to the vendor guidelines in Dulbecco's Modified Eagle's Medium, supplemented with 0.1 mM Non-Essential Amino Acids (NEAA) and fetal bovine serum to a final concentration of 10%. Cells were cultured at 37 ºC, 5 % CO2 and 95% humidity in an active evaporation incubator (Thermo C10). Cells were seeded at a density of 9000 cells per well (96-well plate) in 190 ul of SK-N-AS cell culture medium. The cells were hereafter added 10µl of oligo suspension or PBS (controls) to a final concentration of 5µM from pre-made 96-well dilution plates. The cell culture plates were incubated for 72 hours in the incubator.

After incubation, cells were harvested by removal of media followed by cell lysis and RNA purification using QIAGEN RNeasy 96 Kit (cat 74181), following manufacturers protocol. RNA was diluted 2 fold in water prior to the one-step qPCR reaction. For one-step qPCR reaction qPCR-mix (qScriptTM XLT One-Step RT-qPCR ToughMix® Low ROX from QuantaBio, cat.no 95134-500) and QPCR was run as duplex QPCR using assays from Integrated DNA technologies for ATXN3 (Hs.PT.58.39355049) and TBP (Hs.PT.58v.39858774)

Hs.PT.58.39355049 - Primer Sequences

Probe: 5'-/56-FAM/AAAGGCCAG/ZEN/CCACCAGTTCAGG/3IABkFQ/-3' (SEQ ID NO 1130)

Primer 1: 5'-CTATCAGGACAGAGTTCACATCC-3' (SEQ ID NO 1129)

Primer 2: 5'-GTTTCTAAAGACATGGTCACAGC-3' (SEQ ID NO 1128)

Hs.PT.58v.39858774 – Primer Sequences

Probe: 5'- /5HEX/TGA TCT TTG /ZEN/CAG TGA CCC AGC ATC A/3IABkFQ/ -3' (SEQ ID NO 1131)

Primer 1: 5'- GCT GTT TAA CTT CGC TTC CG-3' (SEQ ID NO 1132)

Primer 2: 5'- CAG CAA CTT CCT CAA TTC CTT G-3' (SEQ ID NO 1133)

The reactions were then mixed in a qPCR plate (MICROAMP®optical 384 well, 4309849). After sealing, the plate was given a quick spin, 1000g for 1 minute at RT, and transferred to a ViiaTM 7 system (Applied Biosystems, Thermo), and the following PCR conditions used: 50°C for 15 minutes; 95°C for 3 minutes; 40 cycles of: 95°C for 5 sec followed by a temperature decrease of 1.6 °C/sec followed by 60 °C for 45 sec. The data was analyzed using the QuantStudioTM Real_time PCR Software and quantity calculated by the delta delta Ct method (Quantity = 2^(-Ct)*1000000000). Quantity is normalized to the calculated quantity for the housekeeping gene assay (TBP) run in the same well. Relative Target Quantity = QUANTITY_target / QUANTITY_housekeeping (RNA knockdown) was calculated for each well by division with the mean of all PBS-treated wells on the same plate. Normalised Target Quantity = (Relative Target Quantity / [mean] Relative Target Quantity]_pbs_wells) * 100.

Compounds targeting selected target sequence regions of SEQ ID NO 1 were evaluated in the above assay.

The target knock-down data is presented in the following Compound and Data Table:

In the Compound table, motif sequences represent the contiguous sequence of nucleobases present in the oligonucleotide.

Oligonucleotide compound represent specific designs of a motif sequence. Capital letters represent beta-D-oxy LNA nucleosides, lowercase letters represent DNA nucleosides, all LNA C are 5-methyl cytosine, all internucleoside linkages are phosphorothioate internucleoside linkages.

Table 4: Compound and Data Table

SEQID	CMPID	Oligonucleotide Base Sequence	Oligonucleotide compound	% of ATXN3 mRNA remaining
1099	1099_1	CCAAAAGAAACCAAACCC	CCAAaagaaaccaaacCC	90,6
1100	1100_1	CCCCATTCAAATATTTATT	CCccattcaaatatttATT	90,5
1101	1101_1	AATCATTTACCCCCAAC	AAtcatttaccccCAAC	92
1102	1102_1	TATCTCAAACTATCCCCA	TAtctcaaactatcccCA	93
1103	1103_1	TCTATTCCTTAACCCAAC	TCTattccttaacccAAC	76,6
1104	1104_1	TCCCCTAAATAATTTAATCA	TCccctaaataatttaATCA	79,3
1105	1105_1	AAACCACTCCATTCCAA	AaaccactccattCCAA	57,7
1106	1106_1	TCTAAACCCCAAACTTTCA	TCtaaaccccaaactttCA	74,3
1107	1107_1	TTCTAAACCCCAAACTTTC	TTCtaaaccccaaacttTC	61,8
1108	1108_1	AGTTCTAAACCCCAAACT	AGttctaaaccccaaACT	73,7
1109	1109_1	TGAAACCATTACTACAACC	TGaaaccattactacAACC	24,9
1110	1110_1	ACATCATTTATCACTACCAC	ACAtcatttatcactaccAC	71,9
1111	1111_1	AACATTAAACCCTCCCA	AacattaaaccctcCCA	80,2
1112	1112_1	TCAGATCCTAAAATCACT	TCAgatcctaaaatcACT	79,5
1113	1113_1	CTATACCTAAAACAATCTA	CTAtacctaaaacaatCTA	99,1
1114	1114_1	TGATTCTTATACTTACTA	TGAttcttatacttaCTA	72,1
1115	1115_1	TAAAAATATAACTACTCCTA	TAaaaatataactactCCTA	93,7
1116	1116_1	TCTTCATTATACCATCAAAT	TCTtcattataccatcaAAT	51,5
1117	1117_1	GTTTCATATTTTTAATCC	GTTtcatatttttaaTCC	37,7
1118	1118_1	TAATATCCTCATTACCCATT	TAatatcctcattacccaTT	84
1119	1119_1	CAAATATTCACAAATCCTA	CAaatattcacaaatCCTA	73,3
1120	1120_1	CATCACAAAATAACCTATCA	CATcacaaaataacctaTCA	79,9
1121	1121_1	CTCTCAACTTCTACTACTAA	CTCtcaacttctactactAA	59,6
1122	1122_1	AATCTTATTTACATCTTCC	AATcttatttacatctTCC	20,7
1123	1123_1	CCAAAATTACTTCTTTTATC	CCAaaattacttcttttATC	56,5
1124	1124_1	AACCCAACTTTCTATTTT	AACCcaactttctattTT	52,7
1125	1125_1	ACAATATATTCCTCAATCA	ACAatatattcctcaaTCA	86,8
1126	1126_1	CCTGTAACAATTATACA	CCTgtaacaattatACA	92,3
1127	1127_1	CATCCCTTTACCACTTT	CAtccctttaccactTT	94,5

In the oligonucleotide compound column, capital letters represent beta-D-oxy LNA nucleosides, LNA cytosines are 5-methyl cytosine, lower case letters are DNA nucleosides, and all internucleoside linkages are phosphorothioate.

As can be seen, most of the above compounds targeting the listed target sequence regions are capable of inhibiting the expression of the human ataxin 3 transcript and that compounds targeting the target sequence region complementary to SEQ ID Nos 1122 and 1109 are particularly effective in inhibiting the human ataxin 3 transcript. Other effective target sites for ATXN3 can be determined from the above table.

Example 3

The screening assay described in Example 2 was performed using a series of further oligonucleotide targeting human ATXN3 pre-mRNA using the qpCR: (ATXN3_exon_8-9(1) PrimeTime® XL qPCR Assay (IDT).

qPCR probe and primers set 2:

Probe: 5'-/56-FAM/CTCCGCAGG/ZEN/GCT ATTCAGCT AAGT /31ABkFQ/-3' (SEQ ID NO 1134)

Primer 1: 5'-AGT AAGATTTGT ACCTGATGTCTGT-3' (SEQ ID NO 1135)

Primer 2: 5'-CATGGAAGATGAGGAAGCAGAT-3' (SEQ ID NO 1136)

The results are shown in the following table

Table 5

SEQID	CMPID	Oligonucleotide Base Sequence	Oligonucleotide compound	% of ATXN3 mRNA remaining
1137	1137_1	CCTACTTCACTTCCTAA	CctacttcacttcCTAA	68,9
1138	1138_1	TTTCCTACTTCACTTCCTA	TttcctacttcacttccTA	95,1
1139	1139_1	TTCCTACTTCACTTCCTA	TtcctacttcacttcCTA	85
1140	1140_1	TTTCCTACTTCACTTCCT	TTtcctacttcacttcCT	88,1
1141	1141_1	TTTCCTACTTCACTTCC	TttcctacttcactTCC	83,1
1142	1142_1	GTTTCCTACTTCACTTC	GTTtcctacttcactTC	60,2
1143	1143_1	ACCAAACCCAAACATCCC	AccaaacccaaacatcCC	88
1144	1144_1	AGAAACCAAACCCAAACATC	AgaaaccaaacccaaaCATC	91,3
1145	1145_1	AGAAACCAAACCCAAACAT	AGaaaccaaacccaaACAT	93,5
1146	1146_1	CTCCTAATACCTAAAAACAAA	CTCCtaatacctaaaaacaAA	100
1147	1147_1	CTCCTAATACCTAAAAACA	CTCCtaatacctaaaaaCA	94,2
1148	1148_1	ACTCCTAATACCTAAAAACA	ACTCctaatacctaaaaaCA	81
1149	1149_1	CACTCCTAATACCTAAAAACA	CACtcctaatacctaaaaACA	90,4
1150	1150_1	CCACTCCTAATACCTAAAAA	CCACtcctaatacctaaaAA	63
1151	1151_1	TCCACTCCTAATACCTAAAAA	TCCactcctaatacctaaaAA	54
1152	1152_1	CCACTCCTAATACCTAAAA	CCACtcctaatacctaaAA	73,7
1153	1153_1	TCCACTCCTAATACCTAAAA	TCCactcctaatacctaAAA	59
1154	1154_1	CCACTCCTAATACCTAAA	CCACtcctaatacctaAA	65,2
1155	1155_1	GTCCACTCCTAATACCTAAA	GtccactcctaataccTAAA	86,8

1156	1156_1	CCACTCCTAATACCTAA	CCactcctaatacCTAA	52,3
1157	1157_1	TCCACTCCTAATACCTAA	TCcactcctaatacCTAA	64,3
1157	1157_2	TCCACTCCTAATACCTAA	TCCActcctaatacctAA	66
1158	1158_1	GTCCACTCCTAATACCTAA	GtccactcctaataccTAA	85,5
1159	1159_1	AGTCCACTCCTAATACCTA	AgtccactcctaataccTA	87,4
1160	1160_1	TCCACTCCTAATACCTA	TCcactcctaatacCTA	70,1
1161	1161_1	AGTCCACTCCTAATACCT	AgtccactcctaatacCT	84,2
1162	1162_1	GTCCACTCCTAATACC	GTCcactcctaataCC	57,8
1163	1163_1	AGTCCACTCCTAATACC	AGtccactcctaataCC	77,1
1164	1164_1	CAGTCCACTCCTAATACC	CagtccactcctaatACC	86,7
1162	1162_2	GTCCACTCCTAATACC	GTCcactcctaatACC	67,8
1165	1165_1	CCAGTCCACTCCTAATAC	CcagtccactcctaaTAC	85,4
1166	1166_1	CAGTCCACTCCTAATAC	CAgtccactcctaaTAC	60,7
1167	1167_1	AGTCCACTCCTAATAC	AGTCcactcctaatAC	78,9
1168	1168_1	CAGTCCACTCCTAATA	CAGtccactcctaaTA	44,5
1169	1169_1	CCAGTCCACTCCTAATA	CCagtccactcctaaTA	33,8
1170	1170_1	GCAACTCTTTCCAAACA	GCAActctttccaaaCA	36
1171	1171_1	AGCAACTCTTTCCAAACA	AGCaactctttccaaaCA	35,3
1172	1172_1	CAGCAACTCTTTCCAAACA	CAgcaactctttccaaACA	58,3
1173	1173_1	CCAGCAACTCTTTCCAAA	CcagcaactctttcCAAA	69,7
1174	1174_1	CCAGCAACTCTTTCCAA	CCagcaactctttcCAA	42,1
1175	1175_1	ACCAGCAACTCTTTCCAA	ACcagcaactctttcCAA	65
1176	1176_1	TTACCAGCAACTCTTTC	TTACcagcaactcttTC	53
1177	1177_1	TGCTCCTCCTATTAAATAA	TGCtcctcctattaaatAA	76,3
1178	1178_1	GCTCCTCCTATTAAATAA	GCtcctcctattaaATAA	61,8
1179	1179_1	GCTCCTCCTATTAAATA	GCtcctcctattaaATA	60,2
1180	1180_1	TGCTCCTCCTATTAAATA	TGctcctcctattaaATA	70,2
1181	1181_1	TGCTCCTCCTATTAAAT	TGCtcctcctattaaAT	80,2
1182	1182_1	TTGCTCCTCCTATTAAAT	TTGCtcctcctattaaAT	79
1183	1183_1	ATTTAATAAAACAAAAACCCT	ATttaataaaacaaaaaCCCT	97,2
1184	1184_1	GCCCAAAAAACTAAATT	GCCCaaaaaactaaaTT	95,5
1185	1185_1	GTTTTTACATTCTAACTT	GTTtttacattctaaCTT	54,1
1186	1186_1	TGTTTTTACATTCTAACT	TGTTtttacattctaaCT	63,8
1187	1187_1	CTGTTTTTACATTCTAAC	CTGTttttacattctaAC	62,5
1188	1188_1	CCCCATTCAAATATTTAT	CCCcattcaaatattTAT	64,9
1189	1189_1	GCCCCATTCAAATATTTAT	GCcccattcaaatattTAT	86,2
1188	1188_2	CCCCATTCAAATATTTAT	CCCCattcaaatatttAT	96,2
1190	1190_1	GCCCCATTCAAATATTTA	GCcccattcaaatatTTA	82,2
1191	1191_1	CCATTCAAATATATACATTTT	CCATtcaaatatatacattTT	72
1191	1191_2	CCATTCAAATATATACATTTT	CCATtcaaataTatacattTT	37,7
1192	1192_1	TCCATTCAAATATATACATTT	TCCAttcaaatatatacatTT	56,8
1193	1193_1	ATCCATTCAAATATATACATT	ATCCattcaaaTatatacaTT	48
1194	1194_1	TCCATTCAAATATATACATT	TCCAttcaaatatatacaTT	53,7
1193	1193_2	ATCCATTCAAATATATACATT	ATCCattcaaatatatacaTT	54,7

1195	1195_1	TATCCATTCAAATATATACAT	TATccattcaaatatataCAT	80,1
1196	1196_1	TCCATTCAAATATATACAT	TCCattcaaatatataCAT	43,1
1197	1197_1	ATCCATTCAAATATATACA	ATCCattcaaatatataCA	53,9
1198	1198_1	TTATCCATTCAAATATATACA	TTatccattcaaatataTACA	69,4
1199	1199_1	TCCATTCAAATATATACA	TCCAttcaaatatataCA	54,7
1200	1200_1	TATCCATTCAAATATATACA	TATCcattcaaatatataCA	53,3
1201	1201_1	CTTTATCCATTCAAATATATA	CTttatccattcaaataTATA	85,5
1202	1202_1	TCTTTATCCATTCAAATATAT	TCTttatccattcaaataTAT	62,6
1203	1203_1	CTCTTTATCCATTCAAATATA	CTCtttatccattcaaatATA	38,4
1204	1204_1	TCTTTATCCATTCAAATATA	TCtttatccattcaaaTATA	70,9
1203	1203_2	CTCTTTATCCATTCAAATATA	CTCTttatccattcaaataTA	33,6
1205	1205_1	CTTTATCCATTCAAATATA	CTttatccattcaaaTATA	78,4
1206	1206_1	TCTCTTTATCCATTCAAATAT	TCtctttatccattcaaaTAT	82
1207	1207_1	CTCTTTATCCATTCAAATAT	CTCtttatccattcaaaTAT	39,8
1208	1208_1	TCTTTATCCATTCAAATAT	TCTttatccattcaaaTAT	63,1
1209	1209_1	TCTCTTTATCCATTCAAATA	TCtctttatccattcaAATA	65,2
1210	1210_1	CTCTTTATCCATTCAAATA	CTCTttatccattcaaaTA	32,2
1211	1211_1	TCTCTTTATCCATTCAAAT	TCTCtttatccattcaaAT	42
1212	1212_1	TCTCTTTATCCATTCAAA	TCTCtttatccattcaAA	42,5
1213	1213_1	AGCACCATATATATCTCA	AgcaccatatatatCTCA	16
1214	1214_1	GCACCATATATATCTCA	GCaccatatatatcTCA	16
1215	1215_1	CAGCACCATATATATCTCA	CagcaccatatatatCTCA	19,2
1215	1215_2	CAGCACCATATATATCTCA	CAgcaccatatatatcTCA	24,1
1216	1216_1	AGCACCATATATATCTC	AGCaccatatatatcTC	19,9
1217	1217_1	GCACCATATATATCTC	GCACcatatatatcTC	82,7
1218	1218_1	CAGCACCATATATATCTC	CAgcaccatatatatCTC	21,1
1219	1219_1	CAGCACCATATATATCT	CAGcaccatatataTCT	28,9
1220	1220_1	ACAGCACCATATATATCT	ACAGcaccatatatatCT	21,9
1221	1221_1	ACAGCACCATATATATC	ACAGcaccatatataTC	25,4
1222	1222_1	CTATGTTATTATCCCCA	CTAtgttattatcccCA	56,1
1223	1223_1	TCTATGTTATTATCCCC	TctatgttattatcCCC	47,7
1224	1224_1	CTCTACACTCTAACTCT	CtctacactctaaCTCT	79,3
1225	1225_1	TCTCTACACTCTAACTCT	TctctacactctaaCTCT	79,6
1226	1226_1	TTCTCTACACTCTAACTCT	TTCtctacactctaactCT	86,9
1227	1227_1	CTTCTCTACACTCTAACTCT	CTtctctacactctaactCT	97
1227	1227_2	CTTCTCTACACTCTAACTCT	CttctctacactctaacTCT	84,5
1228	1228_1	TTCTCTACACTCTAACTC	TTCtctacactctaacTC	81,4
1229	1229_1	CTTCTCTACACTCTAACTC	CttctctacactctaaCTC	89,1
1230	1230_1	TCTCTACACTCTAACTC	TCtctacactctaaCTC	87,3
1231	1231_1	CCTTCTCTACACTCTAACTC	CcttctctacactctaacTC	98,3
1232	1232_1	TTCTCTACACTCTAACT	TTCTctacactctaaCT	80,1
1233	1233_1	CTTCTCTACACTCTAACT	CTTctctacactctaaCT	73,6
1234	1234_1	CCTTCTCTACACTCTAACT	CcttctctacactctAACT	77,7
1235	1235_1	CCTTCTCTACACTCTAAC	CCTtctctacactctaAC	82,4

1236	1236_1	CTTCTCTACACTCTAAC	CTtctctacactcTAAC	90,6
1237	1237_1	AGCCTTCTCTACACTCTAA	AgccttctctacactcTAA	80
1238	1238_1	CCTTCTCTACACTCTAA	CCttctctacactcTAA	72,2
1239	1239_1	GCCTTCTCTACACTCTAA	GCcttctctacactctAA	62,9
1240	1240_1	AGCCTTCTCTACACTCTA	AgccttctctacactcTA	85,2
1241	1241_1	TACTAACTACAACACAAATCA	TACtaactacaacacaaaTCA	91,3
1241	1241_2	TACTAACTACAACACAAATCA	TACtaactacAacacaaaTCA	81,1
1242	1242_1	CTACTAACTACAACACAAATC	CTACtaactacaacacaaaTC	108
1243	1243_1	CACTACTAACTACAACACAAA	CACTactaactacaacacaAA	74
1244	1244_1	CACTACTAACTACAACACAA	CACtactaactacaacaCAA	87,4
1245	1245_1	ACACTACTAACTACAACACAA	ACActactaactacaacaCAA	84,1
1246	1246_1	CACTACTAACTACAACACA	CACTactaactacaacaCA	83,5
1247	1247_1	ACACTACTAACTACAACACA	ACACtactaactacaacaCA	81,3
1248	1248_1	GACACTACTAACTACAACAC	GACactactaactacaaCAC	51,6
1249	1249_1	GACACTACTAACTACAACA	GACActactaactacaaCA	51
1250	1250_1	AGACACTACTAACTACAA	AGAcactactaactaCAA	57,2
1251	1251_1	AGACACTACTAACTACA	AGACactactaactaCA	34,7
1252	1252_1	ATCATTTACCCCCAACCT	AtcatttacccccaacCT	96
1253	1253_1	ATCATTTACCCCCAACC	AtcatttaccccAACC	89,1
1254	1254_1	CAAATCATTTACCCCCAA	CaaatcatttacccCCAA	92
1255	1255_1	CCAAATCATTTACCCCCAA	CcaaatcatttaccccCAA	91
1256	1256_1	ACCAAATCATTTACCCCCA	AccaaatcatttaccccCA	89,9
1257	1257_1	TACCAAATCATTTACCCCC	TaccaaatcatttacccCC	84
1258	1258_1	ACCAAATCATTTACCCC	ACcaaatcatttacCCC	69,9
1259	1259_1	TACCAAATCATTTACCCC	TACcaaatcatttaccCC	56,3
1260	1260_1	CTACCAAATCATTTACCCC	CtaccaaatcatttaccCC	94
1261	1261_1	TACCAAATCATTTACCC	TAccaaatcatttACCC	68,9
1262	1262_1	CTACCAAATCATTTACC	CTACcaaatcatttaCC	70,3
1263	1263_1	TGCTACCAAATCATTTACC	TgctaccaaatcattTACC	79
1264	1264_1	GCTACCAAATCATTTACC	GCtaccaaatcatttACC	83,6
1265	1265_1	TGCTACCAAATCATTTAC	TGCTaccaaatcatttAC	88,3
1266	1266_1	GCTACCAAATCATTTAC	GCTaccaaatcattTAC	71,4
1267	1267_1	TGCTACCAAATCATTTA	TGCtaccaaatcatTTA	79,8
1268	1268_1	CTGCTACCAAATCATTTA	CTGctaccaaatcatTTA	75,3
1269	1269_1	ACTGCTACCAAATCATTT	ACTGctaccaaatcatTT	83,4
1270	1270_1	CTGCTACCAAATCATTT	CTGCtaccaaatcatTT	83
1271	1271_1	ACTGCTACCAAATCATT	ACTGctaccaaatcaTT	71,1
1272	1272_1	CACTTTGCCATAATCAA	CActttgccataaTCAA	26
1273	1273_1	TTATCTCAAACTATCCCCA	TTAtctcaaactatcccCA	92,9
1274	1274_1	ATCTCAAACTATCCCCA	ATctcaaactatccCCA	72,3
1275	1275_1	CTTATCTCAAACTATCCCCA	CttatctcaaactatcccCA	85,5
1276	1276_1	TATCTCAAACTATCCCC	TatctcaaactatcCCC	79,8
1277	1277_1	CTTATCTCAAACTATCCCC	CTtatctcaaactatccCC	84
1278	1278_1	TTATCTCAAACTATCCCC	TTAtctcaaactatccCC	89,7

1279	1279_1	CTTATCTCAAACTATCCC	CttatctcaaactaTCCC	83,5
1280	1280_1	CCTTATCTCAAACTATCCC	CcttatctcaaactatcCC	87,6
1279	1279_2	CTTATCTCAAACTATCCC	CTtatctcaaactatCCC	76,9
1281	1281_1	TTATCTCAAACTATCCC	TtatctcaaactaTCCC	84,7
1282	1282_1	CTTATCTCAAACTATCC	CTTatctcaaactaTCC	78,3
1283	1283_1	CCCTTATCTCAAACTATCC	CccttatctcaaactaTCC	76,4
1284	1284_1	CCTTATCTCAAACTATCC	CCTtatctcaaactatCC	69,3
1285	1285_1	CCTTATCTCAAACTATC	CCttatctcaaacTATC	75,9
1286	1286_1	GCCCTTATCTCAAACTATC	GCccttatctcaaactaTC	76,6
1287	1287_1	CCCTTATCTCAAACTATC	CCcttatctcaaacTATC	67,2
1288	1288_1	TGCCCTTATCTCAAACTAT	TgcccttatctcaaacTAT	90,5
1289	1289_1	GCCCTTATCTCAAACTAT	GCccttatctcaaacTAT	71,9
1290	1290_1	CCCTTATCTCAAACTAT	CCCTtatctcaaactAT	77,7
1291	1291_1	GCCCTTATCTCAAACTA	GCccttatctcaaacTA	68,4
1292	1292_1	TGCCCTTATCTCAAACTA	TgcccttatctcaaaCTA	81,5
1293	1293_1	TGCCCTTATCTCAAACT	TGcccttatctcaaaCT	75,7
1294	1294_1	TTGCCCTTATCTCAAAC	TTGCccttatctcaaAC	89
1295	1295_1	CTTGCCCTTATCTCAA	CTtgcccttatcTCAA	48,2
1296	1296_1	TGAAATCAAACTTCATCA	TGAaatcaaacttcaTCA	66,5
1297	1297_1	GGTCACCATACTTAAT	GGTCaccatacttaAT	89,7
1298	1298_1	TGCTAACACAAATTTCCT	TGctaacacaaattTCCT	47,3
1299	1299_1	GCTAACACAAATTTCCT	GCTaacacaaatttCCT	48,9
1299	1299_2	GCTAACACAAATTTCCT	GCtaacacaaattTCCT	45,7
1300	1300_1	TTGCTAACACAAATTTCC	TTGCtaacacaaatttCC	60,7
1301	1301_1	TGCTAACACAAATTTCC	TGCTaacacaaatttCC	62,6
1302	1302_1	TTGCTAACACAAATTTC	TTGCtaacacaaattTC	72,4
1303	1303_1	CCTTTGCTAACACAAAT	CCTTtgctaacacaaAT	48,1
1304	1304_1	GTATAACCAATAATAACTA	GTAtaaccaataataaCTA	86,1
1305	1305_1	TCTGACATCACACAATTT	TCTGacatcacacaatTT	67,8
1306	1306_1	TCTGACATCACACAATT	TCTGacatcacacaaTT	70,2
1307	1307_1	TATCTGACATCACACAA	TATctgacatcacaCAA	69,8
1308	1308_1	CTATTCCTTAACCCAAC	CTattccttaaccCAAC	77,7
1309	1309_1	GTCTATTCCTTAACCCAAC	GtctattccttaaccCAAC	86,2
1310	1310_1	GTCTATTCCTTAACCCAA	GtctattccttaacCCAA	60,4
1311	1311_1	TCTATTCCTTAACCCAA	TCTattccttaaccCAA	51
1312	1312_1	GTCTATTCCTTAACCCA	GtctattccttaacCCA	67,3
1313	1313_1	GTCTATTCCTTAACCC	GtctattccttaaCCC	77,4
1314	1314_1	GGTCTATTCCTTAACC	GGtctattccttaaCC	83,2
1315	1315_1	AGAACATTTCCTTCTCCT	AgaacatttccttctcCT	84,2
1316	1316_1	AACTGTCCCAAACAACC	AACtgtcccaaacaaCC	75
1317	1317_1	TTAGTCTCCCTCATTTTC	TtagtctccctcattTTC	72,4
1318	1318_1	ATTTAGTCTCCCTCATT	ATttagtctccctCATT	48
1319	1319_1	ATGCATCAAATCTCATA	ATGCatcaaatctcaTA	83,7
1320	1320_1	CCTAAATAATTTAATCATTAA	CCTaaataatttaatcatTAA	94

1321	1321_1	CCCTAAATAATTTAATCATTA	CCCTaaataatttaatcatTA	88,8
1322	1322_1	CCCCTAAATAATTTAATCATT	CCCctaaataatttaatcATT	80,7
1323	1323_1	CCCTAAATAATTTAATCATT	CCCTaaataatttaatcaTT	82,2
1324	1324_1	CCCTAAATAATTTAATCAT	CCCtaaataatttaatCAT	87,1
1325	1325_1	CCCCTAAATAATTTAATCA	CCCctaaataatttaaTCA	79,9
1326	1326_1	CCCTAAATAATTTAATCA	CCCtaaataatttaaTCA	82,5
1327	1327_1	CCCCTAAATAATTTAATC	CCCCtaaataatttaaTC	116
1328	1328_1	TCCCCTAAATAATTTAATC	TCCCctaaataatttaaTC	109
1329	1329_1	TTGCTAATATTTCCAAAA	TTGCtaatatttccaaAA	84,2
1330	1330_1	CTTGCTAATATTTCCAA	CTtgctaatatttCCAA	66,1
1331	1331_1	ACTGTCATCCATATTTCC	ActgtcatccatattTCC	66,2
1332	1332_1	ACTGTCATCCATATTTC	ACTgtcatccatatTTC	48,1
1333	1333_1	AATGCCCCACTCTAATAT	AATGccccactctaatAT	36,9
1334	1334_1	TGCCCCACTCTAATAT	TGCcccactctaatAT	52,8
1335	1335_1	ATGCCCCACTCTAATAT	ATgccccactctaaTAT	43,7
1336	1336_1	AAATGCCCCACTCTAATA	AAATgccccactctaaTA	25,7
1337	1337_1	ATGCCCCACTCTAATA	ATGccccactctaaTA	28,6
1338	1338_1	AATGCCCCACTCTAATA	AATGccccactctaaTA	29,9
1339	1339_1	TTAAATGCCCCACTCTA	TtaaatgccccactCTA	51,3
1340	1340_1	TCTGAAAATTCACTATCT	TCTGaaaattcactatCT	35,7
1341	1341_1	GTCTACTATATACATCT	GTCtactatatacaTCT	30,6
1342	1342_1	AGTCTACTATATACATCT	AGTCtactatatacatCT	45,3
1343	1343_1	AGTCTACTATATACATC	AGTCtactatatacaTC	57
1344	1344_1	GTCTACTATATACATC	GTCTactatatacaTC	46,5
1345	1345_1	TAGTCTACTATATACATC	TAgtctactatataCATC	68,3
1346	1346_1	TAGTCTACTATATACAT	TAGtctactatataCAT	89
1347	1347_1	CTAGTCTACTATATACAT	CTAgtctactatataCAT	86,6
1348	1348_1	CTAGTCTACTATATACA	CTAGtctactatataCA	88,5
1349	1349_1	ACTAGTCTACTATATAC	ACTagtctactataTAC	85,1
1350	1350_1	CTAGTCTACTATATAC	CTAgtctactataTAC	85,3
1351	1351_1	GTATATTCTACCCATAA	GTAtattctacccaTAA	51,3
1352	1352_1	TGTATATTCTACCCATAA	TGTatattctacccaTAA	48,4
1353	1353_1	TGTATATTCTACCCATA	TGtatattctaccCATA	45,6
1354	1354_1	ATGTATATTCTACCCATA	ATgtatattctaccCATA	90,2
1355	1355_1	ATGTATATTCTACCCAT	ATgtatattctacCCAT	51,1
1356	1356_1	GAAAACCACACAATTCCTA	GaaaaccacacaattCCTA	58,9
1357	1357_1	GAAAACCACACAATTCCT	GAaaaccacacaatTCCT	56,4
1358	1358_1	AGAAAACCACACAATTCCT	AGaaaaccacacaattCCT	58,4
1359	1359_1	CAGAAAACCACACAATTCC	CAGaaaaccacacaatTCC	43,3
1360	1360_1	AGAAAACCACACAATTCC	AGAaaaccacacaatTCC	47,6
1361	1361_1	CCAGAAAACCACACAATTC	CCAGaaaaccacacaatTC	26,3
1362	1362_1	CCAGAAAACCACACAATT	CCAGaaaaccacacaaTT	21
1363	1363_1	TCCAGAAAACCACACAAT	TCCAgaaaaccacacaAT	47,1
1364	1364_1	TTCCAGAAAACCACACAA	TTCCagaaaaccacacAA	49,8

1364	1364_2	TTCCAGAAAACCACACAA	TTCcagaaaaccacaCAA	45,8
1365	1365_1	GATATATCACTAAATCCAT	GAtatatcactaaatCCAT	27,4
1366	1366_1	GATATATCACTAAATCCA	GAtatatcactaaaTCCA	43,7
1367	1367_1	AGATATATCACTAAATCCA	AGatatatcactaaaTCCA	37,4
1368	1368_1	AGATATATCACTAAATCC	AGAtatatcactaaaTCC	33,6
1369	1369_1	TCATATATAAATTTCTCTA	TCAtatataaatttctCTA	78
1369	1369_2	TCATATATAAATTTCTCTA	TCATatataaatttctcTA	73,1
1370	1370_1	TCATATATAAATTTCTCT	TCatatataaatttCTCT	27,9
1370	1370_2	TCATATATAAATTTCTCT	TCATatataaatttctCT	60,2
1371	1371_1	AAGATCACACAACCATA	AAGAtcacacaaccaTA	19,8
1372	1372_1	TAAAAGATCACACAACCA	TAaaagatcacacaACCA	47,5
1373	1373_1	CATCACATAAAAACCCACTT	CATcacataaaaacccaCTT	45,4
1374	1374_1	CATCACATAAAAACCCACT	CAtcacataaaaaccCACT	57,9
1375	1375_1	TCATCACATAAAAACCCACT	TCatcacataaaaaccCACT	30,1
1376	1376_1	CATCACATAAAAACCCAC	CAtcacataaaaacCCAC	61,6
1377	1377_1	TCATCACATAAAAACCCAC	TCatcacataaaaacCCAC	30,6
1378	1378_1	GTCATCACATAAAAACCCAC	GTCatcacataaaaaccCAC	24,9
1379	1379_1	GTCATCACATAAAAACCCA	GTCatcacataaaaacCCA	28,7
1380	1380_1	TCATCACATAAAAACCCA	TCatcacataaaaaCCCA	43,9
1381	1381_1	CATCACATAAAAACCCA	CAtcacataaaaaCCCA	71,5
1382	1382_1	TCATCACATAAAAACCC	TCAtcacataaaaaCCC	42,9
1383	1383_1	GTCATCACATAAAAACCC	GTCatcacataaaaaCCC	24,9
1384	1384_1	AGTCATCACATAAAAACCC	AGtcatcacataaaaACCC	35,8
1384	1384_2	AGTCATCACATAAAAACCC	AGTCatcacataaaaacCC	23
1385	1385_1	TAGTCATCACATAAAAACC	TAGTcatcacataaaaaCC	36,3
1386	1386_1	AGTCATCACATAAAAACC	AGTCatcacataaaaaCC	34,9
1387	1387_1	ATGCTAAATACAAATCT	ATGCtaaatacaaatCT	81
1388	1388_1	GAAACCATTACTACAACCAA	GAaaccattactacaaCCAA	20,1
1389	1389_1	GAAACCATTACTACAACCA	GAaaccattactacaACCA	15,9
1390	1390_1	ATGAAACCATTACTACAAC	ATGAaaccattactacaAC	45,6
1391	1391_1	CATGAAACCATTACTACA	CATGaaaccattactaCA	55,9
1392	1392_1	CCATGAAACCATTACTAC	CCatgaaaccattaCTAC	29,5
1393	1393_1	CTCCCATGAAACCATTA	CTCCcatgaaaccatTA	73,7
1394	1394_1	TGCTTACTTTATACAAAA	TGCTtactttatacaaAA	55,9
1395	1395_1	ATGTTAATACTTTTTCCA	ATGttaatacttttttCCA	92,9
1396	1396_1	CCTAATTTAACCCACAA	CCTaatttaacccaCAA	32,2
1397	1397_1	ATCCTAATTTAACCCACAA	ATCctaatttaacccaCAA	38,1
1398	1398_1	TCCTAATTTAACCCACAA	TCCtaatttaacccaCAA	39,9
1399	1399_1	TAATCCTAATTTAACCCACAA	TAAtcctaatttaacccaCAA	72,8
1400	1400_1	TAATCCTAATTTAACCCACA	TAatcctaatttaaccCACA	45
1401	1401_1	AATCCTAATTTAACCCACA	AATCctaatttaacccaCA	41,2
1402	1402_1	TCCTAATTTAACCCACA	TCCtaatttaacccACA	38,3
1403	1403_1	TAATCCTAATTTAACCCAC	TAatcctaatttaacCCAC	37,5
1404	1404_1	ATCCTAATTTAACCCAC	ATcctaatttaacCCAC	34,4

1405	1405_1	AATCCTAATTTAACCCAC	AAtcctaatttaacCCAC	48,2
1406	1406_1	TAATCCTAATTTAACCCA	TAatcctaatttaaCCCA	56,5
1407	1407_1	AATCCTAATTTAACCCA	AAtcctaatttaaCCCA	71,7
1408	1408_1	GTAATCCTAATTTAACCCA	GtaatcctaatttaaCCCA	63,6
1409	1409_1	TAATCCTAATTTAACCC	TAatcctaatttaACCC	56,5
1410	1410_1	GTAATCCTAATTTAACCC	GTaatcctaatttaACCC	44
1411	1411_1	AGTAATCCTAATTTAACCC	AGtaatcctaatttaaCCC	66,2
1410	1410_2	GTAATCCTAATTTAACCC	GTAatcctaatttaaCCC	34,2
1412	1412_1	AGTAATCCTAATTTAACC	AGTAatcctaatttaaCC	42,7
1413	1413_1	TCATTTATCACTACCACA	TCAtttatcactaccACA	26,5
1414	1414_1	CATCATTTATCACTACCACA	CatcatttatcactacCACA	46
1415	1415_1	CATTTATCACTACCACA	CAtttatcactacCACA	19,4
1416	1416_1	ATCATTTATCACTACCACA	ATcatttatcactacCACA	16,8
1416	1416_2	ATCATTTATCACTACCACA	ATCAtttatcactaccaCA	14,1
1417	1417_1	ACATCATTTATCACTACCACA	ACatcatttatcactaccACA	53,4
1418	1418_1	TCATTTATCACTACCAC	TCAtttatcactacCAC	18,9
1419	1419_1	ATCATTTATCACTACCAC	ATcatttatcactaCCAC	21,8
1420	1420_1	CATCATTTATCACTACCAC	CATcatttatcactacCAC	25,1
1421	1421_1	AACATCATTTATCACTACCAC	AACatcatttatcactacCAC	30,5
1421	1421_2	AACATCATTTATCACTACCAC	AacatcatttatcactaCCAC	40,4
1420	1420_2	CATCATTTATCACTACCAC	CatcatttatcactaCCAC	34,3
1422	1422_1	AACATCATTTATCACTACCA	AAcatcatttatcactACCA	34
1423	1423_1	CATCATTTATCACTACCA	CATCatttatcactacCA	11,3
1424	1424_1	TAACATCATTTATCACTACCA	TAacatcatttatcactaCCA	63,1
1425	1425_1	ACATCATTTATCACTACCA	ACATcatttatcactacCA	19
1422	1422_2	AACATCATTTATCACTACCA	AACatcatttatcactaCCA	25
1424	1424_2	TAACATCATTTATCACTACCA	TaacatcatttatcactACCA	61,3
1425	1425_2	ACATCATTTATCACTACCA	ACatcatttatcactACCA	23,5
1426	1426_1	TAACATCATTTATCACTACC	TAACatcatttatcactaCC	33,6
1427	1427_1	ACATCATTTATCACTACC	ACatcatttatcacTACC	32,3
1428	1428_1	TTAACATCATTTATCACTACC	TTAacatcatttatcactaCC	75,5
1429	1429_1	AACATCATTTATCACTACC	AACAtcatttatcactaCC	37,3
1430	1430_1	TTAACATCATTTATCACTAC	TTaacatcatttatcaCTAC	69,1
1431	1431_1	TAACATCATTTATCACTAC	TAacatcatttatcaCTAC	66,6
1432	1432_1	ATTAACATCATTTATCACTAC	ATtaacatcatttatcaCTAC	84,2
1432	1432_2	ATTAACATCATTTATCACTAC	ATtaacatcAtttatcaCTAC	62,8
1433	1433_1	ATTAACATCATTTATCACTA	ATTaacatcatttatcaCTA	81,3
1434	1434_1	TTAACATCATTTATCACTA	TTAacatcatttatcaCTA	74,5
1435	1435_1	TAATTAACATCATTTATCACT	TAattaacatcatttatCACT	84,3
1435	1435_2	TAATTAACATCATTTATCACT	TAattaacaTcatttatCACT	43,3
1436	1436_1	CTAATTAACATCATTTATCAC	CTaattaacatcatttaTCAC	81,4
1436	1436_2	CTAATTAACATCATTTATCAC	CTaattaacAtcatttaTCAC	46,7
1437	1437_1	CCTAATTAACATCATTTATCA	CCtaattaacatcatttaTCA	93,8
1438	1438_1	CTAATTAACATCATTTATCA	CTAattaacatcatttaTCA	89,6

1439	1439_1	CCTAATTAACATCATTTATC	CCTAattaacatcatttaTC	69,4
1440	1440_1	CCCTAATTAACATCATTTATC	CCctaattaacatcatttATC	86,3
1441	1441_1	CCTAATTAACATCATTTAT	CCTaattaacatcattTAT	87,4
1442	1442_1	CCTAATTAACATCATTTA	CCTAattaacatcattTA	66
1443	1443_1	CCCTAATTAACATCATTTA	CCCtaattaacatcattTA	88,7
1444	1444_1	GCCCTAATTAACATCATTT	GCCctaattaacatcatTT	87,9
1445	1445_1	CCCTAATTAACATCATTT	CCCTaattaacatcatTT	75,6
1446	1446_1	CGGCCCTAATTAACAT	CGGCcctaattaacAT	103
1447	1447_1	CTCGGCCCTAATTAA	CTCggccctaatTAA	57,4
1448	1448_1	CACATATAACATATAAACACA	CACAtataacatataaacaCA	61,7
1449	1449_1	TCACATATAACATATAAACAC	TCAcatataacatataaaCAC	43,6
1450	1450_1	ACTATCACATATAACATATA	ACTAtcacatataacataTA	58,5
1451	1451_1	CACTATCACATATAACATATA	CACTatcacatataacataTA	28,1
1452	1452_1	CACTATCACATATAACATAT	CACtatcacatataacaTAT	52
1453	1453_1	CACTATCACATATAACATA	CACTatcacatataacaTA	24,3
1454	1454_1	CACTATCACATATAACAT	CACtatcacatataaCAT	40,1
1455	1455_1	CACTATCACATATAACA	CACTatcacatataaCA	27
1456	1456_1	CAAAGTTTTCCCATTAC	CAaagttttcccaTTAC	21
1457	1457_1	ACAAAGTTTTCCCATTA	ACAaagttttcccaTTA	20,5
1458	1458_1	TCAGTCCAACATAACTC	TCAGtccaacataacTC	15,2
1459	1459_1	CAGTCCAACATAACTC	CAGtccaacataaCTC	23,5
1460	1460_1	ATCAGTCCAACATAACTC	ATCAgtccaacataacTC	13,7
1461	1461_1	ATCAGTCCAACATAACT	ATCAgtccaacataaCT	15,9
1462	1462_1	TAAACATTAAACCCTCCCAAA	TAaacattaaaccctccCAAA	87
1463	1463_1	AACATTAAACCCTCCCAA	AAcattaaaccctcCCAA	68,4
1464	1464_1	TAAACATTAAACCCTCCCAA	TaaacattaaaccctcCCAA	79,2
1465	1465_1	AAACATTAAACCCTCCCAA	AAacattaaaccctcCCAA	70,8
1466	1466_1	TATAAACATTAAACCCTCCCA	TAtaaacattaaaccctccCA	94
1467	1467_1	AACATTAAACCCTCCC	AAcattaaacccTCCC	78,3
1468	1468_1	AAACATTAAACCCTCCC	AAacattaaacccTCCC	89,4
1469	1469_1	TAAACATTAAACCCTCCC	TAAacattaaaccctCCC	72,9
1470	1470_1	ATAAACATTAAACCCTCCC	AtaaacattaaacccTCCC	86
1471	1471_1	TATAAACATTAAACCCTCC	TAtaaacattaaaccCTCC	91,1
1472	1472_1	TAAACATTAAACCCTCC	TAaacattaaaccCTCC	82,2
1473	1473_1	ACTATAAACATTAAACCCTCC	ActataaacattaaaccCTCC	86,5
1474	1474_1	ATAAACATTAAACCCTCC	ATaaacattaaaccCTCC	88,4
1475	1475_1	AACTATAAACATTAAACCCTC	AActataaacattaaacCCTC	92,6
1476	1476_1	CTATAAACATTAAACCCTC	CTataaacattaaacCCTC	82,9
1477	1477_1	ACTATAAACATTAAACCCTC	ACtataaacattaaacCCTC	89,8
1478	1478_1	AAACTATAAACATTAAACCCT	AAactataaacattaaaCCCT	98,9
1479	1479_1	CTATAAACATTAAACCCT	CTataaacattaaaCCCT	82,2
1480	1480_1	ACTATAAACATTAAACCCT	ACtataaacattaaaCCCT	86,6
1481	1481_1	AACTATAAACATTAAACCCT	AActataaacattaaaCCCT	89,5
1482	1482_1	GCTTTAAACTATAAACATT	GCtttaaactataaaCATT	58,2

1483	1483_1	TGCTTTAAACTATAAACA	TGCTttaaactataaaCA	57,2
1484	1484_1	CAGATTTATCACTATTA	CAGAtttatcactatTA	15,4
1485	1485_1	TCACAGCCTATCACCAC	TCacagcctatcacCAC	47,3
1485	1485_2	TCACAGCCTATCACCAC	TCAcagcctatcaccAC	46,3
1486	1486_1	ATCACAGCCTATCACCA	AtcacagcctatcACCA	56,9
1486	1486_2	ATCACAGCCTATCACCA	ATCacagcctatcacCA	23,7
1487	1487_1	AATCACAGCCTATCACC	AATCacagcctatcaCC	32,9
1487	1487_2	AATCACAGCCTATCACC	AatcacagcctatCACC	52,2
1488	1488_1	ATCACAGCCTATCACC	AtcacagcctatCACC	60,1
1489	1489_1	GCGTCACCCAAATCAC	GCgtcacccaaatCAC	11
1490	1490_1	AGCGTCACCCAAATCA	AG^{m}cgtcacccaaaTCA	17,4
1491	1491_1	AGCGTCACCCAAATC	AG^{m}cgtcacccaAATC	18,8
1492	1492_1	CAGATCCTAAAATCACT	CAGAtcctaaaatcaCT	71,8
1493	1493_1	TCAGATCCTAAAATCAC	TCAgatcctaaaatCAC	66,2
1494	1494_1	AGTAAAACCAATCATCAT	AGTaaaaccaatcatCAT	30,8
1495	1495_1	AGTAAAACCAATCATCA	AGTaaaaccaatcaTCA	24,2
1496	1496_1	CCCTTCCATCTCTACTAAAA	CccttccatctctactaaAA	89,7
1497	1497_1	ATAACTACATAACAAACCCA	ATaactacataacaaaCCCA	69,1
1498	1498_1	AATAACTACATAACAAACCCA	AAtaactacataacaaaCCCA	77,8
1499	1499_1	AACTACATAACAAACCCA	AActacataacaaaCCCA	62,9
1500	1500_1	TAACTACATAACAAACCCA	TAactacataacaaaCCCA	65
1501	1501_1	ACTACATAACAAACCCA	ACtacataacaaaCCCA	60,4
1502	1502_1	CAATAACTACATAACAAACCC	CAAtaactacataacaaaCCC	72,6
1503	1503_1	ATAACTACATAACAAACCC	ATAactacataacaaaCCC	60,2
1504	1504_1	ACAATAACTACATAACAAACC	ACAataactacataacaaACC	78,5
1504	1504_2	ACAATAACTACATAACAAACC	ACAAtaactacataacaaaCC	80,9
1505	1505_1	TGAATTCACAATAACTACA	TGaattcacaataacTACA	38,1
1506	1506_1	GCACATTTTTCTTAAACT	GCACatttttcttaaaCT	62,2
1507	1507_1	GCTATACCTAAAACAATCT	GCTatacctaaaacaaTCT	62,2
1508	1508_1	GCTATACCTAAAACAATC	GCTAtacctaaaacaaTC	68,9
1509	1509_1	CCCTTGTAACTAAAAAT	CCCTtgtaactaaaaAT	100
1510	1510_1	CCCCTTGTAACTAAAAA	CCCCttgtaactaaaAA	86,1
1511	1511_1	CCCCTTGTAACTAAAA	CCCCttgtaactaaAA	101
1512	1512_1	ACCCCTTGTAACTAAA	ACCCcttgtaactaAA	88,8
1513	1513_1	CACCCCTTGTAACTAA	CAccccttgtaaCTAA	80,4
1514	1514_1	ACACCCCTTGTAACTA	ACACcccttgtaacTA	72,4
1515	1515_1	GCTAAAACTAATCATCT	GCTaaaactaatcaTCT	72,2
1516	1516_1	GGCTAAAACTAATCAT	GGCtaaaactaatCAT	70,8
1517	1517_1	TTACCCTTCATATATACATCT	TtacccttcatatatacaTCT	89,4
1518	1518_1	ATTACCCTTCATATATACATC	AttacccttcatatataCATC	82,4
1519	1519_1	TTACCCTTCATATATACATC	TTAcccttcatatatacATC	56,3
1520	1520_1	CATTACCCTTCATATATACAT	CAttacccttcatatataCAT	84,2
1521	1521_1	TTACCCTTCATATATACAT	TTAcccttcatatataCAT	55,3
1522	1522_1	ATTACCCTTCATATATACAT	ATTacccttcatatataCAT	49,3

1523	1523_1	ACATTACCCTTCATATATACA	ACAttacccttcatatataCA	55,2
1523	1523_2	ACATTACCCTTCATATATACA	AcattacccttcatataTACA	63,4
1524	1524_1	TTACCCTTCATATATACA	TTACccttcatatataCA	46,9
1525	1525_1	CATTACCCTTCATATATACA	CattacccttcatataTACA	66
1526	1526_1	ATTACCCTTCATATATACA	ATTAcccttcatatataCA	36,7
1527	1527_1	ATTACCCTTCATATATAC	ATTacccttcatataTAC	46,6
1528	1528_1	TTACCCTTCATATATAC	TTAcccttcatataTAC	56,9
1529	1529_1	CATTACCCTTCATATATAC	CATtacccttcatataTAC	63,4
1530	1530_1	ACATTACCCTTCATATATAC	ACAttacccttcatataTAC	34,5
1531	1531_1	TACATTACCCTTCATATATAC	TAcattacccttcatataTAC	76,9
1532	1532_1	CATTACCCTTCATATATA	CAttacccttcataTATA	76,5
1533	1533_1	TACATTACCCTTCATATATA	TACattacccttcatatATA	36,5
1534	1534_1	ATTACCCTTCATATATA	ATtacccttcataTATA	78
1535	1535_1	ACATTACCCTTCATATATA	ACattacccttcataTATA	59,5
1536	1536_1	CATTACCCTTCATATAT	CATtacccttcataTAT	73,7
1537	1537_1	ACATTACCCTTCATATAT	ACAttacccttcataTAT	46,1
1538	1538_1	TACATTACCCTTCATATAT	TACattacccttcataTAT	36,9
1539	1539_1	ACATTACCCTTCATATA	ACattacccttcaTATA	54,2
1540	1540_1	TACATTACCCTTCATATA	TAcattacccttcaTATA	71,5
1541	1541_1	TACATTACCCTTCATAT	TACattacccttcaTAT	34,5
1542	1542_1	GATTCTTATACTTACTA	GATtcttatacttaCTA	46,2
1543	1543_1	TGATTCTTATACTTACT	TGattcttatactTACT	45,7
1544	1544_1	ATGATTCTTATACTTACT	ATGAttcttatacttaCT	54
1545	1545_1	GCCTCATTTTTACCTTT	GCctcatttttaccTTT	82,6
1546	1546_1	ACCAATCTTCTATTTTA	ACCAatcttctatttTA	94,8
1547	1547_1	CAACCAATCTTCTATTTTA	CAACcaatcttctatttTA	90,3
1548	1548_1	GCAACCAATCTTCTATTTT	GCAAccaatcttctattTT	88,3
1549	1549_1	GCAACCAATCTTCTATTT	GCAaccaatcttctaTTT	85
1550	1550_1	GCAACCAATCTTCTATT	GCaaccaatcttcTATT	87,3
1551	1551_1	TGCAACCAATCTTCTATT	TGCaaccaatcttctaTT	90,2
1552	1552_1	TAACTGCAACCAATCTT	TAactgcaaccaaTCTT	88,2
1553	1553_1	TGAATACAACACACATCA	TGAatacaacacacaTCA	97,4
1554	1554_1	ATGAATACAACACACATCA	ATGAatacaacacacatCA	84,4
1555	1555_1	TAAAAATATAACTACTCCT	TAaaaatataactacTCCT	99,8
1556	1556_1	GTAAAAATATAACTACTCC	GTaaaaatataactaCTCC	93,7
1557	1557_1	TCAACTGATACCCACAA	TCAactgatacccaCAA	57,7
1558	1558_1	TGTCTTAACATTTTTCTT	TGTCttaacatttttcTT	63,1
1559	1559_1	CCACTTCAAACTTTTAATTAA	CCActtcaaacttttaatTAA	85
1560	1560_1	CCACTTCAAACTTTTAATTA	CCACttcaaacttttaatTA	84,9
1561	1561_1	CCCACTTCAAACTTTTAATTA	CCcacttcaaacttttaaTTA	88,7
1562	1562_1	CCACTTCAAACTTTTAATT	CCACttcaaacttttaaTT	79,1
1563	1563_1	CCCACTTCAAACTTTTAATT	CCCacttcaaacttttaaTT	86,2
1564	1564_1	ACCCACTTCAAACTTTTAATT	ACCcacttcaaacttttaaTT	100
1565	1565_1	CCACTTCAAACTTTTAAT	CCACttcaaacttttaAT	85,3

1566	1566_1	ACCCACTTCAAACTTTTAAT	ACCcacttcaaacttttAAT	88,8
1567	1567_1	AACCCACTTCAAACTTTTAAT	AACCcacttcaaacttttaAT	92,3
1568	1568_1	CCCACTTCAAACTTTTAA	CCCacttcaaactttTAA	79,9
1569	1569_1	ACCCACTTCAAACTTTTAA	ACCcacttcaaactttTAA	82,5
1570	1570_1	CCCACTTCAAACTTTTA	CCCacttcaaactttTA	79,6
1571	1571_1	ACCCACTTCAAACTTTTA	ACCcacttcaaacttTTA	77,2
1572	1572_1	AACCCACTTCAAACTTTTA	AACCcacttcaaactttTA	86,2
1573	1573_1	ACCCACTTCAAACTTTT	ACCCacttcaaacttTT	93,3
1574	1574_1	AACCCACTTCAAACTTTT	AACCcacttcaaacttTT	82,7
1575	1575_1	AACCCACTTCAAACTTT	AACCcacttcaaactTT	85,8
1576	1576_1	GGACTCTATTAATCAA	GGActctattaatCAA	91,7
1577	1577_1	GAATATTCTACTCTTCT	GAatattctactcTTCT	95,3
1578	1578_1	CTGTATTTACCAATTCAA	CTGtatttaccaattCAA	90,8
1579	1579_1	CTGTATTTACCAATTCA	CTGTatttaccaattCA	88,7
1580	1580_1	ACTGTATTTACCAATTCA	ACTGtatttaccaattCA	97,3
1581	1581_1	ACTGTATTTACCAATTC	ACTGtatttaccaatTC	104
1582	1582_1	CACTGTATTTACCAATT	CACTgtatttaccaaTT	91,1
1583	1583_1	TCACTGTATTTACCAAT	TCACtgtatttaccaAT	98,6
1584	1584_1	CCAACTACTTTACTTTTCAAA	CCaactactttacttttCAAA	84,3
1585	1585_1	CCAACTACTTTACTTTTCAA	CCaactactttacttttTCAA	80
1586	1586_1	ACCAACTACTTTACTTTTCAA	ACcaactactttacttttTCAA	85,1
1585	1585_2	CCAACTACTTTACTTTTCAA	CCAactactttacttttCAA	75,2
1587	1587_1	CCAACTACTTTACTTTTCA	CCAactactttacttttCA	71,9
1588	1588_1	TACCAACTACTTTACTTTTCA	TaccaactactttacttTTCA	82,8
1587	1587_2	CCAACTACTTTACTTTTCA	CCAactactttacttttTCA	67,7
1589	1589_1	ACCAACTACTTTACTTTTCA	ACcaactactttacttttTCA	84
1590	1590_1	TACCAACTACTTTACTTTTC	TACcaactactttacttTTC	75,3
1591	1591_1	GTACCAACTACTTTACTTT	GTACcaactactttactTT	75,8
1592	1592_1	GTACCAACTACTTTACTT	GTAccaactactttaCTT	65,7
1593	1593_1	GTACCAACTACTTTACT	GTACcaactactttaCT	74,5
1594	1594_1	TGTACCAACTACTTTACT	TGtaccaactacttTACT	87,1
1595	1595_1	TTGTACCAACTACTTTAC	TTGtaccaactacttTAC	73,3
1596	1596_1	GTACCAACTACTTTAC	GTAccaactacttTAC	72,5
1597	1597_1	TGTACCAACTACTTTAC	TGTaccaactacttTAC	66
1598	1598_1	TTGTACCAACTACTTTA	TTGTaccaactacttTA	49,3
1599	1599_1	ATTTCATTTTTCTTTTAATA	ATTtcatttttcttttaATA	98,6
1599	1599_2	ATTTCATTTTTCTTTTAATA	ATTTcatttttcttttaaTA	90,7
1600	1600_1	CCTAATTTCATTTTTCTTTT	CCtaatttcatttttcTTTT	69,2
1601	1601_1	TCCTAATTTCATTTTTCTTT	TCctaatttcatttttCTTT	47
1602	1602_1	TTCTTCATTATACCATCAAAT	TTCTtcattataccatcaaAT	29,4
1603	1603_1	TTTCTTCATTATACCATCAAA	TTTCttcattataccatcaAA	24,1
1604	1604_1	TTTTCTTCATTATACCATCAA	TTttcttcattataccaTCAA	14,3
1605	1605_1	TCTTCATTATACCATCAA	TCttcattataccaTCAA	5,02
1606	1606_1	TTTCTTCATTATACCATCAA	TTtcttcattataccaTCAA	21,2

1607	1607_1	TTCTTCATTATACCATCAA	TTCttcattataccatCAA	5,83
1608	1608_1	ATATTTTCTTCATTATACCAT	Atattttcttcattata CCAT	76,1
1609	1609_1	ATATTTTCTTCATTATACCA	ATattttcttcattataCCA	40,2
1610	1610_1	AATATTTTCTTCATTATACCA	AATattttcttcattataCCA	37
1611	1611_1	AAATATTTTCTTCATTATACC	AAatattttcttcattaTACC	23,4
1612	1612_1	ATATTTTCTTCATTATACC	ATattttcttcattaTACC	14,2
1613	1613_1	AATATTTTCTTCATTATACC	AATAttttcttcattataCC	68
1614	1614_1	TAAATATTTTCTTCATTATA	TAaatattttcttcatTATA	96,8
1615	1615_1	TTTTCCTTCATCTACTTCT	TTTtccttcatctacttCT	42,8
1616	1616_1	ATTTTCCTTCATCTACTTCT	ATtttccttcatctacttCT	76
1617	1617_1	AATTTTCCTTCATCTACTTC	AATTttccttcatctactTC	54,9
1618	1618_1	AGAATTTTCCTTCATCTA	Agaattttccttca TCTA	58
1619	1619_1	CAGAATTTTCCTTCATCT	CAgaattttccttcATCT	23,5
1620	1620_1	TCAGAATTTTCCTTCATC	TCAgaattttccttcaTC	29,7
1621	1621_1	CTAGAAATATCTCACATT	CTAGaaatatctcacaTT	64,6
1622	1622_1	CTAGAAATATCTCACAT	CTAgaaatatctcaCAT	75,5
1623	1623_1	ACTAGAAATATCTCACA	ACTAgaaatatctcaCA	53,2
1624	1624_1	ATTAGCCATTAATCTAT	ATtagccattaatCTAT	71,9
1625	1625_1	TTGTTACAAAATAATCCA	TTgttacaaaataaTCCA	12
1625	1625_2	TTGTTACAAAATAATCCA	TTGttacaaaataatCCA	23,8
1626	1626_1	TTATTTTTTACATTAACTA	TTAttttttacattaaCTA	92,1
1627	1627_1	TGCCAAAATACTAACATCA	TGCcaaaatactaacaTCA	32
1628	1628_1	GCCAAAATACTAACATCA	GCCaaaatactaacaTCA	27,8
1629	1629_1	TGCCAAAATACTAACATC	TGCCaaaatactaacaTC	61,5
1630	1630_1	GAGTACAACACTTACA	GAGTacaacacttaCA	31,8
1631	1631_1	CACATCCATTCATTTTAT	CACatccattcatttTAT	30,6
1632	1632_1	CCACATCCATTCATTTTAT	CCAcatccattcattttAT	21,7
1633	1633_1	CCACATCCATTCATTTTA	CCacatccattcattTTA	20
1634	1634_1	TATGCCACATCCATTCAT	Tatgccacatccatt CAT	47
1635	1635_1	TTATGCCACATCCATTCA	Ttatgccacatcca TTCA	20,7
1636	1636_1	TATGCCACATCCATTCA	TAtgccacatccattCA	43,3
1637	1637_1	TTATGCCACATCCATTC	Ttatgccacatcc ATTC	19,5
1638	1638_1	ATTATGCCACATCCATT	ATtatgccacatcCATT	25,1
1639	1639_1	AGTTTCATATTTTTAATC	AGTttcatatttttaATC	65,9
1640	1640_1	ATCACTGCACACTTTCC	ATCactgcacactttCC	12,9
1641	1641_1	AAGCTCTTTCCAAATTCT	AAGCtctttccaaattCT	34,6
1642	1642_1	TAGTTCTTAACTCTTCTC	Tagttcttaactct TCTC	19,2
1643	1643_1	TTAGTTCTTAACTCTTC	TTAGttcttaactctTC	18
1644	1644_1	AGCTTCAAATACTCAAA	AGCTtcaaatactcaAA	74,5
1645	1645_1	TTTCAAAGCCACACCTA	TttcaaagccacacCTA	66,9
1646	1646_1	AATATCCTCATTACCCATT	AATAtcctcattacccaTT	52,3
1647	1647_1	TATCCTCATTACCCATT	TAtcctcattaccCATT	53,4
1647	1647_2	TATCCTCATTACCCATT	TATCctcattacccaTT	22,3
1648	1648_1	ATATCCTCATTACCCATT	ATAtcctcattacccATT	55,8

1649	1649_1	AATATCCTCATTACCCAT	AAtatcctcattacCCAT	46,1
1650	1650_1	TAATATCCTCATTACCCAT	TAAtatcctcattaccCAT	58,3
1651	1651_1	TTAATATCCTCATTACCCAT	TTaatatcctcattaccCAT	61,8
1652	1652_1	ATATCCTCATTACCCAT	ATAtcctcattaccCAT	56,2
1653	1653_1	AATATCCTCATTACCCA	AAtatcctcattaCCCA	49,7
1654	1654_1	TAATATCCTCATTACCCA	TAATatcctcattaccCA	45,6
1655	1655_1	TTTAATATCCTCATTACCCA	TttaatatcctcattacCCA	67,5
1656	1656_1	TTAATATCCTCATTACCCA	TTaatatcctcattacCCA	36
1656	1656_2	TTAATATCCTCATTACCCA	TTAAtatcctcattaccCA	57,9
1654	1654_2	TAATATCCTCATTACCCA	TAAtatcctcattacCCA	40
1653	1653_2	AATATCCTCATTACCCA	AATatcctcattacCCA	44,8
1657	1657_1	ATTTAATATCCTCATTACCC	AtttaatatcctcattaCCC	59,9
1658	1658_1	TAATATCCTCATTACCC	TAATatcctcattacCC	32,9
1659	1659_1	TTAATATCCTCATTACCC	TTAAtatcctcattacCC	42
1660	1660_1	TTTAATATCCTCATTACCC	TttaatatcctcattACCC	41,1
1661	1661_1	AATTTAATATCCTCATTACCC	AatttaatatcctcattaCCC	61
1662	1662_1	TTTAATATCCTCATTACC	TTTAatatcctcattaCC	60,6
1663	1663_1	AATTTAATATCCTCATTACC	AAtttaatatcctcatTACC	58,8
1664	1664_1	TTAATATCCTCATTACC	TTaatatcctcatTACC	42,3
1665	1665_1	AAATTTAATATCCTCATTACC	AAatttaatatcctcatTACC	55,9
1666	1666_1	ATTTAATATCCTCATTACC	ATttaatatcctcatTACC	55,5
1667	1667_1	TAAATTTAATATCCTCATTAC	TAaatttaatatcctcaTTAC	78
1668	1668_1	TTAAATTTAATATCCTCATTA	TTAaatttaatatcctcaTTA	95,2
1669	1669_1	CTTAAATTTAATATCCTCATT	CTtaaatttaatatcctCATT	73,2
1670	1670_1	TCTTAAATTTAATATCCTCAT	TCttaaatttaatatccTCAT	46,8
1671	1671_1	TCTTAAATTTAATATCCTCA	TCttaaatttaatatcCTCA	29,8
1672	1672_1	TTCTTAAATTTAATATCCTCA	TTCttaaatttaatatccTCA	35
1673	1673_1	TTCTTAAATTTAATATCCTC	TTcttaaatttaatatCCTC	36,2
1674	1674_1	TCTTAAATTTAATATCCTC	TCttaaatttaatatCCTC	25,1
1675	1675_1	TTCTTAAATTTAATATCCT	TTCttaaatttaatatCCT	46,9
1676	1676_1	TCTTAAATTTAATATCCT	TCttaaatttaataTCCT	50,9
1677	1677_1	AATAGCCTTTATTCTAC	AAtagcctttattCTAC	33,6
1678	1678_1	CAGCAACAATTATTAATA	CAGCaacaattattaaTA	70,5
1679	1679_1	CCAGCAACAATTATTAAT	CCAGcaacaattattaAT	64,2
1680	1680_1	ACCAGCAACAATTATTAA	ACCagcaacaattatTAA	20,5
1680	1680_2	ACCAGCAACAATTATTAA	ACCAgcaacaattattAA	39,7
1681	1681_1	ACCAGCAACAATTATTA	ACCAgcaacaattatTA	39,4
1682	1682_1	TACCAGCAACAATTATT	TACCagcaacaattaTT	26,4
1683	1683_1	CCCCAAATCTAAAACACTTC	CCccaaatctaaaacacTTC	79,4
1684	1684_1	AACCCCAAATCTAAAACACTT	AACCccaaatctaaaacacTT	82
1685	1685_1	CCCCAAATCTAAAACACTT	CCCcaaatctaaaacacTT	86,4
1686	1686_1	AACCCCAAATCTAAAACACT	AACCccaaatctaaaacaCT	75,2
1687	1687_1	ACCCCAAATCTAAAACACT	ACcccaaatctaaaaCACT	72,5
1688	1688_1	ACCCCAAATCTAAAACAC	ACCccaaatctaaaaCAC	80,9

1689	1689_1	GCAAATATTCACAAATCCT	GCAaatattcacaaatCCT	20,7
1689	1689_2	GCAAATATTCACAAATCCT	GCaaatattcacaaaTCCT	29,3
1690	1690_1	ACTATTTAACACACATTATCA	ACTatttaacacacattaTCA	36,6
1691	1691_1	CTATTTAACACACATTATCA	CTAtttaacacacattaTCA	49,6
1692	1692_1	TACTATTTAACACACATTATC	TACTatttaacacacattaTC	52,4
1693	1693_1	ACTATTTAACACACATTATC	ACTAtttaacacacattaTC	51,8
1694	1694_1	TACTATTTAACACACATTAT	TACtatttaacacacatTAT	91,1
1695	1695_1	CTACTATTTAACACACATTAT	CTActatttaacacacatTAT	72,7
1696	1696_1	CTACTATTTAACACACATTA	CTACtatttaacacacatTA	47,4
1697	1697_1	ACTACTATTTAACACACATTA	ACTActatttaacacacatTA	38,3
1698	1698_1	CTACTATTTAACACACATT	CTACtatttaacacacaTT	41,6
1699	1699_1	ACTACTATTTAACACACATT	ACtactatttaacacaCATT	40,3
1700	1700_1	ACTACTATTTAACACACAT	ACTactatttaacacaCAT	36,8
1701	1701_1	CTACTATTTAACACACA	CTACtatttaacacaCA	45,9
1702	1702_1	ACTACTATTTAACACACA	ACTActatttaacacaCA	32,6
1703	1703_1	TATAGACCCTTAATATT	TATAgacccttaataTT	41,4
1704	1704_1	TTATAGACCCTTAATAT	TTAtagacccttaaTAT	68,5
1705	1705_1	CATCACAAAATAACCTATCAT	CAtcacaaaataacctaTCAT	86,8
1706	1706_1	TCATCACAAAATAACCTATCA	TCAtcacaaaataacctaTCA	67,4
1707	1707_1	TTCATCACAAAATAACCTATC	TTCAtcacaaaataacctaTC	49
1708	1708_1	TTCATCACAAAATAACCTA	TTcatcacaaaataaCCTA	76,4
1709	1709_1	TTTCATCACAAAATAACCTA	TTtcatcacaaaataaCCTA	88,6
1710	1710_1	TCATCACAAAATAACCTA	TCatcacaaaataaCCTA	59,2
1711	1711_1	TTTTCATCACAAAATAACCTA	TTttcatcacaaaataaCCTA	86,1
1712	1712_1	ATTTTCATCACAAAATAACCT	ATTttcatcacaaaataaCCT	64,8
1713	1713_1	TATTTTCATCACAAAATAACC	TATTttcatcacaaaataaCC	76,9
1713	1713_2	TATTTTCATCACAAAATAACC	TATTttcatcaCaaaataaCC	56
1714	1714_1	GTATTTTCATCACAAAATA	GTATtttcatcacaaaaTA	47
1715	1715_1	TTACCTAGATCACTCC	TtacctagatcaCTCC	73,1
1716	1716_1	CTTACCTAGATCACTC	CTTacctagatcaCTC	81,5
1717	1717_1	CCTTACCTAGATCACT	CCTtacctagatcaCT	95,9
1718	1718_1	TAACTGCTCCTTAATCC	TAActgctccttaatCC	34,8
1719	1719_1	TCTAGCAATCCTCTCCT	TCtagcaatcctctcCT	64,2
1720	1720_1	TTCTAGCAATCCTCTCC	TtctagcaatcctcTCC	70,4
1721	1721_1	TTTTCACCTACTAATATTCAT	TTttcacctactaatatTCAT	55,3
1722	1722_1	TTTCACCTACTAATATTCAT	TTtcacctactaatatTCAT	66,2
1723	1723_1	TTCACCTACTAATATTCAT	TTCacctactaatattCAT	17,2
1724	1724_1	TCACCTACTAATATTCAT	TCAcctactaatattCAT	23,5
1725	1725_1	TCACCTACTAATATTCA	TCAcctactaatatTCA	21,1
1726	1726_1	TTTCACCTACTAATATTCA	TTTCacctactaatattCA	16,7
1727	1727_1	TTTTCACCTACTAATATTCA	TTttcacctactaataTTCA	31,3
1728	1728_1	TTTTTCACCTACTAATATTCA	TTtttcacctactaataTTCA	45,3
1729	1729_1	TTCACCTACTAATATTCA	TTCAcctactaatattCA	24,7
1730	1730_1	ATTTTTCACCTACTAATATTC	ATTtttcacctactaataTTC	48,5

1731	1731_1	TTTTTCACCTACTAATATTC	TTTttcacctactaataTTC	31,5
1732	1732_1	TATTTTTCACCTACTAATATT	TAtttttcacctactaaTATT	90,2
1733	1733_1	TATTTTTCACCTACTAATAT	TATttttcacctactaaTAT	89,1
1734	1734_1	TTATTTTTCACCTACTAATAT	TTAtttttcacctactaaTAT	86,1
1735	1735_1	TTATTTTTCACCTACTAATA	TTATttttcacctactaaTA	52,9
1736	1736_1	TATTTTTCACCTACTAATA	TATTtttcacctactaaTA	54,9
1737	1737_1	TTTATTTTTCACCTACTAATA	TTTAtttttcacctactaaTA	52
1738	1738_1	TTTATTTTTCACCTACTAA	TTtatttttcacctaCTAA	51,2
1739	1739_1	TTTATTTTTCACCTACTA	TTTatttttcacctaCTA	19
1740	1740_1	CTCAACTTCTACTACTAATT	CTCAacttctactactaaTT	19,7
1741	1741_1	TCTCAACTTCTACTACTAATT	TCTCaacttctactactaaTT	25,8
1742	1742_1	CTCTCAACTTCTACTACTAAT	CTCtcaacttctactactAAT	43
1743	1743_1	CTCAACTTCTACTACTAAT	CTCAacttctactactaAT	20,1
1744	1744_1	TCTCAACTTCTACTACTAAT	TCTCaacttctactactaAT	22,8
1745	1745_1	TCTCTCAACTTCTACTACTAA	TCtctcaacttctactacTAA	58,4
1746	1746_1	CTCAACTTCTACTACTAA	CTcaacttctactaCTAA	47,3
1747	1747_1	TCTCAACTTCTACTACTAA	TCtcaacttctactaCTAA	56,3
1748	1748_1	CTCAACTTCTACTACTA	CTCaacttctactaCTA	10,7
1749	1749_1	TTCTCTCAACTTCTACTACTA	TtctctcaacttctactaCTA	79,1
1750	1750_1	TCTCTCAACTTCTACTACTA	TCtctcaacttctactacTA	61,2
1751	1751_1	TCTCAACTTCTACTACTA	TCtcaacttctactaCTA	66,8
1752	1752_1	CTCTCAACTTCTACTACTA	CtctcaacttctactACTA	61,7
1753	1753_1	CTCTCAACTTCTACTACT	CTCtcaacttctactaCT	37,9
1754	1754_1	TCTCAACTTCTACTACT	TCtcaacttctacTACT	51,1
1755	1755_1	TCTCTCAACTTCTACTACT	TCtctcaacttctactACT	44,2
1756	1756_1	TTTCTCTCAACTTCTACTACT	TTtctctcaacttctactACT	65,7
1757	1757_1	TTCTCTCAACTTCTACTACT	TTCtctcaacttctactaCT	33,5
1758	1758_1	TTTCTCTCAACTTCTACTAC	TTtctctcaacttctacTAC	67,9
1759	1759_1	CTCTCAACTTCTACTAC	CTCtcaacttctacTAC	34,1
1760	1760_1	TTCTCTCAACTTCTACTAC	TtctctcaacttctaCTAC	63,8
1761	1761_1	TTTTCTCTCAACTTCTACTAC	TTTTctctcaacttctactAC	20,6
1762	1762_1	TCTCTCAACTTCTACTAC	TCtctcaacttctacTAC	49,7
1763	1763_1	TTTCTCTCAACTTCTACTA	TTtctctcaacttctaCTA	60,2
1764	1764_1	TTTTCTCTCAACTTCTACTA	TtttctctcaacttctACTA	52,2
1765	1765_1	TTTTTCTCTCAACTTCTACTA	TTTttctctcaacttctacTA	40,2
1766	1766_1	TCTCTCAACTTCTACTA	TCtctcaacttctaCTA	47,5
1767	1767_1	TTCTCTCAACTTCTACTA	TTCtctcaacttctacTA	35,1
1768	1768_1	TTTCTCTCAACTTCTACT	TTTCtctcaacttctaCT	28,6
1769	1769_1	TTTTCTCTCAACTTCTACT	TTTtctctcaacttctaCT	44,1
1770	1770_1	CTTTTTCTCTCAACTTCTACT	CttttttctctcaacttctaCT	99,8
1771	1771_1	TTTTTCTCTCAACTTCTACT	TTTttctctcaacttctaCT	43,7
1772	1772_1	CTTTTTCTCTCAACTTCTAC	CTTttttctctcaacttctAC	36,2
1773	1773_1	ACTTTTTCTCTCAACTTCTAC	ACTttttctctcaacttctAC	35,6
1774	1774_1	TTTTCTCTCAACTTCTAC	TtttctctcaacttctaCTAC	38,6

1775	1775_1	TTTTTCTCTCAACTTCTAC	TttttctctcaacttCTAC	42,1
1776	1776_1	CTTTTTCTCTCAACTTCTA	CTttttctctcaacttCTA	41,2
1777	1777_1	TACTTTTTCTCTCAACTTCTA	TacttttttctctcaacttctA	69,4
1778	1778_1	ACTTTTTCTCTCAACTTCTA	ActttttctctcaacttctA	66,2
1779	1779_1	TTTTTCTCTCAACTTCTA	TttttctctcaactTCTA	35,5
1780	1780_1	TACTTTTTCTCTCAACTTCT	TActttttctctcaacttCT	65
1781	1781_1	TTACTTTTTCTCTCAACTTCT	Ttacttttttctctcaactt CT	62,1
1782	1782_1	TTACTTTTTCTCTCAACTTC	TTActttttctctcaactTC	38,9
1783	1783_1	TACTTTTTCTCTCAACTTC	TACttttttctctcaactTC	34
1784	1784_1	ACTTTTTCTCTCAACTTC	Actttttctctcaa CTTC	19,7
1785	1785_1	TTACTTTTTCTCTCAACTT	TTActttttctctcaaCTT	22
1786	1786_1	TACTTTTTCTCTCAACTT	TACttttttctctcaaCTT	22,3
1787	1787_1	TTACTTTTTCTCTCAACT	TTACttttttctctcaaCT	11,6
1788	1788_1	GTTACTTTTTCTCTCAACT	GTtacttttttctctcAACT	43,2
1789	1789_1	GTTACTTTTTCTCTCAAC	GTtacttttttctctCAAC	29
1790	1790_1	GTTACTTTTTCTCTCAA	GTtacttttttctcTCAA	5,53
1791	1791_1	AGTTACTTTTTCTCTCAA	AGTtacttttttctctCAA	6,5
1792	1792_1	CTTTTACATTCCCATTAACA	CTTTtacattcccattaaCA	24,5
1793	1793_1	CACTTTTACATTCCCATTAAC	CACttttacattcccattaAC	25,3
1794	1794_1	CTTTTACATTCCCATTAAC	CTtttacattcccatTAAC	21,5
1795	1795_1	ACTTTTACATTCCCATTAAC	ACttttacattcccatTAAC	23
1796	1796_1	ACTTTTACATTCCCATTAA	ACttttacattcccaTTAA	30
1797	1797_1	CTTTTACATTCCCATTAA	CTtttacattcccaTTAA	27,4
1798	1798_1	CACTTTTACATTCCCATTAA	CActttt acattcccaTTAA	28
1798	1798_2	CACTTTTACATTCCCATTAA	CACttttacattcccatTAA	15,9
1799	1799_1	TACACTTTTACATTCCCATTA	TAcacttttacattcccatTA	52,2
1800	1800_1	ACTTTTACATTCCCATTA	ACTtttacattcccaTTA	13,1
1801	1801_1	CACTTTTACATTCCCATTA	CActttt acattcccATTA	15,7
1802	1802_1	ACACTTTTACATTCCCATTA	ACactttt acattcccaTTA	19,1
1802	1802_2	ACACTTTTACATTCCCATTA	ACActttt acattcccatTA	9,66
1803	1803_1	CACTTTTACATTCCCATT	CActttt acattccCATT	10,2
1804	1804_1	TACACTTTTACATTCCCATT	TACacttttacattcccaTT	10,3
1805	1805_1	ACACTTTTACATTCCCATT	ACACttttacattcccaTT	4,51
1805	1805_2	ACACTTTTACATTCCCATT	ACactttt acattccCATT	6,8
1806	1806_1	TACACTTTTACATTCCCAT	TACactttt acattccCAT	3,53
1806	1806_2	TACACTTTTACATTCCCAT	TACActttt acattcccAT	4,79
1807	1807_1	TACACTTTTACATTCCCA	TACactttt acattccCA	6,35
1808	1808_1	GTACACTTTTACATTCCCA	Gtacacttttacattc CCA	3
1808	1808_2	GTACACTTTTACATTCCCA	GTacactttt acattccCA	16,3
1809	1809_1	GTACACTTTTACATTCCC	GTAcacttttacattcCC	4,33
1810	1810_1	TACACTTTTACATTCCC	TACactttt acattcCC	3,26
1811	1811_1	TGTACACTTTTACATTCCC	TGtacacttttacattcCC	12,3
1809	1809_2	GTACACTTTTACATTCCC	Gtacacttttacattc CCC	2,49
1812	1812_1	TGTACACTTTTACATTCC	TGtacacttttacatTCC	2,47

1813	1813_1	CTGTACACTTTTACATTC	CTGtacactttacaTTC	1,89
1814	1814_1	ATCTTATTTACATCTTCC	ATcttatttacatcTTCC	5,41
1815	1815_1	GAATCTTATTTACATCTTC	GAatcttatttacatCTTC	25,8
1816	1816_1	GAATCTTATTTACATCTT	GAatcttatttacaTCTT	19,1
1817	1817_1	TGAATCTTATTTACATCT	TGAatcttatttacaTCT	41,3
1818	1818_1	ATTCAGCTTTTTCAATC	ATTCagctttttcaaTC	16,8
1819	1819_1	TTAATTTTCCCTTCACTCCT	Ttaattttcccttcactcct	85,8
1820	1820_1	TTAATTTTCCCTTCACTCC	Ttaattttcccttcactcc	85,8
1821	1821_1	TTAATTTTCCCTTCACTC	Ttaattttcccttcactc	51
1822	1822_1	GTTAATTTTCCCTTCACTC	Gttaattttcccttcactc	27,2
1823	1823_1	CAAAATTACTTCTTTTATCAT	CAaaattacttcttttaTCAT	86,7
1823	1823_2	CAAAATTACTTCTTTTATCAT	CAaaattacTtcttttaTCAT	51,5
1824	1824_1	CCAAAATTACTTCTTTTATCA	CCAaaattacttcttttaTCA	31,3
1824	1824_2	CCAAAATTACTTCTTTTATCA	CCaaaattacttcttttATCA	36
1825	1825_1	TCCAAAATTACTTCTTTTATC	TCcaaaattacttctttTATC	40,9
1826	1826_1	TCCAAAATTACTTCTTTTAT	TCCaaaattacttctttTAT	50,2
1827	1827_1	CCAAAATTACTTCTTTTAT	CCAaaattacttctttTAT	70
1828	1828_1	TTCCAAAATTACTTCTTTTAT	TTCcaaaattacttctttTAT	64,9
1829	1829_1	TCCAAAATTACTTCTTTTA	TCCAaaattacttctttTA	36,9
1830	1830_1	TTCCAAAATTACTTCTTTTA	TTCCaaaattacttctttTA	52,2
1831	1831_1	GTTCCAAAATTACTTCTTT	GTTCcaaaattacttctTT	54,8
1832	1832_1	GTTCCAAAATTACTTCTT	GTtccaaaattactTCTT	12,5
1833	1833_1	TGTTCCAAAATTACTTCT	TGTtccaaaattactTCT	20,1
1834	1834_1	ATGTTCCAAAATTACTTC	ATGTtccaaaattactTC	23,8
1835	1835_1	CATATTTTACTCTTTTTATT	CATAttttactcttttaTT	90,6
1836	1836_1	CCATATTTTACTCTTTTTAT	CCATattttactcttttAT	35,4
1836	1836_2	CCATATTTTACTCTTTTTAT	CCAtattttactctttTAT	60,8
1837	1837_1	CCCATATTTTACTCTTTTTAT	Cccatattttactctttttat	75,8
1838	1838_1	CATATTTTACTCTTTTTAT	CATattttactctttTAT	83,2
1839	1839_1	CCCATATTTTACTCTTTTTA	CCcatattttactctttTA	81,1
1840	1840_1	CCATATTTTACTCTTTTTA	CCatattttactcttTTTA	24,7
1841	1841_1	ACCCATATTTTACTCTTTTTA	Acccatattttactcttttta	59
1842	1842_1	CCATATTTTACTCTTTTT	CCATattttactctttTT	21,6
1843	1843_1	CCCATATTTTACTCTTTTT	CCcatattttactcttTTT	77,2
1844	1844_1	ACCCATATTTTACTCTTTTT	ACccatattttactctTTTT	97,4
1845	1845_1	TACCCATATTTTACTCTTTTT	TAcccatattttactcttTTT	58,6
1846	1846_1	TACCCATATTTTACTCTTTT	TACccatattttactctTTT	20,4
1847	1847_1	CCCATATTTTACTCTTTT	CCCatattttactcttTT	93,2
1848	1848_1	ACCCATATTTTACTCTTTT	ACCcatattttactcttTT	21,8
1846	1846_2	TACCCATATTTTACTCTTTT	TAcccatattttactcTTTT	22,5
1849	1849_1	TTACCCATATTTTACTCTTTT	TTAcccatattttactcttTT	41,4
1850	1850_1	TACCCATATTTTACTCTTT	TAcccatattttactCTTT	18,9
1851	1851_1	ACCCATATTTTACTCTTT	ACCcatattttactcTTT	13,4
1852	1852_1	TTACCCATATTTTACTCTTT	TTacccatattttactCTTT	14,5

1853	1853_1	TTTACCCATATTTTACTCTTT	TTTacccatattttactcTTT	22,2
1852	1852_2	TTACCCATATTTTACTCTTT	TTACccatattttactctTT	16,7
1853	1853_2	TTTACCCATATTTTACTCTTT	TTTAcccatattttactctTT	16
1854	1854_1	TTACCCATATTTTACTCTT	TTAcccatattttactCTT	14
1855	1855_1	TTTACCCATATTTTACTCTT	TTtacccatattttacTCTT	14,9
1856	1856_1	ACCCATATTTTACTCTT	ACCcatattttactCTT	8,02
1857	1857_1	TACCCATATTTTACTCTT	TACccatattttactCTT	16,7
1858	1858_1	TACCCATATTTTACTCT	TACccatattttacTCT	22,3
1859	1859_1	TTACCCATATTTTACTCT	TTACccatattttactCT	15,2
1860	1860_1	TTTACCCATATTTTACTCT	TTTAcccatattttactCT	11,8
1861	1861_1	TTACCCATATTTTACTC	TTAcccatattttaCTC	24,4
1862	1862_1	TTTACCCATATTTTACTC	TTTacccatattttaCTC	14
1863	1863_1	GTTTACCCATATTTTACTC	GTttacccatattttaCTC	12,2
1864	1864_1	GTTTACCCATATTTTACT	GTttacccatatttTACT	24,9
1865	1865_1	TGTTTACCCATATTTTAC	TGTttacccatatttTAC	13,1
1866	1866_1	GTTTACCCATATTTTAC	GTttacccatattTTAC	13,2
1867	1867_1	TGTTTACCCATATTTTA	TGTttacccatattTTA	6,69
1868	1868_1	TTCTTGCTTCAACCATC	TtcttgcttcaacCATC	13,6
1869	1869_1	GTTACCTCCCTTTATAT	GTtacctccctttatAT	60,9
1870	1870_1	GGTTACCTCCCTTTAT	GgttacctccctTTAT	39
1871	1871_1	AGGTTACCTCCCTTTA	AggttacctcccTTTA	35,4
1872	1872_1	ATGTTCTCTATCTCTATA	ATGttctctatctctATA	53,3
1873	1873_1	TATGTTCTCTATCTCTA	TAtgttctctatctCTA	73,4
1874	1874_1	AGATCAAACTAAAACCT	AGAtcaaactaaaaCCT	88,7
1875	1875_1	TGCCCAATTTCACCCAA	TGcccaatttcacccAA	30,3
1876	1876_1	TTTGCCCAATTTCACCC	Tttgcccaatttcacc	53,3
1877	1877_1	TTTTGCCCAATTTCACC	TTttgcccaatttcaCC	57,8
1878	1878_1	TGTATATCAACAATTCAT	TGTatatcaacaattCAT	20,8
1879	1879_1	ACATTTCTTTAAAATTTCCA	ACatttctttaaaattTCCA	96,4
1879	1879_2	ACATTTCTTTAAAATTTCCA	ACAtttctttaaaatttCCA	96,6
1880	1880_1	CACATTTCTTTAAAATTTCCA	CACAtttctttaaaatttcCA	95,5
1879	1879_3	ACATTTCTTTAAAATTTCCA	AcatttctttaaaattTCCA	98,1
1879	1879_4	ACATTTCTTTAAAATTTCCA	ACATttctttaaaatttcCA	98
1881	1881_1	CCACATTTCTTTAAAATTTCC	CcacatttctttaaaatTTCC	90
1882	1882_1	CACATTTCTTTAAAATTTCC	CAcatttctttaaaattTCC	94,8
1882	1882_2	CACATTTCTTTAAAATTTCC	CAcatttctttaaaatTTCC	89,1
1882	1882_3	CACATTTCTTTAAAATTTCC	CACAtttctttaaaatttCC	94,4
1883	1883_1	ACATTTCTTTAAAATTTCC	ACAtttctttaaaattTCC	91,9
1882	1882_4	CACATTTCTTTAAAATTTCC	CACatttctttaaaattTCC	92,4
1884	1884_1	CCACATTTCTTTAAAATTTC	CCACatttctttaaaattTC	98,3
1885	1885_1	ACCACATTTCTTTAAAATTTC	ACCAcatttctttaaaattTC	97,5
1884	1884_2	CCACATTTCTTTAAAATTTC	CCAcatttctttaaaattTC	102
1884	1884_3	CCACATTTCTTTAAAATTTC	CCacatttctttaaaaTTTC	94,9
1884	1884_4	CCACATTTCTTTAAAATTTC	CCAcatttctttaaaatTTC	87,2

1886	1886_1	ACCACATTTCTTTAAAATTT	ACCAcatttctttaaaatTT	94,8
1887	1887_1	ACAAAACCACATTTCTTTAA	ACAaaaccacatttcttTAA	97,4
1888	1888_1	CTGTTTTCAAATCATTTC	CTGTtttcaaatcattTC	15,8
1889	1889_1	GAACCATTACTATTATCAA	GAaccattactattaTCAA	27,3
1890	1890_1	AGAACCATTACTATTATCA	AGAaccattactattaTCA	19,8
1891	1891_1	AGAACCATTACTATTATC	AGaaccattactatTATC	17,9
1892	1892_1	CTAGAACCATTACTATTA	CTAGaaccattactatTA	35,3
1893	1893_1	TAGAACCATTACTATTA	TAGAaccattactatTA	13,2
1894	1894_1	CTAGAACCATTACTATT	CTAGaaccattactaTT	32,1
1895	1895_1	AGATTACCATCTTTCAAAA	AGATtaccatctttcaaAA	59,5
1895	1895_2	AGATTACCATCTTTCAAAA	AGAttaccatctttcaAAA	54,1
1896	1896_1	AGATTACCATCTTTCAAA	AGATtaccatctttcaAA	50,6
1896	1896_2	AGATTACCATCTTTCAAA	AGattaccatctttCAAA	42,3
1897	1897_1	AGATTACCATCTTTCAA	AGAttaccatctttCAA	32,4
1898	1898_1	AAGATTACCATCTTTCA	AAGAttaccatctttCA	47,9
1899	1899_1	CATGCTCACACATTTTAA	CATgctcacacatttTAA	60,5
1899	1899_2	CATGCTCACACATTTTAA	CAtgctcacacattTTAA	70,3
1899	1899_3	CATGCTCACACATTTTAA	CAtgctcacacatttTAA	69,8
1899	1899_4	CATGCTCACACATTTTAA	CATGctcacacattttAA	55,9
1900	1900_1	CTTAAGCTATCTAAACA	CTTAagctatctaaaCA	82,6
1901	1901_1	TGAACAATTCAACATTCA	TGAacaattcaacatTCA	67,7
1902	1902_1	GATCAAAAAACTTTCCCT	GAtcaaaaaactttCCCT	76,1
1903	1903_1	AGATCAAAAAACTTTCCCT	AGatcaaaaaactttCCCT	70,4
1904	1904_1	AGATCAAAAAACTTTCCC	AGAtcaaaaaactttCCC	73,6
1905	1905_1	TCCTAGATCAAAAAACT	TCCTagatcaaaaaaCT	69,9
1906	1906_1	ATTTTTTCTTCTCTTTTCA	ATTTtttcttctttttCA	8,98
1907	1907_1	TATTTTTTCTTCTCTTTTCA	TATtttttcttctttttCA	63,8
1908	1908_1	ATATTTTTTCTTCTCTTTTC	ATatttttttcttctctTTTC	16,1
1909	1909_1	TCTGCTTTAAAAACTCTC	TCtgctttaaaaacTCTC	34,3
1910	1910_1	CTCTGCTTTAAAAACTC	CTCtgctttaaaaaCTC	51,6
1911	1911_1	ACTACACAAACACATTCAA	ACtacacaaacacatTCAA	37,6
1912	1912_1	CAAACTACACAAACACATTCA	CAaactacacaaacacaTTCA	41,2
1913	1913_1	ACAAACTACACAAACACATTC	ACAaactacacaaacacaTTC	63,1
1914	1914_1	CAACAAACTACACAAACACAT	CAAcaaactacacaaacaCAT	86,1
1915	1915_1	CACAACAAACTACACAAACAC	CACaacaaactacacaaaCAC	62,1
1916	1916_1	TCACAACAAACTACACAAACA	TCACaacaaactacacaaaCA	48,6
1917	1917_1	TTCACAACAAACTACACAAAC	TTCAcaacaaactacacaaAC	58,8
1918	1918_1	ATTTCACAACAAACTACACAA	ATTtcacaacaaactacaCAA	76,8
1919	1919_1	CAATTTCACAACAAACTACAC	CAAtttcacaacaaactaCAC	70,7
1920	1920_1	TGTAACAATTTCACAACAA	TGTaacaatttcacaaCAA	59,5
1921	1921_1	TGTAACAATTTCACAACA	TGTAacaatttcacaaCA	28,7
1922	1922_1	TTAAGCCAACCCCACCA	TtaagccaaccccacCA	83,1
1923	1923_1	TTTAAGCCAACCCCACC	TttaagccaaccccACC	69,2
1924	1924_1	ATTTAAGCCAACCCCAC	Atttaagccaaccccac	60,6

1925	1925_1	CCAGTAATACAAATTATA	CCAGtaatacaaattaTA	69,5
1926	1926_1	CCCAGTAATACAAATTA	CCCAgtaatacaaatTA	55,9
1927	1927_1	TCCCAGTAATACAAATT	TCCCagtaatacaaaTT	64,9
1928	1928_1	ATCCCAGTAATACAAAT	ATCCcagtaatacaaAT	65,9
1929	1929_1	CTACTAGCATCACCACT	CtactagcatcacCACT	19,8
1930	1930_1	TTCTACTAGCATCACC	TtctactagcatCACC	21,8
1931	1931_1	CTTCTACTAGCATCAC	CTtctactagcaTCAC	33,2
1932	1932_1	TAAATTACTCATTAAATCCAT	TAaattactcattaaatCCAT	77,8
1933	1933_1	ATAAATTACTCATTAAATCCA	ATaaattactcattaaaTCCA	52,4
1934	1934_1	TAAATTACTCATTAAATCCA	TAaattactcattaaaTCCA	51,6
1935	1935_1	CATAAATTACTCATTAAATCC	CATaaattactcattaaaTCC	58,5
1935	1935_2	CATAAATTACTCATTAAATCC	CATaaattacTcattaaaTCC	22,3
1936	1936_1	GATTTATTTTTCTACTTA	GAtttatttttctaCTTA	66
1937	1937_1	ATACAACAAACAATTCACTTT	ATacaacaaacaattcaCTTT	53,2
1937	1937_2	ATACAACAAACAATTCACTTT	ATACaacaaacaattcactTT	48,1
1938	1938_1	CGATACAACAAACAATTCA	CGATacaacaaacaattCA	23
1939	1939_1	GAACATCCACACTAACAACA	GAACatccacactaacaaCA	43,6
1940	1940_1	ACATCCACACTAACAACA	ACAtccacactaacaACA	65
1939	1939_2	GAACATCCACACTAACAACA	GAAcatccacactaacaACA	52
1939	1939_3	GAACATCCACACTAACAACA	GAacatccacactaacAACA	58,1
1941	1941_1	GAACATCCACACTAACAAC	GAACatccacactaacaAC	51,3
1941	1941_2	GAACATCCACACTAACAAC	GAacatccacactaaCAAC	63,3
1942	1942_1	TGAACATCCACACTAACAA	TGAacatccacactaaCAA	57,8
1943	1943_1	TTGAACATCCACACTAACA	TTGAacatccacactaaCA	60,3
1944	1944_1	TGAACATCCACACTAACA	TGAAcatccacactaaCA	42,6
1945	1945_1	CATTGAACATCCACACTA	CATtgaacatccacaCTA	59,4
1946	1946_1	ATTGAACATCCACACTA	ATTgaacatccacaCTA	50
1947	1947_1	CATTGAACATCCACACT	CAttgaacatccaCACT	43
1948	1948_1	ACTCATTGAACATCCAC	ACtcattgaacatCCAC	46,8
1949	1949_1	TATCTTTATTTAATAATCTT	TATCtttatttaataatcTT	93,4
1949	1949_2	TATCTTTATTTAATAATCTT	TAtctttatttaataaTCTT	96,9
1950	1950_1	TCTCAAGCTTCACTCTA	TCtcaagcttcactcTA	78,6
1951	1951_1	GACAATATATTCCTCAATC	GACAatatattcctcaaTC	73
1952	1952_1	GACAATATATTCCTCAAT	GACAatatattcctcaAT	82
1952	1952_2	GACAATATATTCCTCAAT	GAcaatatattcctCAAT	76,8
1953	1953_1	TCCTGTAACAATTATAC	TCCtgtaacaattaTAC	95,4
1954	1954_1	ACCCAGAATAAAAACCAC	ACccagaataaaaaCCAC	95,5
1955	1955_1	TTCCACTTTCTTACTCCC	TtccactttcttactcCC	96,6
1956	1956_1	TTCCACTTTCTTACTCC	TtccactttcttacTCC	86,3
1957	1957_1	TTTCCACTTTCTTACTCC	TttccactttcttacTCC	89,2
1958	1958_1	TTTCCACTTTCTTACTC	TTTCcactttcttacTC	89,2
1959	1959_1	ATCCCTTTACCACTTTT	ATCcctttaccactTTT	101
1960	1960_1	CATCCCTTTACCACTTTT	CAtcccttaccactTTT	98
1961	1961_1	TCATCCCTTTACCACTTT	TCatcccttaccactTT	101

1962	1962_1	TCATCCCTTTACCACTT	TCAtccctttaccacTT	96,9
1963	1963_1	CTCATCCCTTTACCACTT	CtcatccctttaccacTT	97,7
1964	1964_1	GTCTACATCTAACCCC	GtctacatctaacCCC	97
1965	1965_1	AGTCTACATCTAACCCC	AGtctacatctaaccCC	99,6
1966	1966_1	CAGTCTACATCTAACCCC	CagtctacatctaaccCC	97,4
1967	1967_1	CAGTCTACATCTAACCC	CagtctacatctaaCCC	99,5
1968	1968_1	TCAGTCTACATCTAACCC	TCagtctacatctaacCC	98,9
1969	1969_1	AGTCTACATCTAACCC	AGTctacatctaacCC	98,2
1970	1970_1	TCAGTCTACATCTAACC	TCagtctacatctAACC	98,3
1971	1971_1	TTCAGTCTACATCTAACC	TTCagtctacatctaaCC	98
1972	1972_1	TTCAGTCTACATCTAAC	TTCAgtctacatctaAC	98,7
1973	1973_1	TTTCAGTCTACATCTAA	TTtcagtctacatCTAA	90,1
1974	1974_1	AGTTTTAACCACACCTCCT	Agttttaaccacacctcct	102
1975	1975_1	GTTTTAACCACACCTCC	GTTttaaccacacctCC	93,7
1976	1976_1	AGTTTTAACCACACCTCC	Agttttaaccacaccтcc	95
1977	1977_1	AGTTTTAACCACACCTC	AGttttaaccacacCTC	88,7
1978	1978_1	GAGTTTTAACCACACC	GAGttttaaccacACC	94,7
1979	1979_1	CAGATCTTCTCTTTATTT	CAGatcttctctttaTTT	96,3
1980	1980_1	TGTTTTCAACAAAACATCA	TGTtttcaacaaaacaTCA	89,9
1981	1981_1	TGTTTTCAACAAAACATC	TGttttcaacaaaaCATC	97,5
1982	1982_1	CTGTTTTCAACAAAACAT	CTGttttcaacaaaaCAT	102
1983	1983_1	TCTGTTTTCAACAAAACA	TCTGttttcaacaaaaCA	98
1984	1984_1	ATCTTTCTAAAACTTACC	ATCTttctaaaacttaCC	96,3
1985	1985_1	CAGAATCTTTCTAAAACT	CAGAatctttctaaaaCT	91,7
1986	1986_1	CTACAGAATCTTTCTAA	CTacagaatctttCTAA	97,6
1986	1986_2	CTACAGAATCTTTCTAA	CTAcagaatctttcTAA	95,6
1987	1987_1	ATTTCCCTTTATTTCCCTT	Atttccctttatttccctt	92
1988	1988_1	GTATTTCCCTTTATTTCC	Gtatttccctttattтcc	99,5

In the oligonucleotide compound column, capital letters represent beta-D-oxy LNA nucleosides, LNA cytosines are 5-methyl cytosine, lower case letters are DNA nucleosides, and all internucleoside linkages are phosphorothioate. ^{m}c represent 5-methyl cytosine DNA nucleosides (used in compounds 1490_1 and 1491_1).

Example 4

The screening assay described in Example 2 was performed using a series of further oligonucleotide targeting human ATXN3 pre-mRNA using the qpCR: (ATXN3_exon_8-9(1) PrimeTime® XL qPCR Assay (IDT).

qPCR probe and primers set 2:

Probe: 5'-/56-FAM/CTCCGCAGG/ZEN/GCT ATTCAGCT AAGT /31ABkFQ/-3' (SEQ ID NO 1134)

Primer 1: 5'-AGT AAGATTTGT ACCTGATGTCTGT-3' (SEQ ID NO 1135)

Primer 2: 5'-CATGGAAGATGAGGAAGCAGAT-3' (SEQ ID NO 1136)

Table 6

SEQID	CMPID	Oligonucleotide Base Sequence	Oligonucleotide compound	% of ATXN3 mRNA remaining
1110	1110_2	ACATCATTTATCACTACCAC	ACatcatttatcactacCAC	44
1102	1102_2	TATCTCAAACTATCCCCA	TatctcaaactatccCCA	74
1104	1104_2	TCCCCTAAATAATTTAATCA	TCCcctaaataatttaaTCA	78
1116	1116_2	TCTTCATTATACCATCAAAT	TCTTcattataccatcaaAT	12
1121	1121_2	CTCTCAACTTCTACTACTAA	CtctcaacttctactaCTAA	68
1114	1114_2	TGATTCTTATACTTACTA	TGATtcttatacttacTA	64
1120	1120_2	CATCACAAAATAACCTATCA	CATCacaaaataacctatCA	38
1100	1100_2	CCCCATTCAAATATTTATT	CCCcattcaaatatttATT	79
1112	1112_2	TCAGATCCTAAAATCACT	TCAGatcctaaaatcaCT	65
1123	1123_2	CCAAAATTACTTCTTTTATC	CCaaaattacttctttTATC	37
1117	1117_2	GTTTCATATTTTTAATCC	GTttcatatttttaATCC	10
1099	1099_2	CCAAAAGAAACCAAACCC	CCaaaagaaaccaaACCC	88
1109	1109_2	TGAAACCATTACTACAACC	TGAaaccattactacaACC	22
1113	1113_2	CTATACCTAAAACAATCTA	CTatacctaaaacaaTCTA	86
1119	1119_2	CAAATATTCACAAATCCTA	CaaatattcacaaatCCTA	78
1125	1125_2	ACAATATATTCCTCAATCA	ACaatatattcctcaATCA	74
1127	1127_2	CATCCCTTTACCACTTT	CatcccttTaccaCTTT	97
1118	1118_2	TAATATCCTCATTACCCATT	TaatatcctcattaccCATT	97
1103	1103_2	TCTATTCCTTAACCCAAC	TCtattccttaaccCAAC	81
1122	1122_2	AATCTTATTTACATCTTCC	AATCttatttacatcttCC	11
1126	1126_2	CCTGTAACAATTATACA	CCTGtaacaattataCA	93
1122	1122_3	AATCTTATTTACATCTTCC	AatcttatttacaTCtTCC	54
1122	1122_4	AATCTTATTTACATCTTCC	AAtcTtatttacAtCttCC	17
1122	1122_5	AATCTTATTTACATCTTCC	AAtcttatttacAtCttCC	21
1122	1122_6	AATCTTATTTACATCTTCC	AatctTatttacaTCttCC	12
1122	1122_7	AATCTTATTTACATCTTCC	AatcttatttacAtCttCC	28
1122	1122_8	AATCTTATTTACATCTTCC	AAtcttatttacAtcTTCC	28
1122	1122_9	AATCTTATTTACATCTTCC	AAtcTtatttacAtctTCC	11
1122	1122_10	AATCTTATTTACATCTTCC	AatctTatttacAtctTCC	9
1122	1122_11	AATCTTATTTACATCTTCC	AatcTtatttacatcTTCC	10
1122	1122_12	AATCTTATTTACATCTTCC	AATcTtatttacAtcTtCC	10
1122	1122_13	AATCTTATTTACATCTTCC	AatCTtatttacAtcttCC	10
1122	1122_14	AATCTTATTTACATCTTCC	AatCttatttacatctTCC	7
1122	1122_15	AATCTTATTTACATCTTCC	AatcttatttacaTCttCC	32
1122	1122_16	AATCTTATTTACATCTTCC	AatCttatttacatcTTCC	4
1122	1122_17	AATCTTATTTACATCTTCC	AAtCttatttacatcTtCC	5
1122	1122_18	AATCTTATTTACATCTTCC	AaTcTtatttacaTcTtCC	9

1122	1122_19	AATCTTATTTACATCTTCC	AatcTTatttacatcTtCC	5
1122	1122_20	AATCTTATTTACATCTTCC	AatcTtatttacatCttCC	13
1122	1122_21	AATCTTATTTACATCTTCC	AAtcttatttacatCttCC	23
1122	1122_22	AATCTTATTTACATCTTCC	AatctTatttacatCttCC	8
1122	1122_23	AATCTTATTTACATCTTCC	AatcTTatttacatCttCC	4
1122	1122_24	AATCTTATTTACATCTTCC	AatctTatttacatcTTCC	8
1122	1122_25	AATCTTATTTACATCTTCC	AATcTTatttacatcTtCC	5
1122	1122_26	AATCTTATTTACATCTTCC	AAtctTatttacatcTtCC	12
1122	1122_27	AATCTTATTTACATCTTCC	AaTCTtatttacatcTtCC	3
1122	1122_28	AATCTTATTTACATCTTCC	AaTcTTatttacatcTtCC	3
1122	1122_29	AATCTTATTTACATCTTCC	AatCTTatttacatcTtCC	3
1122	1122_30	AATCTTATTTACATCTTCC	AAtcTTatttacatctTCC	5
1122	1122_31	AATCTTATTTACATCTTCC	AAtcTtatttacatctTCC	12
1122	1122_32	AATCTTATTTACATCTTCC	AAtcttatttacatctTCC	33
1122	1122_33	AATCTTATTTACATCTTCC	AatCtTatttacatctTCC	3
1122	1122_34	AATCTTATTTACATCTTCC	AatcTTatttacatctTCC	6
1122	1122_35	AATCTTATTTACATCTTCC	AatcTtatttacatctTCC	16
1122	1122_36	AATCTTATTTACATCTTCC	AATCtTatttacatcttCC	8
1122	1122_37	AATCTTATTTACATCTTCC	AAtCTTatttacatcttCC	5
1122	1122_38	AATCTTATTTACATCTTCC	AAtCttatttacatcttCC	16
1122	1122_39	AATCTTATTTACATCTTCC	AaTCTtatttacatcttCC	7
1122	1122_40	AATCTTATTTACATCTTCC	AaTCtTatttacatcttCC	5
1122	1122_41	AATCTTATTTACATCTTCC	AatCTTatttacatcttCC	5
1122	1122_42	AATCTTATTTACATCTTCC	AatCTtatttacatcttCC	13
1122	1122_43	AATCTTATTTACATCTTCC	AatcTTatttacatcttCC	17
1109	1109_3	TGAAACCATTACTACAACC	TgaaaccattacTAcaaCC	58
1109	1109_4	TGAAACCATTACTACAACC	TgaaaccattacTAcAaCC	20
1109	1109_5	TGAAACCATTACTACAACC	TgaAAccattacTacAaCC	23
1109	1109_6	TGAAACCATTACTACAACC	TgAaAccattactAcaaCC	50
1109	1109_7	TGAAACCATTACTACAACC	TgAaaCcattactAcaaCC	46
1109	1109_8	TGAAACCATTACTACAACC	TgaAAccattacTacaaCC	48
1109	1109_9	TGAAACCATTACTACAACC	TgaaaccattactaCAaCC	25
1109	1109_10	TGAAACCATTACTACAACC	TgaaAccattacTaCaACC	24
1109	1109_11	TGAAACCATTACTACAACC	TGaaAccattactaCaaCC	36
1109	1109_12	TGAAACCATTACTACAACC	TgAAAccattactaCaaCC	20
1109	1109_13	TGAAACCATTACTACAACC	TgAAaCcattactaCaaCC	26
1109	1109_14	TGAAACCATTACTACAACC	TgAaaccattactaCaaCC	27
1109	1109_15	TGAAACCATTACTACAACC	TGaAaccattacTacAaCC	14
1109	1109_16	TGAAACCATTACTACAACC	TgAaaCcattactacAACC	12
1109	1109_17	TGAAACCATTACTACAACC	TgaaaCcattacTacAaCC	36
1109	1109_18	TGAAACCATTACTACAACC	TgaaaCcattacTacaaCC	62
1109	1109_19	TGAAACCATTACTACAACC	TGaaAccattactacaaCC	47
1109	1109_20	TGAAACCATTACTACAACC	TgaAaccattactaCAaCC	19
1109	1109_21	TGAAACCATTACTACAACC	TgaAaccattactACaACC	16

1109	1109_22	TGAAACCATTACTACAACC	TgAAaccattactACaACC	9
1109	1109_23	TGAAACCATTACTACAACC	TgAaAccattactAcaACC	29
1109	1109_24	TGAAACCATTACTACAACC	TgaaaCcattactAcaACC	41
1109	1109_25	TGAAACCATTACTACAACC	TgaAACcattactAcaaCC	34
1109	1109_26	TGAAACCATTACTACAACC	TgaAaCcattactaCaaCC	28
1109	1109_27	TGAAACCATTACTACAACC	TGaAaCcattactacAACC	10
1109	1109_28	TGAAACCATTACTACAACC	TgAAaCcattactAcAACC	52
1109	1109_29	TGAAACCATTACTACAACC	TGaAAccattactacaACC	16
1109	1109_30	TGAAACCATTACTACAACC	TGAaaccattactacaaCC	36
1109	1109_31	TGAAACCATTACTACAACC	TgaaaCcattactaCaACC	21
1109	1109_32	TGAAACCATTACTACAACC	TgAAAccattactacAACC	9
1109	1109_33	TGAAACCATTACTACAACC	TgAaaCcattactacAaCC	14
1109	1109_34	TGAAACCATTACTACAACC	TGaaaccattactacaACC	43
1109	1109_35	TGAAACCATTACTACAACC	TgAAaCcattactacaACC	15
1109	1109_36	TGAAACCATTACTACAACC	TgaAACcattactacaaCC	15
1109	1109_37	TGAAACCATTACTACAACC	TGaAaCcattactacaaCC	16
1109	1109_38	TGAAACCATTACTACAACC	TGaaaCcattactacaaCC	38
1109	1109_39	TGAAACCATTACTACAACC	TgAAACcattactacaaCC	14
1109	1109_40	TGAAACCATTACTACAACC	TgAAaCcattactacaaCC	16
1109	1109_41	TGAAACCATTACTACAACC	TgaAaCcattactacaaCC	28
1109	1109_42	TGAAACCATTACTACAACC	TgaaACcattactacaaCC	28
1122	1122_44	AATCTTATTTACATCTTCC	AatcttatttacaTCTtCC	65
1122	1122_45	AATCTTATTTACATCTTCC	AatcTtatttacAtCttCC	38
1122	1122_46	AATCTTATTTACATCTTCC	AatcTtatttacaTcTTCC	34
1122	1122_47	AATCTTATTTACATCTTCC	AAtCttatttacAtcTtCC	10
1122	1122_48	AATCTTATTTACATCTTCC	AAtcTtatttacATcTtCC	35
1122	1122_49	AATCTTATTTACATCTTCC	AatCttatttacAtcTtCC	10
1122	1122_50	AATCTTATTTACATCTTCC	AAtCttatttacAtcttCC	11
1122	1122_51	AATCTTATTTACATCTTCC	AAtctTatttacatCTtCC	9
1122	1122_52	AATCTTATTTACATCTTCC	AatcTTatttacAtcTtCC	12
1122	1122_53	AATCTTATTTACATCTTCC	AatctTatttacatCTtCC	8
1122	1122_54	AATCTTATTTACATCTTCC	AaTcTtatttacatcTTCC	4
1122	1122_55	AATCTTATTTACATCTTCC	AAtcttatttacAtcTtCC	27
1122	1122_56	AATCTTATTTACATCTTCC	AAtCtTatttacAtcttCC	5
1122	1122_57	AATCTTATTTACATCTTCC	AAtcTTatttacatcttCC	14
1122	1122_58	AATCTTATTTACATCTTCC	AaTCttatttacatcttCC	13
1122	1122_59	AATCTTATTTACATCTTCC	AATcttatttacatCttCC	6
1122	1122_60	AATCTTATTTACATCTTCC	AAtcTtatttacatCttCC	10
1122	1122_61	AATCTTATTTACATCTTCC	AAtcTTatttacatcTtCC	6
1122	1122_62	AATCTTATTTACATCTTCC	AatCtTatttacatcTtCC	3
1122	1122_63	AATCTTATTTACATCTTCC	AATCttatttacaTcttCC	5
1122	1122_64	AATCTTATTTACATCTTCC	AatCttatttacatcTtCC	7
1122	1122_65	AATCTTATTTACATCTTCC	AatCttatttacatcttCC	32
1122	1122_66	AATCTTATTTACATCTTCC	Aatcttatttacatc TTCC	19

1122	1122_67	AATCTTATTTACATCTTCC	AATCttatttacatcTtCC	3
1122	1122_68	AATCTTATTTACATCTTCC	AATcTtatttacatcTtCC	4
1122	1122_69	AATCTTATTTACATCTTCC	AAtCTtatttacatcTtCC	3
1122	1122_70	AATCTTATTTACATCTTCC	AAtCtTatttacatcTtCC	3
1122	1122_71	AATCTTATTTACATCTTCC	AAtcTtatttacatcTtCC	13
1122	1122_72	AATCTTATTTACATCTTCC	AaTCttatttacatcTtCC	5
1122	1122_73	AATCTTATTTACATCTTCC	AatCTtatttacatcTtCC	5
1122	1122_74	AATCTTATTTACATCTTCC	AatctTatttacatcTtCC	10
1122	1122_75	AATCTTATTTACATCTTCC	AAtCTtatttacatctTCC	3
1122	1122_76	AATCTTATTTACATCTTCC	AAtCttatttacatctTCC	5
1122	1122_77	AATCTTATTTACATCTTCC	AaTCttatttacatctTCC	5
1122	1122_78	AATCTTATTTACATCTTCC	AatCTtatttacatctTCC	4
1122	1122_79	AATCTTATTTACATCTTCC	AAtCTtatttacatcttCC	7
1122	1122_80	AATCTTATTTACATCTTCC	AAtCtTatttacatcttCC	5
1122	1122_81	AATCTTATTTACATCTTCC	AatCtTatttacatcttCC	8
1109	1109_43	TGAAACCATTACTACAACC	TgAAaccattacTAcAaCC	18
1109	1109_44	TGAAACCATTACTACAACC	TgAaAccattacTacAaCC	27
1109	1109_45	TGAAACCATTACTACAACC	TgaAaCcattacTacAaCC	65
1109	1109_46	TGAAACCATTACTACAACC	TgAaaccattacTacaACC	25
1109	1109_47	TGAAACCATTACTACAACC	TgaAaccattacTacaACC	35
1109	1109_48	TGAAACCATTACTACAACC	TgaaAccattacTacaACC	48
1109	1109_49	TGAAACCATTACTACAACC	TgaAaCcattacTacaaCC	44
1109	1109_50	TGAAACCATTACTACAACC	TgaAaccattacTaCaaCC	34
1109	1109_51	TGAAACCATTACTACAACC	TGaaaccattacTacaACC	29
1109	1109_52	TGAAACCATTACTACAACC	TgAAaccattacTacaACC	23
1109	1109_53	TGAAACCATTACTACAACC	TgaaaCcattacTaCaaCC	39
1109	1109_54	TGAAACCATTACTACAACC	TGaaaccattactaCaaCC	33
1109	1109_55	TGAAACCATTACTACAACC	TgAaAccattactaCaaCC	29
1109	1109_56	TGAAACCATTACTACAACC	TGaaAccattactacAACC	16
1109	1109_57	TGAAACCATTACTACAACC	TGaaAccattactacAaCC	18
1109	1109_58	TGAAACCATTACTACAACC	TgAaACcattactacaaCC	12
1109	1109_59	TGAAACCATTACTACAACC	TgAaaccattactaCAaCC	13
1109	1109_60	TGAAACCATTACTACAACC	TgaaAccattactACaaCC	36
1109	1109_61	TGAAACCATTACTACAACC	TGaaaccattactAcaACC	34
1109	1109_62	TGAAACCATTACTACAACC	TgAaaCcattactACaaCC	43
1109	1109_63	TGAAACCATTACTACAACC	TGaAAccattactaCaaCC	19
1109	1109_64	TGAAACCATTACTACAACC	TGaaaCcattactACaaCC	29
1109	1109_65	TGAAACCATTACTACAACC	TGaAaccattactAcaaCC	40
1109	1109_66	TGAAACCATTACTACAACC	TgaAAccattactAcAACC	14
1109	1109_67	TGAAACCATTACTACAACC	TGaAaccattactAcAaCC	14
1109	1109_68	TGAAACCATTACTACAACC	TGaaaCcattactAcAaCC	27
1109	1109_69	TGAAACCATTACTACAACC	TgAaaCcattactAcAACC	31
1109	1109_70	TGAAACCATTACTACAACC	TgAaAccattactAcAaCC	24
1109	1109_71	TGAAACCATTACTACAACC	TgaaACcattactacAACC	10

1109	1109_72	TGAAACCATTACTACAACC	TGAaaccattactacAaCC	11
1109	1109_73	TGAAACCATTACTACAACC	TgaAACcattactAcAaCC	34
1109	1109_74	TGAAACCATTACTACAACC	TGaAaCcattactacaACC	15
1109	1109_75	TGAAACCATTACTACAACC	TGaaACcattactacaaCC	14
1109	1109_76	TGAAACCATTACTACAACC	TGaAaccattactaCaaCC	22
1109	1109_77	TGAAACCATTACTACAACC	TgaAAccattactaCaaCC	30
1109	1109_78	TGAAACCATTACTACAACC	TgaaAccattactaCaaCC	50
1109	1109_79	TGAAACCATTACTACAACC	TgaAACcattactacAaCC	9
1109	1109_80	TGAAACCATTACTACAACC	TGaAaccattactacaaCC	31
1109	1109_81	TGAAACCATTACTACAACC	TgAaaCcattactacaaCC	31

In the oligonucleotide compound column, capital letters represent beta-D-oxy LNA nucleosides, LNA cytosines are 5-methyl cytosine, lower case letters are DNA nucleosides, and all internucleoside linkages are phosphorothioate.

Example 5 Testing in vitro efficacy of LNA oligonucleotides in iCell GlutaNeurons at 25µM

An oligonucleotide screen was performed in a human cell line using selected LNA oligonucleotides from the previous examples.

The iCell GlutaNeurons derived from human induced pluripotent stem cell were purchased from the vendor listed in table 3, and were maintained as recommended by the supplier in a humidified incubator at 37°C with 5% CO_2. For the screening assays, cells were seeded in 96 multi well plates in media recommended by the supplier (see table 3 in the Materials and Methods section). The number of cells/well was optimized (Table 3).

Cells were grown for 7 days before addition of the oligonucleotide in concentration of 25 µM (dissolved in medium). 4 days after addition of the oligonucleotide, the cells were harvested.

RNA extraction and qPCR was performed as described for “Example 1”

Primer assays for ATXN3 and house keeping gene were:

ATXN3 primer assay (Assay ID: N/A, Item Name: Hs.PT.58.39355049):

Forward primer: GTTTCTAAAGACATGGTCACAGC (SEQ ID NO 1128)

Reverse: CTATCAGGACAGAGTTCACATCC (SEQ ID NO 1129)

Probe: 56-FAM/AAAGGCCAG/ZEN/CCACCAGTTCAGG/3IABkFQ/ (SEQ ID NO 1030)

TBP primer assay (Assay ID: N/A, Item name: Hs.PT.58v.39858774

Probe: 5’- /5HEX/TGA TCT TTG /ZEN/CAG TGA CCC AGC ATC A/3IABkFQ/ -3’ (SEQ ID NO 1131)

Primer 1: 5’- GCT GTT TAA CTT CGC TTC CG-3’ (SEQ ID NO 1132)

Primer 2: 5’- CAG CAA CTT CCT CAA TTC CTT G-3’ (SEQ ID NO 1133)

The relative ATXN3 mRNA expression levels were determined as % of control (medium-treated cells) i.e. the lower the value the larger the inhibition.
The compounds tested and the target knock-down data is presented in the Table 7.

Example 6 Determination of EC50 values of LNA gapmers targeting ATXN3

Values for EC50 (concentration at which half effect on target knockdown is observed) was determined for the cell lines SK-N-AS, A431 and iPSCs (iCell GlutaNeurons). The following oligoconcentrations were used:

- SK-N-AS: 50µM – half log dilution (3.16 fold) – 8 steps including blank control
- A431: 50µM – half log dilution (3.16 fold) – 8 steps including blank control
- iPCS: 10µM – 10 fold dilution – 8 steps including blank control

The cells were treated with oligo, lysed and analysed as indicated in previous exapmles.
The compounds tested and their EC50 values is shown in table 7.

Example 7 *In vitro* toxicity Evaluation

The criterion for selection of oligonucleotides assessed in the various safety assays is based on the magnitude and frequency of signals obtained. Safety assays used were: Caspase activation, hepatotoxicity, nephrotoxicity toxicity and immunotoxicity assays. The signals obtained in the individual in vitro safety assays result in a score (0-safe, 0.5 borderline toxicity, 1-mild toxicity, 2- medium toxicity and 3- severe toxicity) and are summarized into a cumulative score for each sequence (See table 7), providing an objective ranking of compounds. As reported in the references provided, the signal strength is a measure of risk for *in vivo* toxicity based on validation of the assays using in vivo relevant reference molecules

In vitro toxicity assays were performed as described in the following references:

Caspase activation assay: Dieckmann et al., Molecular Therapy: Nucleic Acids Vol. 10 March 2018, pp45 - 54.

Hepatotoxicity toxicity assay: Sewing et al., Methods in Molecular Biology Oligonucleotide-Based Therapies MIMB, volume 2036, pp 249-259 2019, Sewing et al., PLOS ONE | DOI:10.1371/journal.pone.0159431 July 21, 2016.

Nephrotoxicity toxicity assay: Moisan et al., Mol Ther Nucleic Acids. 2017 Mar 17;6:89-105. doi: 10.1016/j.omtn.2016.11.006. Epub 2016 Dec 10.

Immunotoxicity: Sewing et al., PLoS One. 2017 Nov 6;12(11):e0187574. doi: 10.1371/journal.pone.0187574. eCollection 2017.

As part of the screening cascade 1170 compounds were evaluated in the cell lines SK-N-AS and A431 where compound efficacy was evaluated (Tables 4 - 6). Of these, 50 of the most effective compounds were evaluated for caspase activation of which 18 underwent further evaluation in the descrived in the three other in vitro tox assays (cumulative score is shown in Table 7).

Conclusively, 8 compounds were identified as being highly effective and potent in vitro, and with a low or absent toxicity in the 4 in vitro assays – these compounds were therefore selected for evaluated in transgenic mice expressing human ATNX3 pre-mRNA: Compounds # 1856_1, 1813_1, 1812_1, 1809_2, 1607_1, 1122_62, 1122_67 and 1122_33.

Table 7 – Data obtained from examples 5, 6 & 7

CMPID	Total tox score	SK-N-AS EC50 (µM)	A-431 EC50 (µM)	HiPSC EC50 (µM)	HiPCS, Maximal efficacy at 25µM (% remaining ATXN3 transcript)
1856_1	1,5	0,53	0,22	0,23	2,87
1806_2	2	0,35	0,19	0,03	0,91
1888_1	-	0,72	0,54	-	
1813_1	2	0,24	0,08	0,04	1,85
1640_1	-	1,50	0,19	-	
1812_1	1,5	0,20	0,09	0,09	0,59
1117_2	-	0,73	0,57	-	
1810_1	-	0,36	0,14	-	
1809_2	1,25	0,22	0,09	0,05	1,44
1489_1	-	1,16	0,30	-	
1867_1	-	0,54	0,50	-	
1893_1	-	0,95	0,34	0,41	4
1906_1	-	0,36	0,57	0,04	2,55
1214_1	-	1,05	0,38	-	
1213_1	-	1,01	0,38	-	
1423_1	-	0,75	0,23	0,03	3,58
1790_1	-	0,42	0,47	-	
1605_1	-	0,47	0,17	-	
1607_1	2,5	0,32	0,25	0,08	4,46
1805_1	-	0,75	0,23	-	
1806_1	-	0,45	0,20	0,04	1,3
1809_1	3	0,24	0,20	0,02	1,81
1808_1	2	0,26	0,22	0,06	1,4
1625_1	0,5	0,94	0,25	0,66	7,16
1122_54	-	0,62	0,15	-	
1122_16	-	0,30	0,15	-	
1122_17	-	0,33	0,17	0,11	1,07
1122_62	0,5	0,21	0,10	0,03	3,53
1122_19	-	0,28	0,24	-	

1122_23	-	0,54	0,18	0,05	0,59
1122_67	0	0,29	0,10	0,01	0,52
1122_68	-	0,28	0,13	0,01	
1122_69	-	0,27	0,12	-	
1122_70	-	0,20	0,10	-	
1122_27	1	0,23	0,12	0,03	0,55
1122_72	0,5	0,25	0,15	0,06	2,28
1122_28	1	0,20	0,12	0,01	0,37
1122_29	-	0,19	0,09	0,02	1,6
1122_73	-	0,29	0,18	0,04	1,59
1122_75	1	0,44	0,12	0,03	2
1122_76	-	0,33	0,19	-	
1122_77	1	0,30	0,20	0,04	1,97
1122_78	-	0,29	0,18	0,02	1,91
1122_33	1,25	0,18	0,10	0,02	1,84
1122_37	-	0,25	0,13	0,03	0,89
1122_80	-	0,33	0,17	-	
1122_41	-	0,24	0,16	0,01	0,47
1109_22	-	0,90	0,23	0,11	8,41
1109_32	0	0,75	0,17	0,09	3,49
1109_79	-	1,48	0,20	-	

Example 7: *In vivo* transgenic mouse Study

Animal Care

In vivo activity and tolerability of the compounds were tested in 10 - 13 week old B6;CBA-Tg(ATXN3*)84.2Cce/IbezJ male and female mice (JAX® Mice,The Jackson Laboratory) housed 3-5 per cage. The mice are transgenic mice which express the human ATXN3 pre-mRNA sequence, with 84 CAG repeats motif, an allele which is associated with MJD in humans). Animals were held in colony rooms maintained at constant temperature (22 ± 2°C) and humidity (40 + 80%) and illuminated for 12 hours per day (lights on at 0600 hours). All animals had ad libitum access to food and water throughout the studies. All procedures are performed in accordance with the respective Swiss regulations and approved by the Cantonal Ethical Committee for Animal Research.

Administration Route -Intra-cisterna Magna injections.

The compounds were administered to mice by intra cisterna magna (ICM) injections. Prior to ICM injection the animals received 0.05 mg/kg Buprenorphine dosed sc as analgesia. For the ICM injection animals were placed in isofluran. Intracerebroventricular injections were performed using a Hamilton micro syringe with a FEP catheter fitted with a 36 gauge needle. The skin was incised, muscles retracted and the atlanto-occipital membrane exposed. Intracerebroventricular injections were performed using a Hamilton micro syringe with a catheter fitted with a 36 gauge needle. The 4 microliter bolus of test compound or vehicle was injected over 30 seconds. Muscles were repositioned and skin closed with 2-3

sutures. Animals were placed in a varm environment until they recovered from the procedure.

2 independent experiments were performed with groups of different compounds as shown in Table 8.

Table 8

Compound ID	Dose, µg	Time-point	Group Size
Saline only	0	4wk	6
1856_1	250	4wk	8
1813_1	250	4wk	8
1812_1	250	4wk	8
1809_2	250	4wk	8
1607_1	250	4wk	8
1122_62	250	4wk	8
1122_67	250	4wk	8
1122_33	250	4wk	8

Tolerability Results:

All compounds were found to be tolerated up to the 4 weeks timepoint. Acute toxicity was measured by monitoring the animal's behavior as described in WO2016/126995 (see example 9). Sub-acute toxicity was measured by monitoring the body weight of each animal during the time course of the experiment, with >5% weight reduction indicative of sub-acute toxicity. In some groups 1 or 2 animals did show some distress after the ICM administration and were euthanized, but this was likely to be due to the procedure rather than a adverse toxicity of any of the compounds. All eight compounds were therefore considered to be well tolerated in vivo.

4 weeks post administration, the animals were sacrificed, and tissues from the cortex, midbrain, cerebellum, hippocampus pons/medulla and striatum were collected weighed and snap frozen in liquid N2 directly after sampling. Samples were stored on dry ice until storage at -80 °C.

Analysis of *in vivo* samples. Description of tissue preparation for content measurement and qPCR.

Mouse tissue samples were homogenized in the MagNA Pure LC RNA Isolation Tissue Lysis Buffer (Roche, Indianapolis, IN) using a Qiagen TissueLyzer II. The homogenates were incubated for 30 minutes at room temperature for complete lysis. After lysis the homogenates were centrifuged for 3 minutes at 13000rpm and the supernatant used for analysis. Half was set aside for bioanalysis and for the other half, RNA extraction was continued directly.

Oligo content analysis

For bioanalysis, the samples were diluted 10-50 fold for oligo content measurements with a hybridization ELISA method. A biotinylated LNA-capture probe and a digoxigenin-conjugated LNA-detection probe (both 35nM in 5xSSCT, each complementary to one end of the LNA oligonucleotide to be detected) was mixed with the diluted homogenates or relevant standards, incubated for 30 minutes at RT and then added to a streptavidine-coated ELISA plates (Nunc cat. no. 436014).

The plates were incubated for 1 hour at RT, washed in 2xSSCT (300mM sodium chloride, 30mM sodium citrate and 0,05% v/v Tween-20, pH 7.0) The captured LNA duplexes were detected using an anti-DIG antibodies conjugated with alkaline phosphatase (Roche Applied Science cat. No. 11093274910) and an alkaline phosphatase substrate system (Blue Phos substrate, KPL product code 50-88-00). The amount of oligo complexes was measured as absorbance at 615 nm on a Biotek reader.

Data was normalized to the tissue weight and expressed as nM of oligo.

mRNA Analysis

RNA was purified from 350µL of supernatant using the MagNA Pure 96 instrument using the kit Cellular RNA Large Volume Kit (Roche, Indianapolis, IN). RNA samples were normalized to 2ng/µL in RNase-Free water and stored at -20° C until further use.

For one-step qPCR (cDNA synthesis and qPCR), each sample was run in duplicates with four probe sets (IDT, Leuven, Belgium) run in duplex.

To each reaction 4µL of previously diluted RNA, 0.5µL of water and 5.5µL of TaqMan MasterMix was added. Plates were centrifuged and heat-chocked at 90° C for 40sek followed by a short incubation on ice before analyzing the samples using qPCR (Incubation at 50° C for 15 minutes and 90° C for 3 minutes followed by 40 cycles at 95° C for 5 sec and 60° C for 45sec). Assay probes are described below.

Data was analyzed using the relative standard curve method where each is first normalized to the housekeeping gene (RPL4) and then expressed as percent of untreated control animals.

qPCR assays for in vivo studies:

Human ATXN3, qPR assay: (ATXN3_exon_8-9(1) PrimeTime® XL qPCR Assay (IDT).

qPCR probe and primers:
Probe: 5'-/56-FAM/CTCCGCAGG/ZEN/GCT ATTCAGCT AAGT /31ABkFQ/-3' (SEQ ID NO 1134)
Primer 1: 5'-AGT AAGATTTGT ACCTGATGTCTGT-3' (SEQ ID NO 1135)
Primer 2: 5'-CATGGAAGATGAGGAAGCAGAT-3' (SEQ ID NO 1136)

House keeping gene used:

Mouse RPL4, qPCR assay (Mm.PT.58.17609218) PrimeTime® XL qPCR Assay (IDT).

qPCR probe and primers:
Probe: 5'- /5HEX/CTG AAC AGC /ZEN/CTC CTT GGT CTT CTT GTA /3IABkFQ/-3' (SEQ ID NO 1090)
Primer 1: 5'- CTT GCC AGC TCT CAT TCT CTG-3' (SEQ ID NO 1091)
Primer 2: 5'- TGG TGG TTG AAG ATA AGG TTG A-3' (SEQ ID NO 1092)

Example 8: Testing in vitro efficacy of LNA oligonucleotides and Reference Compounds *in a time course, dose range experiment in human iPSC-derived neurons*

Compounds used: 1122_67 and 1813_1 & the following reference compounds disclosed in WO2019/217708, as referenced by the Compound ID numbers used in WO2019/217708: 1100673, 1101657, 1102130, 1103014 & 1102987. Compounds 1100673, 1101657, 1102130 are highlighted in WO2019/217708 as providing potent in vivo inhibition, compounds 1103014 and 1102987 were not evaluated in vivo in WO2019/217708, but are included as reference compounds due to the sequence similarity to compound 1122_67 (1103014) and 1813_1 (1102987).

The iCell GlutaNeurons cells were prepared and maintained as described in example 5 & Table 3. Cells were grown for 7 days before addition of the oligonucleotide in concentration of 0 - 10 µM (dissolved in medium).

Cells were harvested at 4 days, 6 days, 9 days, 12 days and 20 days after oligo treatment, and RNA extraction and qPCR was performed as described for “Example 1”, using the ATXN3 primar assay described in example 5. The relative ATXN3 mRNA expression levels were determined as % of control (medium-treated cells) i.e. the lower the value the larger the inhibition. The results are shown in Table 9

Table 9

Compound	EC50 in hiPSC-derived neurons, nM				
	Day 4	Day 6	Day 9	Day 12	Day 20
1122_67	7,2	1,3	1,4	1,1	1,1
1813_1	23	6,3	10	8,9	7,7
1100673	110	27	30	34	44
1101657	515	204	69	90	73
1102130	315	164	390	101	133
1103014	662	64	435	98	369
1102987	944	305	135	391	200

Compounds 1122_67 and 1813_1 were remarkably more potent than the 5 reference compounds, with compound 1122_67 being the most potent compound at all time points and both 1122_67 and 1813_1 gave a remarkably effective and long lasting inhibition of ATXN3 mRNA.

Example 9: Comparative *In vivo* transgenic mouse study

A further *in vivo* study was performed at Charles River Laboratories Den Bosch B.V., Groningen, NL, using compound 1122_67 and 1813_1, and reference compound 1100673 (WO2019/217708). The study used male and female B6;CBA-Tg(ATXN3*)84.2Cce/IbezJ mice with the compounds administered via intracisternal (ICM) administration. At two timepoints after compound administration, 1 or 4 weeks, animals were euthanized and terminal plasma samples and tissues were collected.

Animal Care

In vivo activity and tolerability of the compounds were tested in 62 B6;CBA-Tg(ATXN3*)84.2Cce/IbezJ male and female mice (JAX® Mice,The Jackson Laboratory) at the age between 7-10 weeks. Following arrival, animals were housed in groups up to 5 in individually vented cages (IVC, 40 x 20 x 16 cm) in a temperature (22 ± 2 °C) and humidity (55 ± 15%) controlled environment on a 12 hour light cycle (07.00 – 19.00h). Males and females were kept in separate cages. Standard diet (SDS Diets, RM1 PL) and domestic quality mains water were available ad libitum. If required, animals received soaked chow and/or Royal Canin in addition to Standard diet as part of pamper care. The experiments were conducted in strict accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council 2011) and were in accordance with European Union directive 2010/63 and

the Dutch law. The in vivo experiment described was performed at Charles River Laboratories Den Bosch B.V. location Groningen (Groningen, the Netherlands).

Administration Route -Intra-cisterna Magna injections.

The compounds were administered to mice by intra cisterna magna (ICM) injections. Mice were anesthetized using isoflurane (2.5-3% and 500 mL/min O2). Before surgery, Finadyne (1 mg/kg, s.c.) was administered for analgesia during surgery and the post-surgical recovery period. A mixture of bupivacaine and epinephrine was applied to the incision site and periost of the skull for local analgesia.

Animals were placed in a stereotaxic frame (Kopf instruments, USA) and an incision made at the back of the head towards the neck. Then, the skin was spread and the coordinates marked prior to drilling a hole in the occipital bone of the skull, where a cannula was placed. Next, the compounds were injected into the cisterna magna (ICM). A volume of 4 µL of the assigned test item was injected over 30 seconds. After injection, the needle and cannula were held in place for 30 seconds to ensure no back flow occurred. The cannula was then retracted, the hole was covered with skin and the incision was closed by sutures.

Animals were placed in a warm environment until recovered from the procedure.

Compound 1122_67 was administered at a single dose of 90, 150 or 250 µg, and compound 1813_1 was administered at a single dose of 150µg or 250µg. The reference compound 1100673 was administered at a single dose of 250µg only.

From three days prior to ICM injections, up to one week after administration, animal's weight was registered daily. Animal's weight was monitored and registered at least twice a week for the rest of the experiment.

At the end of the experiment, on day 8 or 29 (1 or 4 weeks), the animals were euthanized by Euthasol® overdose. Terminal plasma was collected in Li-Hep tubes. Terminal tissues were harvested from the animals and were dissected on a chilled surface. Half of the tissue samples were stored in 2.0 mL Safe-Lock tubes, PCR clean, pre-weighted and precooled. Immediately after collection, samples were weighed and flash frozen in liquid N2 prior to storage at -80 ºC. The other half was fixed in 4% PFA for 72 hours and subsequently transferred to 70% ethanol awaiting shipment. Tissue dissection and collection was performed, collecting tissue from a range of tissues: Midbrain, Cortex, Striatum, Hippocampus, Cerebellum, Brainstem, and spinal cord (Cervical, Thoracic & Lumbar).

Tolerability Results:

Acute toxicity was measured by monitoring the animal's behavior as described in WO2016/126995 (see example 9). Chronic toxicity was measured by monitoring the body weight of each animal during the time course of the experiment, with >5% weight reduction indicative of chronic toxicity. In some groups 1 or 2 animals did show some distress after the ICM administration and were euthanized, but this was likely to be due to the nature of the surgical procedure rather than a adverse toxicity of any of the compounds.

There were signs of acute toxicity at the 250µg dose of 1813_1 is 3 mice, leading to early euthanisation of this group of animals. Otherwise all compounds were found to be tolerated up to the 4 weeks timepoint.

After 4 weeks the animals were eutyhanised and brain and CNS tissue collected: Spinal cord, cortex, striatum, hippocampus, midbrain, brainstem and cerebellum as well as liver and kidney was collected in liquid nitrogen for drug concentration analysis an ATAXN3 mRNA analysis at 1 or 4 weeks following dosing.

Analysis of *in vivo* samples: Description of tissue preparation for content measurement and qPCR was performed as per Example 7. The EC50 was calculated, and maximum KD achieved recorded – this data is provided in Table 10.

Compound 1122_67 was the most effective compound in all brain tissues tested and gave an excellent effective knock-down in all brain tissues tested, indicating good bio-distribution to all key tissues (1813_1 was as effective as 1122_67 in spinal cord, brainstem and midbrain). Notably compound 1122_67 gave highly effective knock-down in cerebellum, a tissue which the reference compound 1100673 was notably less effective. A further key observation at the after 4weeks of treatment is that the efficacy of 1122_67 was even further improved as compared to the 1week timepoint in all brain tissues. Notably, the efficacy of the reference compound, 1100673 was notably lower at the 4week stage vs. the 1week timepoint, particularly in key cerebellum and cortex tissues. The long duration of action and high potency of 1122_67 indicates that this compound should require a less frequent administration in a therapeutic setting.

Example 10 Compound Stability to SVPD

Methodology: 3´- exonuclease snake venom phosphodiesterase I (SVP) (Art. No. LS003926, Lot. No. 58H18367) was purchased by Worthington Biochemical Corp. (Lakewood, New York, USA). The reaction mix for the 3´- exonuclease snake venom phosphodiesterase I (SVP) assay consisted of 50 mM TRIS/HCl pH 8 buffer, 10 mM MgCl2, 30 U CIP (NEB, Ipswich, Massachusetts, USA), 0.02 U SVP and the oligonucleotide compound. The stability of the ASOs against SVPD was determined by performing the nuclease assays over a one day time course. In each reaction mix an amount about 0.2 mg/mL ASO in a totaly volume of 150 µl was used.

The incubation period of 24 h at 37°C was performed on an autosampler, the SVPD and reactions and the ASO stabilities were monitored in time intervals by an UHPLC system equipped with a diode-array detector and coupled with electrospray ionization-time of flight–mass spectrometry (ESI-ToF-MS). To generate the t=0 h time point, the enzyme was added into the reaction mix, directly before the first injection. Further injections took place at regular intervals over a period of 24 hours.

Compounds tested, 1122_67, 1813_1 and the reference compounds 1100673, 1101657, 1102130, 1103014, and 1102987.

The data is illustrated in Figure 9. Whilst the three highlighted reference compounds from WO2019/217708 and the 1122_67 and 1813_1 compouinds had good stability in the SVPD assay, the 2 reference compounds from WO2019/217708 with the closest sequence to 1122_67 and 1813_1, compounds 1103014 and 1102987 were notably more vulnerable to SVPD degradation as compared to 1122_67 and 1813_1.

Example 11 WT and polyQ Ataxin 3 protein levels in human SCA3 patient derived fibroblasts treated with selected oligonucleotides (ASO)

This experiment was performed to investigate the efficacy of effiacty of knock down of the LNA oligonucleotides, 1122_67 and 1122_33, as compared to the prior art compounds, 1100673 and 1102130 in SCA3 patient derived fibroblasts, allowing for an assessment of the efficacy on the disease causing ataxin3 allele and the ataxin3 WT allele.

Cell line used for the ASO treatment, human SCA3 patient derived fibroblasts (GM06153 – Coriell Institute). One hundred thousand cells were seeded per well in a 24 well plate with a total volume of 1 ml. ASOs were added immediately after to a final concentration of 10 µM (gymnotic uptake). After 4 days of incubation at, cells were washed twice with PBS, and harvested in 200 µl RIPA buffer (Thermo Scientific, Pierce).

Western blots were performed on the capillary-based immunoassay platform (WES, ProteinSimple) using a WES 12-230 kDa Wes Separation Module. Cell lysate were diluted 10x in Sample load buffer (ProteinSimple) prior loading on the cartridge. Primary antibody for Ataxin 3 (rabbit monoclonal antibody, prod. # 702788 from Invitrogen) and for HPRT (rabbit monoclonal antibody, cat. # Ab109021 from Abcam). Both antibodies were used in 1/100 dilutions. Goat anti-rabbit HRP conjugate (Part. # DM-001, ProteinSimple) was used as secondary antibody.

Compass software (ProteinSimple) was for quantification of the protein bands.

Results

To show an efficient KD of both the wild type as well as the polyQ extended Ataxin 3 protein, GM06153 cells were treated with 10 uM of ASO for four days prior to protein analysis on the WES. Ataxin 3 antibody recognize both isoforms, and the intensity (area under peak) was normalized to the protein input based on the signal from HPRT. As seen from the figure 10A and B, we observe that upon treatment with 1122_67 and 1122_33, there is an increased reduction in the polyQ extended Ataxin 3 compared to the wild type Ataxin 3. This trend is not observed for the other ASOs (Scrambled control, 1100673 or 1102130) where we observe a higher amount of the polyQ extended Ataxin 3, compared to the wild type Ataxin 3. A higher activity on the disease causing polyQ extended Ataxin 3 than the WT Ataxin 3 is preferable as it allows a selective reduction of the disease causing allele.

Table 8

	Cortex		Midbrain		Cerebellum		Hippocampus		Pons/medulla		Striatum	
Compounds	EC50 (nM)	Max efficacy (% remaining)	EC50 (nM)	Max efficacy (% remaining)	EC50 (nM)	Max efficacy (% remaining)	EC50 (nM)	Max efficacy (% remaining)	EC50 (nM)	Max efficacy (% remaining)	EC50 (nM)	Max efficacy (% remaining)
1856_1	251	33	77	20	434	49	202	41	-	24	103	27
1813_1	260	22	93	20	347	47	279	30	-	22	89	18
1812_1	307	52	156	28	603	50	233	35	-	26	184	32
1809_2	134	57	153	34	511	50	111	46	-	21	93	29
1607_1	193	40	89	17	120	42	81	21	-	15	63	26
1122_62	125	56	74	26	226	16	86	46	-	19	54	36
1122_67	125	23	79	14	261	27	146	22	-	13	88	19
1122_33	102	47	38	16	166	35	79	24	-	17	63	29

All compounds tested gave efficacious target inhibition in the tissues tested and were tolerated at the doses tested. Compound 1122_33 across the compounds tested has either the best or second ranked highest specific activity (lower EC50) in all tissues, followed by 1122_62 and 1122_67.

Compounds 1122_67, 1607_1, 1813_1 and 1122_33 provided high efficacy *in vivo* in all tissues tested, illustrating a remarkable consistent inhibition of ATXN3 expression across the brain tissues tested. Based on an accumulative rank score compound 1122_67 was consistently either the best or second ranked compound in terms of efficacy of ATXN3 knock down in the tissues tested.

Table 10

Tissue		Cortex (A1)		Cerebellum		Brainstem		Midbrain		Striatum	
		EC50 (nM)	Max KD observed	EC50 (nM)	Max KD observed	EC50 (nM)	Max KD observed	EC50 (nM)	Max KD observed	EC50 (nM)	Max KD observed
1 week of treatment	1122_67	242	88%	833	74%	196	87%	165	89%	148	77%
	1813_1	278	61%	966	57%	377	85%	183	90%	118	51%
	1100673	391	67%	2012	48%	769	79%	279	81%	331	69%
4 week of treatment	1122_67	100	92%	365	81%	81	93%	94	95%	46	89%
	1813_1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
	1100673	199	49%	1229	33%	419	72%	129	74%	130	35%

Tissue		Hippocampus		Spinal cord, cervical		Spinal cord, thoracic		Spinal cord, lumbar	
		EC50 (nM)	Max KD observed	EC50 (nM)	Max KD observed	EC50 (nM)	Max KD observed	EC50 (nM)	Max KD observed
1 week of treatment	1122_67	243	75%	41	89%	39	90%	54	89%
	1813_1	341	63%	45	90%	36	92%	48	91%
	1100673	516	66%	83	83%	51	83%	68	82%
4 week of treatment	1122_67	89	92%	16	93%	Imprecise	93%	18	93%
	1813_1	ND	ND	ND	ND	ND	ND	ND	ND
	1100673	329	52%	48	83%	Imprecise	84%	56	84%

CLAIMS

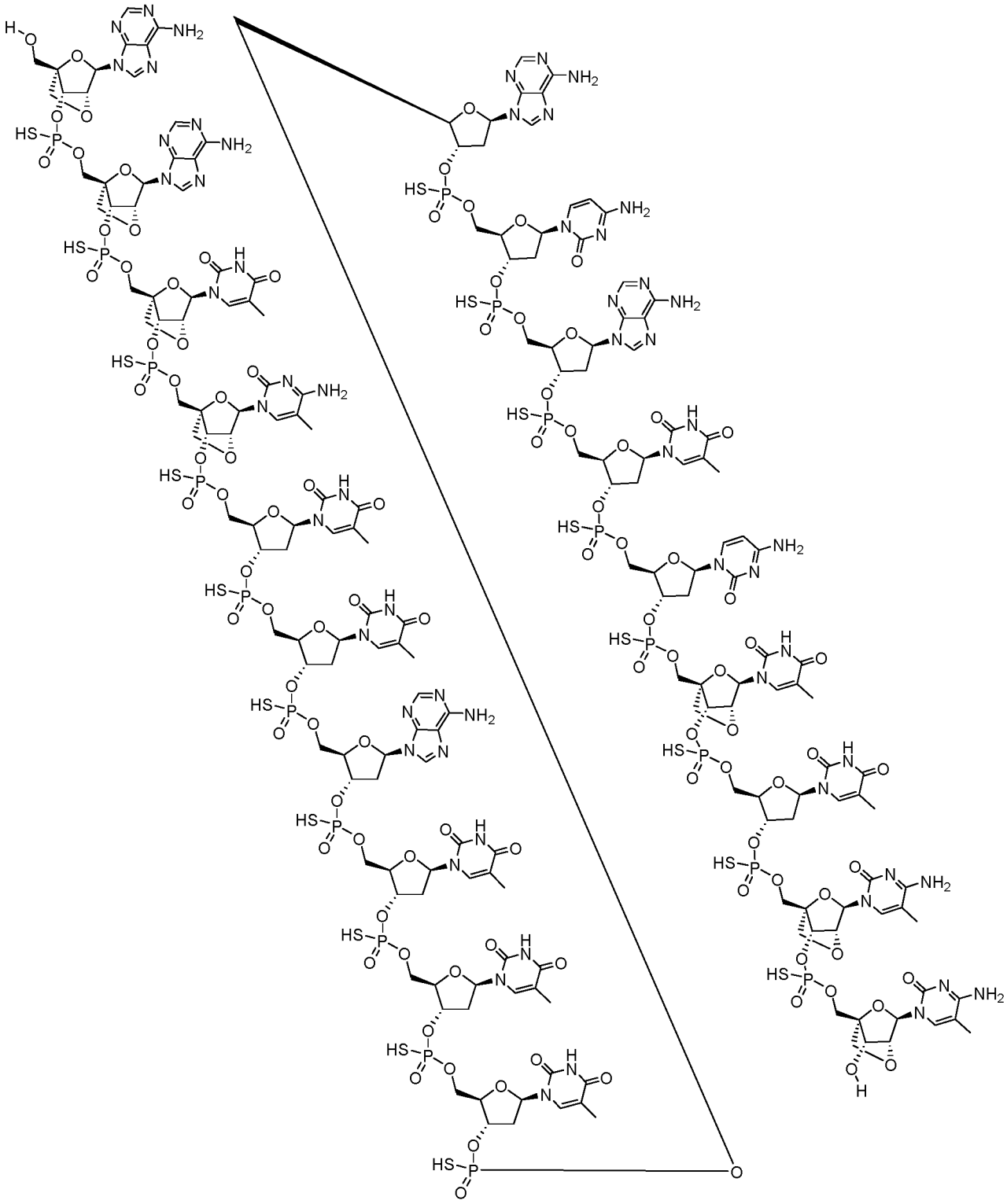
1. An antisense oligonucleotide selected from the group consisting of Compound No 1122_62, 1122_67, 1856_1, 1813_1, 1812_1, 1809_2, 1607_1, and 1122_33, or a pharmaceutically acceptable salt thereof.
2. The antisense oligonucleotide according to claim 1, wherein the antisense oligonucleotide is ACCcatattttactCTT (Compound No 1856_1), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.
3. The antisense oligonucleotide according to claim 1, wherein the antisense oligonucleotide is CTGtacacttttacaTT (Compound No 1813_1), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.
4. The antisense oligonucleotide according to claim 1, wherein the antisense oligonucleotide is, TGtacacttttacatTCC (Compound No 1812_1), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.
5. The antisense oligonucleotide according to claim 1, wherein the antisense oligonucleotide is GtacacttttacattCCC (Compound No 1809_2), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.
6. The antisense oligonucleotide according to claim 1, wherein the antisense oligonucleotide is TTCttcattataccatCAA (Compound No 1607_1), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.

7. The antisense oligonucleotide according to claim 1, wherein the antisense oligonucleotide is AatCtTatttacatcTtCC (Compound No 1122_62), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.
8. The antisense oligonucleotide according to claim 1, wherein the antisense oligonucleotide is AATCttatttacatcTtCC (Compound No 1122_67), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.
9. The antisense oligonucleotide according to claim 1, wherein the antisense oligonucleotide is AatCtTatttacatctTCC (Compound No 1122_33), wherein a capital letter represents a beta-D-oxy LNA nucleoside, a lower case letter represents a DNA nucleoside, wherein each LNA cytosine is 5-methyl cytosine, and wherein the internucleoside linkages between the nucleosides are phosphorothioate internucleoside linkages; or a pharmaceutically acceptable salt thereof.

10. A conjugate comprising the oligonucleotide according to any one of claims 1 – 9, and at least one conjugate moiety covalently attached to said oligonucleotide; or a pharmaceutically acceptable salt thereof.
11. A pharmaceutical composition comprising the oligonucleotide of claim 1-9 or the conjugate of claim 10 and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.
12. An *in vivo* or *in vitro* method for modulating *ATXN3* expression in a target cell which is expressing *ATXN3*, said method comprising administering an oligonucleotide or salt of any one of claims 1-9, the conjugate according to claim 10, or the pharmaceutical composition of claim 11 in an effective amount to said cell.
13. A method for treating or preventing a disease comprising administering a therapeutically or prophylactically effective amount of an oligonucleotide or salt of any one of claims 1 - 9 or the conjugate according to claim 10 or the pharmaceutical composition of claim 11 to a subject suffering from or susceptible to the disease.
14. The method of claim 13, wherein the disease is spinocerebellar ataxia, such as spinocerebellar ataxia 3, such as Machado-Joseph disease

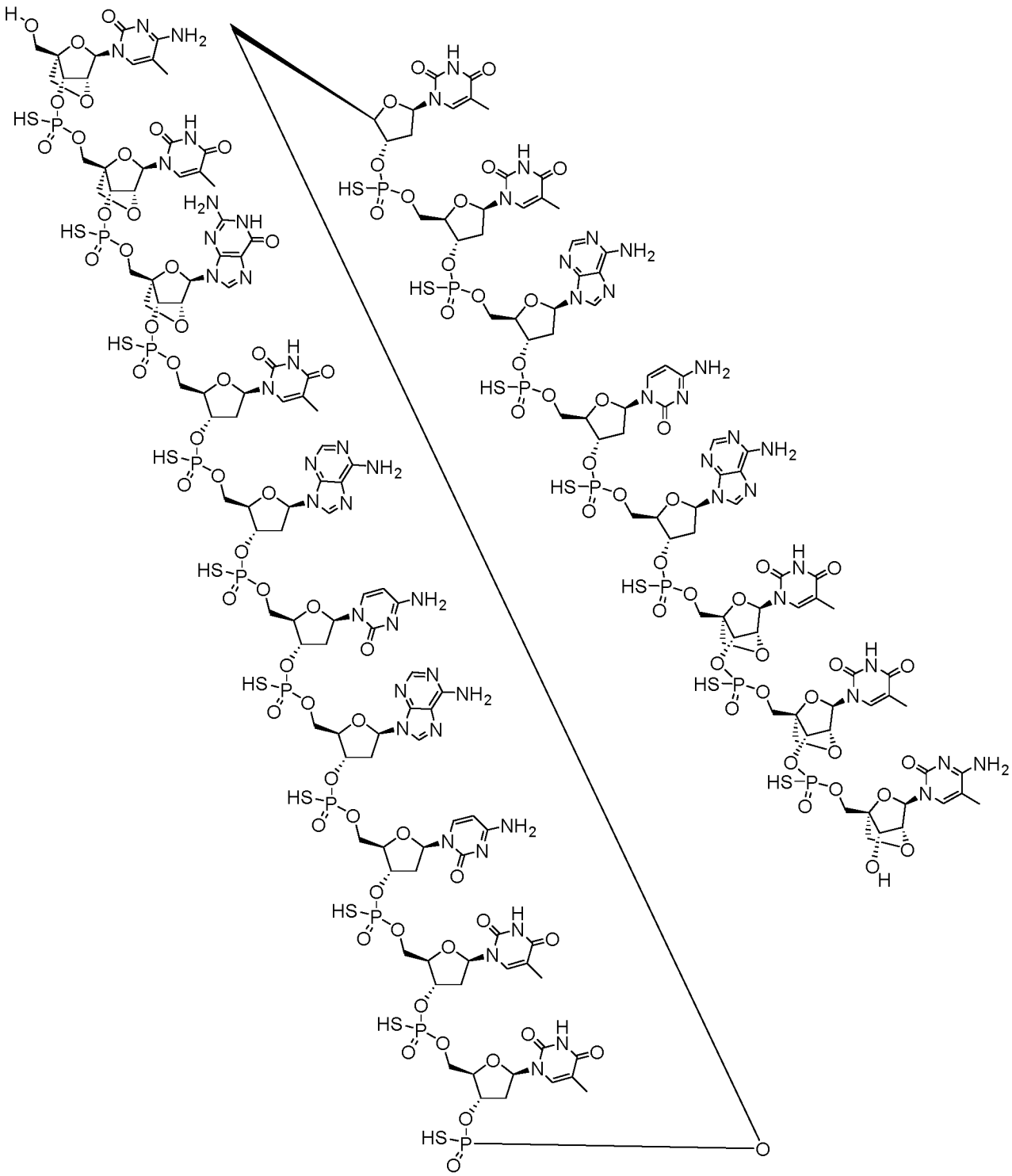
15. The oligonucleotide or salt of any one of claims 1 - 9 or the conjugate according to claim 10 or the pharmaceutical composition of claim 11 for use in medicine.
16. The oligonucleotide or salt of any one of claims 1 - 9 or the conjugate according to claim 10 or the pharmaceutical composition of claim 11 for use in the treatment or prevention of spinocerebellar ataxia, such as spinocerebellar ataxia 3, such as Machado-Joseph disease, (MJD).
17. Use of the oligonucleotide or salt of claim 1 - 9 or the conjugate according to claim 10 or the pharmaceutical composition of claim 11, for the preparation of a medicament for treatment or prevention of spinocerebellar ataxia, such as spinocerebellar ataxia 3, such as Machado-Joseph disease.

Figure 1



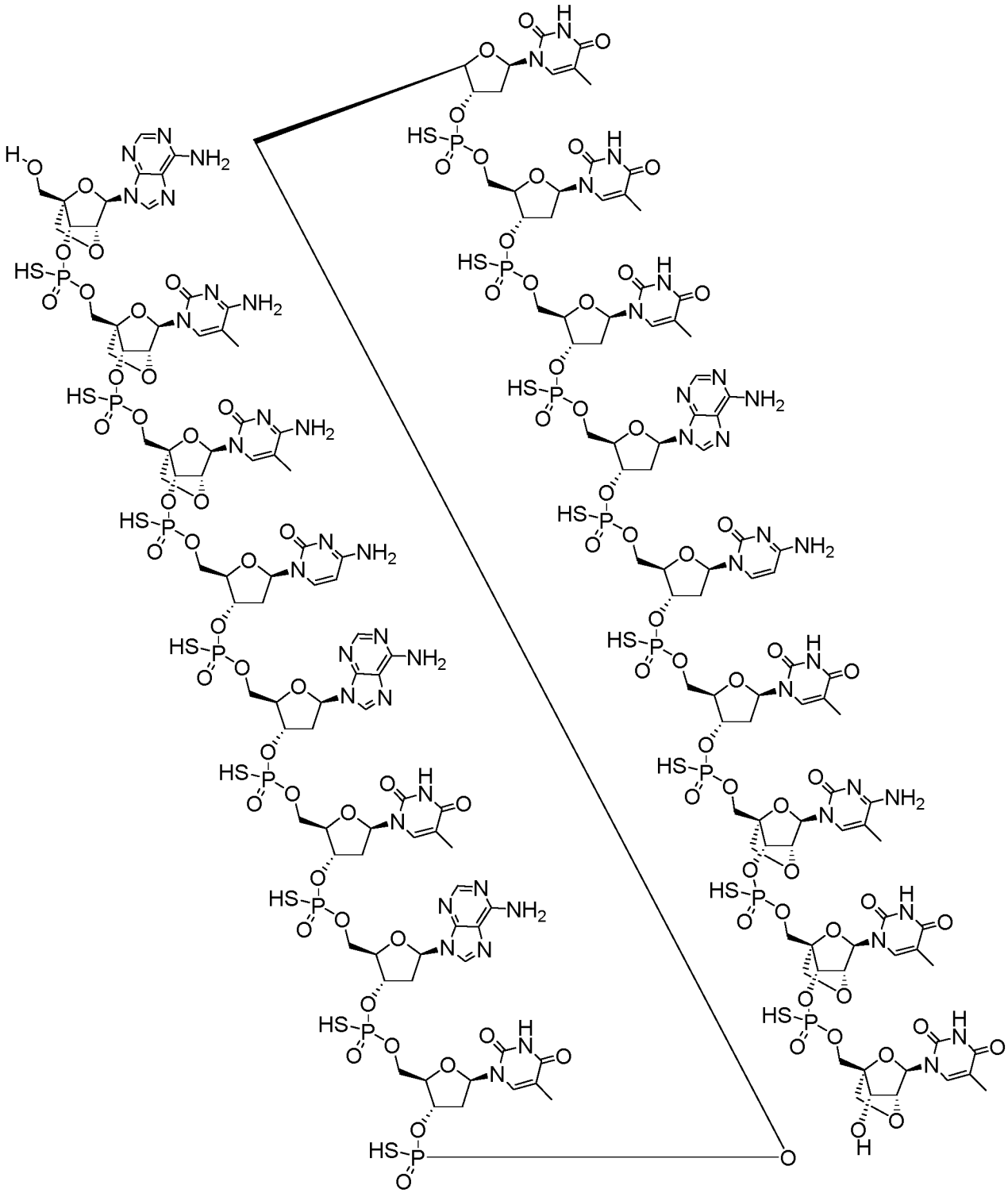
Compound # 1122_67

FIGURE 2



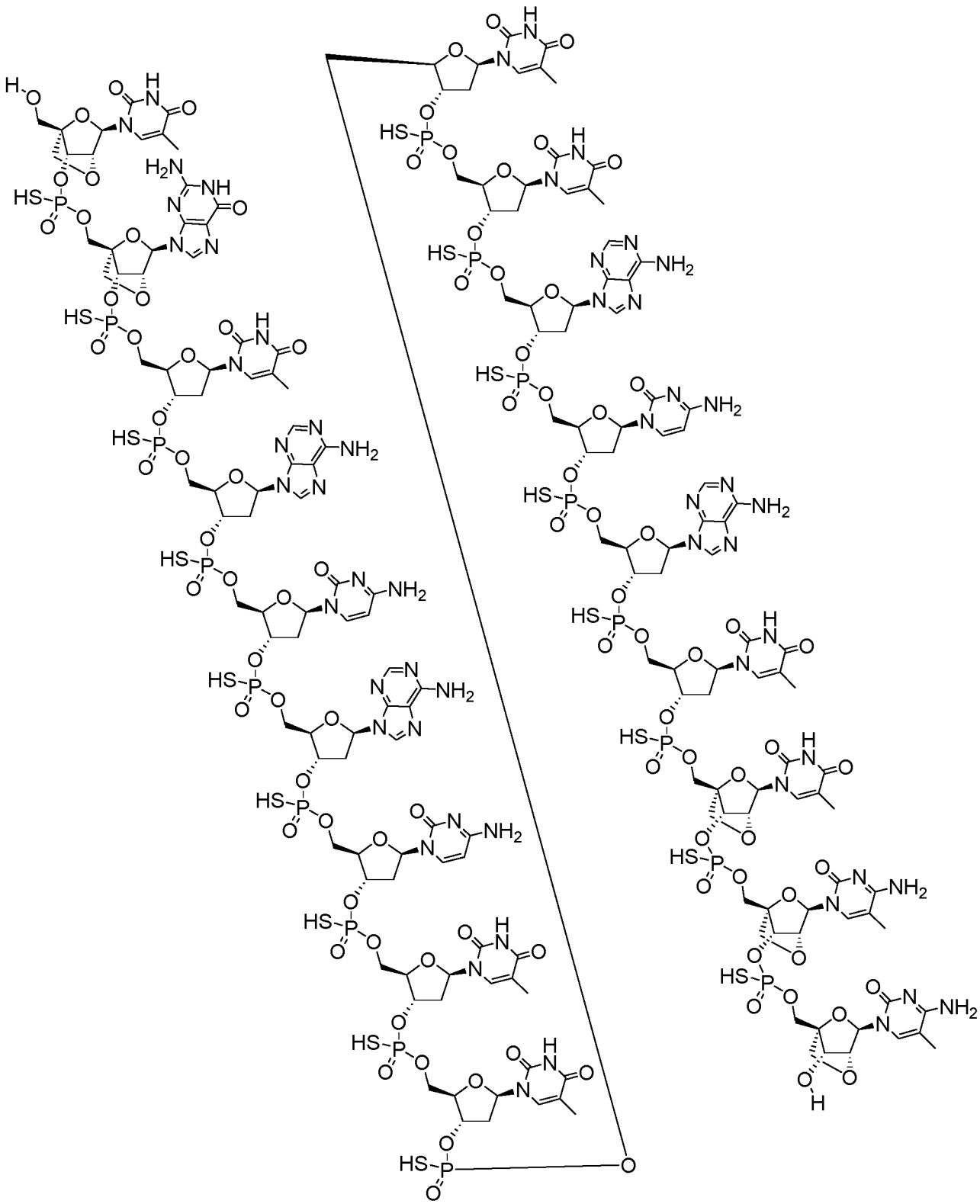
Compound # 1813_1

FIGURE 3



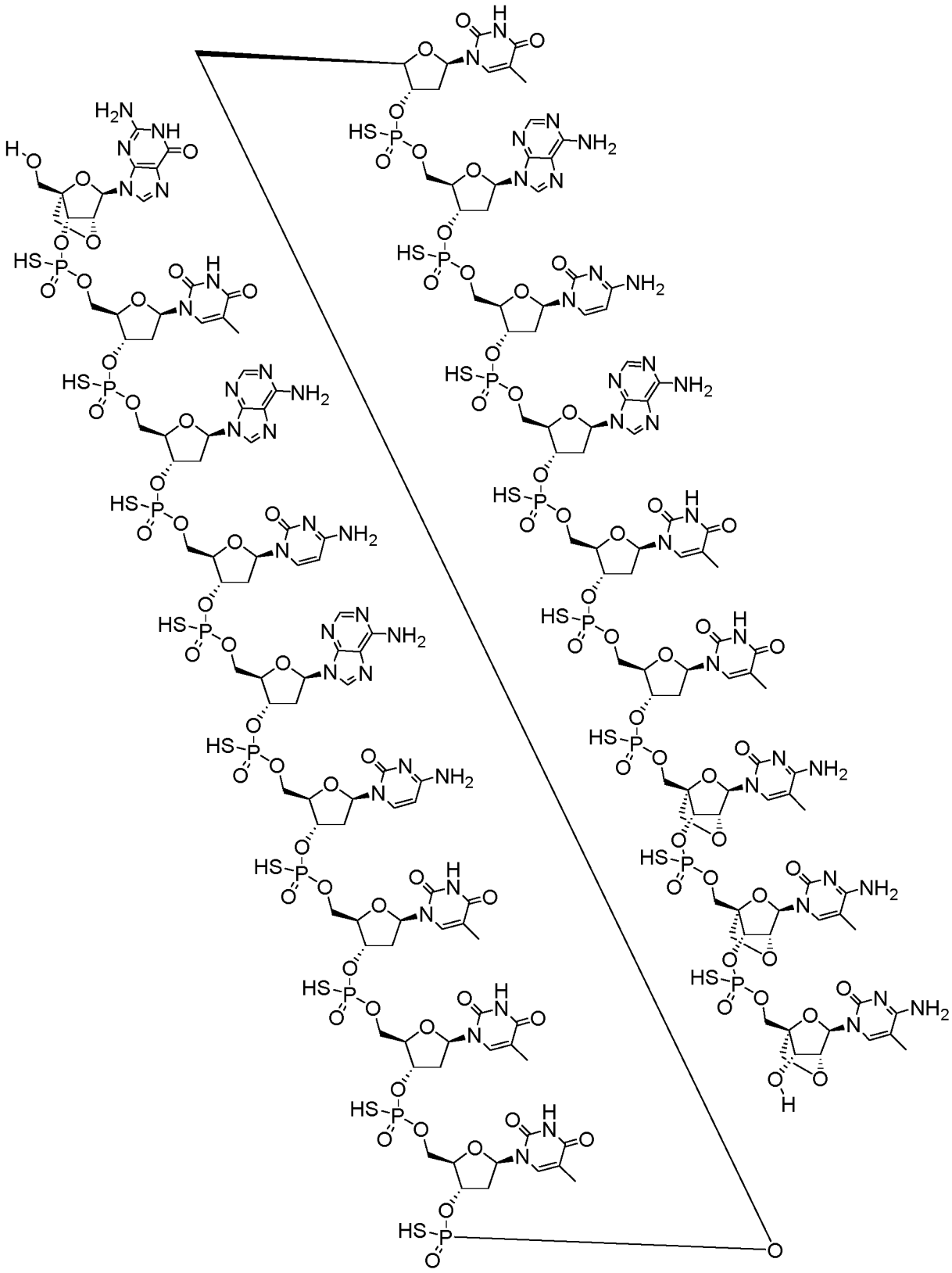
Compound # 1856_1

FIGURE 4



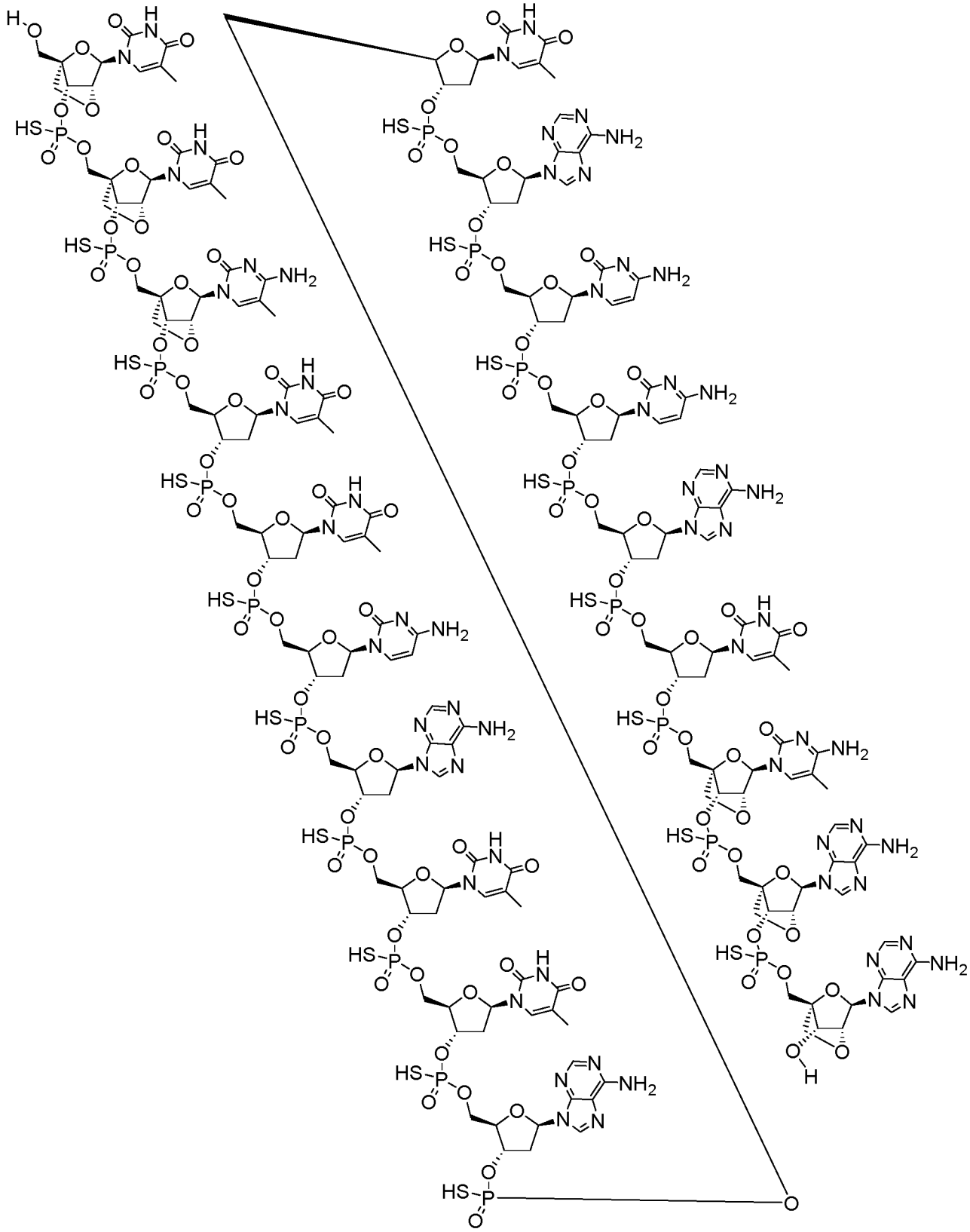
Compound # 1812_1

FIGURE 5



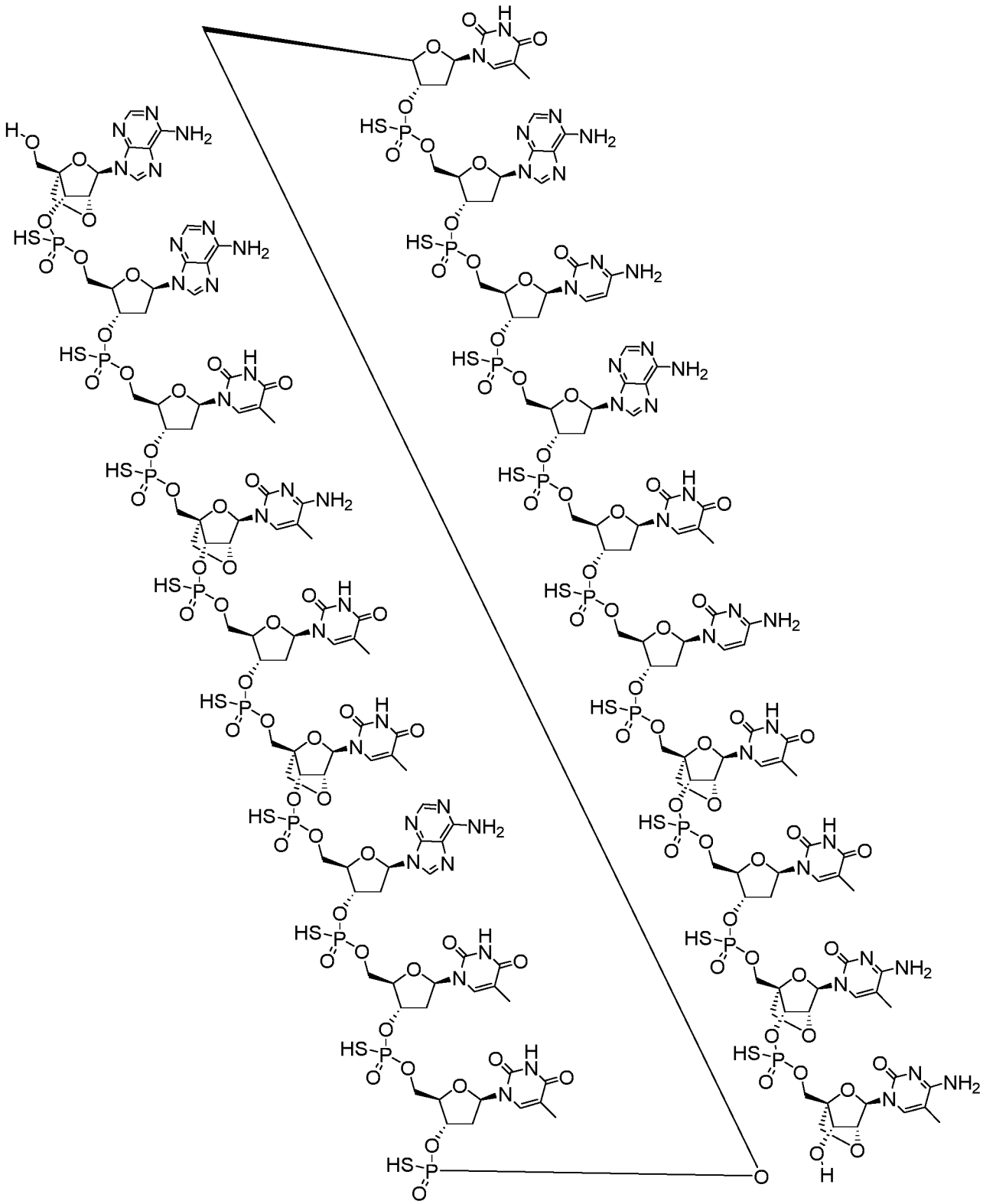
Compound ID 1809_2

FIGURE 6



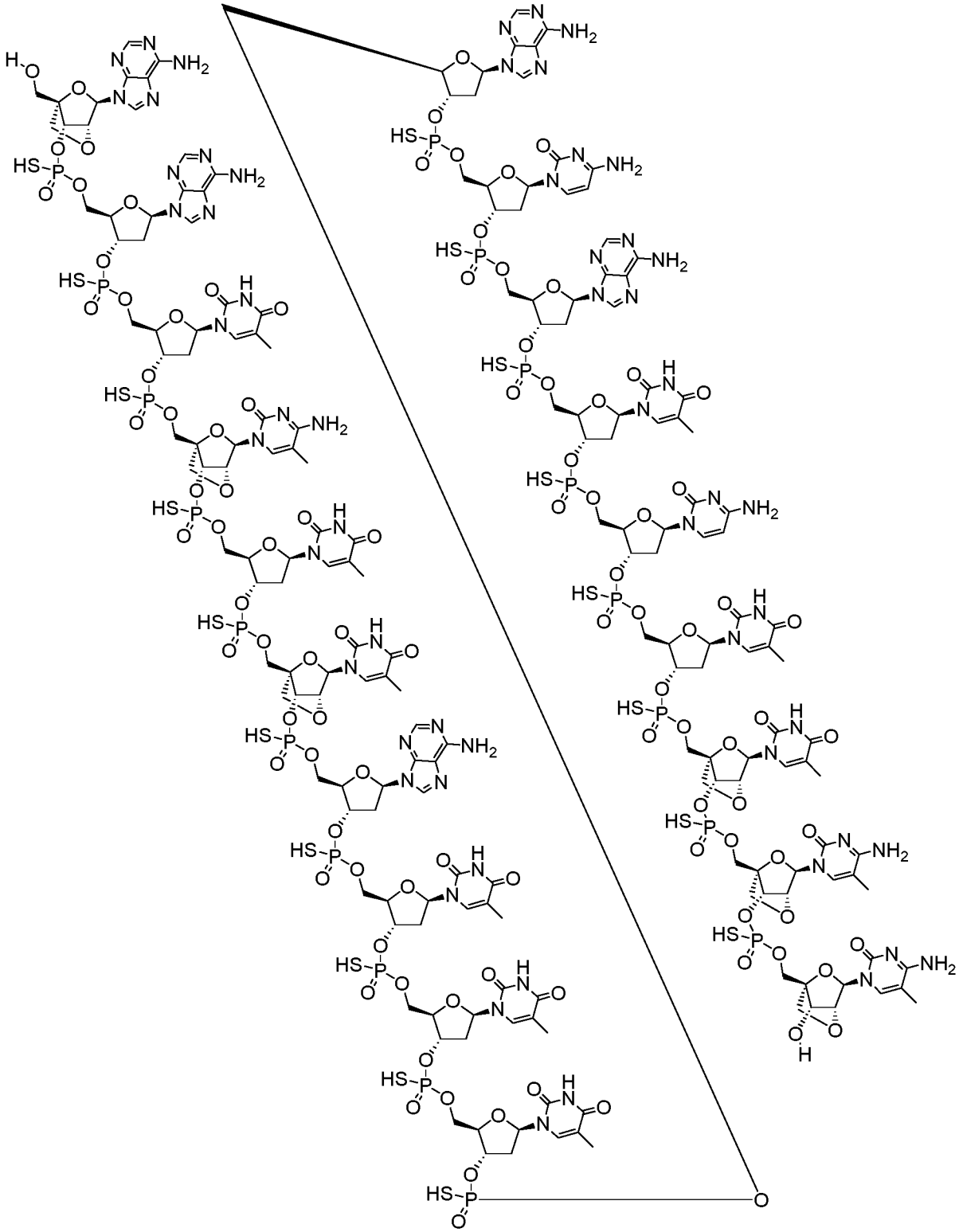
Compound ID 1607_1

FIGURE 7



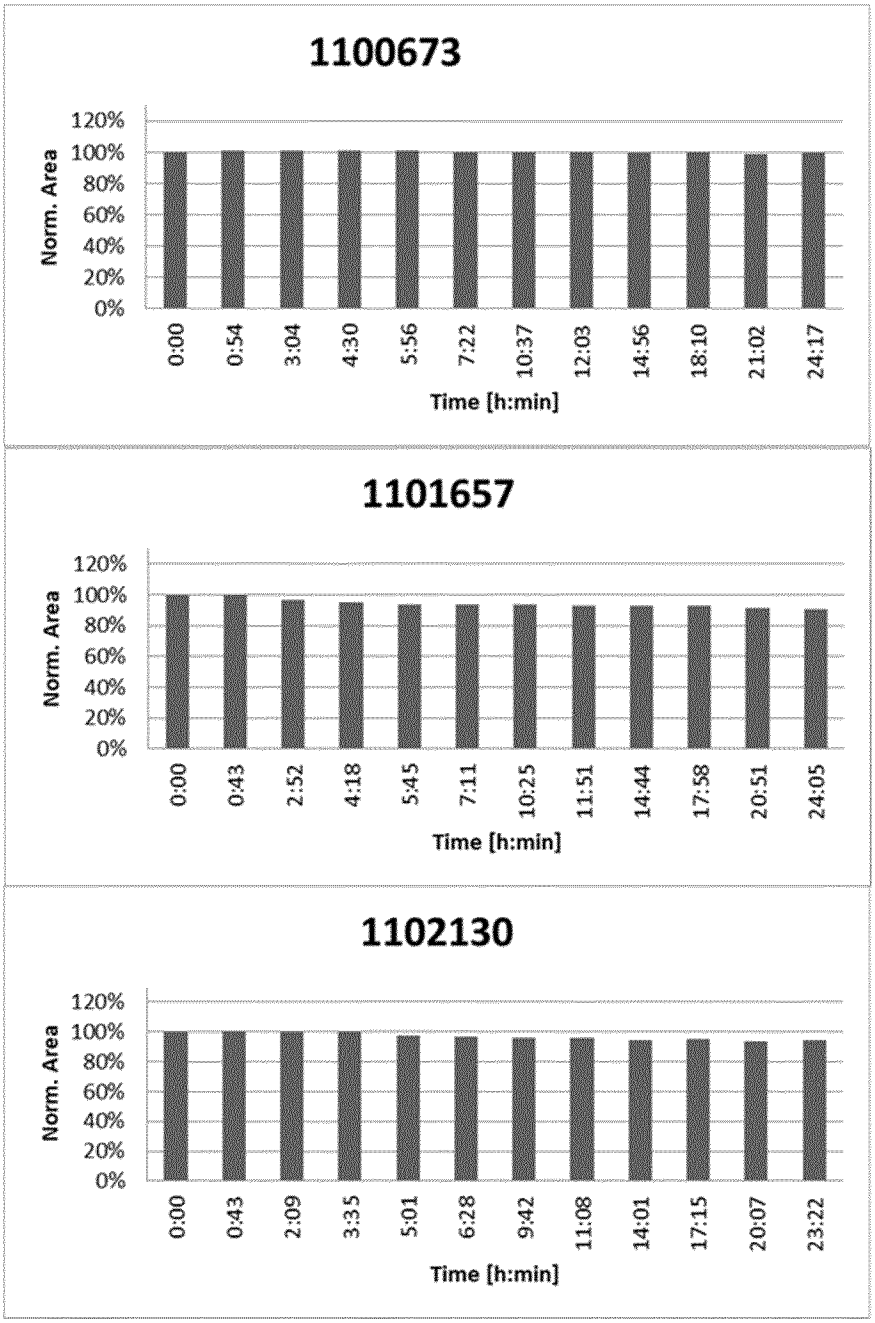
Compound # 1122_62

FIGURE 8



Compound # 1122_33

FIGURE 9


1100673
Norm. Area
120%
100%
80%
60%
40%
20%
0%
0:00
0:54
3:04
4:30
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7:22
10:37
12:03
14:56
18:10
21:02
24:17
Time [h:min]
1101657
Norm. Area
120%
100%
80%
60%
40%
20%
0%
0:00
0:43
2:52
4:18
5:45
7:11
10:25
11:51
14:44
17:58
20:51
24:05
Time [h:min]
1102130
Norm. Area
120%
100%
80%
60%
40%
20%
0%
0:00
0:43
2:09
3:35
5:01
6:28
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14:01
17:15
20:07
23:22
Time [h:min]

FIGURE 9 (continued)

FIGURE 10A

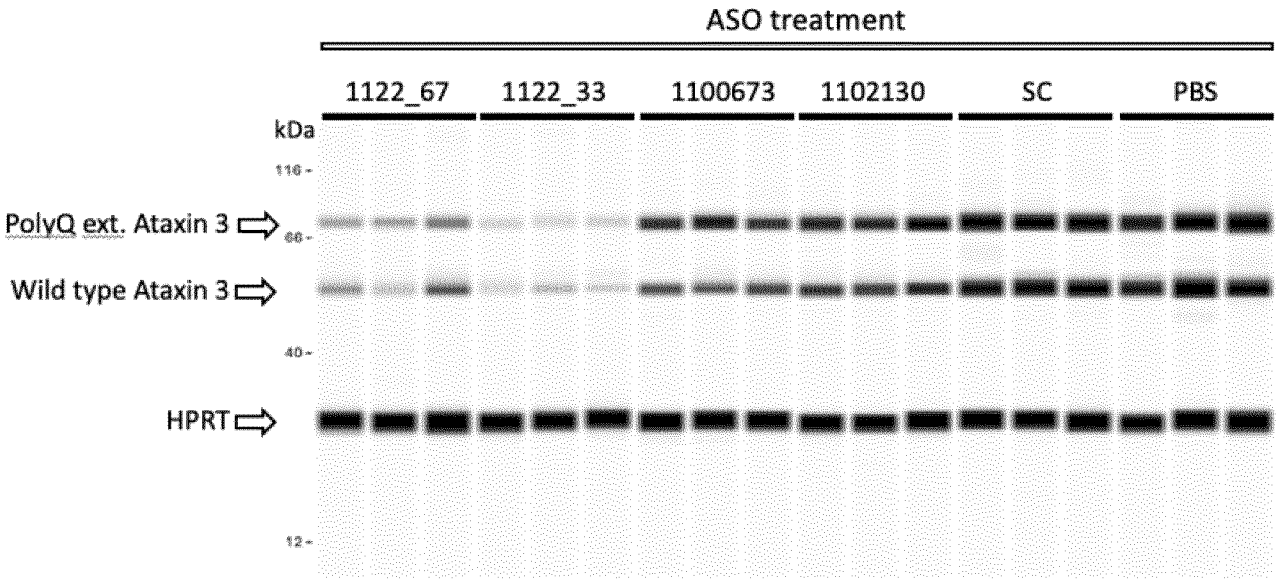
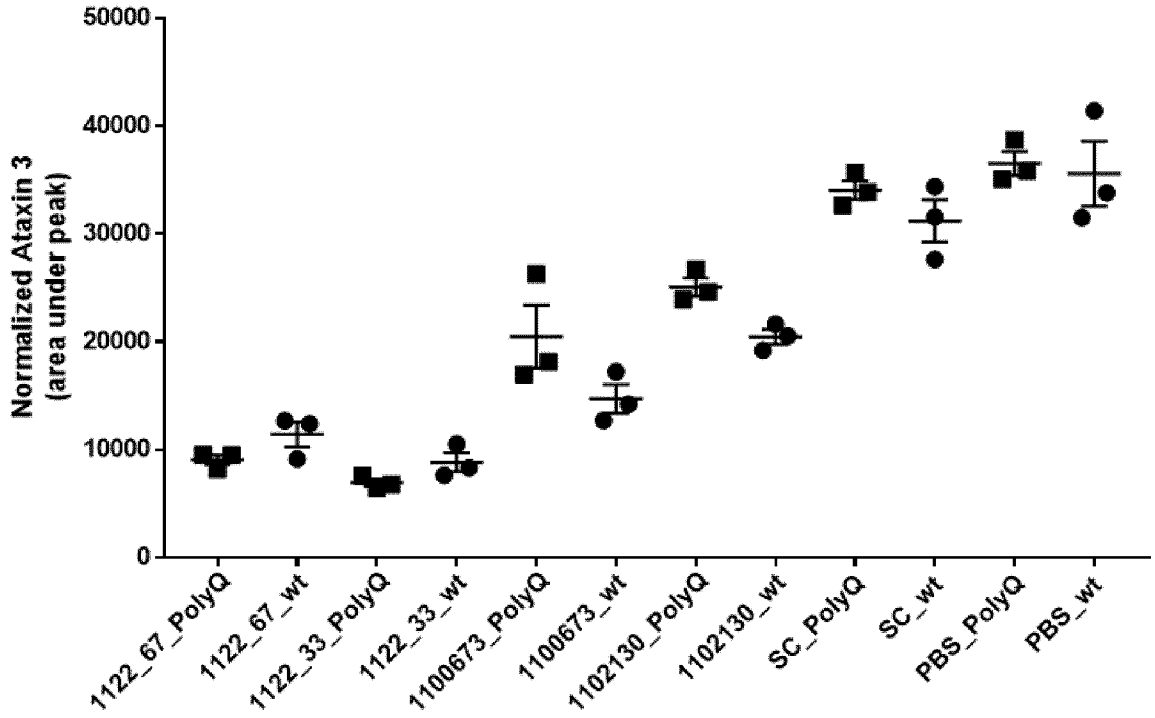


FIGURE 10B



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/065401

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N15/113 A61K31/712 A61K31/7125 A61K31/7115
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, COMPENDEX, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LAUREN R. MOORE ET AL: "Evaluation of Antisense Oligonucleotides Targeting ATXN3 in SCA3 Mouse Models", MOLECULAR THERAPY-NUCLEIC ACIDS, vol. 7, 1 June 2017 (2017-06-01), pages 200-210, XP055674189, US ISSN: 2162-2531, DOI: 10.1016/j.omtn.2017.04.005 figure 1 ----- -/--	1,10-17

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 August 2020	31/08/2020

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Piret, Bernard

1

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HU JIAXIN ET AL: "Allele-selective inhibition of ataxin-3 (ATX3) expression by antisense oligomers and duplex RNAs", BIOLOGICAL CHEMISTRY, WALTER DE GRUYTER GMBH & CO, BERLIN, DE, vol. 392, no. 4, 1 April 2011 (2011-04-01) , pages 315-325, XP008154586, ISSN: 1431-6730, DOI: 10.1515/BC.2011.045 [retrieved on 2011-07-25] table 2	1,10-17
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X	DANIEL R. SCOLES ET AL: "Antisense oligonucleotides : A primer", NEUROLOGY GENETICS, vol. 5, no. 2, 1 April 2019 (2019-04-01), page e323, XP055712472, DOI: 10.1212/NXG.0000000000000323 the whole document	1
X	SWAYZE ERIC E ET AL: "Antisense oligonucleotides containing locked nucleic acid improve potency but cause significant hepatotoxicity in animals", NUCLEIC ACIDS RESEARCH, INFORMATION RETRIEVAL LTD , vol. 35, no. 2 1 January 2007 (2007-01-01), pages 687-700, XP002539513, ISSN: 0305-1048, DOI: 10.1093/NAR/GKL1071 Retrieved from the Internet: URL:20061219 the whole document	1
X,P	WO 2019/217708 A1 (IONIS PHARMACEUTICALS INC [US]) 14 November 2019 (2019-11-14) cited in the application the whole document	1,10-17

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2020/065401

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