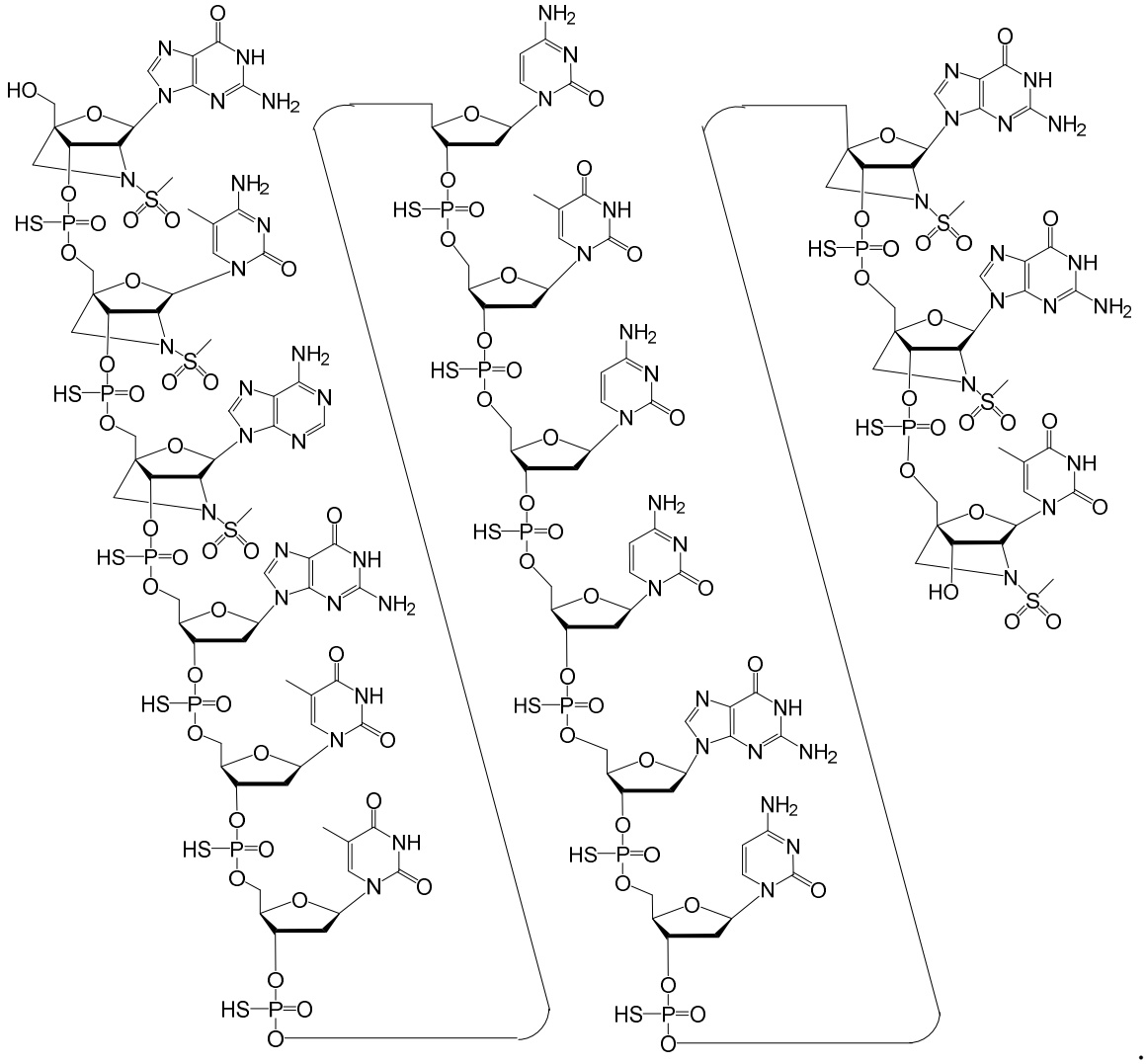
[0011d]
In a further aspect of the present disclosure, there is provided a modified oligonucleotide represented by the following formula or a salt thereof,



[0011e]
In another aspect of the present disclosure, there is provided a pharmaceutical composition, comprising:

the modified oligonucleotide disclosed herein or a pharmaceutically acceptable salt thereof;

wherein the modified oligonucleotide comprising:

1) a gap segment;

2) a 5' wing segment; and

3) a 3' wing segment,

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, all nucleosides of the 5' wing segment and the 3' wing segment each include at least one modified sugar, and the gap segment includes only nucleosides that contain no modified sugar, or includes one or two nucleosides that each contain a modified sugar, and includes other nucleosides that contain no modified sugar;

wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage;

and

a pharmaceutically acceptable carrier.

[0011f]

In yet another aspect of the present disclosure, there is provided a pharmaceutical composition disclosed herein, for use in therapeutically treating or delaying progress of a DUX4-related disease.

[0011g]

In a further aspect of the present disclosure, there is provided a use of a modified oligonucleotide disclosed herein, in manufacture of a medicament for therapeutically treating or delaying progress of a DUX4-related disease.

[Problems to Be Solved by the Invention]

[0012]

An object of the present invention is to provide a compound, a method and a pharmaceutical composition for inhibiting expression of DUX4 and for treating, that is, therapeutically treating, preventing, delaying or ameliorating, DUX4-related diseases and/or symptoms thereof. The compound and pharmaceutical composition disclosed herein also inhibit mutant DUX4 such as SNP and DUX4 splicing variants.

[0013]

Claims

[Claim 1]

A modified oligonucleotide consisting of 12 – 30 residues, comprising:

a nucleobase sequence that includes at least 8 contiguous nucleobase sequences and is complementary to an equal length portion at positions 126 – 147, 232 – 248, 1306 – 1325 or 1480 – 1495 from a 5’ end of a nucleobase sequence of a mature mRNA of DUX4 of SEQ ID NO: 1,

wherein the nucleobase sequence of the modified oligonucleotide has at least 90% complementarity to the equal length portion in the nucleobase sequence of the mature mRNA of DUX4 of SEQ ID NO: 1, and when the at least 8 contiguous nucleobase sequences include a nucleobase sequence that is complementary to the equal length portion at the positions 1480 – 1495 from the 5' end of the nucleobase sequence of SEQ ID NO: 1, the modified oligonucleotide consists of a nucleobase sequence having at a 3’ end a complementary base of a base of the position 1480 from the 5’ end of the nucleobase of SEQ ID NO: 1,

wherein one or more modified nucleotides of the modified oligonucleotide each include a modified sugar, wherein the modified sugar is selected from a group consisting of ALNA [Ms], ALNA [mU], ALNA [ipU], ALNA [Oxz], and ALNA [Trz].

[Claim 2]

A modified oligonucleotide consisting of 12-30 residues, comprising:

a nucleobase sequence that includes at least 8 contiguous nucleobase sequences and is complementary to an equal length portion at positions 1472 – 1495 from a 5' end of a nucleobase sequence of a mature mRNA of DUX4 of SEQ ID NO: 1,

wherein the nucleobase sequence of the modified oligonucleotide has at least 90% complementarity to the equal length portion in the nucleobase sequence of the mature mRNA of DUX4 of SEQ ID NO: 1, and the modified oligonucleotide includes at least one nucleoside that includes a modified sugar selected from the group consisting of ALNA [Ms], ALNA [mU], ALNA [ipU], ALNA [Oxz], and ALNA [Trz].

[Claim 3]

The modified oligonucleotide according to claim 2, further comprising:

a 2'-O-methoxyethyl modified sugar and/or a 2'-O-methyl modified sugar.

[Claim 4]

The modified oligonucleotide according to any one of claims 1 – 3, wherein at least one modified nucleotide of the modified oligonucleotide includes a modified nucleobase.

[Claim 5]

The modified oligonucleotide according to claim 4, wherein the modified nucleobase is a 5-methylcytosine.

[Claim 6]

The modified oligonucleotide according to any one of claims 1 – 5, wherein at least one internucleoside linkage is a modified internucleoside linkage.

[Claim 7]

The modified oligonucleotide according to claim 6, wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage.

[Claim 8]

The modified oligonucleotide according to any one of claims 1 – 7, comprising:

1) a gap segment;

2) a 5' wing segment; and

3) a 3' wing segment,

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, all nucleosides of the 5' wing segment and the 3' wing segment each include at least one modified sugar, and the gap segment includes only nucleosides that contain no modified

sugar, or includes one or two nucleosides that each contain a modified sugar, and includes other nucleosides that contain no modified sugar.

[Claim 9]

The modified oligonucleotide according to any one of claims 1 – 8, consisting of:

a nucleobase sequence that is complementary to a nucleobase sequence of positions 128 – 143 from the 5' end of the nucleobase sequence, a nucleobase sequence of positions 232 – 247 from the 5 'end, a nucleobase sequence of positions 233 – 248 from the 5' end, a nucleobase sequence of positions 1309 – 1323 from the 5' end, or a nucleobase sequence of positions 1480 – 1495 from the 5' end of the mature mRNA of DUX4 of SEQ ID NO: 1.

[Claim 10]

The modified oligonucleotide according to any one of claims 1 – 9, consisting of:

a base sequence of gtggcgatgc ccgggt (SEQ ID NO: 75), gagattcccg cnggtg (SEQ ID NO: 78: n represents a 5-methylcytosine), ngagattcccgccggt (SEQ ID NO: 2: n represents a 5-methylcytosine), gnagttctccgcggt (SEQ ID NO: 3: n represents a 5-methylcytosine), or gnntagacagcgtngg (SEQ ID NO: 4: n represents a 5-methylcytosine).

[Claim 11]

The modified oligonucleotide according to claim 10 represented by the following formula,

GmsMmsMmsTdsAdsGdsAdsCdsAdsGdsCdsGdsTdsMmsGmsGm,

wherein nucleobases are represented by the following symbols: A = adenine, T = thymine, G = guanine, C = cytosine, and M = 5-methylcytosine; sugar moieties are represented by the following symbols: m = ALNA [Ms], and d = 2'-deoxyribose; and internucleoside linkages are represented by the following symbol: s = phosphorothioate.

[Claim 12]

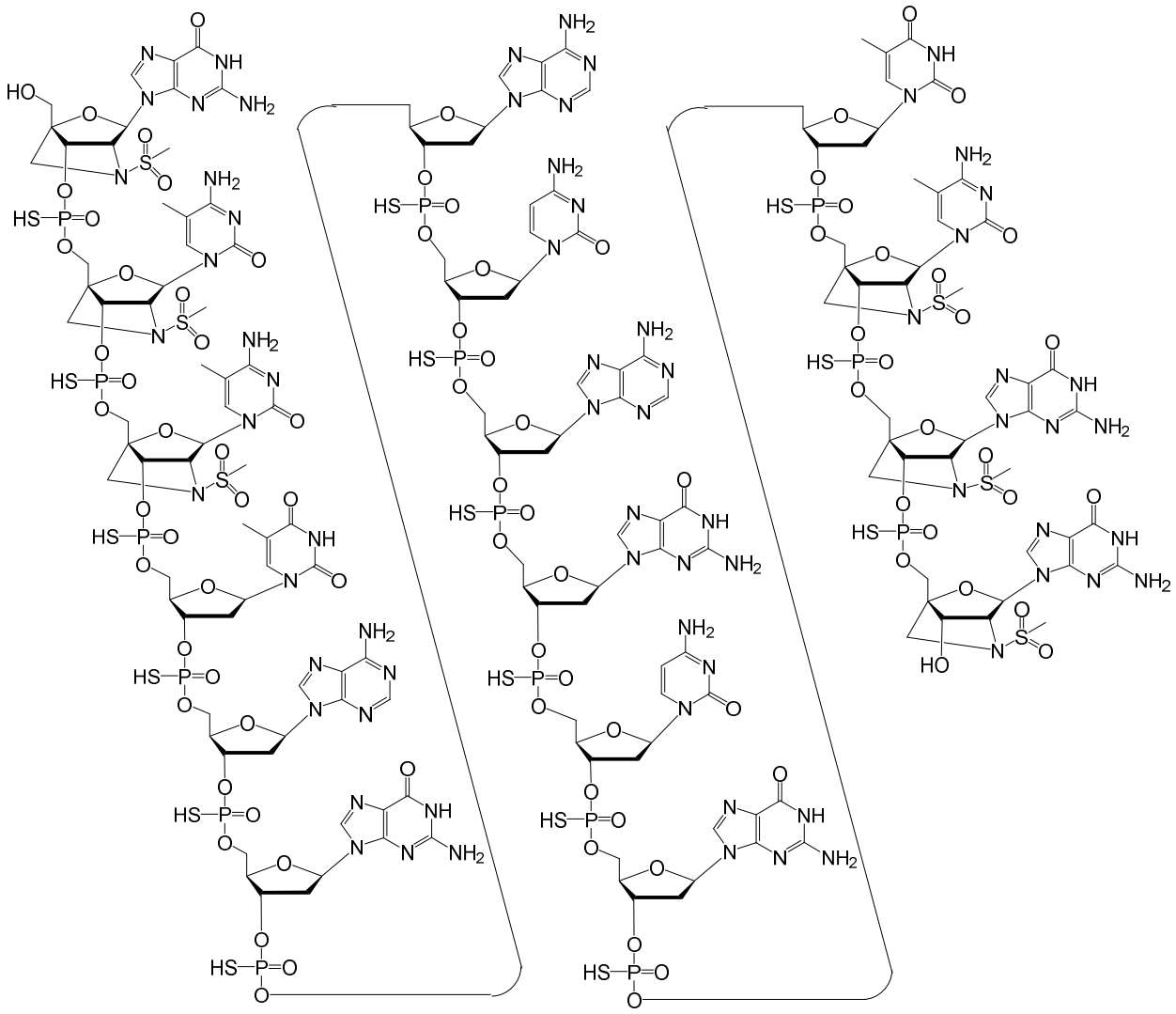
The modified oligonucleotide according to claim 10 represented by the following formula,

GmsMmsAmsGdsTdsTdsCdsTdsCdsCdsGdsCdsGmsGmsTm,

wherein nucleobases are represented by the following symbols: A = adenine, T = thymine, G = guanine, C = cytosine, and M = 5-methylcytosine; sugar moieties are represented by the following symbols: m = ALNA [Ms], and d = 2'-deoxyribose; and internucleoside linkages are represented by the following symbol: s = phosphorothioate.

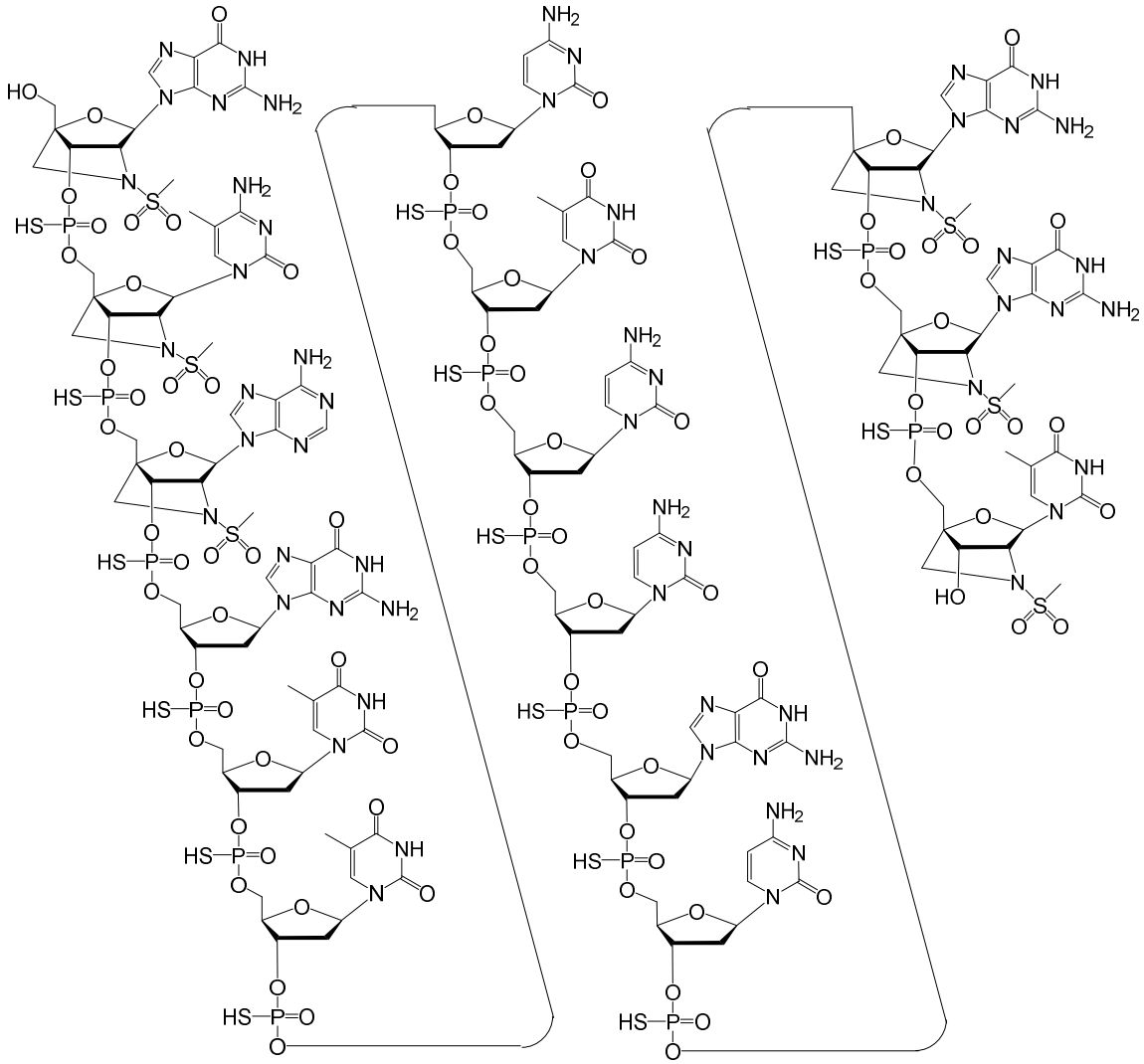
[Claim 13]

A modified oligonucleotide represented by the following formula or a salt thereof,



[Claim 14]

A modified oligonucleotide represented by the following formula or a salt thereof,



[Claim 15]

A pharmaceutical composition, comprising:

the modified oligonucleotide according to any one of claims 1 – 14 or a pharmaceutically acceptable salt thereof;

wherein the modified oligonucleotide comprising:

1) a gap segment;

2) a 5' wing segment; and

3) a 3' wing segment,

wherein the gap segment is positioned between the 5' wing segment and the 3' wing segment, all nucleosides of the 5' wing segment and the 3' wing segment each include at least one modified sugar, and the gap segment includes only nucleosides that contain no modified sugar, or includes one or two nucleosides that each contain a modified sugar, and includes other nucleosides that contain no modified sugar;

wherein the modified internucleoside linkage is a phosphorothioate internucleoside linkage;

and

a pharmaceutically acceptable carrier.

[Claim 16]

The pharmaceutical composition according to claim 15, for use in therapeutically treating or delaying progress of a DUX4-related disease.

[Claim 17]

The pharmaceutical composition for use according to claim 16, wherein the DUX4-related disease is facioscapulohumeral muscular dystrophy.

[Claim 18]

Use of the modified oligonucleotide according to any one of claims 1 – 14, in manufacture of a medicament for therapeutically treating or delaying progress of a DUX4-related disease.

[Claim 19]

The use according to claim 18, wherein the DUX4-related disease is facioscapulohumeral muscular dystrophy.

COMPOUND, METHOD AND PHARMACEUTICAL COMPOSITION FOR MODULATING EXPRESSION OF DUX4

Abstract

An object of the present invention is to provide a compound, a method and a pharmaceutical composition for normalizing double homeobox 4 (DUX4) of an individual in which the DUX4 gene has abnormally expressed. Provided is a modified oligonucleotide consisting of 12 – 30 residues. The modified oligonucleotide includes a nucleobase sequence that includes at least 8 contiguous nucleobase sequences and is complementary to an equal length portion at positions 126 – 147, 232 – 248, 1306 – 1325 or 1472 – 1495 from a 5’ end of a nucleobase of a mature mRNA of DUX4 of SEQ ID NO: 1. The nucleobase sequence of the modified oligonucleotide has at least 90% complementarity to the equal length portion in the nucleobase sequence of the mature mRNA of DUX4 of SEQ ID NO: 1.

[No suitable figure]