Description

Title of Invention: COMBINATION OF ANTISENSE OLIGOMERS

Technical Field

[0001]

The present invention relates to a pharmaceutical composition or a pharmaceutical combination for use in treatment of muscular dystrophy, a method for treatment of muscular dystrophy, and the like.

Background Art

[0002]

In recent years, exon skipping therapy has received attention which involves causing exon skipping of a gene having a mutation that causes a disease so that a protein having partial functions arises, thereby treating the disease. Examples of the disease that may be treated by such exon skipping therapy include Duchenne muscular dystrophy (DMD).

[0003]

DMD is the most frequent form of hereditary progressive muscular disease that affects one in about 3,500 newborn boys. Although DMD patients exhibit motor functions rarely different from healthy humans in their infancy and childhood, muscle weakness is observed in children from around 4 to 5 years old. Then, muscle

weakness in DMD patients progresses with age to the loss of ambulation by about 12 years old and death due to cardiac or respiratory insufficiency in the twenties. Therefore, it has been strongly desired to develop an effective therapeutic agent.

[0004]

DMD is known to be caused by a mutation in the dystrophin gene. The dystrophin gene is located on X chromosome and is a huge gene consisting of 2.2 million DNA base pairs. DNA is transcribed into pre-mRNA, and introns are removed by splicing to synthesize mRNA of 13,993 bases in which 79 exons are joined together. This mRNA is translated into 3,685 amino acids to produce dystrophin protein. The dystrophin protein is associated with the maintenance of membrane stability in muscle cells and necessary to make muscle cells less fragile. Patients with DMD have a mutation in the dystrophin gene and hence, the functional dystrophin protein is rarely expressed in muscle cells of the patients. Therefore, the structure of muscle cells cannot be maintained at the time of muscle contraction in the body of the patients with DMD, leading to a large influx of calcium ions into muscle cells. Consequently, muscle cell necrosis and fibrosis progress so that muscle cells can be eventually regenerated only with difficulty.

[0005]

Becker muscular dystrophy (BMD) is also caused by a mutation in the dystrophin gene. The symptoms involve muscle weakness but are typically mild and slow in the progress of muscle weakness, when compared to DMD. In many cases, its onset is in adulthood. Differences in clinical symptoms between DMD and BMD are considered to reside in whether the reading frame for amino acids on the translation of dystrophin mRNA into the dystrophin protein is disrupted by the mutation or not (Non Patent Literature 1). More specifically, in DMD, the presence of mutation shifts the amino acid reading frame so that the expression of functional dystrophin protein is abolished, whereas in BMD the dystrophin protein that is capable of functioning, though imperfectly, is produced because the amino acid reading frame is preserved, while a part of the exons are deleted by the mutation.

[0006]

Exon skipping is expected to serve as a method for treating DMD. This method involves modifying splicing to restore the amino acid reading frame of dystrophin mRNA and induce expression of the dystrophin protein having the function partially restored (Non Patent Literature 2). The amino acid sequence part to be translated from an exon, which is a target for exon skipping, will be lost. For this reason, the dystrophin protein expressed by this treatment becomes shorter than normal one but since the amino acid reading frame is maintained, the

function to stabilize muscle cells is partially retained. Consequently, it is expected that exon skipping will lead DMD to the similar symptoms to that of BMD which is milder. The exon skipping approach has passed the animal tests using mice or dogs and now is currently assessed in clinical trials on human DMD patients.

[0007]

The skipping of an exon can be induced by binding of antisense nucleic acids targeting site(s) surrounding either 5' or 3' splice site or both sites, or exon-internal sites. An exon will only be included in the mRNA when both splice sites thereof are recognized by the spliceosome complex. Thus, exon skipping can be induced by targeting the sites surrounding the splice sites with antisense nucleic acids. Furthermore, the binding of an SR protein rich in serine and arginine to an exonic splicing enhancer (ESE) is considered necessary for an exon to be recognized by the splicing mechanism. Accordingly, exon skipping can also be induced by targeting ESE.

[0008]

Since a mutation of the dystrophin gene may vary depending on DMD patients, antisense nucleic acids need to be designed based on the site or type of respective genetic mutation. There are a plurality of reports on an antisense nucleic acid that induces exon skipping targeting one sequence of consecutive bases for a single

exon in the dystrophin gene (Patent Literatures 1 to 6 and Non Patent Literatures 1 and 2). It has also been reported that when two types of antisense nucleic acids that target the same exon in the dystrophin gene are mixed and allowed to act (dual targeting), skipping activity may be enhanced as compared to use of each antisense nucleic acid alone (Patent Literature 7).

[0009]

A method called multi-exon skipping has received attention which involves causing skipping of a plurality of exons (exon group), not one exon as described above. This method enables a wide range of mutations in the dystrophin gene to be treated by exon skipping. For example, exons 45 to 55 in the dystrophin gene are known as hot spots of genetic mutation, and it has been reported that skipping of these 11 exons enables about 60% of DMD patients having a deletion mutation to be treated (Non Patent Literature 3). Most of patients congenitally lacking exons 45 to 55 are known to manifest no or mild symptoms, though developing BMD (Non Patent Literature 4). Thus, it is expected that drugs capable of inducing exon 45 to 55 skipping are promising as therapeutic agents for DMD.

[0010]

For example, a method using antisense nucleic acids respectively targeting all exons in a region which is the target of exon skipping (Non Patent Literatures 5, 7, 8,

and 10), a method using antisense nucleic acids respectively targeting two different exons on the 3' side and 5' side of a region which is the target of exon skipping (Non Patent Literatures 6 and 9 and Patent Literatures 8, 9, and 11), and a method using an antisense nucleic acid targeting only an exon on the 5' side of a region which is the target of exon skipping (Patent Literature 10) have been reported as methods for inducing multi-exon skipping.

Citation List

Patent Literature

[0011]

Patent Literature 1: International Publication WO2004/048570

Patent Literature 2: International Publication W2009/139630

Patent Literature 3: International Publication W2010/048586

Patent Literature 4: U.S. Patent Publication Nos. 2010/0168212

Patent Literature 5: International Publication W2011/057350

Patent Literature 6: International Publication W2006/000057

Patent Literature 7: International Publication W2007/135105

Patent Literature 8: International Publication W2004/083446

Non Patent Literature

Patent Literature 9: International Publication W2014/007620

Patent Literature 10: International Publication W2019/200185

Patent Literature 11: International Publication W2020/219820

Non Patent Literature

[0012]

Non Patent Literature 1: Annemieke Aartsma-Rus et al., (2002) Neuromuscular Disorders 12: S71-S77

Non Patent Literature 2: Wilton S. D., e t al., Molecular Therapy 2007: 15: p. 1288-96

Non Patent Literature 3: Christophe Beroud et al., Human Mutation, 28(2), 2007, 196-202

Non Patent Literature 4: Yusuke Echigoya et al., Molecular Therapy-Nucleic Acids, 4(2), 2015, e225

Non Patent Literature 5: Yoshitsugu Aoki et al., PNAS, 109(34), 2012, 13763-13768

Non Patent Literature 6: Laura van Vliet et al., BMC Medical Genetics, 9, 105, 2008

Non Patent Literature 7: Joshua Lee et al., PLoS ONE, 13(5), e0197084, 2018

Non Patent Literature 8: Joshua Lee et al., Methods in Molecular Biology, 1828, 141-150, 2018

Non Patent Literature 9: Annemieke Aartsma-Rus et al, Am. J. Hum. Genet. 74(1), 83-92, 2004
Non Patent Literature 10: Yusuke Echigoya et al., Molecular Therapy, 27(11), 1-13, 2019

Summary of Invention

Technical Problem

[0013]

The effects of drugs causing simultaneous skipping a plurality of exons (exon group) in objective pre-mRNA are not always sufficient. Under the foregoing circumstances, medicaments for treating patients having various mutations by causing simultaneous skipping of a plurality of exons (exon group) in objective pre-mRNA have been desired.

Solution to Problem

[0014]

The present invention provides a combination of antisense oligomers or pharmaceutically acceptable salts thereof, or hydrates thereof, a pharmaceutical composition, a pharmaceutical combination, a method for treatment of muscular dystrophy, and the like as follows:

(1)

A combination of antisense oligomers or pharmaceutically acceptable salts thereof, or hydrates thereof which cause simultaneous skipping of any two or

more numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA,

the combination comprising:

(i) a first antisense oligomer or a pharmaceutically acceptable salt thereof, or a hydrate thereof, comprising:

a first unit oligomer comprising a base sequence complementary to a base sequence consisting of a base sequence of 11 bases in the upstream direction from the 3' end of the 44th intron and a base sequence of 69 bases in the downstream direction from the 5' end of the 45th exon in the human dystrophin pre-mRNA, or a partial base sequence thereof; and

a second unit oligomer comprising a base sequence complementary to a base sequence of from the 52nd to 75th bases in the upstream direction from the 3' end of the 44th intron in the human dystrophin pre-mRNA, or a partial base sequence thereof; and

(ii) a second antisense oligomer or a pharmaceutically acceptable salt thereof, or a hydrate thereof, comprising a base sequence complementary to a base sequence consisting of a base sequence of 33 bases in the upstream direction from the 3' end of the 54th intron and a base sequence of 53 bases in the downstream direction from the 5' end of the 55th exon in the human dystrophin pre-mRNA, or a partial base sequence thereof.

(2)

The combination according to (1), wherein

the first unit oligomer comprises a base sequence complementary to consecutive 15 to 30 bases of a base sequence consisting of a base sequence of 11 bases in the upstream direction from the 3' end of the 44th intron and a base sequence of 69 bases in the downstream direction from the 5' end of the 45th exon in the human dystrophin pre-mRNA,

the second unit oligomer comprises a base sequence complementary to consecutive 1 to 10 bases of a base sequence of from the 52nd to 75th bases in the upstream direction from the 3' end of the 44th intron in the human dystrophin pre-mRNA, and

the second antisense oligomer comprises a base sequence complementary to consecutive 15 to 30 bases of a base sequence consisting of a base sequence of 33 bases in the upstream direction from the 3' end of the 54th intron and a base sequence of 53 bases in the downstream direction from the 5' end of the 55th exon in the human dystrophin pre-mRNA.

(3)

The combination according to (1) or (2), wherein

the first unit oligomer comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c), and/or

the second unit oligomer comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

(4)

The combination according to any one of (1) to (3), wherein

the second antisense oligomer comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

(5)

The combination according to any one of (1) to (4), wherein the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, the first unit oligomer comprises any

one base sequence selected from SEQ ID NOs: 907 to 1602, the second unit oligomer comprises any one base sequence selected from SEQ ID NOs: 106 to 210, and the second antisense oligomer comprises any one base sequence selected from SEQ ID NOs: 4299 to 5090.

(6)

The combination according to any one of (1) to (5), wherein the first unit oligomer comprises any one base sequence selected from the group consisting of SEQ ID NOs: 1180, 1190, 1201, 1212, 1222, 1224, and 1239.

(7)

The combination according to any one of (1) to (6), wherein the second unit oligomer comprises any one base sequence selected from the group consisting of SEQ ID NOs: 114, 124, 151, 201, 203, and 205.

(8)

The combination according to (6) or (7), wherein

the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, and

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, and the second unit oligomer comprises a base sequence of SEQ ID NO: 151,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, and the second unit oligomer comprises a base sequence of SEQ ID NO: 201,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, and the second unit oligomer comprises a base sequence of SEQ ID NO: 203,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, and the second unit oligomer comprises a base sequence of SEQ ID NO: 205,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1239, and the second unit oligomer comprises a base sequence of SEQ ID NO: 114,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1224, and the second unit oligomer comprises a base sequence of SEQ ID NO: 124,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1180, and the second unit oligomer comprises a base sequence of SEQ ID NO: 151,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1190, and the second unit oligomer comprises a base sequence of SEQ ID NO: 151,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1212, and the second unit oligomer comprises a base sequence of SEQ ID NO: 151, or

the first unit oligomer comprises a base sequence of SEQ ID NO: 1222, and the second unit oligomer comprises a base sequence of SEQ ID NO: 151.

(9)

The combination according to any one of (1) to (8), wherein the second antisense oligomer comprises a base

sequence selected from the group consisting of SEQ ID NOs: 4698, 4702, 4752, 4923, 4926, 4936, and 4977.

(10)

The combination according to any one of (1) to (9), wherein

the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, and

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 201, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 203, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 205, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1239, the second unit oligomer comprises a

base sequence of SEQ ID NO: 114, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1224, the second unit oligomer comprises a base sequence of SEQ ID NO: 124, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1180, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1190, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1212, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1222, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4698,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4702,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4752,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4923,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4926,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4936,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4977, or

the first unit oligomer comprises a base sequence of SEQ ID NO: 1180, the second unit oligomer comprises a

base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4977.

(11)

The combination according to any one of (5) to (10), wherein the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950 or 4880.

(12)

The combination according to any one of (1) to (11), further comprising:

(iii) a third antisense oligomer or a pharmaceutically acceptable salt thereof, or a hydrate thereof, comprising a base sequence complementary to a base sequence consisting of a base sequence of 23 bases in the upstream direction from the 3' end of the 45th exon and a base sequence of 73 bases in the downstream direction from the 5' end of the 45th intron in the human dystrophin pre-mRNA, or a partial base sequence thereof.

(13)

The combination according to (12), wherein the third antisense oligomer comprises a base sequence complementary to consecutive 15 to 30 bases of a base sequence consisting of a base sequence of 23 bases in the upstream direction from the 3' end of the 45th exon and a base sequence of 73 bases in the downstream direction

from the 5' end of the 45th intron in the human dystrophin pre-mRNA.

(14)

The combination according to (12) or (13), wherein the third antisense oligomer comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

(15-1)

The combination according to (14), wherein the third antisense oligomer comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 1611 to 1654, 1664 to 1707, 1718 to 1761, 1773 to 1816, 1829 to 1872, 1886 to 1929,

1944 to 1987, 2003 to 2046, 2063 to 2106, 2124 to 2167, 2186 to 2229, 2249 to 2292, 2313 to 2356, 2378 to 2421, 2444 to 2487, and 2511 to 2554;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 1611 to 1654, 1664 to 1707, 1718 to 1761, 1773 to 1816, 1829 to 1872, 1886 to 1929, 1944 to 1987, 2003 to 2046, 2063 to 2106, 2124 to 2167, 2186 to 2229, 2249 to 2292, 2313 to 2356, 2378 to 2421, 2444 to 2487, and 2511 to 2554;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1611 to 1654, 1664 to 1707, 1718 to 1761, 1773 to 1816, 1829 to 1872, 1886 to 1929, 1944 to 1987, 2003 to 2046, 2063 to 2106, 2124 to 2167, 2186 to 2229, 2249 to 2292, 2313 to 2356, 2378 to 2421, 2444 to 2487, and 2511 to 2554, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

(15-2)

The combination according to (14), wherein the third antisense oligomer comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 1614 to 1654, 1667 to 1707, 1721 to 1761, 1776 to 1816, 1832 to 1872, 1889 to 1929, 1947 to 1987, 2006 to 2046, 2066 to 2106, 2127 to 2167, 2189 to 2229, 2252 to 2292, 2316 to 2356, 2381 to 2421, 2447 to 2487, and 2514 to 2554;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 1614 to 1654, 1667 to 1707, 1721 to 1761, 1776 to 1816, 1832 to 1872, 1889 to 1929, 1947 to 1987, 2006 to 2046, 2066 to 2106, 2127 to 2167, 2189 to 2229, 2252 to 2292, 2316 to 2356, 2381 to 2421, 2447 to 2487, and 2514 to 2554;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1614 to 1654, 1667 to 1707, 1721 to 1761, 1776 to 1816, 1832 to 1872, 1889 to 1929, 1947 to 1987, 2006 to 2046, 2066 to 2106, 2127 to 2167, 2189 to 2229, 2252 to 2292, 2316 to 2356, 2381 to 2421, 2447 to 2487, and 2514 to 2554, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

(16)

The combination according to (14), wherein the third antisense oligomer comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 1617 to 1654, 1670 to 1707, 1724 to 1761, 1779 to 1816, 1835 to 1872, 1892 to 1929, 1950 to 1987, 2009 to 2046, 2069 to 2106, 2130 to 2167, 2192 to 2229, 2255 to 2292, 2319 to 2356, 2384 to 2421, 2450 to 2487, and 2517 to 2554;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 1617 to 1654, 1670 to 1707, 1724 to 1761, 1779 to 1816, 1835 to 1872, 1892 to 1929, 1950 to 1987, 2009 to 2046, 2069 to 2106, 2130 to 2167, 2192 to 2229, 2255 to 2292, 2319 to 2356, 2384 to 2421, 2450 to 2487, and 2517 to 2554;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1617 to 1654, 1670 to 1707, 1724 to 1761, 1779 to 1816, 1835 to 1872, 1892 to 1929, 1950 to 1987, 2009 to 2046, 2069 to 2106, 2130 to 2167, 2192 to 2229, 2255 to 2292, 2319 to 2356, 2384 to 2421, 2450 to 2487, and 2517 to 2554, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

(17-1)

The combination according to any one of (1) to (14), wherein the third antisense oligomer comprises a base sequence selected from the group consisting of SEQ ID NOs: 3060, 3065, 3077, 3082, 3087, 3090, 3096, 3108, 3119, and 3320.

(17-2)

The combination according to any one of (1) to (14), wherein the third antisense oligomer comprises a base sequence selected from the group consisting of SEQ ID NOs: 3077, 3082, 3087, 3090, 3096, 3108, and 3119.

(17-3)

The combination according to any one of (1) to (14), wherein the third antisense oligomer comprises a base sequence selected from the group consisting of SEQ ID NOs: 3082, 3087, 3090, 3096, 3108, and 3119.

(18)

The combination according to any one of (12) to (17), wherein the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, the first unit oligomer comprises any one base sequence selected from SEQ ID NOs: 907 to 1602, the second unit oligomer comprises any one base sequence selected from SEQ ID NOs: 106 to 210, the second

antisense oligomer comprises any one base sequence selected from SEQ ID NOs: 4299 to 5090, and the third antisense oligomer comprises any one base sequence selected from SEQ ID NOs: 2555 to 3506.

(19)

The combination according to any one of (1) to (18), wherein

the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, and

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 201, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 203, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 205, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1239, the second unit oligomer comprises a base sequence of SEQ ID NO: 114, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1224, the second unit oligomer comprises a base sequence of SEQ ID NO: 124, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1180, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1190, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1212, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1222, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3060,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense

oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3065,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3077,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3087,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3090,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3096,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3108,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3119,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3320,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4698, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense

oligomer comprises a base sequence of SEQ ID NO: 4702, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4752, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4923, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4926, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4936, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4977, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4977, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3096, or

the first unit oligomer comprises a base sequence of SEQ ID NO: 1180, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4977, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3096.

(20)

The combination according to (18) or (19), wherein the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950 or 4880, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082, 3090, or 3096.

(21)

The combination according to any one of (1) to (20), the combination causing skipping of all exons from the 45th exon to the 55th exon in the human dystrophin pre-mRNA.

(22)

The combination according to any one of (1) to (11), wherein the first and second antisense oligomers are oligonucleotides, or the combination according to any one of (12) to (21), wherein the first to third antisense oligomers are oligonucleotides.

(23)

The combination according to (22), wherein a sugar moiety and/or a phosphate-binding region of at least one nucleotide constituting the oligonucleotide is modified.

(24)

The combination according to (22) or (23), wherein the sugar moiety of at least one nucleotide constituting the oligonucleotide is a ribose in which the 2'-OH group is replaced by any one group selected from the group consisting of -OR, -R, -R'OR, -SH, -SR, $-NH_2$, -NHR, $-NR_2$, $-N_3$, -CN, -F, -Cl, -Br, and -I
(wherein R is an alkyl or an aryl and R' is an alkylene).

(25)

The combination according to any one of (22) to (24), wherein the phosphate-binding region of at least one nucleotide constituting the oligonucleotide is any one selected from the group consisting of a

phosphorothioate bond, a phosphorodithioate bond, an alkylphosphonate bond, a phosphoramidate bond and a boranophosphate bond.

(26)

The combination according to any one of (1) to (11), wherein the first and second antisense oligomers are morpholino oligomers, or the combination according to any one of (12) to (21), wherein the first to third antisense oligomers are oligonucleotides.

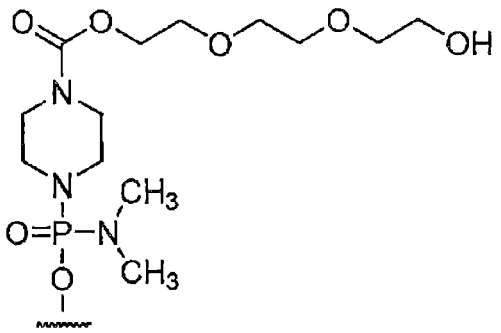
(27)

The combination according to (26), wherein the first to third antisense oligomers are phosphorodiamidate morpholino oligomers.

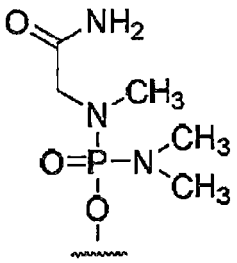
(28)

The combination according to (26) or (27), wherein the 5' end of each of the first to third antisense oligomers is a group represented by any one of the following chemical formulae (1) to (3):

[Chem. 1]



(1)



(2)



(3)

(29)

(a) A pharmaceutical composition comprising the first and second antisense oligomers according to any one of (1) to (28), or pharmaceutically acceptable salts thereof, or hydrates thereof, or

(b) a pharmaceutical combination comprising (i) a pharmaceutical composition comprising the first antisense oligomer according to any one of (1) to (28), or a pharmaceutically acceptable salt thereof, or a hydrate thereof, and (ii) a pharmaceutical composition comprising the second antisense oligomer according to any one of (1) to (28), or a pharmaceutically acceptable salt thereof, or a hydrate thereof.

(30)

(a) A pharmaceutical composition comprising the first to third antisense oligomers according to any one of (12) to (28), or pharmaceutically acceptable salts thereof, or hydrates thereof, or

(b) a pharmaceutical combination comprising (i) a pharmaceutical composition comprising the first antisense oligomer according to any one of (12) to (28), or a pharmaceutically acceptable salt thereof, or a hydrate thereof, (ii) a pharmaceutical composition comprising the second antisense oligomer according to any one of (12) to (28), or a pharmaceutically acceptable salt thereof, or a hydrate thereof, and (iii) a pharmaceutical composition comprising the third antisense oligomer according to any

one of (12) to (28), or a pharmaceutically acceptable salt thereof, or a hydrate thereof.

(31)

The pharmaceutical composition or the pharmaceutical combination according to (29) or (30), wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

(32)

The pharmaceutical composition or the pharmaceutical combination according to any one of (29) to (31), for treatment of muscular dystrophy.

(33)

The pharmaceutical composition or the pharmaceutical combination according to any one of (29) to (32), for being administered to a human patient.

(34)

A method for treatment of muscular dystrophy, comprising administering to a patient with muscular dystrophy (i) the first and second antisense oligomers according to any one of (1) to (28), or pharmaceutically acceptable salts thereof, or hydrates thereof, (ii) the first to third antisense oligomers according to any one of (12) to (28), or pharmaceutically acceptable salts thereof, or hydrates thereof, or (iii) the pharmaceutical composition or the pharmaceutical combination according to any one of (29) to (33).

(35)

The method for treatment according to (34), wherein the muscular dystrophy patient is a patient with a mutation that is a target of exon 45 to 55 skipping in dystrophin gene.

(36)

The method for treatment according to (34) or (35), wherein the patient is a human.

[0015]

The present invention provides a combination of antisense oligomers that cause simultaneous skipping of a plurality of exons in a target. Another aspect of the present invention provides a pharmaceutical composition or combination for treating muscular dystrophy patients having various mutations by causing simultaneous skipping of a plurality of exons in objective pre-mRNA. An alternative aspect of the present invention enables simultaneous skipping of exons 45 to 55 in human dystrophin pre-mRNA to be caused with a high efficiency.

Brief Description of Drawings

[0016]

[Figure 1] Figure 1 is a diagram showing results of studying exon 45 to 55 skipping in mouse dystrophin pre-mRNA in H2K-mdx52 cells by RT-PCR (total concentration of added PMO: 30 μM).

[Figure 2] Figure 2 is a diagram showing results of studying exon 45 skipping in mouse dystrophin pre-mRNA in

H2K-mdx52 cells by RT-PCR (total concentration of added PMO: 30 μM).

[Figure 3] Figure 3 is a diagram showing results of studying exon 45 to 55 skipping in mouse dystrophin pre-mRNA in H2K-mdx52 cells by RT-PCR. In the drawing, "2-2" indicates a result obtained by treatment with Mixture 2 + PMO No. 3 (1:1), "2-4" indicates a result obtained by treatment with Mixture 2 + PMO No. 3 (1:2), "2-5" indicates a result obtained by treatment with PMO No. 3 singly, "2-7" indicates a result obtained by treatment with Mixture 2 singly, and "NT" means "not treated" (total concentration of added PMO: 15 μM).

[Figure 4] Figure 4 is a diagram showing results of studying exon 45 skipping in mouse dystrophin pre-mRNA in H2K-mdx52 cells by RT-PCR. In the drawing, "2-2" indicates a result obtained by treatment with Mixture 2 + PMO No. 3 (1:1), "2-4" indicates a result obtained by treatment with Mixture 2 + PMO No. 3 (1:2), "2-5" indicates a result obtained by treatment with PMO No. 3 singly, "2-7" indicates a result obtained by treatment with Mixture 2 singly, and NT means "not treated" (total concentration of added PMO: 15 μM).

[Figure 5] Figure 5 is a diagram showing results of studying exon 45 to 55 skipping in mouse dystrophin pre-mRNA in H2K-mdx52 cells by RT-PCR. In the drawing, "3-2" indicates a result obtained by treatment with Mixture 2 + PMO No. 4 (1:1), "3-4" indicates a result obtained by

treatment with Mixture 2 + PMO No. 4 (1:2), "3-5" indicates a result obtained by treatment with PMO No. 4 singly, "3-7" indicates a result obtained by treatment with Mixture 2 singly, and "NT" means "not treated" (total concentration of added PMO: 15 μM).

[Figure 6] Figure 6 is a diagram showing results of studying exon 45 skipping in mouse dystrophin pre-mRNA in H2K-mdx52 cells by RT-PCR. In the drawing, "3-2" indicates a result obtained by treatment with Mixture 2 + PMO No. 4 (1:1), "3-4" indicates a result obtained by treatment with Mixture 2 + PMO No. 4 (1:2), "3-5" indicates a result obtained by treatment with PMO No. 4 singly, "3-7" indicates a result obtained by treatment with Mixture 2 singly, and NT means "not treated" (total concentration of added PMO: 15 μM).

[Figure 7] Figure 7 is a diagram showing results of studying exon 45 to 55 skipping in mouse dystrophin pre-mRNA in H2K-mdx52 cells by RT-PCR. In the drawing, "2-1" indicates a result obtained by treatment with Mixture 2 singly, "2-2" indicates a result obtained by treatment with Mixture 2 + PMO No. 3 (1:1), "2-3" indicates a result obtained by treatment with Mixture 2 + PMO No. 3 (2:1), "2-4" indicates a result obtained by treatment with Mixture 2 + PMO No. 3 (3:1), and "NT" means "not treated" (total concentration of added PMO: 15 μM).

[Figure 8] Figure 8 is a diagram showing results of studying exon 45 skipping in mouse dystrophin pre-mRNA in

H2K-mdx52 cells by RT-PCR. In the drawing, "2-1" indicates a result obtained by treatment with Mixture 2 singly, "2-2" indicates a result obtained by treatment with Mixture 2 + PMO No. 3 (1:1), "2-3" indicates a result obtained by treatment with Mixture 2 + PMO No. 3 (2:1), "2-4" indicates a result obtained by treatment with Mixture 2 + PMO No. 3 (3:1), and "NT" means "not treated" (total concentration of added PMO: 15 μM).

[Figure 9] Figure 9 is a diagram showing results of studying exon 45 to 55 skipping in mouse dystrophin pre-mRNA in H2K-mdx52 cells by RT-PCR. In the drawing, "NC" indicates a result obtained by treatment with Endo-porter singly, "Mix 2" indicates a result obtained by treatment with a mixture of PMO No. 1 and PMO No. 2 both in a final concentration of 25 μM, and "Mix 2 + hnRNP A1" indicates a result obtained by treatment with a mixture of PMO No. 1 and PMO No. 2 both in a final concentration of 18.75 μM, and PMO No. 3 in a final concentration of 12.5 μM (total concentration of added PMO: 50 μM).

[Figure 10] Figure 10 is a diagram showing results of studying exon 45 skipping in mouse dystrophin pre-mRNA in H2K-mdx52 cells by RT-PCR. In the drawing, "NC" indicates a result obtained by treatment with Endo-porter singly, "Mix 2" indicates a result obtained by treatment with a mixture of PMO No. 1 and PMO No. 2 both in a final concentration of 25 μM, and "Mix 2 + hnRNP A1" indicates a result obtained by treatment with a mixture of PMO No.

1 and PMO No. 2 both in a final concentration of 18.75 μM, and PMO No. 3 in a final concentration of 12.5 μM (total concentration of added PMO: 50 μM).

[Figure 11] Figure 11 is a diagram showing results of studying, by Western blotting, expression of dystrophin protein by exon 45 to 55 skipping in mouse dystrophin pre-mRNA in H2K-mdx52 cells. In the drawing, "NC" indicates a result obtained by treatment with Endo-porter singly, "Mix 2" indicates a result obtained by treatment with a mixture of PMO No. 1 and PMO No. 2 both in a final concentration of 25 μM, "Mix 2 + hnRNP A1" indicates a result obtained by treatment with a mixture of PMO No. 1 and PMO No. 2 both in a final concentration of 18.75 μM, and PMO No. 3 in a final concentration of 12.5 μM, and "NT" means "not treated" (total concentration of added PMO: 50 μM).

[Figure 12] Figure 12 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in normal human-derived myoblasts by RT-PCR.

[Figure 13] Figure 13 is a diagram showing results of studying exon 45 skipping in normal human-derived myoblasts by RT-PCR.

[Figure 14] Figure 14 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 48 to 50 deletion by RT-PCR.

[Figure 15] Figure 15 is a diagram showing results of studying exon 45 skipping in DMD patient-derived myoblasts with exon 48 to 50 deletion by RT-PCR.

[Figure 16] Figure 16 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 48 to 50 deletion by RT-PCR.

[Figure 17] Figure 17 is a diagram showing results of studying exon 45 skipping in DMD patient-derived myoblasts with exon 48 to 50 deletion by RT-PCR.

[Figure 18] Figure 18 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 48 to 50 deletion by Western blotting.

[Figure 19] Figure 19 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 46 to 51 deletion by RT-PCR.

[Figure 20] Figure 20 is a diagram showing results of studying exon 45 skipping in DMD patient-derived myoblasts with exon 46 to 51 deletion by RT-PCR.

[Figure 21] Figure 21 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 46 to 51 deletion by RT-PCR.

[Figure 22] Figure 22 is a diagram showing results of studying exon 45 skipping in DMD patient-derived myoblasts with exon 46 to 51 deletion by RT-PCR.

[Figure 23] Figure 23 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 46 to 51 deletion by Western blotting.

[Figure 24] Figure 24 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion by RT-PCR.

[Figure 25] Figure 25 is a diagram showing results of studying exon 45 skipping in DMD patient-derived myoblasts with exon 51 deletion by RT-PCR.

[Figure 26] Figure 26 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion by RT-PCR.

[Figure 27] Figure 27 is a diagram showing results of studying exon 45 skipping in DMD patient-derived myoblasts with exon 51 deletion by RT-PCR.

[Figure 28] Figure 28 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion by RT-PCR.

[Figure 29] Figure 29 is a diagram showing results of studying exon 45 skipping in DMD patient-derived myoblasts with exon 51 deletion by RT-PCR.

[Figure 30] Figure 30 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion by RT-PCR.

[Figure 31] Figure 31 is a diagram showing results of studying exon 45 skipping in DMD patient-derived myoblasts with exon 51 deletion by RT-PCR.

[Figure 32] Figure 32 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion by RT-PCR.

[Figure 33] Figure 33 is a diagram showing results of studying exon 45 skipping in DMD patient-derived myoblasts with exon 51 deletion by RT-PCR.

[Figure 34] Figure 34 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion by RT-PCR.

[Figure 35] Figure 35 is a diagram showing results of studying exon 45 skipping in DMD patient-derived myoblasts with exon 51 deletion by RT-PCR.

[Figure 36] Figure 36 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in DMD

patient-derived myoblasts with exon 51 deletion by RT-PCR.

[Figure 37] Figure 37 is a diagram showing results of studying exon 45 skipping in DMD patient-derived myoblasts with exon 51 deletion by RT-PCR.

[Figure 38] Figure 38 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion by Western blotting.

[Figure 39] Figure 39 is a diagram showing results of studying exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion by Western blotting.

Description of Embodiments

[0017]

Hereinafter, the present invention is described in detail. The embodiments described below are intended to be presented by way of example merely to describe the invention but not to limit the invention only to the following embodiments. The present invention may be implemented in various ways without departing from the gist of the invention.

[0018]

1. Combination of antisense oligomers

The present invention provides a combination of antisense oligomers or pharmaceutically acceptable salts

thereof, or hydrates thereof which cause simultaneous skipping of two or more numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA, the combination comprising:

(i) a first antisense oligomer or a pharmaceutically acceptable salt thereof, or a hydrate thereof, comprising:

a first unit oligomer comprising a base sequence complementary to a base sequence consisting of a base sequence of 11 bases in the upstream direction from the 3' end of the 44th intron and a base sequence of 69 bases in the downstream direction from the 5' end of the 45th exon in the human dystrophin pre-mRNA, or a partial base sequence thereof; and

a second unit oligomer comprising a base sequence complementary to a base sequence of from the 52nd to 75th bases in the upstream direction from the 3' end of the 44th intron in the human dystrophin pre-mRNA, or a partial base sequence thereof; and

(ii) a second antisense oligomer or a pharmaceutically acceptable salt thereof, or a hydrate thereof, comprising a base sequence complementary to a base sequence consisting of a base sequence of 33 bases in the upstream direction from the 3' end of the 54th intron and a base sequence of 53 bases in the downstream direction from the 5' end of the 55th exon in the human

dystrophin pre-mRNA, or a partial base sequence thereof. The foregoing combination is hereinafter referred to also as the "combination of the present invention".

[0019]

As used herein, the term "combination" means a substance combination, a pharmaceutical combination, an agent combination, and the like. In one embodiment, respective antisense oligomers in the combination of the present invention are comprised in one pharmaceutical composition, and simultaneously administered. In another embodiment, respective antisense oligomers in the combination of the present invention are comprised in a plurality of pharmaceutical compositions, and separately (simultaneously or sequentially) administered. As used herein, the term "simultaneously" administering a plurality of pharmaceutical compositions means that a plurality of pharmaceutical compositions are administered at the same time. As used herein, the term "sequentially" administering a plurality of pharmaceutical compositions means that these are administered at different times. Specifically, one pharmaceutical composition may be administered before or after another pharmaceutical composition, and an administration interval in this case is not limited, but may be, for example, a few minutes, a few hours, or a few days.

[0020]

Hereinafter, a first antisense oligomer or a pharmaceutically acceptable salt thereof, or a hydrate thereof, and a second antisense oligomer or a pharmaceutically acceptable salt thereof, or a hydrate thereof (and optionally a third antisense oligomer or a pharmaceutically acceptable salt thereof, or a hydrate thereof described herein) may be collectively referred to as the "antisense oligomer of the present invention". The antisense oligomer of the present invention may refer to each of antisense oligomers or pharmaceutically acceptable salts thereof, or hydrates thereof. A first antisense oligomer or a pharmaceutically acceptable salt thereof, or a hydrate thereof described above as (i) may be referred to as the "first antisense oligomer of the present invention", and a second antisense oligomer or a pharmaceutically acceptable salt thereof, or a hydrate thereof described above as (ii) may be referred to as the "second antisense oligomer of the present invention".

[0021]

As used herein, the term "gene" is intended to mean a genomic gene and also include cDNA, pre-mRNA and mRNA. Preferably, the gene is pre-mRNA. As used herein, the term "pre-mRNA" is an RNA molecule comprising an exon and an intron transcribed from a target gene on the genome and is a mRNA precursor.

[0022]

The human dystrophin pre-mRNA is an RNA molecule comprising an exon and an intron transcribed from the human dystrophin gene on the genome and is a mRNA precursor. Those skilled in the art can obtain information on the base sequence of the human dystrophin pre-mRNA by analogy from the genomic sequence of the human dystrophin gene (GenBank Accession Nos. NG_012232.1).

[0023]

In the human genome, the human dystrophin gene locates at locus Xp21.2. The human dystrophin gene has a size of about 3.0 Mbp and is the largest gene among known human genes. However, the coding regions of the human dystrophin gene are only about 14 kb, distributed as 79 exons throughout the human dystrophin gene (Roberts, RG, et al., Genomics, 16: 536-538 (1993)). The pre-mRNA, which is the transcript of the human dystrophin gene, undergoes splicing to generate mature mRNA of about 14 kb. The base sequence of mature mRNA of human wild-type dystrophin gene is known (GenBank Accession Nos. NM_004006).

[0024]

The first antisense oligomer of the present invention comprises the first unit oligomer and the second unit oligomer, or consists of the first unit oligomer and the second unit oligomer.

[0025]

The first unit oligomer targets a base sequence of 11 bases in the upstream direction from the 3' end of the 44th intron and a base sequence of 69 bases in the downstream direction from the 5' end of the 45th exon in the human dystrophin pre-mRNA. As used herein, the term "targeting" means that an intended base sequence is a base sequence complementary to the base sequence of a target region or a partial base sequence of the target sequence.

[0026]

A target sequence of the first unit oligomer can be indicated by the range of -11 bases to +69 bases when the boundary between the 3' end of intron 44 and the 5' end of exon 45 is defined as basing point 0, a base sequence region on the 5' side (upstream) from the basing point in the dystrophin gene is indicated by "-" (minus), and a base sequence region on the 3' side (downstream) therefrom is indicated by "+". In this respect, the region indicated by the range of -11 bases to -1 base belongs to intron 44, and the region indicated by the range of +1 base to +69 bases belongs to exon 45.

[0027]

The first unit oligomer comprises a base sequence complementary to a base sequence consisting of a base sequence of 11 bases in the upstream direction from the 3' end of the 44th intron and a base sequence of 69 bases in the downstream direction from the 5' end of the 45th

exon in the human dystrophin pre-mRNA, or a partial base sequence thereof.

[0028]

The second unit oligomer targets a base sequence of from the 52nd to 75th bases in the upstream direction from the 3' end of the 44th intron in the human dystrophin pre-mRNA.

[0029]

A target sequence of the second unit oligomer can be indicated by the range of -75 bases to -52 bases when the boundary between the 3' end of intron 44 and the 5' end of exon 45 is defined as basing point 0, a base sequence region on the 5' side (upstream) from the basing point in the dystrophin gene is indicated by "-" (minus), and a base sequence region on the 3' side (downstream) therefrom is indicated by "+". In this respect, the region indicated by the range of -75 bases to -52 bases belongs to intron 44.

[0030]

The second unit oligomer comprises a base sequence complementary to a base sequence of from the 52nd to 75th bases in the upstream direction from the 3' end of the 44th intron in the human dystrophin pre-mRNA, or a partial base sequence thereof.

[0031]

The second antisense oligomer of the present invention targets a base sequence consisting of a base

sequence of 33 bases in the upstream direction from the 3' end of the 54th intron and a base sequence of 53 bases in the downstream direction from the 5' end of the 55th exon in the human dystrophin pre-mRNA.

[0032]

A target sequence of the second antisense oligomer can be indicated by the range of -33 bases to +53 bases when the boundary between the 3' end of intron 54 and the 5' end of exon 55 is defined as basing point 0, a base sequence region on the 5' side (upstream) from the basing point in the dystrophin gene is indicated by "-" (minus), and a base sequence region on the 3' side (downstream) therefrom is indicated by "+". In this respect, the region indicated by the range of -33 bases to -1 base belongs to intron 54, and the region indicated by the range of +1 base to +53 bases belongs to exon 55.

[0033]

The second antisense oligomer comprises a base sequence complementary to a base sequence of 33 bases in the upstream direction from the 3' end of the 54th intron and a base sequence of 53 bases in the downstream direction from the 5' end of the 55th exon in the human dystrophin pre-mRNA, or a partial base sequence thereof.

[0034]

The combination of the present invention may further comprise, in addition to the first antisense oligomer and the second antisense oligomer of the present invention, a

third antisense oligomer or a pharmaceutically acceptable salt thereof, or a hydrate thereof, comprising a base sequence complementary to a base sequence consisting of a base sequence of 23 bases in the upstream direction from the 3' end of the 45th exon, and a base sequence of 73 bases in the downstream direction from the 5' end of the 45th intron in the human dystrophin pre-mRNA, or a partial base sequence thereof. Hereinafter, a third antisense oligomer or a pharmaceutically acceptable salt thereof, or a hydrate thereof is referred to also as the "third antisense oligomer of the present invention".

[0035]

The third antisense oligomer of the present invention targets a base sequence consisting of a base sequence of 23 bases in the upstream direction from the 3' end of the 45th exon and a base sequence of 73 bases in the downstream direction from the 5' end of the 45th intron in the human dystrophin pre-mRNA.

[0036]

A target sequence of the third antisense oligomer can be indicated by the range of -23 bases to +73 bases when the boundary between the 3' end of exon 45 and the 5' end of intron 46 is defined as basing point 0, a base sequence region on the 5' side (upstream) from the basing point in the dystrophin gene is indicated by "-" (minus), and a base sequence region on the 3' side (downstream) therefrom is indicated by "+". In this respect, the

region indicated by the range of -23 bases to -1 base belongs to exon 45, and the region indicated by the range of +1 base to +73 bases belongs to intron 46.

[0037]

The third antisense oligomer comprises a base sequence complementary to a base sequence consisting of a base sequence of 23 bases in the upstream direction from the 3' end of the 45th exon and a base sequence of 73 bases in the downstream direction from the 5' end of the 45th intron in the human dystrophin pre-mRNA, or a partial base sequence thereof.

[0038]

Specific examples of surrounding sequences of the target sequences of the first unit oligomer and the second unit oligomer comprised in the first antisense oligomer, the second antisense oligomer, and the third antisense oligomer of the present invention include those shown in Table 1 below.

[0039]

[Table 1]

Table 1

Target surrounding sequence	
Range of -600 to +69 bases based on basing point of 3' end of intron 44 (including H45_ (-75)-(-52): range of -75 to -52 bases based on basing point of 3' end of intron 44, and H45_(-11)-(69): range of -11 to +69 bases based on basing point of 3' end of intron 44)	SEQ ID NO:
TCTTGATGGGATGCTCCTGAAAGCAATTAATTCTCAGTTTTTTGTGGCTTCTAATGCAAAATACATTGACGCAGACAGAATTTGAA ATGAATTTTCTTCTAATATAGCAATTAATTTTATTTAAATATCTCTAGAGTTTTTTTTTAATACTGTGACTAACCTATGTTTGTTC TTTTTCACCTCTCGTATCCACGATCACTAAGAAACCCAAATACTTTGTTCATGTTTAAATTTTACAACATTTCATAGACTATTAAA CATGGAACATCCTTGTGGGGACAAGAAATCGAATTTGCTCTTGAAAAGGTTTCCAACTAATTGATTTGTAGGACATTATAACATCC TCTAGCTGACAAGCTTACAAAAATAAAAACTGGAGCTAACCGAGAGGGTGCTTTTTTCCCTGACACATAAAAGGTGTCTTTCTGTC TTGTATCCTTTGGATATGGGCATGTCAGTTTCATAGGGAAATTTTCACATGGAGCTTTTGTATTTCTTTCTTTGCCAGTACAACTG CATGTGGTAGCACACTGTTTAATCTTTTCTCAAATAAAAAGACATGGGGCTTCATTTTTGTTTTGCCTTTTTGGTATCTTACAGGA ACTCCAGGATGGCATTGGGCAGCGGCAAACTGTTGTCAGAACATTGAATGCAACTGGGGAAGAAATA	5091
Ragne of -23 to +400 bases based on basing point of 5' end of intron 45 (including H45_(154)-(249): range of -23 to +73 bases based on basing point of 5' end of intron 45)	
CAGCTGTCAGACAGAAAAAAGAGGTAGGGCGACAGATCTAATAGGAATGAAAACATTTTAGCAGACTTTTTAAGCTTTCTTTAGAA GAATATTTCATGAGAGATTATAAGCAGGGTGAAAGGCACTAACATTAAAGAACCTATCAACCATTAATCAACAGCAGTAAAGAAAT TTTTTATTTCTTTTTTTCATATACTAAAATATATACTTGTGGCTAGTTAGTGGTTTTCTGCTATTTTAAACTTGAAGTTTGCTTTA AAAATCACCCATGATTGCTTAAAGGTGAATATCTTCAATATATTTTAACTTCAACAAGCTGAATCTCAGTTGTTTTTCAAGAAGAT TTTAGAAAGCAATTATAAATGATTGTTTTGTAGGAAAGACAGATCTTTGCTTAGTTTTAAAAATAGCTATGAATATGAC	5092
Range of -400 to +53 bases based on basing point of 3' end of intron 54 (including H55_(-33)-(+53): range of -33 to +53 bases based on basing point of 3' end of intron 54)	
TCTCAAATTTGGCAGTATATTAAAAATAAGCTTTCAAAATTGACCAACAAAAACTACAAAATTGAAAAAAAGGTACTTTGAACTTT CACATGTTCAAATATATGTATATATATTTCACATATATATATGAAACCTCCTCTGTGGAGAGGGGTTTATAGAAATCTGTAATTGT CATTCTTGCATGCCTTCCCCCATACAAACGCCTTTAAGTTAAATAAAAATGAAAGTAAATAGACTGCACAATATTATAGTTGTTGC TTAAAGGAAGAGCTGTAGCAACAACTCACCCCATTGTTGGTATATTACAATTTAGTTCCTCCATCTTTCTCTTTTTATGGAGTTCA CTAGGTGCACCATTCTGATATTTAATAATTGCATCTGAACATTTGGTCCTTTGCAGGGTGAGTGAGCGAGAGGCTGCTTTGGAAGA AACTCATAGATTACTGCAACAGT	5093

[0040]

Specific examples of the target sequences of the first unit oligomer and the second unit oligomer comprised in the first antisense oligomer, the second antisense oligomer, and the third antisense oligomer of the present invention include those shown in Table 2 below.

[Table 2]

Table 2

Target sequence	SEQ ID NO:
H45_(-75)-(-52) (range of -75 to -52 bases based on basing point of 3' end of intron 44) GCACACTGTTTAATCTTTTCTCAA	5094
H45_(-11)-(+69) (range of -11 to +69 bases based on basing point of 3' end of intron 44) GTATCTTACAGGAACTCCAGGATGGCATTGGGCAGCGGCAAACTGTTGTCAGAACATTGAATGCAACTGGGGAAGAAATA	5095
H45_(+154)-(+249) (range of -23 to +73 bases based on basing point of 5' end of intron 45) CAGCTGTCAGACAGAAAAAAGAGGTAGGGCGACAGATCTAATAGGAATGAAAACATTTTAGCAGACTTTTTAAGCTTTCTTTAGAAGAATATTTCA	5096
H55_(-33)-(+53) (range of -33 to +53 bases based on basing point of 3' end of intron 54) AATAATTGCATCTGAACATTTGGTCCTTTGCAGGGTGAGTGAGCGAGAGGCTGCTTTGGAAGAAACTCATAGATTACTGCAACAGT	5097

[0041]

As used herein, thymine "T" and uracil "U" are interchangeable with each other. Neither "T" nor "U" essentially influences the exon skipping activity of the antisense oligomer of the present invention. Therefore, as used herein, identical base sequences except for "T" or "U" are represented by the same SEQ ID NO. In the tables below, "U" may be described as "T" even in the base sequence of pre-mRNA. Those skilled in the art can understand an RNA sequence by appropriately replacing "T" with "U".

[0042]

Herein, a target base sequence is described as "Ha_b-c".

[0043]

"Ha" represents the ath exon of the human dystrophin gene, "b" represents the 5'-terminal base of the target base sequence, and "c" represents the 3'-terminal base of the target base sequence.

When "b" and "c" are positive integers, "b" and "c" each represent a base number in the downstream direction when the 5'-terminal base of the ath exon is counted as

the 1st base. On the other hand, when "b" and "c" are negative integers, "b" and "c" each represent a base number in the upstream direction when the 3'-terminal base of the (a - 1)th intron is counted as the 1st base.

[0044]

For example, "H55_(-75)-(-52)" means a base sequence in which the 5' end of the target base sequence is the 75th base in the upstream direction from the 3' end of the 54th intron and the 3' end of the target base sequence is the 52nd base in the upstream direction from the 3' end of the 54th intron.

[0045]

The surrounding sequence of the target region or the target sequence of the antisense oligomer of the present invention includes both wild (e.g., the base sequences represented by SEQ ID NOs: 5021 to 5027) and mutant types in relation to the human dystrophin pre-mRNA. Such a mutant type has, for example, any one base sequence selected from the group consisting of base sequences (B0) and (B1) to (B16) below:

(B0) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027;

(B1) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting

of SEQ ID NOs: 5021 to 5027, and has a length within ±15% of the length of the any one base sequence selected;

(B2) a base sequence that has at least 86% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027, and has a length within ±14% of the length of the any one base sequence selected;

(B3) a base sequence that has at least 87% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027, and has a length within ±13% of the length of the any one base sequence selected;

(B4) a base sequence that has at least 88% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027, and has a length within ±12% of the length of the any one base sequence selected;

(B5) a base sequence that has at least 89% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027, and has a length within ±11% of the length of the any one base sequence selected;

(B6) a base sequence that has at least 90% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027, and has a length within ±10% of the length of the any one base sequence selected;

(B7) a base sequence that has at least 91% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027, and has a length within ±9% of the length of the any one base sequence selected;

(B8) a base sequence that has at least 92% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027, and has a length within ±8% of the length of the any one base sequence selected;
(B9) a base sequence that has at least 93% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027, and has a length within ±7% of the length of the any one base sequence selected;
(B10) a base sequence that has at least 94% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027, and has a length within ±6% of the length of the any one base sequence selected;
(B11) a base sequence that has at least 95% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027, and has a length within ±5% of the length of the any one base sequence selected;
(B12) a base sequence that has at least 96% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027, and has a length within ±4% of the length of the any one base sequence selected;
(B13) a base sequence that has at least 97% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027, and has a length within ±3% of the length of the any one base sequence selected;
(B14) a base sequence that has at least 98% identity with any one base sequence selected from the group consisting

of SEQ ID NOs: 5021 to 5027, and has a length within ±2% of the length of the any one base sequence selected;
(B15) a base sequence that has at least 99% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027, and has a length within ±1% of the length of the any one base sequence selected; and
(B16) a base sequence that has at least 99.5% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027, and has a length within ±0.5% of the length of the any one base sequence selected.

[0046]

As used herein, the term "base sequence that hybridizes under stringent conditions" refers to, for example, a base sequence obtained by colony hybridization, plaque hybridization, Southern hybridization or the like, using as a probe all or part of a base sequence complementary to, *e.g.*, any one base sequence selected from the group consisting of SEQ ID NOs: 5021 to 5027. The hybridization method which may be used includes methods described in, for example, "Sambrook & Russell, Molecular Cloning: A Laboratory Manual Vol. 3, Cold Spring Harbor, Laboratory Press, 2001," "Ausubel, Current Protocols in Molecular Biology, John Wiley & Sons, 1987-1997," etc.

[0047]

As used herein, the term "complementary base sequence" is not limited to a base sequence that forms Watson-Crick pairs with an intended base sequence, and also includes a base sequence that forms wobble base pairs therewith. Herein, the Watson-Crick pair means a base pair that forms a hydrogen bond between adenine and thymine, between adenine and uracil, or between guanine and cytosine, and the wobble base pair means a base pair that forms a hydrogen bond between guanine and uracil, between inosine and uracil, between inosine and adenine, or between inosine and cytosine. The term "complementary base sequence" does not have to have 100% complementarity with the intended base sequence and may contain, for example, 1, 2, 3, 4, or 5 noncomplementary bases based on the intended base sequence or may be a base sequence shorter by 1 base, 2 bases, 3 bases, 4 bases, or 5 bases than the intended base sequence.

[0048]

As used herein, the term "stringent conditions" may be any of low stringent conditions, moderate stringent conditions or high stringent conditions. The term "low stringent condition" is, for example, 5 × SSC, 5 × Denhardt's solution, 0.5% SDS, 50% formamide at 32°C. The term "moderate stringent condition" is, for example, 5 × SSC, 5 × Denhardt's solution, 0.5% SDS, 50% formamide at 42°C, or 5 × SSC, 1% SDS, 50 mM Tris-HCl (pH 7.5), 50% formamide at 42°C. The term "high stringent condition"

is, for example, 5 × SSC, 5 × Denhardt's solution, 0.5% SDS, 50% formamide at 50°C, or 0.2 × SSC, 0.1% SDS at 65°C. Under these conditions, base sequences with higher homology are expected to be obtained efficiently at higher temperatures, although multiple factors are involved in hybridization stringency including temperature, probe concentration, probe length, ionic strength, time, salt concentration and others, and those skilled in the art may approximately select these factors to achieve similar stringency.

When commercially available kits are used for hybridization, for example, an Alkphos Direct Labelling and Detection System (GE Healthcare) may be used. In this case, according to the attached protocol, after cultivation with a labeled probe overnight, the membrane can be washed with a primary wash buffer containing 0.1% (w/v) SDS at 55°C, thereby detecting hybridization. Alternatively, when the probe is labeled with digoxigenin (DIG) using a commercially available reagent (*e.g.*, a PCR Labelling Mix (Roche Diagnostics), etc.) in producing a probe based on all or part of the complementary sequence to any one base sequence selected from the group consisting of SEQ ID NOs: 233 to 256, 341 to 369, and 385 to 389, hybridization can be detected with a DIG Nucleic Acid Detection Kit (Roche Diagnostics) or the like.

[0049]

The identity between base sequences may be determined using algorithm BLAST (Basic Local Alignment Search Tool) by Karlin and Altschul (Proc. Natl. Acad. Sci. USA 872264-2268, 1990; Proc. Natl. Acad. Sci. USA 90: 5873, 1993). Programs called BLASTN and BLASTX based on the BLAST algorithm have been developed (Altschul SF, et al: J. Mol. Biol. 215: 403, 1990). When a base sequence is sequenced using BLASTN, the parameters are, for example, score = 100 and wordlength = 12. When BLAST and Gapped BLAST programs are used, the default parameters for each program are employed.

[0050]

The antisense oligomer of the present invention comprises a base sequence complementary to a base sequence of the target regions of the present invention, or a partial base sequence thereof. The term "partial" means a region, except for the full length, of the target regions, i.e., a partial region of the target regions. The partial region may be 10 to 60 bases long, 10 to 55 bases long, 10 to 50 bases long, 10 to 45 bases long, 10 to 40 bases long, 10 to 35 bases long, 10 to 30 bases long, 10 to 25 bases long, 15 to 60 bases long, 15 to 55 bases long, 15 to 50 bases long, 15 to 45 bases long, 15 to 40 bases long, 15 to 35 bases long, 15 to 30 bases long, 15 to 25 bases long, 16 to 60 bases long, 16 to 55 bases long, 16 to 50 bases long, 16 to 45 bases long, 16 to 40 bases long, 16 to 35 bases long, 16 to 30 bases

long, 16 to 25 bases long, 17 to 60 bases long, 17 to 55 bases long, 17 to 50 bases long, 17 to 45 bases long, 17 to 40 bases long, 17 to 35 bases long, 17 to 30 bases long, 17 to 25 bases long, 18 to 60 bases long, 18 to 55 bases long, 18 to 50 bases long, 18 to 45 bases long, 18 to 40 bases long, 18 to 35 bases long, 18 to 30 bases long, 18 to 25 bases long, 19 to 60 bases long, 19 to 55 bases long, 19 to 50 bases long, 19 to 45 bases long, 19 to 40 bases long, 19 to 35 bases long, 19 to 30 bases long, 19 to 25 bases long, 20 to 60 bases long, 20 to 55 bases long, 20 to 50 bases long, 20 to 45 bases long, 20 to 40 bases long, 20 to 35 bases long, 20 to 30 bases long, 20 to 25 bases long, 15 to 30 bases long, 15 to 29 bases long, 15 to 28 bases long, 15 to 27 bases long, 15 to 26 bases long, 15 to 25 bases long, 15 to 24 bases long, 15 to 23 bases long, 15 to 22 bases long, 15 to 21 bases long, 15 to 20 bases long, 15 to 19 bases long, 15 to 18 bases long, 16 to 30 bases long, 16 to 29 bases long, 16 to 28 bases long, 16 to 27 bases long, 16 to 26 bases long, 16 to 25 bases long, 16 to 24 bases long, 16 to 23 bases long, 16 to 22 bases long, 16 to 21 bases long, 16 to 20 bases long, 16 to 19 bases long, 16 to 18 bases long, 17 to 30 bases long, 17 to 29 bases long, 17 to 28 bases long, 17 to 27 bases long, 17 to 26 bases long, 17 to 25 bases long, 17 to 24 bases long, 17 to 23 bases long, 17 to 22 bases long, 17 to 21 bases long, 17 to 20 bases long, 17 to 19 bases long, 17 to 18 bases

long, 18 to 30 bases long, 18 to 29 bases long, 18 to 28 bases long, 18 to 27 bases long, 18 to 26 bases long, 18 to 25 bases long, 18 to 24 bases long, 18 to 23 bases long, 18 to 22 bases long, 18 to 21 bases long, 18 to 20 bases long, 18 to 19 bases long, 19 to 30 bases long, 19 to 29 bases long, 19 to 28 bases long, 19 to 27 bases long, 19 to 26 bases long, 19 to 25 bases long, 19 to 24 bases long, 19 to 23 bases long, 19 to 22 bases long, 19 to 21 bases long, 19 to 20 bases long, 20 to 30 bases long, 20 to 29 bases long, 20 to 28 bases long, 20 to 27 bases long, 20 to 26 bases long, 20 to 25 bases long, 20 to 24 bases long, 20 to 23 bases long, 20 to 22 bases long, 20 to 21 bases long, 5 to 25 bases long, 5 to 24 bases long, 5 to 23 bases long, 5 to 22 bases long, 5 to 21 bases long, 5 to 20 bases long, 5 to 19 bases long, 5 to 18 bases long, 5 to 17 bases long, 5 to 16 bases long, 5 to 15 bases long, 5 to 14 bases long, 5 to 13 bases long, 5 to 12 bases long, 7 to 25 bases long, 7 to 24 bases long, 7 to 23 bases long, 7 to 22 bases long, 7 to 21 bases long, 7 to 20 bases long, 7 to 19 bases long, 7 to 18 bases long, 7 to 17 bases long, 7 to 16 bases long, 7 to 15 bases long, 7 to 14 bases long, 7 to 13 bases long, 7 to 12 bases long, 9 to 25 bases long, 9 to 24 bases long, 9 to 23 bases long, 9 to 22 bases long, 9 to 21 bases long, 9 to 20 bases long, 9 to 19 bases long, 9 to 18 bases long, 9 to 17 bases long, 9 to 16 bases long, 9 to 15 bases long, 9 to 14 bases long, 9 to 13 bases

long, 9 to 12 bases long, 10 to 25 bases long, 10 to 24 bases long, 10 to 23 bases long, 10 to 22 bases long, 10 to 21 bases long, 10 to 20 bases long, 10 to 19 bases long, 10 to 18 bases long, 10 to 17 bases long, 10 to 16 bases long, 10 to 15 bases long, 10 to 14 bases long, 10 to 13 bases long, 10 to 12 bases long, 60 bases long, 59 bases long, 58 bases long, 57 bases long, 56 bases long, 55 bases long, 54 bases long, 53 bases long, 52 bases long, 51 bases long, 50 bases long, 49 bases long, 48 bases long, 47 bases long, 46 bases long, 45 bases long, 44 bases long, 43 bases long, 42 bases long, 41 bases long, 40 bases long, 39 bases long, 38 bases long, 37 bases long, 36 bases long, 35 bases long, 34 bases long, 33 bases long, 32 bases long, 31 bases long, 30 bases long, 29 bases long, 28 bases long, 27 bases long, 26 bases long, 25 bases long, 24 bases long, 23 bases long, 22 bases long, 21 bases long, 20 bases long, 19 bases long, 18 bases long, 17 bases long, 16 bases long, 15 bases long, 14 bases long, 13 bases long, 12 bases long, 11 bases long, 10 bases long, 9 bases long, 8 bases long, 7 bases long, 6 bases long, or 5 bases long, but not limited thereto. These lengths may be increased or decreased by 1, 2, or 3 bases.

[0051]

The antisense oligomer of the present invention has an activity to cause simultaneous skipping of any two or more numerically consecutive exons selected from the

group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA. As used herein, such skipping of two or more numerically consecutive exons from objective pre-mRNA is referred to as "multi-exon skipping" or "multi-skipping", and this activity is referred to as "multi-exon skipping activity" or "multi-skipping activity".

[0052]

As used herein, the term "cause simultaneous skipping" of two or more numerically consecutive exons includes not only removal of the respective exons from pre-mRNA at completely the same timings but also sequential removal of the respective exons within a period from pre-mRNA to mature mRNA. Specifically, the term "cause simultaneous skipping" of two or more numerically consecutive exons refers to removal of a plurality of (two or more) numerically consecutive exons from pre-mRNA.

[0053]

As used herein, the term "two or more numerically consecutive exons" means a plurality of exons that increase one by one in exon number among exons (the total number of exons is referred to as Texon) contained in objective pre-mRNA. The exon number means a number assigned to exons in order from the 5' end to the 3' end with an exon at the most upstream position of pre-mRNA defined as the first exon, followed by the second, the

third, ... In the case of skipping of two or more numerically consecutive exons in a certain gene, its exon numbers a_1, ..., a_j can be represented by the sequence $\{a_j\}$. The general term a_j in the sequence $\{a_j\}$ is represented by the expression below:

[Expression 1]

$a_j = m + (j - 1)$

wherein m is a given natural number that satisfies $1 \leq m \leq (Texon - 1)$, and j is a natural number that satisfies $2 \leq (m + j) \leq Texon + 1$.

When the objective pre-mRNA is, for example, human dystrophin pre-mRNA, Texon is 79.

In a certain aspect, j is a given natural number selected from 1 to 11. In another aspect, j is 11, j is 10, j is 9, j is 8, j is 7, j is 6, j is 5, j is 4, j is 3, j is 2, or j is 1.

[0054]

Herein, the any two or more numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon mean a plurality of exons that increase one by one in exon number among 11 exons from the 45th exon to the 55th exon contained in pre-mRNA. The exon number means a number assigned to exons in order from the 5' end to the 3' end with an exon at the most upstream position of pre-mRNA defined as the first exon, followed by the second, the third, ..., and the 79th exons among 79 exons contained in human dystrophin pre-mRNA. An

intron is numbered as the same number as that of an exon positioned on the 5' side thereof. Specifically, the 45th intron is flanked by the 45th exon positioned on the 5' side thereof and the 46th exon positioned on the 3' side thereof. As used herein, the "nth" exon or intron means the nth exon or intron counted from the 5' end toward the 3' end in pre-mRNA.

[0055]

Table 3 shows combinations of exons included in the any two or more numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon.

[0056]

[Table 3]

Table 3

Combination	Exons included	Combination	Exons included
Combination 1	45、46	Combination 29	48～50
Combination 2	45～47	Combination 30	48～51
Combination 3	45～48	Combination 31	48～52
Combination 4	45～49	Combination 32	48～53
Combination 5	45～50	Combination 33	48～54
Combination 6	45～51	Combination 34	48～55
Combination 7	45～52	Combination 35	49、50
Combination 8	45～53	Combination 36	49～51
Combination 9	45～54	Combination 37	49～52
Combination 10	45～55	Combination 38	49～53
Combination 11	46、47	Combination 39	49～54
Combination 12	46～48	Combination 40	49～55
Combination 13	46～49	Combination 41	50、51
Combination 14	46～50	Combination 42	50～52
Combination 15	46～51	Combination 43	50～53
Combination 16	46～52	Combination 44	50～54
Combination 17	46～53	Combination 45	50～55
Combination 18	46～54	Combination 46	51、52
Combination 19	46～55	Combination 47	51～53
Combination 20	47、48	Combination 48	51～54
Combination 21	47～49	Combination 49	51～55
Combination 22	47～50	Combination 50	52、53
Combination 23	47～51	Combination 51	52～54
Combination 24	47～52	Combination 52	52～55
Combination 25	47～53	Combination 53	53、54
Combination 26	47～54	Combination 54	53～55
Combination 27	47～55	Combination 55	54、55
Combination 28	48、49		

[0057]

Among the combinations of exons described in Table 3, for example, the combination 1, 2, 3, 4, 6, 8, 10, 18, 20, 21, 23, 25, 27, 28, 30, 32, 34, 36, 38, 40, 41, 43, 45, 46, 50, 52, or 55 is a skipping pattern expected to exert higher therapeutic effects on DMD. Multi-exon skipping in such a combination is expected to exert therapeutic effects on more patients with DMD. In one embodiment, the combination of the present invention

causes skipping of all exons from the 45th exon to the 55th exon in human dystrophin pre-mRNA.

[0058]

The any two or more numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon may include a plurality of groups of consecutive exons and may be, for example, but not limited to, (example 1) exons 45 and 46 (first exon group) and exons 48 to 53 (second exon group), or (example 2) exons 46 and 47 (first exon group), exons 49 and 50 (second exon group), and exons 52 to 54 (third exon group).

[0059]

In the present invention, the term "activity to cause skipping" (i.e., multi-skipping activity) means, when human dystrophin pre-mRNA is taken as an example, an activity to produce human dystrophin mRNA having deletion of any two or more numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in the human dystrophin pre-mRNA.

In other words, this activity means that by binding of the antisense oligomer of the present invention to a target site in human dystrophin pre-mRNA, the 5'-terminal nucleotide of an exon immediately downstream of the exons to be deleted is linked to the 3'-terminal nucleotide of an exon immediately upstream of the exons to be deleted when the pre-mRNA undergoes splicing, thus resulting in

formation of mature mRNA which is free of codon frame shift (i.e., mature mRNA having deletion of the exons without frame shift).

[0060]

The antisense oligomer of the present invention exhibits a multi-skipping activity under physiological conditions. The term "under physiological conditions" refers to conditions set to mimic the *in vivo* environment in terms of pH, salt composition and temperature. The conditions are, for example, 25 to 40°C, preferably 37°C, pH 5 to 8, preferably pH 7.4 and 150 mM of sodium chloride concentration.

[0061]

Whether multi-skipping is caused or not can be confirmed by introducing the combination of the present invention into a dystrophin expression cell (e.g., human rhabdomyosarcoma cells), amplifying the region surrounding exons 45 to 55 of mRNA of the human dystrophin gene from the total RNA of the dystrophin expression cell by RT-PCR, and performing nested PCR or sequence analysis on the PCR amplified product. The multi-skipping efficiency can be determined as follows. The mRNA for the human dystrophin gene is collected from test cells; in the mRNA, the polynucleotide level "A" of the band where any two or more numerically consecutive exons among exons 45 to 55 are skipped, the polynucleotide level "B" of the band where any one exon

among exons 45 to 55 is skipped, and the polynucleotide level "C" of the band where no skipping is caused are measured. Using these measurement values of "A", "B", and "C", the efficiency is calculated by the following equation.

Skipping efficiency (%) = A / (A + B + C) × 100

[0062]

For example, the multi-skipping efficiency of exons 45 to 55 can be determined by using a forward primer for exon 44 and a reverse primer for exon 56 to measure the polynucleotide level "A" of the band where exons 45 to 55 are multi-skipped, using the forward primer for exon 44 and a reverse primer for exon 46 to measure the polynucleotide level "B" of the band where exon 45 is single-skipped, and using the forward primer for exon 44 and the reverse primer for exon 46 to measure the polynucleotide level "C" of the band where no skipping is caused, followed by calculation by the equation using these measurement values of "A", "B", and "C".

[0063]

The number of exons to be deleted in human dystrophin mRNA by the antisense oligomer of the present invention is 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11. This is referred to as a deletion pattern, and various deletion patterns may exist in admixture in results obtained in one skipping experiment or skipping treatment. For example, mRNA admixture having deletion of 2, 3, 4, 5, 6,

7, 8, 9, 10, or 11 exons is obtained by introducing the antisense oligomer of the present invention to cells expressing human dystrophin pre-mRNA, and collecting its mRNA.

[0064]

In a certain aspect, the term "activity to cause skipping" can be defined as (C1) to (C10) below.

[0065]

(C1) Any two numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA are skipped with the efficiency of 5% or higher, 10% or higher, 15% or higher, 20% or higher, 25% or higher, 30% or higher, 35% or higher, 40% or higher, 45% or higher, 50% or higher, 55% or higher, 60% or higher, 65% or higher, 70% or higher, 75% or higher, 80% or higher, 85% or higher, 90% or higher, or 95% or higher.

Herein, the two numerically consecutive exons may be the 45th and the 46th exons, the 46th and the 47th exons, the 47th and the 48th exons, the 48th and the 49th exons, the 49th and the 50th exons, the 50th and the 51st exons, the 51st and the 52nd exons, the 52nd and the 53rd exons, the 53rd and the 54th exons, or the 54th and the 55th exons.

[0066]

(C2) Any three numerically consecutive exons selected from the group consisting of the 45th exon to

the 55th exon in human dystrophin pre-mRNA are skipped with the efficiency of 5% or higher, 10% or higher, 15% or higher, 20% or higher, 25% or higher, 30% or higher, 35% or higher, 40% or higher, 45% or higher, 50% or higher, 55% or higher, 60% or higher, 65% or higher, 70% or higher, 75% or higher, 80% or higher, 85% or higher, 90% or higher, or 95% or higher.

Herein, the three numerically consecutive exons may be the 45th to the 47th exons, the 46th to the 48th exons, the 47th to the 49th exons, the 48th to the 50th exons, the 49th to the 51st exons, the 50th to the 52nd exons, the 51st to the 53rd exons, the 52nd to the 54th exons, or the 53rd to the 55th exons.

[0067]

(C3) Any four numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA are skipped with the efficiency of 5% or higher, 10% or higher, 15% or higher, 20% or higher, 25% or higher, 30% or higher, 35% or higher, 40% or higher, 45% or higher, 50% or higher, 55% or higher, 60% or higher, 65% or higher, 70% or higher, 75% or higher, 80% or higher, 85% or higher, 90% or higher, or 95% or higher.

Herein, the four numerically consecutive exons may be the 45th to the 48th exons, the 46th to the 49th exons, the 47th to the 50th exons, the 48th to the 51st exons, the 49th to the 52nd exons, the 50th to the 53rd

exons, the 51st to the 54th exons, or the 52nd to the 55th exons.

[0068]

(C4) Any five numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA are skipped with the efficiency of 5% or higher, 10% or higher, 15% or higher, 20% or higher, 25% or higher, 30% or higher, 35% or higher, 40% or higher, 45% or higher, 50% or higher, 55% or higher, 60% or higher, 65% or higher, 70% or higher, 75% or higher, 80% or higher, 85% or higher, 90% or higher, or 95% or higher.

Herein, the five numerically consecutive exons may be the 45th to the 49th exons, the 46th to the 50th exons, the 47th to the 51st exons, the 48th to the 52nd exons, the 49th to the 53rd exons, the 50th to the 54th exons, or the 51st to the 55th exons.

[0069]

(C5) Any six numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA are skipped with the efficiency of 5% or higher, 10% or higher, 15% or higher, 20% or higher, 25% or higher, 30% or higher, 35% or higher, 40% or higher, 45% or higher, 50% or higher, 55% or higher, 60% or higher, 65% or higher, 70% or higher, 75% or higher, 80% or higher, 85% or higher, 90% or higher, or 95% or higher.

Herein, the six numerically consecutive exons may be the 45th to the 50th exons, the 46th to the 51st exons, the 47th to the 52nd exons, the 48th to the 53rd exons, the 49th to the 54th exons, or the 50th to the 55th exons.

[0070]

(C6) Any seven numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA are skipped with the efficiency of 5% or higher, 10% or higher, 15% or higher, 20% or higher, 25% or higher, 30% or higher, 35% or higher, 40% or higher, 45% or higher, 50% or higher, 55% or higher, 60% or higher, 65% or higher, 70% or higher, 75% or higher, 80% or higher, 85% or higher, 90% or higher, or 95% or higher.

Herein, the seven numerically consecutive exons may be the 45th to the 51st exons, the 46th to the 52nd exons, the 47th to the 53rd exons, the 48th to the 54th exons, or the 49th to the 55th exons.

[0071]

(C7) Any eight numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA are skipped with the efficiency of 5% or higher, 10% or higher, 15% or higher, 20% or higher, 25% or higher, 30% or higher, 35% or higher, 40% or higher, 45% or higher, 50% or higher, 55% or higher, 60% or higher, 65% or higher, 70%

or higher, 75% or higher, 80% or higher, 85% or higher, 90% or higher, or 95% or higher.

Herein, the eight numerically consecutive exons may be the 45th to the 52nd exons, the 46th to the 53rd exons, the 47th to the 54th exons, or the 48th to the 55th exons.

[0072]

(C8) Any nine numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA are skipped with the efficiency of 5% or higher, 10% or higher, 15% or higher, 20% or higher, 25% or higher, 30% or higher, 35% or higher, 40% or higher, 45% or higher, 50% or higher, 55% or higher, 60% or higher, 65% or higher, 70% or higher, 75% or higher, 80% or higher, 85% or higher, 90% or higher, or 95% or higher.

Herein, the nine numerically consecutive exons may be the 45th to the 53rd exons, the 46th to the 54th exons, or the 47th to the 55th exons.

[0073]

(C9) Any ten numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA are skipped with the efficiency of 5% or higher, 10% or higher, 15% or higher, 20% or higher, 25% or higher, 30% or higher, 35% or higher, 40% or higher, 45% or higher, 50% or higher, 55% or higher, 60% or higher, 65% or higher, 70% or higher,

75% or higher, 80% or higher, 85% or higher, 90% or higher, or 95% or higher.

Herein, the ten numerically consecutive exons may be the 45th to the 54th exons, or the 46th to the 55th exons.

[0074]

(C10) Eleven numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA are skipped with the efficiency of 5% or higher, 10% or higher, 15% or higher, 20% or higher, 25% or higher, 30% or higher, 35% or higher, 40% or higher, 45% or higher, 50% or higher, 55% or higher, 60% or higher, 65% or higher, 70% or higher, 75% or higher, 80% or higher, 85% or higher, 90% or higher, or 95% or higher.

Herein, the eleven numerically consecutive exons may be the 45th to the 55th exons.

[0075]

The antisense oligomer of the present invention may be 10 to 60 bases long, 10 to 55 bases long, 10 to 50 bases long, 10 to 45 bases long, 10 to 40 bases long, 10 to 35 bases long, 10 to 30 bases long, 10 to 25 bases long, 15 to 60 bases long, 15 to 55 bases long, 15 to 50 bases long, 15 to 45 bases long, 15 to 40 bases long, 15 to 35 bases long, 15 to 30 bases long, 15 to 25 bases long, 16 to 60 bases long, 16 to 55 bases long, 16 to 50 bases long, 16 to 45 bases long, 16 to 40 bases long, 16

to 35 bases long, 16 to 30 bases long, 16 to 25 bases long, 17 to 60 bases long, 17 to 55 bases long, 17 to 50 bases long, 17 to 45 bases long, 17 to 40 bases long, 17 to 35 bases long, 17 to 30 bases long, 17 to 25 bases long, 18 to 60 bases long, 18 to 55 bases long, 18 to 50 bases long, 18 to 45 bases long, 18 to 40 bases long, 18 to 35 bases long, 18 to 30 bases long, 18 to 25 bases long, 19 to 60 bases long, 19 to 55 bases long, 19 to 50 bases long, 19 to 45 bases long, 19 to 40 bases long, 19 to 35 bases long, 19 to 30 bases long, 19 to 25 bases long, 20 to 60 bases long, 20 to 55 bases long, 20 to 50 bases long, 20 to 45 bases long, 20 to 40 bases long, 20 to 35 bases long, 20 to 30 bases long, 20 to 25 bases long, 15 to 30 bases long, 15 to 29 bases long, 15 to 28 bases long, 15 to 27 bases long, 15 to 26 bases long, 15 to 25 bases long, 15 to 24 bases long, 15 to 23 bases long, 15 to 22 bases long, 15 to 21 bases long, 15 to 20 bases long, 15 to 19 bases long, 15 to 18 bases long, 16 to 30 bases long, 16 to 29 bases long, 16 to 28 bases long, 16 to 27 bases long, 16 to 26 bases long, 16 to 25 bases long, 16 to 24 bases long, 16 to 23 bases long, 16 to 22 bases long, 16 to 21 bases long, 16 to 20 bases long, 16 to 19 bases long, 16 to 18 bases long, 17 to 30 bases long, 17 to 29 bases long, 17 to 28 bases long, 17 to 27 bases long, 17 to 26 bases long, 17 to 25 bases long, 17 to 24 bases long, 17 to 23 bases long, 17 to 22 bases long, 17 to 21 bases long, 17 to 20 bases long, 17

to 19 bases long, 17 to 18 bases long, 18 to 30 bases long, 18 to 29 bases long, 18 to 28 bases long, 18 to 27 bases long, 18 to 26 bases long, 18 to 25 bases long, 18 to 24 bases long, 18 to 23 bases long, 18 to 22 bases long, 18 to 21 bases long, 18 to 20 bases long, 18 to 19 bases long, 19 to 30 bases long, 19 to 29 bases long, 19 to 28 bases long, 19 to 27 bases long, 19 to 26 bases long, 19 to 25 bases long, 19 to 24 bases long, 19 to 23 bases long, 19 to 22 bases long, 19 to 21 bases long, 19 to 20 bases long, 20 to 30 bases long, 20 to 29 bases long, 20 to 28 bases long, 20 to 27 bases long, 20 to 26 bases long, 20 to 25 bases long, 20 to 24 bases long, 20 to 23 bases long, 20 to 22 bases long, 20 to 21 bases long, 60 bases long, 59 bases long, 58 bases long, 57 bases long, 56 bases long, 55 bases long, 54 bases long, 53 bases long, 52 bases long, 51 bases long, 50 bases long, 49 bases long, 48 bases long, 47 bases long, 46 bases long, 45 bases long, 44 bases long, 43 bases long, 42 bases long, 41 bases long, 40 bases long, 39 bases long, 38 bases long, 37 bases long, 36 bases long, 35 bases long, 34 bases long, 33 bases long, 32 bases long, 31 bases long, 30 bases long, 29 bases long, 28 bases long, 27 bases long, 26 bases long, 25 bases long, 24 bases long, 23 bases long, 22 bases long, 21 bases long, 20 bases long, 19 bases long, 18 bases long, 17 bases long, 16 bases long, 15 bases long, 14 bases long, 13 bases long, 12 bases long, 11 bases long, or 10 bases

long, but not limited thereto. These lengths may be increased or decreased by 1, 2, or 3 bases.

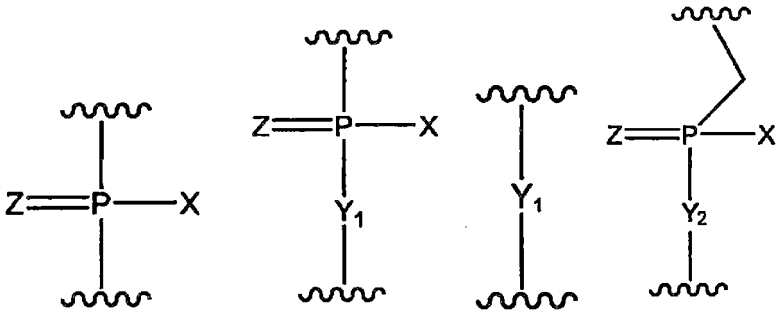
[0076]

The first antisense oligomer of the present invention is a linked-type antisense oligomer configured to comprise a plurality of unit oligomers linked to each other, a pharmaceutically acceptable salt thereof, or a hydrate thereof (hereinafter, also referred to as the "linked-type antisense oligomer of the present invention"). The unit oligomers mean respective oligomers constituting the linked-type antisense oligomer of the present invention. Specifically, the unit oligomers mean moieties (units) comprising base sequences that hybridize with target base sequences having consecutive base sequences when the linked-type antisense oligomer of the present invention binds to the target base sequences in human dystrophin pre-mRNA.

[0077]

The unit oligomers may be linked via a linker that does not contribute to hybridization, or may be linked directly without the mediation of a linker. When the unit oligomers are linked directly to each other, the 3' end of the unit positioned on the 5' side and the 5' end of the unit positioned on the 3' side form a phosphate bond or any one of the following groups.

[Chem. 2]



wherein X represents -OH, $-CH_2R^1$, $-O-CH_2R^1$, $-S-CH_2R^1$, $-NR^2R^3$ or F;

R^1 represents H or an alkyl;

R^2 and R^3, which may be the same or different, each represents H, an alkyl, a cycloalkyl or an aryl;

Y_1 represents O, S, CH_2, or NR^1;

Y_2 represents O, S, or NR^1;

Z represents O or S.

[0078]

The first unit oligomer constituting the linked-type antisense oligomer of the present invention may comprise a base sequence complementary to a base sequence consisting of a base sequence of 11 bases in the upstream direction from the 3' end of the 44th intron and a base sequence of 69 bases in the downstream direction from the 5' end of the 45th exon in human dystrophin pre-mRNA, or a partial base sequence thereof. The second unit oligomer constituting the linked-type antisense oligomer of the present invention may comprise a base sequence complementary to a base sequence of from the 52nd to 75th bases in the upstream direction from the 3' end of the

44th intron in human dystrophin pre-mRNA, or a partial base sequence thereof.

[0079]

In relation to the target sequence of the unit oligomer, the term "partial" means a partial region of consecutive bases, except for the full length, of the target sequence. The partial region may be 5 to 30 bases long, 5 to 29 bases long, 5 to 28 bases long, 5 to 27 bases long, 5 to 26 bases long, 5 to 25 bases long, 5 to 24 bases long, 5 to 23 bases long, 5 to 22 bases long, 5 to 21 bases long, 5 to 20 bases long, 5 to 19 bases long, 5 to 18 bases long, 5 to 17 bases long, 5 to 16 bases long, 5 to 15 base long, 5 to 14 bases long, 5 to 13 bases long, 5 to 12 bases long, 7 to 30 bases long, 7 to 29 bases long, 7 to 28 bases long, 7 to 27 bases long, 7 to 26 bases long, 7 to 25 bases long, 7 to 24 bases long, 7 to 23 bases long, 7 to 22 bases long, 7 to 21 bases long, 7 to 20 bases long, 7 to 19 bases long, 7 to 18 bases long, 7 to 17 bases long, 7 to 16 bases long, 7 to 15 bases long, 7 to 14 bases long, 7 to 13 bases long, 7 to 12 bases long, 9 to 30 bases long, 9 to 29 bases long, 9 to 28 bases long, 9 to 27 bases long, 9 to 26 bases long, 9 to 25 bases long, 9 to 24 bases long, 9 to 23 bases long, 9 to 22 bases long, 9 to 21 bases long, 9 to 20 bases long, 9 to 19 bases long, 9 to 18 bases long, 9 to 17 bases long, 9 to 16 bases long, 9 to 15 bases long, 9 to 14 bases long, 9 to 13 bases long, 9 to 12 bases

long, 10 to 30 bases long, 10 to 29 bases long, 10 to 28 bases long, 10 to 27 bases long, 10 to 26 bases long, 10 to 25 bases long, 10 to 24 bases long, 10 to 23 bases long, 10 to 22 bases long, 10 to 21 bases long, 10 to 20 bases long, 10 to 19 bases long, 10 to 18 bases long, 10 to 17 bases long, 10 to 16 bases long, 10 to 15 bases long, 10 to 14 bases long, 10 to 13 bases long, 10 to 12 bases long, 30 bases long, 29 bases long, 28 bases long, 27 bases long, 26 bases long, 25 bases long, 24 bases long, 23 bases long, 22 bases long, 21 bases long, 20 bases long, 19 bases long, 18 bases long, 17 bases long, 16 bases long, 15 bases long, 14 bases long, 13 bases long, 12 bases long, 11 bases long, 10 bases long, 9 bases long, 8 bases long, 7 bases long, 6 bases long, or 5 bases long, but is not limited thereto. These lengths may be increased or decreased by 1, 2, or 3 bases.

[0080]

The size of each unit oligomer may be 5 to 30 bases long, 5 to 29 bases long, 5 to 28 bases long, 5 to 27 bases long, 5 to 26 bases long, 5 to 25 bases long, 5 to 24 bases long, 5 to 23 bases long, 5 to 22 bases long, 5 to 21 bases long, 5 to 20 bases long, 5 to 19 bases long, 5 to 18 bases long, 5 to 17 bases long, 5 to 16 bases long, 5 to 15 bases long, 5 to 14 bases long, 5 to 13 bases long, 5 to 12 bases long, 7 to 30 bases long, 7 to 29 bases long, 7 to 28 bases long, 7 to 27 bases long, 7 to 26 bases long, 7 to 25 bases long, 7 to 24 bases long,

7 to 23 bases long, 7 to 22 bases long, 7 to 21 bases long, 7 to 20 bases long, 7 to 19 bases long, 7 to 18 bases long, 7 to 17 bases long, 7 to 16 bases long, 7 to 15 bases long, 7 to 14 bases long, 7 to 13 bases long, 7 to 12 bases long, 9 to 30 bases long, 9 to 29 bases long, 9 to 28 bases long, 9 to 27 bases long, 9 to 26 bases long, 9 to 25 bases long, 9 to 24 bases long, 9 to 23 bases long, 9 to 22 bases long, 9 to 21 bases long, 9 to 20 bases long, 9 to 19 bases long, 9 to 18 bases long, 9 to 17 bases long, 9 to 16 bases long, 9 to 15 bases long, 9 to 14 bases long, 9 to 13 bases long, 9 to 12 bases long, 10 to 30 bases long, 10 to 29 bases long, 10 to 28 bases long, 10 to 27 bases long, 10 to 26 bases long, 10 to 25 bases long, 10 to 24 bases long, 10 to 23 bases long, 10 to 22 bases long, 10 to 21 bases long, 10 to 20 bases long, 10 to 19 bases long, 10 to 18 bases long, 10 to 17 bases long, 10 to 16 bases long, 10 to 15 bases long, 10 to 14 bases long, 10 to 13 bases long, 10 to 12 bases long, 30 bases long, 29 bases long, 28 bases long, 27 bases long, 26 bases long, 25 bases long, 24 bases long, 23 bases long, 22 bases long, 21 bases long, 20 bases long, 19 bases long, 18 bases long, 17 bases long, 16 bases long, 15 bases long, 14 bases long, 13 bases long, 12 bases long, 11 bases long, 10 bases long, 9 bases long, 8 bases long, 7 bases long, 6 bases long, 5 bases long, but not limited thereto. These lengths may

be increased or decreased by 1, 2, or 3 bases. The unit oligomers may have the same size or different sizes.

[0081]

In the first antisense oligomer, the order of the first unit oligomer and the second unit oligomer is not limited. The first antisense oligomer may comprise the first unit oligomer and the second unit oligomer from the 5' ends in this order, or may comprise the second unit oligomer and the first unit oligomer from the 5' ends in this order.

[0082]

In one embodiment, the first unit oligomer comprises or consists of a base sequence complementary to consecutive 15 to 30 bases of a base sequence consisting of a base sequence 11 bases in the upstream direction from the 3' end of the 44th intron and a base sequence of 69 bases in the downstream direction from the 5' end of the 45th exon in human dystrophin pre-mRNA. In one embodiment, the second unit oligomer comprises or consists of a base sequence complementary to consecutive 1 to 10 bases of a base sequence of from the 52nd to 75th bases in the upstream direction from the 3' end of the 44th intron in human dystrophin pre-mRNA. In one embodiment, the second antisense oligomer comprises a base sequence complementary to consecutive 15 to 30 bases of a base sequence consisting of a base sequence of 33 bases in the upstream direction from the 3' end of the

54th intron and a base sequence of 53 bases in the downstream direction from the 5' end of the 55th exon in human dystrophin pre-mRNA. In one embodiment, the third antisense oligomer comprises or consists of a base sequence complementary to consecutive 15 to 30 bases of a base sequence consisting of a base sequence of 23 bases in the upstream direction from the 3' end of the 45th exon and a base sequence of 73 bases in the downstream direction from the 5' end of the 45th intron in the human dystrophin pre-mRNA.

[0083]

Table 4 below shows examples of the target sequence of the first unit oligomer, and the complementary sequence (antisense sequence) thereof.

[Table 4-1]

Table 4

Length mer	Target site	Targe sequence	SEQ ID NO:	Antisense sequence (5' to 3')	SEQ ID NO:
15	H45_5-19	TCCAGGATGGCATTG	211	CAATGCCATCCTGGA	907
15	H45_6-20	CCAGGATGGCATTGG	212	CCAATGCCATCCTGG	908
15	H45_7-21	CAGGATGGCATTGGG	213	CCCAATGCCATCCTG	909
15	H45_8-22	AGGATGGCATTGGGC	214	GCCCAATGCCATCCT	910

15	H45_9-23	GGATGGCATTGGGCA	215	TGCCCAATGCCATCC	911
15	H45_10-24	GATGGCATTGGGCAG	216	CTGCCCAATGCCATC	912
15	H45_11-25	ATGGCATTGGGCAGC	217	GCTGCCCAATGCCAT	913
15	H45_12-26	TGGCATTGGGCAGCG	218	CGCTGCCCAATGCCA	914
15	H45_13-27	GGCATTGGGCAGCGG	219	CCGCTGCCCAATGCC	915
15	H45_14-28	GCATTGGGCAGCGGC	220	GCCGCTGCCCAATGC	916
15	H45_15-29	CATTGGGCAGCGGCA	221	TGCCGCTGCCCAATG	917
15	H45_16-30	ATTGGGCAGCGGCAA	222	TTGCCGCTGCCCAAT	918
15	H45_17-31	TTGGGCAGCGGCAAA	223	TTTGCCGCTGCCCAA	919
15	H45_18-32	TGGGCAGCGGCAAAC	224	GTTTGCCGCTGCCCA	920
15	H45_19-33	GGGCAGCGGCAAACT	225	AGTTTGCCGCTGCCC	921
15	H45_20-34	GGCAGCGGCAAACTG	226	CAGTTTGCCGCTGCC	922
15	H45_21-35	GCAGCGGCAAACTGT	227	ACAGTTTGCCGCTGC	923
15	H45_22-36	CAGCGGCAAACTGTT	228	AACAGTTTGCCGCTG	924
15	H45_23-37	AGCGGCAAACTGTTG	229	CAACAGTTTGCCGCT	925
15	H45_24-38	GCGGCAAACTGTTGT	230	ACAACAGTTTGCCGC	926
15	H45_25-39	CGGCAAACTGTTGTC	231	GACAACAGTTTGCCG	927
15	H45_26-40	GGCAAACTGTTGTCA	232	TGACAACAGTTTGCC	928

[Table 4-3]

15	H45_27-41	GCAAACTGTTGTCAG	233	CTGACAACAGTTTGC	929
15	H45_28-42	CAAACTGTTGTCAGA	234	TCTGACAACAGTTTG	930
15	H45_29-43	AAACTGTTGTCAGAA	235	TTCTGACAACAGTTT	931
15	H45_30-44	AACTGTTGTCAGAAC	236	GTTCTGACAACAGTT	932
15	H45_31-45	ACTGTTGTCAGAACA	237	TGTTCTGACAACAGT	933
15	H45_32-46	CTGTTGTCAGAACAT	238	ATGTTCTGACAACAG	934
15	H45_33-47	TGTTGTCAGAACATT	239	AATGTTCTGACAACA	935
15	H45_34-48	GTTGTCAGAACATTG	240	CAATGTTCTGACAAC	936
15	H45_35-49	TTGTCAGAACATTGA	241	TCAATGTTCTGACAA	937
15	H45_36-50	TGTCAGAACATTGAA	242	TTCAATGTTCTGACA	938
15	H45_37-51	GTCAGAACATTGAAT	243	ATTCAATGTTCTGAC	939
15	H45_38-52	TCAGAACATTGAATG	244	CATTCAATGTTCTGA	940
15	H45_39-53	CAGAACATTGAATGC	245	GCATTCAATGTTCTG	941
15	H45_40-54	AGAACATTGAATGCA	246	TGCATTCAATGTTCT	942
16	H45_4-19	CTCCAGGATGGCATTG	247	CAATGCCATCCTGGAG	943
16	H45_5-20	TCCAGGATGGCATTGG	248	CCAATGCCATCCTGGA	944
16	H45_6-21	CCAGGATGGCATTGGG	249	CCCAATGCCATCCTGG	945
16	H45_7-22	CAGGATGGCATTGGGC	250	GCCCAATGCCATCCTG	946
16	H45_8-23	AGGATGGCATTGGGCA	251	TGCCCAATGCCATCCT	947
16	H45_9-24	GGATGGCATTGGGCAG	252	CTGCCCAATGCCATCC	948
16	H45_10-	GATGGCATTGGGCAGC	253	GCTGCCCAATGCCATC	949

[Table 4-4]

	25				
16	H45_11-26	ATGGCATTGGGCAGCG	254	CGCTGCCCAATGCCAT	950
16	H45_12-27	TGGCATTGGGCAGCGG	255	CCGCTGCCCAATGCCA	951
16	H45_13-28	GGCATTGGGCAGCGGC	256	GCCGCTGCCCAATGCC	952
16	H45_14-29	GCATTGGGCAGCGGCA	257	TGCCGCTGCCCAATGC	953
16	H45_15-30	CATTGGGCAGCGGCAA	258	TTGCCGCTGCCCAATG	954
16	H45_16-31	ATTGGGCAGCGGCAAA	259	TTTGCCGCTGCCCAAT	955
16	H45_17-32	TTGGGCAGCGGCAAAC	260	GTTTGCCGCTGCCCAA	956
16	H45_18-33	TGGGCAGCGGCAAACT	261	AGTTTGCCGCTGCCCA	957
16	H45_19-34	GGGCAGCGGCAAACTG	262	CAGTTTGCCGCTGCCC	958
16	H45_20-35	GGCAGCGGCAAACTGT	263	ACAGTTTGCCGCTGCC	959
16	H45_21-36	GCAGCGGCAAACTGTT	264	AACAGTTTGCCGCTGC	960
16	H45_22-37	CAGCGGCAAACTGTTG	265	CAACAGTTTGCCGCTG	961
16	H45_23-38	AGCGGCAAACTGTTGT	266	ACAACAGTTTGCCGCT	962
16	H45_24-39	GCGGCAAACTGTTGTC	267	GACAACAGTTTGCCGC	963
16	H45_25-40	CGGCAAACTGTTGTCA	268	TGACAACAGTTTGCCG	964
16	H45_26-41	GGCAAACTGTTGTCAG	269	CTGACAACAGTTTGCC	965
16	H45_27-42	GCAAACTGTTGTCAGA	270	TCTGACAACAGTTTGC	966

[Table 4-5]

16	H45_28-43	CAAACTGTTGTCAGAA	271	TTCTGACAACAGTTTG	967
16	H45_29-44	AAACTGTTGTCAGAAC	272	GTTCTGACAACAGTTT	968
16	H45_30-45	AACTGTTGTCAGAACA	273	TGTTCTGACAACAGTT	969
16	H45_31-46	ACTGTTGTCAGAACAT	274	ATGTTCTGACAACAGT	970
16	H45_32-47	CTGTTGTCAGAACATT	275	AATGTTCTGACAACAG	971
16	H45_33-48	TGTTGTCAGAACATTG	276	CAATGTTCTGACAACA	972
16	H45_34-49	GTTGTCAGAACATTGA	277	TCAATGTTCTGACAAC	973
16	H45_35-50	TTGTCAGAACATTGAA	278	TTCAATGTTCTGACAA	974
16	H45_36-51	TGTCAGAACATTGAAT	279	ATTCAATGTTCTGACA	975
16	H45_37-52	GTCAGAACATTGAATG	280	CATTCAATGTTCTGAC	976
16	H45_38-53	TCAGAACATTGAATGC	281	GCATTCAATGTTCTGA	977
16	H45_39-54	CAGAACATTGAATGCA	282	TGCATTCAATGTTCTG	978
16	H45_40-55	AGAACATTGAATGCAA	283	TTGCATTCAATGTTCT	979
17	H45_3-19	ACTCCAGGATGGCATTG	284	CAATGCCATCCTGGAGT	980
17	H45_4-20	CTCCAGGATGGCATTGG	285	CCAATGCCATCCTGGAG	981
17	H45_5-21	TCCAGGATGGCATTGGG	286	CCCAATGCCATCCTGGA	982
17	H45_6-22	CCAGGATGGCATTGGGC	287	GCCCAATGCCATCCTGG	983
17	H45_7-23	CAGGATGGCATTGGGCA	288	TGCCCAATGCCATCCTG	984
17	H45_8-24	AGGATGGCATTGGGCAG	289	CTGCCCAATGCCATCCT	985
17	H45_9-25	GGATGGCATTGGGCAGC	290	GCTGCCCAATGCCATCC	986
17	H45_10-26	GATGGCATTGGGCAGCG	291	CGCTGCCCAATGCCATC	987

[Table 4-6]

17	H45_11-27	ATGGCATTGGGCAGCGG	292	CCGCTGCCCAATGCCAT	988
17	H45_12-28	TGGCATTGGGCAGCGGC	293	GCCGCTGCCCAATGCCA	989
17	H45_13-29	GGCATTGGGCAGCGGCA	294	TGCCGCTGCCCAATGCC	990
17	H45_14-30	GCATTGGGCAGCGGCAA	295	TTGCCGCTGCCCAATGC	991
17	H45_15-31	CATTGGGCAGCGGCAAA	296	TTTGCCGCTGCCCAATG	992
17	H45_16-32	ATTGGGCAGCGGCAAAC	297	GTTTGCCGCTGCCCAAT	993
17	H45_17-33	TTGGGCAGCGGCAAACT	298	AGTTTGCCGCTGCCCAA	994
17	H45_18-34	TGGGCAGCGGCAAACTG	299	CAGTTTGCCGCTGCCCA	995
17	H45_19-35	GGGCAGCGGCAAACTGT	300	ACAGTTTGCCGCTGCCC	996
17	H45_20-36	GGCAGCGGCAAACTGTT	301	AACAGTTTGCCGCTGCC	997
17	H45_21-37	GCAGCGGCAAACTGTTG	302	CAACAGTTTGCCGCTGC	998
17	H45_22-38	CAGCGGCAAACTGTTGT	303	ACAACAGTTTGCCGCTG	999
17	H45_23-39	AGCGGCAAACTGTTGTC	304	GACAACAGTTTGCCGCT	1000
17	H45_24-40	GCGGCAAACTGTTGTCA	305	TGACAACAGTTTGCCGC	1001
17	H45_25-41	CGGCAAACTGTTGTCAG	306	CTGACAACAGTTTGCCG	1002
17	H45_26-42	GGCAAACTGTTGTCAGA	307	TCTGACAACAGTTTGCC	1003
17	H45_27-43	GCAAACTGTTGTCAGAA	308	TTCTGACAACAGTTTGC	1004
17	H45_28-44	CAAACTGTTGTCAGAAC	309	GTTCTGACAACAGTTTG	1005

[Table 4-7]

17	H45_29-45	AAACTGTTGTCAGAACA	310	TGTTCTGACAACAGTTT	1006
17	H45_30-46	AACTGTTGTCAGAACAT	311	ATGTTCTGACAACAGTT	1007
17	H45_31-47	ACTGTTGTCAGAACATT	312	AATGTTCTGACAACAGT	1008
17	H45_32-48	CTGTTGTCAGAACATTG	313	CAATGTTCTGACAACAG	1009
17	H45_33-49	TGTTGTCAGAACATTGA	314	TCAATGTTCTGACAACA	1010
17	H45_34-50	GTTGTCAGAACATTGAA	315	TTCAATGTTCTGACAAC	1011
17	H45_35-51	TTGTCAGAACATTGAAT	316	ATTCAATGTTCTGACAA	1012
17	H45_36-52	TGTCAGAACATTGAATG	317	CATTCAATGTTCTGACA	1013
17	H45_37-53	GTCAGAACATTGAATGC	318	GCATTCAATGTTCTGAC	1014
17	H45_38-54	TCAGAACATTGAATGCA	319	TGCATTCAATGTTCTGA	1015
17	H45_39-55	CAGAACATTGAATGCAA	320	TTGCATTCAATGTTCTG	1016
17	H45_40-56	AGAACATTGAATGCAAC	321	GTTGCATTCAATGTTCT	1017
18	H45_2-19	AACTCCAGGATGGCATTG	322	CAATGCCATCCTGGAGTT	1018
18	H45_3-20	ACTCCAGGATGGCATTGG	323	CCAATGCCATCCTGGAGT	1019
18	H45_4-21	CTCCAGGATGGCATTGGG	324	CCCAATGCCATCCTGGAG	1020
18	H45_5-22	TCCAGGATGGCATTGGGC	325	GCCCAATGCCATCCTGGA	1021
18	H45_6-23	CCAGGATGGCATTGGGCA	326	TGCCCAATGCCATCCTGG	1022
18	H45_7-24	CAGGATGGCATTGGGCAG	327	CTGCCCAATGCCATCCTG	1023
18	H45_8-25	AGGATGGCATTGGGCAGC	328	GCTGCCCAATGCCATCCT	1024
18	H45_9-26	GGATGGCATTGGGCAGCG	329	CGCTGCCCAATGCCATCC	1025
18	H45_10-27	GATGGCATTGGGCAGCGG	330	CCGCTGCCCAATGCCATC	1026
18	H45_11-	ATGGCATTGGGCAGCGGC	331	GCCGCTGCCCAATGCCAT	1027

[Table 4-8]

	28				
18	H45_12-29	TGGCATTGGGCAGCGGCA	332	TGCCGCTGCCCAATGCCA	1028
18	H45_13-30	GGCATTGGGCAGCGGCAA	333	TTGCCGCTGCCCAATGCC	1029
18	H45_14-31	GCATTGGGCAGCGGCAAA	334	TTTGCCGCTGCCCAATGC	1030
18	H45_15-32	CATTGGGCAGCGGCAAAC	335	GTTTGCCGCTGCCCAATG	1031
18	H45_16-33	ATTGGGCAGCGGCAAACT	336	AGTTTGCCGCTGCCCAAT	1032
18	H45_17-34	TTGGGCAGCGGCAAACTG	337	CAGTTTGCCGCTGCCCAA	1033
18	H45_18-35	TGGGCAGCGGCAAACTGT	338	ACAGTTTGCCGCTGCCCA	1034
18	H45_19-36	GGGCAGCGGCAAACTGTT	339	AACAGTTTGCCGCTGCCC	1035
18	H45_20-37	GGCAGCGGCAAACTGTTG	340	CAACAGTTTGCCGCTGCC	1036
18	H45_21-38	GCAGCGGCAAACTGTTGT	341	ACAACAGTTTGCCGCTGC	1037
18	H45_22-39	CAGCGGCAAACTGTTGTC	342	GACAACAGTTTGCCGCTG	1038
18	H45_23-40	AGCGGCAAACTGTTGTCA	343	TGACAACAGTTTGCCGCT	1039
18	H45_24-41	GCGGCAAACTGTTGTCAG	344	CTGACAACAGTTTGCCGC	1040
18	H45_25-42	CGGCAAACTGTTGTCAGA	345	TCTGACAACAGTTTGCCG	1041
18	H45_26-43	GGCAAACTGTTGTCAGAA	346	TTCTGACAACAGTTTGCC	1042
18	H45_27-44	GCAAACTGTTGTCAGAAC	347	GTTCTGACAACAGTTTGC	1043
18	H45_28-45	CAAACTGTTGTCAGAACA	348	TGTTCTGACAACAGTTTG	1044

[Table 4-9]

18	H45_29-46	AAACTGTTGTCAGAACAT	349	ATGTTCTGACAACAGTTT	1045
18	H45_30-47	AACTGTTGTCAGAACATT	350	AATGTTCTGACAACAGTT	1046
18	H45_31-48	ACTGTTGTCAGAACATTG	351	CAATGTTCTGACAACAGT	1047
18	H45_32-49	CTGTTGTCAGAACATTGA	352	TCAATGTTCTGACAACAG	1048
18	H45_33-50	TGTTGTCAGAACATTGAA	353	TTCAATGTTCTGACAACA	1049
18	H45_34-51	GTTGTCAGAACATTGAAT	354	ATTCAATGTTCTGACAAC	1050
18	H45_35-52	TTGTCAGAACATTGAATG	355	CATTCAATGTTCTGACAA	1051
18	H45_36-53	TGTCAGAACATTGAATGC	356	GCATTCAATGTTCTGACA	1052
18	H45_37-54	GTCAGAACATTGAATGCA	357	TGCATTCAATGTTCTGAC	1053
18	H45_38-55	TCAGAACATTGAATGCAA	358	TTGCATTCAATGTTCTGA	1054
18	H45_39-56	CAGAACATTGAATGCAAC	359	GTTGCATTCAATGTTCTG	1055
18	H45_40-57	AGAACATTGAATGCAACT	360	AGTTGCATTCAATGTTCT	1056
19	H45_1-19	GAACTCCAGGATGGCATTG	361	CAATGCCATCCTGGAGTTC	1057
19	H45_2-20	AACTCCAGGATGGCATTGG	362	CCAATGCCATCCTGGAGTT	1058
19	H45_3-21	ACTCCAGGATGGCATTGGG	363	CCCAATGCCATCCTGGAGT	1059
19	H45_4-22	CTCCAGGATGGCATTGGGC	364	GCCCAATGCCATCCTGGAG	1060
19	H45_5-23	TCCAGGATGGCATTGGGCA	365	TGCCCAATGCCATCCTGGA	1061
19	H45_6-24	CCAGGATGGCATTGGGCAG	366	CTGCCCAATGCCATCCTGG	1062
19	H45_7-25	CAGGATGGCATTGGGCAGC	367	GCTGCCCAATGCCATCCTG	1063
19	H45_8-26	AGGATGGCATTGGGCAGCG	368	CGCTGCCCAATGCCATCCT	1064
19	H45_9-27	GGATGGCATTGGGCAGCGG	369	CCGCTGCCCAATGCCATCC	1065
19	H45_10-28	GATGGCATTGGGCAGCGGC	370	GCCGCTGCCCAATGCCATC	1066

[Table 4-10]

19	H45_11-29	ATGGCATTGGGCAGCGGCA	371	TGCCGCTGCCCAATGCCAT	1067
19	H45_12-30	TGGCATTGGGCAGCGGCAA	372	TTGCCGCTGCCCAATGCCA	1068
19	H45_13-31	GGCATTGGGCAGCGGCAAA	373	TTTGCCGCTGCCCAATGCC	1069
19	H45_14-32	GCATTGGGCAGCGGCAAAC	374	GTTTGCCGCTGCCCAATGC	1070
19	H45_15-33	CATTGGGCAGCGGCAAACT	375	AGTTTGCCGCTGCCCAATG	1071
19	H45_16-34	ATTGGGCAGCGGCAAACTG	376	CAGTTTGCCGCTGCCCAAT	1072
19	H45_17-35	TTGGGCAGCGGCAAACTGT	377	ACAGTTTGCCGCTGCCCAA	1073
19	H45_18-36	TGGGCAGCGGCAAACTGTT	378	AACAGTTTGCCGCTGCCCA	1074
19	H45_19-37	GGGCAGCGGCAAACTGTTG	379	CAACAGTTTGCCGCTGCCC	1075
19	H45_20-38	GGCAGCGGCAAACTGTTGT	380	ACAACAGTTTGCCGCTGCC	1076
19	H45_21-39	GCAGCGGCAAACTGTTGTC	381	GACAACAGTTTGCCGCTGC	1077
19	H45_22-40	CAGCGGCAAACTGTTGTCA	382	TGACAACAGTTTGCCGCTG	1078
19	H45_23-41	AGCGGCAAACTGTTGTCAG	383	CTGACAACAGTTTGCCGCT	1079
19	H45_24-42	GCGGCAAACTGTTGTCAGA	384	TCTGACAACAGTTTGCCGC	1080
19	H45_25-43	CGGCAAACTGTTGTCAGAA	385	TTCTGACAACAGTTTGCCG	1081
19	H45_26-44	GGCAAACTGTTGTCAGAAC	386	GTTCTGACAACAGTTTGCC	1082
19	H45_27-45	GCAAACTGTTGTCAGAACA	387	TGTTCTGACAACAGTTTGC	1083
19	H45_28-46	CAAACTGTTGTCAGAACAT	388	ATGTTCTGACAACAGTTTG	1084

[Table 4-11]

19	H45_29-47	AAACTGTTGTCAGAACATT	389	AATGTTCTGACAACAGTTT	1085
19	H45_30-48	AACTGTTGTCAGAACATTG	390	CAATGTTCTGACAACAGTT	1086
19	H45_31-49	ACTGTTGTCAGAACATTGA	391	TCAATGTTCTGACAACAGT	1087
19	H45_32-50	CTGTTGTCAGAACATTGAA	392	TTCAATGTTCTGACAACAG	1088
19	H45_33-51	TGTTGTCAGAACATTGAAT	393	ATTCAATGTTCTGACAACA	1089
19	H45_34-52	GTTGTCAGAACATTGAATG	394	CATTCAATGTTCTGACAAC	1090
19	H45_35-53	TTGTCAGAACATTGAATGC	395	GCATTCAATGTTCTGACAA	1091
19	H45_36-54	TGTCAGAACATTGAATGCA	396	TGCATTCAATGTTCTGACA	1092
19	H45_37-55	GTCAGAACATTGAATGCAA	397	TTGCATTCAATGTTCTGAC	1093
19	H45_38-56	TCAGAACATTGAATGCAAC	398	GTTGCATTCAATGTTCTGA	1094
19	H45_39-57	CAGAACATTGAATGCAACT	399	AGTTGCATTCAATGTTCTG	1095
19	H45_40-58	AGAACATTGAATGCAACTG	400	CAGTTGCATTCAATGTTCT	1096
20	H45_(-1)-19	GGAACTCCAGGATGGCATTG	401	CAATGCCATCCTGGAGTTCC	1097
20	H45_1-20	GAACTCCAGGATGGCATTGG	402	CCAATGCCATCCTGGAGTTC	1098
20	H45_2-21	AACTCCAGGATGGCATTGGG	403	CCCAATGCCATCCTGGAGTT	1099
20	H45_3-22	ACTCCAGGATGGCATTGGGC	404	GCCCAATGCCATCCTGGAGT	1100
20	H45_4-23	CTCCAGGATGGCATTGGGCA	405	TGCCCAATGCCATCCTGGAG	1101
20	H45_5-24	TCCAGGATGGCATTGGGCAG	406	CTGCCCAATGCCATCCTGGA	1102
20	H45_6-25	CCAGGATGGCATTGGGCAGC	407	GCTGCCCAATGCCATCCTGG	1103
20	H45_7-26	CAGGATGGCATTGGGCAGCG	408	CGCTGCCCAATGCCATCCTG	1104
20	H45_8-27	AGGATGGCATTGGGCAGCGG	409	CCGCTGCCCAATGCCATCCT	1105
20	H45_9-28	GGATGGCATTGGGCAGCGGC	410	GCCGCTGCCCAATGCCATCC	1106

[Table 4-12]

20	H45_10-29	GATGGCATTGGGCAGCGGCA	411	TGCCGCTGCCCAATGCCATC	1107
20	H45_11-30	ATGGCATTGGGCAGCGGCAA	412	TTGCCGCTGCCCAATGCCAT	1108
20	H45_12-31	TGGCATTGGGCAGCGGCAAA	413	TTTGCCGCTGCCCAATGCCA	1109
20	H45_13-32	GGCATTGGGCAGCGGCAAAC	414	GTTTGCCGCTGCCCAATGCC	1110
20	H45_14-33	GCATTGGGCAGCGGCAAACT	415	AGTTTGCCGCTGCCCAATGC	1111
20	H45_15-34	CATTGGGCAGCGGCAAACTG	416	CAGTTTGCCGCTGCCCAATG	1112
20	H45_16-35	ATTGGGCAGCGGCAAACTGT	417	ACAGTTTGCCGCTGCCCAAT	1113
20	H45_17-36	TTGGGCAGCGGCAAACTGTT	418	AACAGTTTGCCGCTGCCCAA	1114
20	H45_18-37	TGGGCAGCGGCAAACTGTTG	419	CAACAGTTTGCCGCTGCCCA	1115
20	H45_19-38	GGGCAGCGGCAAACTGTTGT	420	ACAACAGTTTGCCGCTGCCC	1116
20	H45_20-39	GGCAGCGGCAAACTGTTGTC	421	GACAACAGTTTGCCGCTGCC	1117
20	H45_21-40	GCAGCGGCAAACTGTTGTCA	422	TGACAACAGTTTGCCGCTGC	1118
20	H45_22-41	CAGCGGCAAACTGTTGTCAG	423	CTGACAACAGTTTGCCGCTG	1119
20	H45_23-42	AGCGGCAAACTGTTGTCAGA	424	TCTGACAACAGTTTGCCGCT	1120
20	H45_24-43	GCGGCAAACTGTTGTCAGAA	425	TTCTGACAACAGTTTGCCGC	1121
20	H45_25-44	CGGCAAACTGTTGTCAGAAC	426	GTTCTGACAACAGTTTGCCG	1122
20	H45_26-45	GGCAAACTGTTGTCAGAACA	427	TGTTCTGACAACAGTTTGCC	1123
20	H45_27-46	GCAAACTGTTGTCAGAACAT	428	ATGTTCTGACAACAGTTTGC	1124

[Table 4-13]

20	H45_28-47	CAAACTGTTGTCAGAACATT	429	AATGTTCTGACAACAGTTTG	1125
20	H45_29-48	AAACTGTTGTCAGAACATTG	430	CAATGTTCTGACAACAGTTT	1126
20	H45_30-49	AACTGTTGTCAGAACATTGA	431	TCAATGTTCTGACAACAGTT	1127
20	H45_31-50	ACTGTTGTCAGAACATTGAA	432	TTCAATGTTCTGACAACAGT	1128
20	H45_32-51	CTGTTGTCAGAACATTGAAT	433	ATTCAATGTTCTGACAACAG	1129
20	H45_33-52	TGTTGTCAGAACATTGAATG	434	CATTCAATGTTCTGACAACA	1130
20	H45_34-53	GTTGTCAGAACATTGAATGC	435	GCATTCAATGTTCTGACAAC	1131
20	H45_35-54	TTGTCAGAACATTGAATGCA	436	TGCATTCAATGTTCTGACAA	1132
20	H45_36-55	TGTCAGAACATTGAATGCAA	437	TTGCATTCAATGTTCTGACA	1133
20	H45_37-56	GTCAGAACATTGAATGCAAC	438	GTTGCATTCAATGTTCTGAC	1134
20	H45_38-57	TCAGAACATTGAATGCAACT	439	AGTTGCATTCAATGTTCTGA	1135
20	H45_39-58	CAGAACATTGAATGCAACTG	440	CAGTTGCATTCAATGTTCTG	1136
20	H45_40-59	AGAACATTGAATGCAACTGG	441	CCAGTTGCATTCAATGTTCT	1137
21	H45_(-2)-19	AGGAACTCCAGGATGGCATTG	442	CAATGCCATCCTGGAGTTCCT	1138
21	H45_(-1)-20	GGAACTCCAGGATGGCATTGG	443	CCAATGCCATCCTGGAGTTCC	1139
21	H45_1-21	GAACTCCAGGATGGCATTGGG	444	CCCAATGCCATCCTGGAGTTC	1140
21	H45_2-22	AACTCCAGGATGGCATTGGGC	445	GCCCAATGCCATCCTGGAGTT	1141
21	H45_3-23	ACTCCAGGATGGCATTGGGCA	446	TGCCCAATGCCATCCTGGAGT	1142

[Table 4-14]

21	H45_4-24	CTCCAGGATGGCATTGGGCAG	447	CTGCCCAATGCCATCCTGGAG	1143
21	H45_5-25	TCCAGGATGGCATTGGGCAGC	448	GCTGCCCAATGCCATCCTGGA	1144
21	H45_6-26	CCAGGATGGCATTGGGCAGCG	449	CGCTGCCCAATGCCATCCTGG	1145
21	H45_7-27	CAGGATGGCATTGGGCAGCGG	450	CCGCTGCCCAATGCCATCCTG	1146
21	H45_8-28	AGGATGGCATTGGGCAGCGGC	451	GCCGCTGCCCAATGCCATCCT	1147
21	H45_9-29	GGATGGCATTGGGCAGCGGCA	452	TGCCGCTGCCCAATGCCATCC	1148
21	H45_10-30	GATGGCATTGGGCAGCGGCAA	453	TTGCCGCTGCCCAATGCCATC	1149
21	H45_11-31	ATGGCATTGGGCAGCGGCAAA	454	TTTGCCGCTGCCCAATGCCAT	1150
21	H45_12-32	TGGCATTGGGCAGCGGCAAAC	455	GTTTGCCGCTGCCCAATGCCA	1151
21	H45_13-33	GGCATTGGGCAGCGGCAAACT	456	AGTTTGCCGCTGCCCAATGCC	1152
21	H45_14-34	GCATTGGGCAGCGGCAAACTG	457	CAGTTTGCCGCTGCCCAATGC	1153
21	H45_15-35	CATTGGGCAGCGGCAAACTGT	458	ACAGTTTGCCGCTGCCCAATG	1154
21	H45_16-36	ATTGGGCAGCGGCAAACTGTT	459	AACAGTTTGCCGCTGCCCAAT	1155
21	H45_17-37	TTGGGCAGCGGCAAACTGTTG	460	CAACAGTTTGCCGCTGCCCAA	1156
21	H45_18-38	TGGGCAGCGGCAAACTGTTGT	461	ACAACAGTTTGCCGCTGCCCA	1157
21	H45_19-39	GGGCAGCGGCAAACTGTTGTC	462	GACAACAGTTTGCCGCTGCCC	1158
21	H45_20-40	GGCAGCGGCAAACTGTTGTCA	463	TGACAACAGTTTGCCGCTGCC	1159
21	H45_21-41	GCAGCGGCAAACTGTTGTCAG	464	CTGACAACAGTTTGCCGCTGC	1160

[Table 4-15]

21	H45_22-42	CAGCGGCAAACTGTTGTCAGA	465	TCTGACAACAGTTTGCCGCTG	1161
21	H45_23-43	AGCGGCAAACTGTTGTCAGAA	466	TTCTGACAACAGTTTGCCGCT	1162
21	H45_24-44	GCGGCAAACTGTTGTCAGAAC	467	GTTCTGACAACAGTTTGCCGC	1163
21	H45_25-45	CGGCAAACTGTTGTCAGAACA	468	TGTTCTGACAACAGTTTGCCG	1164
21	H45_26-46	GGCAAACTGTTGTCAGAACAT	469	ATGTTCTGACAACAGTTTGCC	1165
21	H45_27-47	GCAAACTGTTGTCAGAACATT	470	AATGTTCTGACAACAGTTTGC	1166
21	H45_28-48	CAAACTGTTGTCAGAACATTG	471	CAATGTTCTGACAACAGTTTG	1167
21	H45_29-49	AAACTGTTGTCAGAACATTGA	472	TCAATGTTCTGACAACAGTTT	1168
21	H45_30-50	AACTGTTGTCAGAACATTGAA	473	TTCAATGTTCTGACAACAGTT	1169
21	H45_31-51	ACTGTTGTCAGAACATTGAAT	474	ATTCAATGTTCTGACAACAGT	1170
21	H45_32-52	CTGTTGTCAGAACATTGAATG	475	CATTCAATGTTCTGACAACAG	1171
21	H45_33-53	TGTTGTCAGAACATTGAATGC	476	GCATTCAATGTTCTGACAACA	1172
21	H45_34-54	GTTGTCAGAACATTGAATGCA	477	TGCATTCAATGTTCTGACAAC	1173
21	H45_35-55	TTGTCAGAACATTGAATGCAA	478	TTGCATTCAATGTTCTGACAA	1174
21	H45_36-56	TGTCAGAACATTGAATGCAAC	479	GTTGCATTCAATGTTCTGACA	1175
21	H45_37-57	GTCAGAACATTGAATGCAACT	480	AGTTGCATTCAATGTTCTGAC	1176
21	H45_38-58	TCAGAACATTGAATGCAACTG	481	CAGTTGCATTCAATGTTCTGA	1177
21	H45_39-59	CAGAACATTGAATGCAACTGG	482	CCAGTTGCATTCAATGTTCTG	1178

[Table 4-16]

21	H45_40-60	AGAACATTGAATGCAACTGGG	483	CCCAGTTGCATTCAATGTTCT	1179
22	H45_(-3)-19	CAGGAACTCCAGGATGGCATTG	484	CAATGCCATCCTGGAGTTCCTG	1180
22	H45_(-2)-20	AGGAACTCCAGGATGGCATTGG	485	CCAATGCCATCCTGGAGTTCCT	1181
22	H45_(-1)-21	GGAACTCCAGGATGGCATTGGG	486	CCCAATGCCATCCTGGAGTTCC	1182
22	H45_1-22	GAACTCCAGGATGGCATTGGGC	487	GCCCAATGCCATCCTGGAGTTC	1183
22	H45_2-23	AACTCCAGGATGGCATTGGGCA	488	TGCCCAATGCCATCCTGGAGTT	1184
22	H45_3-24	ACTCCAGGATGGCATTGGGCAG	489	CTGCCCAATGCCATCCTGGAGT	1185
22	H45_4-25	CTCCAGGATGGCATTGGGCAGC	490	GCTGCCCAATGCCATCCTGGAG	1186
22	H45_5-26	TCCAGGATGGCATTGGGCAGCG	491	CGCTGCCCAATGCCATCCTGGA	1187
22	H45_6-27	CCAGGATGGCATTGGGCAGCGG	492	CCGCTGCCCAATGCCATCCTGG	1188
22	H45_7-28	CAGGATGGCATTGGGCAGCGGC	493	GCCGCTGCCCAATGCCATCCTG	1189
22	H45_8-29	AGGATGGCATTGGGCAGCGGCA	494	TGCCGCTGCCCAATGCCATCCT	1190
22	H45_9-30	GGATGGCATTGGGCAGCGGCAA	495	TTGCCGCTGCCCAATGCCATCC	1191
22	H45_10-31	GATGGCATTGGGCAGCGGCAAA	496	TTTGCCGCTGCCCAATGCCATC	1192
22	H45_11-32	ATGGCATTGGGCAGCGGCAAAC	497	GTTTGCCGCTGCCCAATGCCAT	1193
22	H45_12-33	TGGCATTGGGCAGCGGCAAACT	498	AGTTTGCCGCTGCCCAATGCCA	1194
22	H45_13-34	GGCATTGGGCAGCGGCAAACTG	499	CAGTTTGCCGCTGCCCAATGCC	1195
22	H45_14-35	GCATTGGGCAGCGGCAAACTGT	500	ACAGTTTGCCGCTGCCCAATGC	1196

[Table 4-17]

22	H45_15-36	CATTGGGCAGCGGCAAACTGTT	501	AACAGTTTGCCGCTGCCCAATG	1197
22	H45_16-37	ATTGGGCAGCGGCAAACTGTTG	502	CAACAGTTTGCCGCTGCCCAAT	1198
22	H45_17-38	TTGGGCAGCGGCAAACTGTTGT	503	ACAACAGTTTGCCGCTGCCCAA	1199
22	H45_18-39	TGGGCAGCGGCAAACTGTTGTC	504	GACAACAGTTTGCCGCTGCCCA	1200
22	H45_19-40	GGGCAGCGGCAAACTGTTGTCA	505	TGACAACAGTTTGCCGCTGCCC	1201
22	H45_20-41	GGCAGCGGCAAACTGTTGTCAG	506	CTGACAACAGTTTGCCGCTGCC	1202
22	H45_21-42	GCAGCGGCAAACTGTTGTCAGA	507	TCTGACAACAGTTTGCCGCTGC	1203
22	H45_22-43	CAGCGGCAAACTGTTGTCAGAA	508	TTCTGACAACAGTTTGCCGCTG	1204
22	H45_23-44	AGCGGCAAACTGTTGTCAGAAC	509	GTTCTGACAACAGTTTGCCGCT	1205
22	H45_24-45	GCGGCAAACTGTTGTCAGAACA	510	TGTTCTGACAACAGTTTGCCGC	1206
22	H45_25-46	CGGCAAACTGTTGTCAGAACAT	511	ATGTTCTGACAACAGTTTGCCG	1207
22	H45_26-47	GGCAAACTGTTGTCAGAACATT	512	AATGTTCTGACAACAGTTTGCC	1208
22	H45_27-48	GCAAACTGTTGTCAGAACATTG	513	CAATGTTCTGACAACAGTTTGC	1209
22	H45_28-49	CAAACTGTTGTCAGAACATTGA	514	TCAATGTTCTGACAACAGTTTG	1210
22	H45_29-50	AAACTGTTGTCAGAACATTGAA	515	TTCAATGTTCTGACAACAGTTT	1211
22	H45_30-51	AACTGTTGTCAGAACATTGAAT	516	ATTCAATGTTCTGACAACAGTT	1212
22	H45_31-52	ACTGTTGTCAGAACATTGAATG	517	CATTCAATGTTCTGACAACAGT	1213
22	H45_32-53	CTGTTGTCAGAACATTGAATGC	518	GCATTCAATGTTCTGACAACAG	1214

[Table 4-18]

22	H45_33-54	TGTTGTCAGAACATTGAATGCA	519	TGCATTCAATGTTCTGACAACA	1215
22	H45_34-55	GTTGTCAGAACATTGAATGCAA	520	TTGCATTCAATGTTCTGACAAC	1216
22	H45_35-56	TTGTCAGAACATTGAATGCAAC	521	GTTGCATTCAATGTTCTGACAA	1217
22	H45_36-57	TGTCAGAACATTGAATGCAACT	522	AGTTGCATTCAATGTTCTGACA	1218
22	H45_37-58	GTCAGAACATTGAATGCAACTG	523	CAGTTGCATTCAATGTTCTGAC	1219
22	H45_38-59	TCAGAACATTGAATGCAACTGG	524	CCAGTTGCATTCAATGTTCTGA	1220
22	H45_39-60	CAGAACATTGAATGCAACTGGG	525	CCCAGTTGCATTCAATGTTCTG	1221
22	H45_40-61	AGAACATTGAATGCAACTGGGG	526	CCCCAGTTGCATTCAATGTTCT	1222
23	H45_(-4)-19	ACAGGAACTCCAGGATGGCATTG	527	CAATGCCATCCTGGAGTTCCTGT	1223
23	H45_(-3)-20	CAGGAACTCCAGGATGGCATTGG	528	CCAATGCCATCCTGGAGTTCCTG	1224
23	H45_(-2)-21	AGGAACTCCAGGATGGCATTGGG	529	CCCAATGCCATCCTGGAGTTCCT	1225
23	H45_(-1)-22	GGAACTCCAGGATGGCATTGGGC	530	GCCCAATGCCATCCTGGAGTTCC	1226
23	H45_1-23	GAACTCCAGGATGGCATTGGGCA	531	TGCCCAATGCCATCCTGGAGTTC	1227
23	H45_2-24	AACTCCAGGATGGCATTGGGCAG	532	CTGCCCAATGCCATCCTGGAGTT	1228
23	H45_3-25	ACTCCAGGATGGCATTGGGCAGC	533	GCTGCCCAATGCCATCCTGGAGT	1229
23	H45_4-26	CTCCAGGATGGCATTGGGCAGCG	534	CGCTGCCCAATGCCATCCTGGAG	1230
23	H45_5-27	TCCAGGATGGCATTGGGCAGCGG	535	CCGCTGCCCAATGCCATCCTGGA	1231
23	H45_6-28	CCAGGATGGCATTGGGCAGCGGC	536	GCCGCTGCCCAATGCCATCCTGG	1232

[Table 4-19]

23	H45_7-29	CAGGATGGCATTGGGCAGCGGCA	537	TGCCGCTGCCCAATGCCATCCTG	1233
23	H45_8-30	AGGATGGCATTGGGCAGCGGCAA	538	TTGCCGCTGCCCAATGCCATCCT	1234
23	H45_9-31	GGATGGCATTGGGCAGCGGCAAA	539	TTTGCCGCTGCCCAATGCCATCC	1235
23	H45_10-32	GATGGCATTGGGCAGCGGCAAAC	540	GTTTGCCGCTGCCCAATGCCATC	1236
23	H45_11-33	ATGGCATTGGGCAGCGGCAAACT	541	AGTTTGCCGCTGCCCAATGCCAT	1237
23	H45_12-34	TGGCATTGGGCAGCGGCAAACTG	542	CAGTTTGCCGCTGCCCAATGCCA	1238
23	H45_13-35	GGCATTGGGCAGCGGCAAACTGT	543	ACAGTTTGCCGCTGCCCAATGCC	1239
23	H45_14-36	GCATTGGGCAGCGGCAAACTGTT	544	AACAGTTTGCCGCTGCCCAATGC	1240
23	H45_15-37	CATTGGGCAGCGGCAAACTGTTG	545	CAACAGTTTGCCGCTGCCCAATG	1241
23	H45_16-38	ATTGGGCAGCGGCAAACTGTTGT	546	ACAACAGTTTGCCGCTGCCCAAT	1242
23	H45_17-39	TTGGGCAGCGGCAAACTGTTGTC	547	GACAACAGTTTGCCGCTGCCCAA	1243
23	H45_18-40	TGGGCAGCGGCAAACTGTTGTCA	548	TGACAACAGTTTGCCGCTGCCCA	1244
23	H45_19-41	GGGCAGCGGCAAACTGTTGTCAG	549	CTGACAACAGTTTGCCGCTGCCC	1245
23	H45_20-42	GGCAGCGGCAAACTGTTGTCAGA	550	TCTGACAACAGTTTGCCGCTGCC	1246
23	H45_21-43	GCAGCGGCAAACTGTTGTCAGAA	551	TTCTGACAACAGTTTGCCGCTGC	1247
23	H45_22-44	CAGCGGCAAACTGTTGTCAGAAC	552	GTTCTGACAACAGTTTGCCGCTG	1248
23	H45_23-45	AGCGGCAAACTGTTGTCAGAACA	553	TGTTCTGACAACAGTTTGCCGCT	1249
23	H45_24-46	GCGGCAAACTGTTGTCAGAACAT	554	ATGTTCTGACAACAGTTTGCCGC	1250

[Table 4-20]

23	H45_25-47	CGGCAAACTGTTGTCAGAACATT	555	AATGTTCTGACAACAGTTTGCCG	1251
23	H45_26-48	GGCAAACTGTTGTCAGAACATTG	556	CAATGTTCTGACAACAGTTTGCC	1252
23	H45_27-49	GCAAACTGTTGTCAGAACATTGA	557	TCAATGTTCTGACAACAGTTTGC	1253
23	H45_28-50	CAAACTGTTGTCAGAACATTGAA	558	TTCAATGTTCTGACAACAGTTTG	1254
23	H45_29-51	AAACTGTTGTCAGAACATTGAAT	559	ATTCAATGTTCTGACAACAGTTT	1255
23	H45_30-52	AACTGTTGTCAGAACATTGAATG	560	CATTCAATGTTCTGACAACAGTT	1256
23	H45_31-53	ACTGTTGTCAGAACATTGAATGC	561	GCATTCAATGTTCTGACAACAGT	1257
23	H45_32-54	CTGTTGTCAGAACATTGAATGCA	562	TGCATTCAATGTTCTGACAACAG	1258
23	H45_33-55	TGTTGTCAGAACATTGAATGCAA	563	TTGCATTCAATGTTCTGACAACA	1259
23	H45_34-56	GTTGTCAGAACATTGAATGCAAC	564	GTTGCATTCAATGTTCTGACAAC	1260
23	H45_35-57	TTGTCAGAACATTGAATGCAACT	565	AGTTGCATTCAATGTTCTGACAA	1261
23	H45_36-58	TGTCAGAACATTGAATGCAACTG	566	CAGTTGCATTCAATGTTCTGACA	1262
23	H45_37-59	GTCAGAACATTGAATGCAACTGG	567	CCAGTTGCATTCAATGTTCTGAC	1263
23	H45_38-60	TCAGAACATTGAATGCAACTGGG	568	CCCAGTTGCATTCAATGTTCTGA	1264
23	H45_39-61	CAGAACATTGAATGCAACTGGGG	569	CCCCAGTTGCATTCAATGTTCTG	1265
23	H45_40-62	AGAACATTGAATGCAACTGGGGA	570	TCCCCAGTTGCATTCAATGTTCT	1266
24	H45_(-5)-19	TACAGGAACTCCAGGATGGCATTG	571	CAATGCCATCCTGGAGTTCCTGTA	1267
24	H45_(-4)-20	ACAGGAACTCCAGGATGGCATTGG	572	CCAATGCCATCCTGGAGTTCCTGT	1268

[Table 4-21]

24	H45_(-3)-21	CAGGAACTCCAGGATGGCATTGGG	573	CCCAATGCCATCCTGGAGTTCCTG	1269
24	H45_(-2)-22	AGGAACTCCAGGATGGCATTGGGC	574	GCCCAATGCCATCCTGGAGTTCCT	1270
24	H45_(-1)-23	GGAACTCCAGGATGGCATTGGGCA	575	TGCCCAATGCCATCCTGGAGTTCC	1271
24	H45_1-24	GAACTCCAGGATGGCATTGGGCAG	576	CTGCCCAATGCCATCCTGGAGTTC	1272
24	H45_2-25	AACTCCAGGATGGCATTGGGCAGC	577	GCTGCCCAATGCCATCCTGGAGTT	1273
24	H45_3-26	ACTCCAGGATGGCATTGGGCAGCG	578	CGCTGCCCAATGCCATCCTGGAGT	1274
24	H45_4-27	CTCCAGGATGGCATTGGGCAGCGG	579	CCGCTGCCCAATGCCATCCTGGAG	1275
24	H45_5-28	TCCAGGATGGCATTGGGCAGCGGC	580	GCCGCTGCCCAATGCCATCCTGGA	1276
24	H45_6-29	CCAGGATGGCATTGGGCAGCGGCA	581	TGCCGCTGCCCAATGCCATCCTGG	1277
24	H45_7-30	CAGGATGGCATTGGGCAGCGGCAA	582	TTGCCGCTGCCCAATGCCATCCTG	1278
24	H45_8-31	AGGATGGCATTGGGCAGCGGCAAA	583	TTTGCCGCTGCCCAATGCCATCCT	1279
24	H45_9-32	GGATGGCATTGGGCAGCGGCAAAC	584	GTTTGCCGCTGCCCAATGCCATCC	1280
24	H45_10-33	GATGGCATTGGGCAGCGGCAAACT	585	AGTTTGCCGCTGCCCAATGCCATC	1281
24	H45_11-34	ATGGCATTGGGCAGCGGCAAACTG	586	CAGTTTGCCGCTGCCCAATGCCAT	1282
24	H45_12-35	TGGCATTGGGCAGCGGCAAACTGT	587	ACAGTTTGCCGCTGCCCAATGCCA	1283
24	H45_13-36	GGCATTGGGCAGCGGCAAACTGTT	588	AACAGTTTGCCGCTGCCCAATGCC	1284
24	H45_14-37	GCATTGGGCAGCGGCAAACTGTTG	589	CAACAGTTTGCCGCTGCCCAATGC	1285
24	H45_15-38	CATTGGGCAGCGGCAAACTGTTGT	590	ACAACAGTTTGCCGCTGCCCAATG	1286

[Table 4-22]

24	H45_16-39	ATTGGGCAGCGGCAAACTGTTGTC	591	GACAACAGTTTGCCGCTGCCCAAT	1287
24	H45_17-40	TTGGGCAGCGGCAAACTGTTGTCA	592	TGACAACAGTTTGCCGCTGCCCAA	1288
24	H45_18-41	TGGGCAGCGGCAAACTGTTGTCAG	593	CTGACAACAGTTTGCCGCTGCCCA	1289
24	H45_19-42	GGGCAGCGGCAAACTGTTGTCAGA	594	TCTGACAACAGTTTGCCGCTGCCC	1290
24	H45_20-43	GGCAGCGGCAAACTGTTGTCAGAA	595	TTCTGACAACAGTTTGCCGCTGCC	1291
24	H45_21-44	GCAGCGGCAAACTGTTGTCAGAAC	596	GTTCTGACAACAGTTTGCCGCTGC	1292
24	H45_22-45	CAGCGGCAAACTGTTGTCAGAACA	597	TGTTCTGACAACAGTTTGCCGCTG	1293
24	H45_23-46	AGCGGCAAACTGTTGTCAGAACAT	598	ATGTTCTGACAACAGTTTGCCGCT	1294
24	H45_24-47	GCGGCAAACTGTTGTCAGAACATT	599	AATGTTCTGACAACAGTTTGCCGC	1295
24	H45_25-48	CGGCAAACTGTTGTCAGAACATTG	600	CAATGTTCTGACAACAGTTTGCCG	1296
24	H45_26-49	GGCAAACTGTTGTCAGAACATTGA	601	TCAATGTTCTGACAACAGTTTGCC	1297
24	H45_27-50	GCAAACTGTTGTCAGAACATTGAA	602	TTCAATGTTCTGACAACAGTTTGC	1298
24	H45_28-51	CAAACTGTTGTCAGAACATTGAAT	603	ATTCAATGTTCTGACAACAGTTTG	1299
24	H45_29-52	AAACTGTTGTCAGAACATTGAATG	604	CATTCAATGTTCTGACAACAGTTT	1300
24	H45_30-53	AACTGTTGTCAGAACATTGAATGC	605	GCATTCAATGTTCTGACAACAGTT	1301
24	H45_31-54	ACTGTTGTCAGAACATTGAATGCA	606	TGCATTCAATGTTCTGACAACAGT	1302
24	H45_32-55	CTGTTGTCAGAACATTGAATGCAA	607	TTGCATTCAATGTTCTGACAACAG	1303
24	H45_33-56	TGTTGTCAGAACATTGAATGCAAC	608	GTTGCATTCAATGTTCTGACAACA	1304

[Table 4-23]

24	H45_34-57	GTTGTCAGAACATTGAATGCAACT	609	AGTTGCATTCAATGTTCTGACAAC	1305
24	H45_35-58	TTGTCAGAACATTGAATGCAACTG	610	CAGTTGCATTCAATGTTCTGACAA	1306
24	H45_36-59	TGTCAGAACATTGAATGCAACTGG	611	CCAGTTGCATTCAATGTTCTGACA	1307
24	H45_37-60	GTCAGAACATTGAATGCAACTGGG	612	CCCAGTTGCATTCAATGTTCTGAC	1308
24	H45_38-61	TCAGAACATTGAATGCAACTGGGG	613	CCCCAGTTGCATTCAATGTTCTGA	1309
24	H45_39-62	CAGAACATTGAATGCAACTGGGGA	614	TCCCCAGTTGCATTCAATGTTCTG	1310
24	H45_40-63	AGAACATTGAATGCAACTGGGGAA	615	TTCCCCAGTTGCATTCAATGTTCT	1311
25	H45_(-6)-19	TTACAGGAACTCCAGGATGGCATTG	616	CAATGCCATCCTGGAGTTCCTGTAA	1312
25	H45_(-5)-20	TACAGGAACTCCAGGATGGCATTGG	617	CCAATGCCATCCTGGAGTTCCTGTA	1313
25	H45_(-4)-21	ACAGGAACTCCAGGATGGCATTGGG	618	CCCAATGCCATCCTGGAGTTCCTGT	1314
25	H45_(-3)-22	CAGGAACTCCAGGATGGCATTGGGC	619	GCCCAATGCCATCCTGGAGTTCCTG	1315
25	H45_(-2)-23	AGGAACTCCAGGATGGCATTGGGCA	620	TGCCCAATGCCATCCTGGAGTTCCT	1316
25	H45_(-1)-24	GGAACTCCAGGATGGCATTGGGCAG	621	CTGCCCAATGCCATCCTGGAGTTCC	1317
25	H45_1-25	GAACTCCAGGATGGCATTGGGCAGC	622	GCTGCCCAATGCCATCCTGGAGTTC	1318
25	H45_2-26	AACTCCAGGATGGCATTGGGCAGCG	623	CGCTGCCCAATGCCATCCTGGAGTT	1319
25	H45_3-27	ACTCCAGGATGGCATTGGGCAGCGG	624	CCGCTGCCCAATGCCATCCTGGAGT	1320
25	H45_4-28	CTCCAGGATGGCATTGGGCAGCGGC	625	GCCGCTGCCCAATGCCATCCTGGAG	1321
25	H45_5-29	TCCAGGATGGCATTGGGCAGCGGCA	626	TGCCGCTGCCCAATGCCATCCTGGA	1322

[Table 4-24]

25	H45_6-30	CCAGGATGGCATTGGGCAGCGGCAA	627	TTGCCGCTGCCCAATGCCATCCTGG	1323
25	H45_7-31	CAGGATGGCATTGGGCAGCGGCAAA	628	TTTGCCGCTGCCCAATGCCATCCTG	1324
25	H45_8-32	AGGATGGCATTGGGCAGCGGCAAAC	629	GTTTGCCGCTGCCCAATGCCATCCT	1325
25	H45_9-33	GGATGGCATTGGGCAGCGGCAAACT	630	AGTTTGCCGCTGCCCAATGCCATCC	1326
25	H45_10-34	GATGGCATTGGGCAGCGGCAAACTG	631	CAGTTTGCCGCTGCCCAATGCCATC	1327
25	H45_11-35	ATGGCATTGGGCAGCGGCAAACTGT	632	ACAGTTTGCCGCTGCCCAATGCCAT	1328
25	H45_12-36	TGGCATTGGGCAGCGGCAAACTGTT	633	AACAGTTTGCCGCTGCCCAATGCCA	1329
25	H45_13-37	GGCATTGGGCAGCGGCAAACTGTTG	634	CAACAGTTTGCCGCTGCCCAATGCC	1330
25	H45_14-38	GCATTGGGCAGCGGCAAACTGTTGT	635	ACAACAGTTTGCCGCTGCCCAATGC	1331
25	H45_15-39	CATTGGGCAGCGGCAAACTGTTGTC	636	GACAACAGTTTGCCGCTGCCCAATG	1332
25	H45_16-40	ATTGGGCAGCGGCAAACTGTTGTCA	637	TGACAACAGTTTGCCGCTGCCCAAT	1333
25	H45_17-41	TTGGGCAGCGGCAAACTGTTGTCAG	638	CTGACAACAGTTTGCCGCTGCCCAA	1334
25	H45_18-42	TGGGCAGCGGCAAACTGTTGTCAGA	639	TCTGACAACAGTTTGCCGCTGCCCA	1335
25	H45_19-43	GGGCAGCGGCAAACTGTTGTCAGAA	640	TTCTGACAACAGTTTGCCGCTGCCC	1336
25	H45_20-44	GGCAGCGGCAAACTGTTGTCAGAAC	641	GTTCTGACAACAGTTTGCCGCTGCC	1337
25	H45_21-45	GCAGCGGCAAACTGTTGTCAGAACA	642	TGTTCTGACAACAGTTTGCCGCTGC	1338
25	H45_22-46	CAGCGGCAAACTGTTGTCAGAACAT	643	ATGTTCTGACAACAGTTTGCCGCTG	1339
25	H45_23-47	AGCGGCAAACTGTTGTCAGAACATT	644	AATGTTCTGACAACAGTTTGCCGCT	1340

[Table 4-25]

25	H45_24-48	GCGGCAAACTGTTGTCAGAACATTG	645	CAATGTTCTGACAACAGTTTGCCGC	1341
25	H45_25-49	CGGCAAACTGTTGTCAGAACATTGA	646	TCAATGTTCTGACAACAGTTTGCCG	1342
25	H45_26-50	GGCAAACTGTTGTCAGAACATTGAA	647	TTCAATGTTCTGACAACAGTTTGCC	1343
25	H45_27-51	GCAAACTGTTGTCAGAACATTGAAT	648	ATTCAATGTTCTGACAACAGTTTGC	1344
25	H45_28-52	CAAACTGTTGTCAGAACATTGAATG	649	CATTCAATGTTCTGACAACAGTTTG	1345
25	H45_29-53	AAACTGTTGTCAGAACATTGAATGC	650	GCATTCAATGTTCTGACAACAGTTT	1346
25	H45_30-54	AACTGTTGTCAGAACATTGAATGCA	651	TGCATTCAATGTTCTGACAACAGTT	1347
25	H45_31-55	ACTGTTGTCAGAACATTGAATGCAA	652	TTGCATTCAATGTTCTGACAACAGT	1348
25	H45_32-56	CTGTTGTCAGAACATTGAATGCAAC	653	GTTGCATTCAATGTTCTGACAACAG	1349
25	H45_33-57	TGTTGTCAGAACATTGAATGCAACT	654	AGTTGCATTCAATGTTCTGACAACA	1350
25	H45_34-58	GTTGTCAGAACATTGAATGCAACTG	655	CAGTTGCATTCAATGTTCTGACAAC	1351
25	H45_35-59	TTGTCAGAACATTGAATGCAACTGG	656	CCAGTTGCATTCAATGTTCTGACAA	1352
25	H45_36-60	TGTCAGAACATTGAATGCAACTGGG	657	CCCAGTTGCATTCAATGTTCTGACA	1353
25	H45_37-61	GTCAGAACATTGAATGCAACTGGGG	658	CCCCAGTTGCATTCAATGTTCTGAC	1354
25	H45_38-62	TCAGAACATTGAATGCAACTGGGGA	659	TCCCCAGTTGCATTCAATGTTCTGA	1355
25	H45_39-63	CAGAACATTGAATGCAACTGGGGAA	660	TTCCCCAGTTGCATTCAATGTTCTG	1356
25	H45_40-64	AGAACATTGAATGCAACTGGGGAAG	661	CTTCCCCAGTTGCATTCAATGTTCT	1357
26	H45_(-7)-19	CTTACAGGAACTCCAGGATGGCATTG	662	CAATGCCATCCTGGAGTTCCTGTAAG	1358

[Table 4-26]

26	H45_(-6)-20	TTACAGGAACTCCAGGATGGCATTGG	663	CCAATGCCATCCTGGAGTTCCTGTAA	1359
26	H45_(-5)-21	TACAGGAACTCCAGGATGGCATTGGG	664	CCCAATGCCATCCTGGAGTTCCTGTA	1360
26	H45_(-4)-22	ACAGGAACTCCAGGATGGCATTGGGC	665	GCCCAATGCCATCCTGGAGTTCCTGT	1361
26	H45_(-3)-23	CAGGAACTCCAGGATGGCATTGGGCA	666	TGCCCAATGCCATCCTGGAGTTCCTG	1362
26	H45_(-2)-24	AGGAACTCCAGGATGGCATTGGGCAG	667	CTGCCCAATGCCATCCTGGAGTTCCT	1363
26	H45_(-1)-25	GGAACTCCAGGATGGCATTGGGCAGC	668	GCTGCCCAATGCCATCCTGGAGTTCC	1364
26	H45_1-26	GAACTCCAGGATGGCATTGGGCAGCG	669	CGCTGCCCAATGCCATCCTGGAGTTC	1365
26	H45_2-27	AACTCCAGGATGGCATTGGGCAGCGG	670	CCGCTGCCCAATGCCATCCTGGAGTT	1366
26	H45_3-28	ACTCCAGGATGGCATTGGGCAGCGGC	671	GCCGCTGCCCAATGCCATCCTGGAGT	1367
26	H45_4-29	CTCCAGGATGGCATTGGGCAGCGGCA	672	TGCCGCTGCCCAATGCCATCCTGGAG	1368
26	H45_5-30	TCCAGGATGGCATTGGGCAGCGGCAA	673	TTGCCGCTGCCCAATGCCATCCTGGA	1369
26	H45_6-31	CCAGGATGGCATTGGGCAGCGGCAAA	674	TTTGCCGCTGCCCAATGCCATCCTGG	1370
26	H45_7-32	CAGGATGGCATTGGGCAGCGGCAAAC	675	GTTTGCCGCTGCCCAATGCCATCCTG	1371
26	H45_8-33	AGGATGGCATTGGGCAGCGGCAAACT	676	AGTTTGCCGCTGCCCAATGCCATCCT	1372
26	H45_9-34	GGATGGCATTGGGCAGCGGCAAACTG	677	CAGTTTGCCGCTGCCCAATGCCATCC	1373
26	H45_10-35	GATGGCATTGGGCAGCGGCAAACTGT	678	ACAGTTTGCCGCTGCCCAATGCCATC	1374
26	H45_11-36	ATGGCATTGGGCAGCGGCAAACTGTT	679	AACAGTTTGCCGCTGCCCAATGCCAT	1375
26	H45_12-37	TGGCATTGGGCAGCGGCAAACTGTTG	680	CAACAGTTTGCCGCTGCCCAATGCCA	1376

[Table 4-27]

26	H45_13-38	GGCATTGGGCAGCGGCAAACTGTTGT	681	ACAACAGTTTGCCGCTGCCCAATGCC	1377
26	H45_14-39	GCATTGGGCAGCGGCAAACTGTTGTC	682	GACAACAGTTTGCCGCTGCCCAATGC	1378
26	H45_15-40	CATTGGGCAGCGGCAAACTGTTGTCA	683	TGACAACAGTTTGCCGCTGCCCAATG	1379
26	H45_16-41	ATTGGGCAGCGGCAAACTGTTGTCAG	684	CTGACAACAGTTTGCCGCTGCCCAAT	1380
26	H45_17-42	TTGGGCAGCGGCAAACTGTTGTCAGA	685	TCTGACAACAGTTTGCCGCTGCCCAA	1381
26	H45_18-43	TGGGCAGCGGCAAACTGTTGTCAGAA	686	TTCTGACAACAGTTTGCCGCTGCCCA	1382
26	H45_19-44	GGGCAGCGGCAAACTGTTGTCAGAAC	687	GTTCTGACAACAGTTTGCCGCTGCCC	1383
26	H45_20-45	GGCAGCGGCAAACTGTTGTCAGAACA	688	TGTTCTGACAACAGTTTGCCGCTGCC	1384
26	H45_21-46	GCAGCGGCAAACTGTTGTCAGAACAT	689	ATGTTCTGACAACAGTTTGCCGCTGC	1385
26	H45_22-47	CAGCGGCAAACTGTTGTCAGAACATT	690	AATGTTCTGACAACAGTTTGCCGCTG	1386
26	H45_23-48	AGCGGCAAACTGTTGTCAGAACATTG	691	CAATGTTCTGACAACAGTTTGCCGCT	1387
26	H45_24-49	GCGGCAAACTGTTGTCAGAACATTGA	692	TCAATGTTCTGACAACAGTTTGCCGC	1388
26	H45_25-50	CGGCAAACTGTTGTCAGAACATTGAA	693	TTCAATGTTCTGACAACAGTTTGCCG	1389
26	H45_26-51	GGCAAACTGTTGTCAGAACATTGAAT	694	ATTCAATGTTCTGACAACAGTTTGCC	1390
26	H45_27-52	GCAAACTGTTGTCAGAACATTGAATG	695	CATTCAATGTTCTGACAACAGTTTGC	1391
26	H45_28-53	CAAACTGTTGTCAGAACATTGAATGC	696	GCATTCAATGTTCTGACAACAGTTTG	1392
26	H45_29-54	AAACTGTTGTCAGAACATTGAATGCA	697	TGCATTCAATGTTCTGACAACAGTTT	1393
26	H45_30-55	AACTGTTGTCAGAACATTGAATGCAA	698	TTGCATTCAATGTTCTGACAACAGTT	1394

[Table 4-28]

26	H45_31-56	ACTGTTGTCAGAACATTGAATGCAAC	699	GTTGCATTCAATGTTCTGACAACAGT	1395
26	H45_32-57	CTGTTGTCAGAACATTGAATGCAACT	700	AGTTGCATTCAATGTTCTGACAACAG	1396
26	H45_33-58	TGTTGTCAGAACATTGAATGCAACTG	701	CAGTTGCATTCAATGTTCTGACAACA	1397
26	H45_34-59	GTTGTCAGAACATTGAATGCAACTGG	702	CCAGTTGCATTCAATGTTCTGACAAC	1398
26	H45_35-60	TTGTCAGAACATTGAATGCAACTGGG	703	CCCAGTTGCATTCAATGTTCTGACAA	1399
26	H45_36-61	TGTCAGAACATTGAATGCAACTGGGG	704	CCCCAGTTGCATTCAATGTTCTGACA	1400
26	H45_37-62	GTCAGAACATTGAATGCAACTGGGGA	705	TCCCCAGTTGCATTCAATGTTCTGAC	1401
26	H45_38-63	TCAGAACATTGAATGCAACTGGGGAA	706	TTCCCCAGTTGCATTCAATGTTCTGA	1402
26	H45_39-64	CAGAACATTGAATGCAACTGGGGAAG	707	CTTCCCCAGTTGCATTCAATGTTCTG	1403
26	H45_40-65	AGAACATTGAATGCAACTGGGGAAGA	708	TCTTCCCCAGTTGCATTCAATGTTCT	1404
27	H45_(-8)-19	TCTTACAGGAACTCCAGGATGGCATTG	709	CAATGCCATCCTGGAGTTCCTGTAAGA	1405
27	H45_(-7)-20	CTTACAGGAACTCCAGGATGGCATTGG	710	CCAATGCCATCCTGGAGTTCCTGTAAG	1406
27	H45_(-6)-21	TTACAGGAACTCCAGGATGGCATTGGG	711	CCCAATGCCATCCTGGAGTTCCTGTAA	1407
27	H45_(-5)-22	TACAGGAACTCCAGGATGGCATTGGGC	712	GCCCAATGCCATCCTGGAGTTCCTGTA	1408
27	H45_(-4)-23	ACAGGAACTCCAGGATGGCATTGGGCA	713	TGCCCAATGCCATCCTGGAGTTCCTGT	1409
27	H45_(-3)-24	CAGGAACTCCAGGATGGCATTGGCAG	714	CTGCCCAATGCCATCCTGGAGTTCCTG	1410
27	H45_(-2)-25	AGGAACTCCAGGATGGCATTGGGCAGC	715	GCTGCCCAATGCCATCCTGGAGTTCCT	1411
27	H45_(-1)-26	GGAACTCCAGGATGGCATTGGGCAGCG	716	CGCTGCCCAATGCCATCCTGGAGTTCC	1412

[Table 4-29]

27	H45_1-27	GAACTCCAGGATGGCATTGGGCAGCGG	717	CCGCTGCCCAATGCCATCCTGGAGTTC	1413
27	H45_2-28	AACTCCAGGATGGCATTGGGCAGCGGC	718	GCCGCTGCCCAATGCCATCCTGGAGTT	1414
27	H45_3-29	ACTCCAGGATGGCATTGGGCAGCGGCA	719	TGCCGCTGCCCAATGCCATCCTGGAGT	1415
27	H45_4-30	CTCCAGGATGGCATTGGGCAGCGGCAA	720	TTGCCGCTGCCCAATGCCATCCTGGAG	1416
27	H45_5-31	TCCAGGATGGCATTGGGCAGCGGCAAA	721	TTTGCCGCTGCCCAATGCCATCCTGGA	1417
27	H45_6-32	CCAGGATGGCATTGGGCAGCGGCAAAC	722	GTTTGCCGCTGCCCAATGCCATCCTGG	1418
27	H45_7-33	CAGGATGGCATTGGGCAGCGGCAAACT	723	AGTTTGCCGCTGCCCAATGCCATCCTG	1419
27	H45_8-34	AGGATGGCATTGGGCAGCGGCAAACTG	724	CAGTTTGCCGCTGCCCAATGCCATCCT	1420
27	H45_9-35	GGATGGCATTGGGCAGCGGCAAACTGT	725	ACAGTTTGCCGCTGCCCAATGCCATCC	1421
27	H45_10-36	GATGGCATTGGGCAGCGGCAAACTGTT	726	AACAGTTTGCCGCTGCCCAATGCCATC	1422
27	H45_11-37	ATGGCATTGGGCAGCGGCAAACTGTTG	727	CAACAGTTTGCCGCTGCCCAATGCCAT	1423
27	H45_12-38	TGGCATTGGGCAGCGGCAAACTGTTGT	728	ACAACAGTTTGCCGCTGCCCAATGCCA	1424
27	H45_13-39	GGCATTGGGCAGCGGCAAACTGTTGTC	729	GACAACAGTTTGCCGCTGCCCAATGCC	1425
27	H45_14-40	GCATTGGGCAGCGGCAAACTGTTGTCA	730	TGACAACAGTTTGCCGCTGCCCAATGC	1426
27	H45_15-41	CATTGGGCAGCGGCAAACTGTTGTCAG	731	CTGACAACAGTTTGCCGCTGCCCAATG	1427
27	H45_16-42	ATTGGGCAGCGGCAAACTGTTGTCAGA	732	TCTGACAACAGTTTGCCGCTGCCCAAT	1428
27	H45_17-43	TTGGGCAGCGGCAAACTGTTGTCAGAA	733	TTCTGACAACAGTTTGCCGCTGCCCAA	1429
27	H45_18-44	TGGGCAGCGGCAAACTGTTGTCAGAAC	734	GTTCTGACAACAGTTTGCCGCTGCCCA	1430

[Table 4-30]

27	H45_19-45	GGGCAGCGGCAAACTGTTGTCAGAACA	735	TGTTCTGACAACAGTTTGCCGCTGCCC	1431
27	H45_20-46	GGCAGCGGCAAACTGTTGTCAGAACAT	736	ATGTTCTGACAACAGTTTGCCGCTGCC	1432
27	H45_21-47	GCAGCGGCAAACTGTTGTCAGAACATT	737	AATGTTCTGACAACAGTTTGCCGCTGC	1433
27	H45_22-48	CAGCGGCAAACTGTTGTCAGAACATTG	738	CAATGTTCTGACAACAGTTTGCCGCTG	1434
27	H45_23-49	AGCGGCAAACTGTTGTCAGAACATTGA	739	TCAATGTTCTGACAACAGTTTGCCGCT	1435
27	H45_24-50	GCGGCAAACTGTTGTCAGAACATTGAA	740	TTCAATGTTCTGACAACAGTTTGCCGC	1436
27	H45_25-51	CGGCAAACTGTTGTCAGAACATTGAAT	741	ATTCAATGTTCTGACAACAGTTTGCCG	1437
27	H45_26-52	GGCAAACTGTTGTCAGAACATTGAATG	742	CATTCAATGTTCTGACAACAGTTTGCC	1438
27	H45_27-53	GCAAACTGTTGTCAGAACATTGAATGC	743	GCATTCAATGTTCTGACAACAGTTTGC	1439
27	H45_28-54	CAAACTGTTGTCAGAACATTGAATGCA	744	TGCATTCAATGTTCTGACAACAGTTTG	1440
27	H45_29-55	AAACTGTTGTCAGAACATTGAATGCAA	745	TTGCATTCAATGTTCTGACAACAGTTT	1441
27	H45_30-56	AACTGTTGTCAGAACATTGAATGCAAC	746	GTTGCATTCAATGTTCTGACAACAGTT	1442
27	H45_31-57	ACTGTTGTCAGAACATTGAATGCAACT	747	AGTTGCATTCAATGTTCTGACAACAGT	1443
27	H45_32-58	CTGTTGTCAGAACATTGAATGCAACTG	748	CAGTTGCATTCAATGTTCTGACAACAG	1444
27	H45_33-59	TGTTGTCAGAACATTGAATGCAACTGG	749	CCAGTTGCATTCAATGTTCTGACAACA	1445
27	H45_34-60	GTTGTCAGAACATTGAATGCAACTGGG	750	CCCAGTTGCATTCAATGTTCTGACAAC	1446
27	H45_35-61	TTGTCAGAACATTGAATGCAACTGGGG	751	CCCCAGTTGCATTCAATGTTCTGACAA	1447
27	H45_36-62	TGTCAGAACATTGAATGCAACTGGGGA	752	TCCCCAGTTGCATTCAATGTTCTGACA	1448

[Table 4-31]

27	H45_37-63	GTCAGAACATTGAATGCAACTGGGGAA	753	TTCCCCAGTTGCATTCAATGTTCTGAC	1449
27	H45_38-64	TCAGAACATTGAATGCAACTGGGGAAG	754	CTTCCCCAGTTGCATTCAATGTTCTGA	1450
27	H45_39-65	CAGAACATTGAATGCAACTGGGGAAGA	755	TCTTCCCCAGTTGCATTCAATGTTCTG	1451
27	H45_40-66	AGAACATTGAATGCAACTGGGGAAGAA	756	TTCTTCCCCAGTTGCATTCAATGTTCT	1452
28	H45_(-9)-19	ATCTTACAGGAACTCCAGGATGGCATTG	757	CAATGCCATCCTGGAGTTCCTGTAAGAT	1453
28	H45_(-8)-20	TCTTACAGGAACTCCAGGATGGCATTGG	758	CCAATGCCATCCTGGAGTTCCTGTAAGA	1454
28	H45_(-7)-21	CTTACAGGAACTCCAGGATGGCATTGGG	759	CCCAATGCCATCCTGGAGTTCCTGTAAG	1455
28	H45_(-6)-22	TTACAGGAACTCCAGGATGGCATTGGGC	760	GCCCAATGCCATCCTGGAGTTCCTGTAA	1456
28	H45_(-5)-23	TACAGGAACTCCAGGATGGCATTGGGCA	761	TGCCCAATGCCATCCTGGAGTTCCTGTA	1457
28	H45_(-4)-24	ACAGGAACTCCAGGATGGCATTGGGCAG	762	CTGCCCAATGCCATCCTGGAGTTCCTGT	1458
28	H45_(-3)-25	CAGGAACTCCAGGATGGCATTGGGCAGC	763	GCTGCCCAATGCCATCCTGGAGTTCCTG	1459
28	H45_(-2)-26	AGGAACTCCAGGATGGCATTGGGCAGCG	764	CGCTGCCCAATGCCATCCTGGAGTTCCT	1460
28	H45_(-1)-27	GGAACTCCAGGATGGCATTGGGCAGCGG	765	CCGCTGCCCAATGCCATCCTGGAGTTCC	1461
28	H45_1-28	GAACTCCAGGATGGCATTGGGCAGCGGC	766	GCCGCTGCCCAATGCCATCCTGGAGTTC	1462
28	H45_2-29	AACTCCAGGATGGCATTGGGCAGCGGCA	767	TGCCGCTGCCCAATGCCATCCTGGAGTT	1463
28	H45_3-30	ACTCCAGGATGGCATTGGGCAGCGGCAA	768	TTGCCGCTGCCCAATGCCATCCTGGAGT	1464
28	H45_4-31	CTCCAGGATGGCATTGGGCAGCGGCAAA	769	TTTGCCGCTGCCCAATGCCATCCTGGAG	1465
28	H45_5-32	TCCAGGATGGCATTGGGCAGCGGCAAAC	770	GTTTGCCGCTGCCCAATGCCATCCTGGA	1466

[Table 4-32]

28	H45_6-33	CCAGGATGGCATTGGGCAGCGG CAAACT	771	AGTTTGCCGCTGCCCAATGC CATCCTGG	1467
28	H45_7-34	CAGGATGGCATTGGGCAGCGGC AAACTG	772	CAGTTTGCCGCTGCCCAATG CCATCCTG	1468
28	H45_8-35	AGGATGGCATTGGGCAGCGGCA AACTGT	773	ACAGTTTGCCGCTGCCCAAT GCCATCCT	1469
28	H45_9-36	GGATGGCATTGGGCAGCGGCAA ACTGTT	774	AACAGTTTGCCGCTGCCCAA TGCCATCC	1470
28	H45_10-37	GATGGCATTGGGCAGCGGCAAA CTGTTG	775	CAACAGTTTGCCGCTGCCCA ATGCCATC	1471
28	H45_11-38	ATGGCATTGGGCAGCGGCAAAC TGTTGT	776	ACAACAGTTTGCCGCTGCCC AATGCCAT	1472
28	H45_12-39	TGGCATTGGGCAGCGGCAAACT GTTGTC	777	GACAACAGTTTGCCGCTGCC CAATGCCA	1473
28	H45_13-40	GGCATTGGGCAGCGGCAAACTG TTGTCA	778	TGACAACAGTTTGCCGCTGC CCAATGCC	1474
28	H45_14-41	GCATTGGGCAGCGGCAAACTGT TGTCAG	779	CTGACAACAGTTTGCCGCTG CCCAATGC	1475
28	H45_15-42	CATTGGGCAGCGGCAAACTGTT GTCAGA	780	TCTGACAACAGTTTGCCGCT GCCCAATG	1476
28	H45_16-43	ATTGGGCAGCGGCAAACTGTTG TCAGAA	781	TTCTGACAACAGTTTGCCGC TGCCCAAT	1477
28	H45_17-44	TTGGGCAGCGGCAAACTGTTGT CAGAAC	782	GTTCTGACAACAGTTTGCCG CTGCCCAA	1478
28	H45_18-45	TGGGCAGCGGCAAACTGTTGTC AGAACA	783	TGTTCTGACAACAGTTTGCC GCTGCCCA	1479
28	H45_19-46	GGGCAGCGGCAAACTGTTGTCA GAACAT	784	ATGTTCTGACAACAGTTTGC CGCTGCCC	1480
28	H45_20-47	GGCAGCGGCAAACTGTTGTCAG AACATT	785	AATGTTCTGACAACAGTTTG CCGCTGCC	1481
28	H45_21-48	GCAGCGGCAAACTGTTGTCAGA ACATTG	786	CAATGTTCTGACAACAGTTT GCCGCTGC	1482
28	H45_22-49	CAGCGGCAAACTGTTGTCAGAA CATTGA	787	TCAATGTTCTGACAACAGTT TGCCGCTG	1483
28	H45_23-50	AGCGGCAAACTGTTGTCAGAAC ATTGAA	788	TTCAATGTTCTGACAACAGT TTGCCGCT	1484

[Table 4-33]

28	H45_24-51	GCGGCAAACTGTTGTCAGAACATTGAAT	789	ATTCAATGTTCTGACAACAGTTTGCCGC	1485
28	H45_25-52	CGGCAAACTGTTGTCAGAACATTGAATG	790	CATTCAATGTTCTGACAACAGTTTGCCG	1486
28	H45_26-53	GGCAAACTGTTGTCAGAACATTGAATGC	791	GCATTCAATGTTCTGACAACAGTTTGCC	1487
28	H45_27-54	GCAAACTGTTGTCAGAACATTGAATGCA	792	TGCATTCAATGTTCTGACAACAGTTTGC	1488
28	H45_28-55	CAAACTGTTGTCAGAACATTGAATGCAA	793	TTGCATTCAATGTTCTGACAACAGTTTG	1489
28	H45_29-56	AAACTGTTGTCAGAACATTGAATGCAAC	794	GTTGCATTCAATGTTCTGACAACAGTTT	1490
28	H45_30-57	AACTGTTGTCAGAACATTGAATGCAACT	795	AGTTGCATTCAATGTTCTGACAACAGTT	1491
28	H45_31-58	ACTGTTGTCAGAACATTGAATGCAACTG	796	CAGTTGCATTCAATGTTCTGACAACAGT	1492
28	H45_32-59	CTGTTGTCAGAACATTGAATGCAACTGG	797	CCAGTTGCATTCAATGTTCTGACAACAG	1493
28	H45_33-60	TGTTGTCAGAACATTGAATGCAACTGGG	798	CCCAGTTGCATTCAATGTTCTGACAACA	1494
28	H45_34-61	GTTGTCAGAACATTGAATGCAACTGGGG	799	CCCCAGTTGCATTCAATGTTCTGACAAC	1495
28	H45_35-62	TTGTCAGAACATTGAATGCAACTGGGGA	800	TCCCCAGTTGCATTCAATGTTCTGACAA	1496
28	H45_36-63	TGTCAGAACATTGAATGCAACTGGGGAA	801	TTCCCCAGTTGCATTCAATGTTCTGACA	1497
28	H45_37-64	GTCAGAACATTGAATGCAACTGGGGAAG	802	CTTCCCCAGTTGCATTCAATGTTCTGAC	1498
28	H45_38-65	TCAGAACATTGAATGCAACTGGGGAAGA	803	TCTTCCCCAGTTGCATTCAATGTTCTGA	1499
28	H45_39-66	CAGAACATTGAATGCAACTGGGGAAGAA	804	TTCTTCCCCAGTTGCATTCAATGTTCTG	1500
28	H45_40-67	AGAACATTGAATGCAACTGGGGAAGAAA	805	TTTCTTCCCCAGTTGCATTCAATGTTCT	1501
29	H45_(-10)-19	TATCTTACAGGAACTCCAGGATGGCATTG	806	CAATGCCATCCTGGAGTTCCTGTAAGATA	1502

[Table 4-34]

29	H45_(-9)-20	ATCTTACAGGAACTCCAGGATGGCATTGG	807	CCAATGCCATCCTGGAGTTCCTGTAAGAT	1503
29	H45_(-8)-21	TCTTACAGGAACTCCAGGATGGCATTGGG	808	CCCAATGCCATCCTGGAGTTCCTGTAAGA	1504
29	H45_(-7)-22	CTTACAGGAACTCCAGGATGGCATTGGGC	809	GCCCAATGCCATCCTGGAGTTCCTGTAAG	1505
29	H45_(-6)-23	TTACAGGAACTCCAGGATGGCATTGGGCA	810	TGCCCAATGCCATCCTGGAGTTCCTGTAA	1506
29	H45_(-5)-24	TACAGGAACTCCAGGATGGCATTGGGCAG	811	CTGCCCAATGCCATCCTGGAGTTCCTGTA	1507
29	H45_(-4)-25	ACAGGAACTCCAGGATGGCATTGGGCAGC	812	GCTGCCCAATGCCATCCTGGAGTTCCTGT	1508
29	H45_(-3)-26	CAGGAACTCCAGGATGGCATTGGGCAGCG	813	CGCTGCCCAATGCCATCCTGGAGTTCCTG	1509
29	H45_(-2)-27	AGGAACTCCAGGATGGCATTGGGCAGCGG	814	CCGCTGCCCAATGCCATCCTGGAGTTCCT	1510
29	H45_(-1)-28	GGAACTCCAGGATGGCATTGGGCAGCGGC	815	GCCGCTGCCCAATGCCATCCTGGAGTTCC	1511
29	H45_1-29	GAACTCCAGGATGGCATTGGGCAGCGGCA	816	TGCCGCTGCCCAATGCCATCCTGGAGTTC	1512
29	H45_2-30	AACTCCAGGATGGCATTGGGCAGCGGCAA	817	TTGCCGCTGCCCAATGCCATCCTGGAGTT	1513
29	H45_3-31	ACTCCAGGATGGCATTGGGCAGCGGCAAA	818	TTTGCCGCTGCCCAATGCCATCCTGGAGT	1514
29	H45_4-32	CTCCAGGATGGCATTGGGCAGCGGCAAAC	819	GTTTGCCGCTGCCCAATGCCATCCTGGAG	1515
29	H45_5-33	TCCAGGATGGCATTGGGCAGCGGCAAACT	820	AGTTTGCCGCTGCCCAATGCCATCCTGGA	1516
29	H45_6-34	CCAGGATGGCATTGGGCAGCGGCAAACTG	821	CAGTTTGCCGCTGCCCAATGCCATCCTGG	1517
29	H45_7-35	CAGGATGGCATTGGGCAGCGGCAAACTGT	822	ACAGTTTGCCGCTGCCCAATGCCATCCTG	1518
29	H45_8-36	AGGATGGCATTGGGCAGCGGCAAACTGTT	823	AACAGTTTGCCGCTGCCCAATGCCATCCT	1519
29	H45_9-37	GGATGGCATTGGGCAGCGGCAAACTGTTG	824	CAACAGTTTGCCGCTGCCCAATGCCATCC	1520

[Table 4-35]

29	H45_10-38	GATGGCATTGGGCAGCGGCAAACTGTTGT	825	ACAACAGTTTGCCGCTGCCCAATGCCATC	1521
29	H45_11-39	ATGGCATTGGGCAGCGGCAAACTGTTGTC	826	GACAACAGTTTGCCGCTGCCCAATGCCAT	1522
29	H45_12-40	TGGCATTGGGCAGCGGCAAACTGTTGTCA	827	TGACAACAGTTTGCCGCTGCCCAATGCCA	1523
29	H45_13-41	GGCATTGGGCAGCGGCAAACTGTTGTCAG	828	CTGACAACAGTTTGCCGCTGCCCAATGCC	1524
29	H45_14-42	GCATTGGGCAGCGGCAAACTGTTGTCAGA	829	TCTGACAACAGTTTGCCGCTGCCCAATGC	1525
29	H45_15-43	CATTGGGCAGCGGCAAACTGTTGTCAGAA	830	TTCTGACAACAGTTTGCCGCTGCCCAATG	1526
29	H45_16-44	ATTGGGCAGCGGCAAACTGTTGTCAGAAC	831	GTTCTGACAACAGTTTGCCGCTGCCCAAT	1527
29	H45_17-45	TTGGGCAGCGGCAAACTGTTGTCAGAACA	832	TGTTCTGACAACAGTTTGCCGCTGCCCAA	1528
29	H45_18-46	TGGGCAGCGGCAAACTGTTGTCAGAACAT	833	ATGTTCTGACAACAGTTTGCCGCTGCCCA	1529
29	H45_19-47	GGGCAGCGGCAAACTGTTGTCAGAACATT	834	AATGTTCTGACAACAGTTTGCCGCTGCCC	1530
29	H45_20-48	GGCAGCGGCAAACTGTTGTCAGAACATTG	835	CAATGTTCTGACAACAGTTTGCCGCTGCC	1531
29	H45_21-49	GCAGCGGCAAACTGTTGTCAGAACATTGA	836	TCAATGTTCTGACAACAGTTTGCCGCTGC	1532
29	H45_22-50	CAGCGGCAAACTGTTGTCAGAACATTGAA	837	TTCAATGTTCTGACAACAGTTTGCCGCTG	1533
29	H45_23-51	AGCGGCAAACTGTTGTCAGAACATTGAAT	838	ATTCAATGTTCTGACAACAGTTTGCCGCT	1534
29	H45_24-52	GCGGCAAACTGTTGTCAGAACATTGAATG	839	CATTCAATGTTCTGACAACAGTTTGCCGC	1535
29	H45_25-53	CGGCAAACTGTTGTCAGAACATTGAATGC	840	GCATTCAATGTTCTGACAACAGTTTGCCG	1536
29	H45_26-54	GGCAAACTGTTGTCAGAACATTGAATGCA	841	TGCATTCAATGTTCTGACAACAGTTTGCC	1537
29	H45_27-55	GCAAACTGTTGTCAGAACATTGAATGCAA	842	TTGCATTCAATGTTCTGACAACAGTTTGC	1538

[Table 4-36]

29	H45_28-56	CAAACTGTTGTCAGAACATTGAATGCAAC	843	GTTGCATTCAATGTTCTGACAACAGTTTG	1539
29	H45_29-57	AAACTGTTGTCAGAACATTGAATGCAACT	844	AGTTGCATTCAATGTTCTGACAACAGTTT	1540
29	H45_30-58	AACTGTTGTCAGAACATTGAATGCAACTG	845	CAGTTGCATTCAATGTTCTGACAACAGTT	1541
29	H45_31-59	ACTGTTGTCAGAACATTGAATGCAACTGG	846	CCAGTTGCATTCAATGTTCTGACAACAGT	1542
29	H45_32-60	CTGTTGTCAGAACATTGAATGCAACTGGG	847	CCCAGTTGCATTCAATGTTCTGACAACAG	1543
29	H45_33-61	TGTTGTCAGAACATTGAATGCAACTGGGG	848	CCCCAGTTGCATTCAATGTTCTGACAACA	1544
29	H45_34-62	GTTGTCAGAACATTGAATGCAACTGGGGA	849	TCCCCAGTTGCATTCAATGTTCTGACAAC	1545
29	H45_35-63	TTGTCAGAACATTGAATGCAACTGGGGAA	850	TTCCCCAGTTGCATTCAATGTTCTGACAA	1546
29	H45_36-64	TGTCAGAACATTGAATGCAACTGGGGAAG	851	CTTCCCCAGTTGCATTCAATGTTCTGACA	1547
29	H45_37-65	GTCAGAACATTGAATGCAACTGGGGAAGA	852	TCTTCCCCAGTTGCATTCAATGTTCTGAC	1548
29	H45_38-66	TCAGAACATTGAATGCAACTGGGGAAGAA	853	TTCTTCCCCAGTTGCATTCAATGTTCTGA	1549
29	H45_39-67	CAGAACATTGAATGCAACTGGGGAAGAAA	854	TTTCTTCCCCAGTTGCATTCAATGTTCTG	1550
29	H45_40-68	AGAACATTGAATGCAACTGGGGAAGAAAT	855	ATTTCTTCCCCAGTTGCATTCAATGTTCT	1551
30	H45_(-11)-19	GTATCTTACAGGAACTCCAGGATGGCATTG	856	CAATGCCATCCTGGAGTTCCTGTAAGATAC	1552
30	H45_(-10)-20	TATCTTACAGGAACTCCAGGATGGCATTGG	857	CCAATGCCATCCTGGAGTTCCTGTAAGATA	1553
30	H45_(-9)-21	ATCTTACAGGAACTCCAGGATGGCATTGGG	858	CCCAATGCCATCCTGGAGTTCCTGTAAGAT	1554
30	H45_(-8)-22	TCTTACAGGAACTCCAGGATGGCATTGGGC	859	GCCCAATGCCATCCTGGAGTTCCTGTAAGA	1555
30	H45_(-7)-23	CTTACAGGAACTCCAGGATGGCATTGGGCA	860	TGCCCAATGCCATCCTGGAGTTCCTGTAAG	1556

[Table 4-37]

30	H45_(-6)-24	TTACAGGAACTCCAGGATGGCATTGGGCAG	861	CTGCCCAATGCCATCCTGGAGTTCCTGTAA	1557
30	H45_(-5)-25	TACAGGAACTCCAGGATGGCATTGGGCAGC	862	GCTGCCCAATGCCATCCTGGAGTTCCTGTA	1558
30	H45_(-4)-26	ACAGGAACTCCAGGATGGCATTGGGCAGCG	863	CGCTGCCCAATGCCATCCTGGAGTTCCTGT	1559
30	H45_(-3)-27	CAGGAACTCCAGGATGGCATTGGCAGCGG	864	CCGCTGCCCAATGCCATCCTGGAGTTCCTG	1560
30	H45_(-2)-28	AGGAACTCCAGGATGGCATTGGGCAGCGGC	865	GCCGCTGCCCAATGCCATCCTGGAGTTCCT	1561
30	H45_(-1)-29	GGAACTCCAGGATGGCATTGGGCAGCGGCA	866	TGCCGCTGCCCAATGCCATCCTGGAGTTCC	1562
30	H45_1-30	GAACTCCAGGATGGCATTGGGCAGCGGCAA	867	TTGCCGCTGCCCAATGCCATCCTGGAGTTC	1563
30	H45_2-31	AACTCCAGGATGGCATTGGGCAGCGGCAAA	868	TTTGCCGCTGCCCAATGCCATCCTGGAGTT	1564
30	H45_3-32	ACTCCAGGATGGCATTGGGCAGCGGCAAAC	869	GTTTGCCGCTGCCCAATGCCATCCTGGAGT	1565
30	H45_4-33	CTCCAGGATGGCATTGGGCAGCGGCAAACT	870	AGTTTGCCGCTGCCCAATGCCATCCTGGAG	1566
30	H45_5-34	TCCAGGATGGCATTGGGCAGCGGCAAACTG	871	CAGTTTGCCGCTGCCCAATGCCATCCTGGA	1567
30	H45_6-35	CCAGGATGGCATTGGGCAGCGGCAAACTGT	872	ACAGTTTGCCGCTGCCCAATGCCATCCTGG	1568
30	H45_7-36	CAGGATGGCATTGGGCAGCGGCAAACTGTT	873	AACAGTTTGCCGCTGCCCAATGCCATCCTG	1569
30	H45_8-37	AGGATGGCATTGGGCAGCGGCAAACTGTTG	874	CAACAGTTTGCCGCTGCCCAATGCCATCCT	1570
30	H45_9-38	GGATGGCATTGGGCAGCGGCAAACTGTTGT	875	ACAACAGTTTGCCGCTGCCCAATGCCATCC	1571
30	H45_10-39	GATGGCATTGGGCAGCGGCAAACTGTTGTC	876	GACAACAGTTTGCCGCTGCCCAATGCCATC	1572
30	H45_11-40	ATGGCATTGGGCAGCGGCAAACTGTTGTCA	877	TGACAACAGTTTGCCGCTGCCCAATGCCAT	1573
30	H45_12-41	TGGCATTGGGCAGCGGCAAACTGTTGTCAG	878	CTGACAACAGTTTGCCGCTGCCCAATGCCA	1574

[Table 4-38]

30	H45_13-42	GGCATTGGGCAGCGGCAAACTGTTGTCAGA	879	TCTGACAACAGTTTGCCGCTGCCCAATGCC	1575
30	H45_14-43	GCATTGGGCAGCGGCAAACTGTTGTCAGAA	880	TTCTGACAACAGTTTGCCGCTGCCCAATGC	1576
30	H45_15-44	CATTGGGCAGCGGCAAACTGTTGTCAGAAC	881	GTTCTGACAACAGTTTGCCGCTGCCCAATG	1577
30	H45_16-45	ATTGGGCAGCGGCAAACTGTTGTCAGAACA	882	TGTTCTGACAACAGTTTGCCGCTGCCCAAT	1578
30	H45_17-46	TTGGGCAGCGGCAAACTGTTGTCAGAACAT	883	ATGTTCTGACAACAGTTTGCCGCTGCCCAA	1579
30	H45_18-47	TGGGCAGCGGCAAACTGTTGTCAGAACATT	884	AATGTTCTGACAACAGTTTGCCGCTGCCCA	1580
30	H45_19-48	GGGCAGCGGCAAACTGTTGTCAGAACATTG	885	CAATGTTCTGACAACAGTTTGCCGCTGCCC	1581
30	H45_20-49	GGCAGCGGCAAACTGTTGTCAGAACATTGA	886	TCAATGTTCTGACAACAGTTTGCCGCTGCC	1582
30	H45_21-50	GCAGCGGCAAACTGTTGTCAGAACATTGAA	887	TTCAATGTTCTGACAACAGTTTGCCGCTGC	1583
30	H45_22-51	CAGCGGCAAACTGTTGTCAGAACATTGAAT	888	ATTCAATGTTCTGACAACAGTTTGCCGCTG	1584
30	H45_23-52	AGCGGCAAACTGTTGTCAGAACATTGAATG	889	CATTCAATGTTCTGACAACAGTTTGCCGCT	1585
30	H45_24-53	GCGGCAAACTGTTGTCAGAACATTGAATGC	890	GCATTCAATGTTCTGACAACAGTTTGCCGC	1586
30	H45_25-54	CGGCAAACTGTTGTCAGAACATTGAATGCA	891	TGCATTCAATGTTCTGACAACAGTTTGCCG	1587
30	H45_26-55	GGCAAACTGTTGTCAGAACATTGAATGCAA	892	TTGCATTCAATGTTCTGACAACAGTTTGCC	1588
30	H45_27-56	GCAAACTGTTGTCAGAACATTGAATGCAAC	893	GTTGCATTCAATGTTCTGACAACAGTTTGC	1589
30	H45_28-57	CAAACTGTTGTCAGAACATTGAATGCAACT	894	AGTTGCATTCAATGTTCTGACAACAGTTTG	1590
30	H45_29-58	AAACTGTTGTCAGAACATTGAATGCAACTG	895	CAGTTGCATTCAATGTTCTGACAACAGTTT	1591
30	H45_30-59	AACTGTTGTCAGAACATTGAATGCAACTGG	896	CCAGTTGCATTCAATGTTCTGACAACAGTT	1592

[Table 4-39]

30	H45_31-60	ACTGTTGTCAGAACATTGAATGCAACTGGG	897	CCCAGTTGCATTCAATGTTCTGACAACAGT	1593
30	H45_32-61	CTGTTGTCAGAACATTGAATGCAACTGGGG	898	CCCCAGTTGCATTCAATGTTCTGACAACAG	1594
30	H45_33-62	TGTTGTCAGAACATTGAATGCAACTGGGGA	899	TCCCCAGTTGCATTCAATGTTCTGACAACA	1595
30	H45_34-63	GTTGTCAGAACATTGAATGCAACTGGGGAA	900	TTCCCCAGTTGCATTCAATGTTCTGACAAC	1596
30	H45_35-64	TTGTCAGAACATTGAATGCAACTGGGGAAG	901	CTTCCCCAGTTGCATTCAATGTTCTGACAA	1597
30	H45_36-65	TGTCAGAACATTGAATGCAACTGGGGAAGA	902	TCTTCCCCAGTTGCATTCAATGTTCTGACA	1598
30	H45_37-66	GTCAGAACATTGAATGCAACTGGGGAAGAA	903	TTCTTCCCCAGTTGCATTCAATGTTCTGAC	1599
30	H45_38-67	TCAGAACATTGAATGCAACTGGGGAAGAAA	904	TTTCTTCCCCAGTTGCATTCAATGTTCTGA	1600
30	H45_39-68	CAGAACATTGAATGCAACTGGGGAAGAAAT	905	ATTTCTTCCCCAGTTGCATTCAATGTTCTG	1601
30	H45_40-69	AGAACATTGAATGCAACTGGGGAAGAAATA	906	TATTTCTTCCCCAGTTGCATTCAATGTTCT	1602

[0084]

In one embodiment, the first unit oligomer comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length

within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

[0085]

Herein, the base sequence (c) is a mutant type of the base sequence (a), and examples of such a mutant type also include

(c-1) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID Nos: 211 to 906, and has a length within ±15% of the length of the any one base sequence selected,

(c-2) a base sequence that has at least 86% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length within ±14% of the length of the any one base sequence selected,

(c-3) a base sequence that has at least 87% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length within ±13% of the length of the any one base sequence selected,

(c-4) a base sequence that has at least 88% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length within ±12% of the length of the any one base sequence selected,

(c-5) a base sequence that has at least 89% identity with any one base sequence selected from the group consisting

of SEQ ID NOs: 211 to 906, and has a length within ±11% of the length of the any one base sequence selected,

(c-6) a base sequence that has at least 90% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length within ±10% of the length of the any one base sequence selected,

(c-7) a base sequence that has at least 91% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length within ±9% of the length of the any one base sequence selected,

(c-8) a base sequence that has at least 92% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length within ±8% of the length of the any one base sequence selected,

(c-9) a base sequence that has at least 93% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length within ±7% of the length of the any one base sequence selected,

(c-10) a base sequence that has at least 94% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length within ±6% of the length of the any one base sequence selected,

(c-11) a base sequence that has at least 95% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length

within ±5% of the length of the any one base sequence selected,

(c-12) a base sequence that has at least 96% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length within ±4% of the length of the any one base sequence selected,

(c-13) a base sequence that has at least 97% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length within ±3% of the length of the any one base sequence selected,

(c-14) a base sequence that has at least 98% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length within ±2% of the length of the any one base sequence selected,

(c-15) a base sequence that has at least 99% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length within ±1% of the length of the any one base sequence selected, and

(c-16) a base sequence that has at least 99.5% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length within ±0.5% of the length of the any one base sequence selected.

[0086]

In one embodiment, the first unit oligomer comprises or consists of:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602; or

(b) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±15% of the length of the any one base sequence selected.

[0087]

Herein, the base sequence (b) is a mutant type of the base sequence (a), and examples of such a mutant type also include:

(b-1) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±15% of the length of the any one base sequence selected,

(b-2) a base sequence that has at least 86% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±14% of the length of the any one base sequence selected,

(b-3) a base sequence that has at least 87% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length

within ±13% of the length of the any one base sequence selected,

(b-4) a base sequence that has at least 88% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±12% of the length of the any one base sequence selected,

(b-5) a base sequence that has at least 89% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±11% of the length of the any one base sequence selected,

(b-6) a base sequence that has at least 90% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±10% of the length of the any one base sequence selected,

(b-7) a base sequence that has at least 91% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±9% of the length of the any one base sequence selected,

(b-8) a base sequence that has at least 92% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±8% of the length of the any one base sequence selected,

(b-9) a base sequence that has at least 93% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±7% of the length of the any one base sequence selected,

(b-10) a base sequence that has at least 94% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±6% of the length of the any one base sequence selected,

(b-11) a base sequence that has at least 95% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±5% of the length of the any one base sequence selected,

(b-12) a base sequence that has at least 96% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±4% of the length of the any one base sequence selected,

(b-13) a base sequence that has at least 97% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±3% of the length of the any one base sequence selected,

(b-14) a base sequence that has at least 98% identity with any one base sequence selected from the

group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±2% of the length of the any one base sequence selected,

(b-15) a base sequence that has at least 99% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±1% of the length of the any one base sequence selected, and

(b-16) a base sequence that has at least 99.5% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, and has a length within ±0.5% of the length of the any one base sequence selected.

[0088]

In one embodiment, the first unit oligomer comprises or consists of any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602.

[0089]

In one embodiment, the first unit oligomer comprises or consists of any one base sequence selected from the group consisting of SEQ ID NOs: 1180, 1190, 1201, 1212, 1222, 1224, and 1239.

[0090]

Table 5 below shows examples of the target sequence of the second unit oligomer, and a complementary sequence (antisense sequence) thereof.

[Table 5-1]

Table 5

Length mer	Target site	Targe sequence	SEQ ID NO:	Antisense sequence (5' to 3')	SEQ ID NO:
1	H45_(-61)	C	1	G	106
1	H45_(-62)	T	2	A	107
1	H45_(-63)	A	3	T	108
1	H45_(-64)	A	4	T	109
1	H45_(-65)	T	5	A	110
1	H45_(-66)	T	6	A	111
2	H45_(-61)-(-60)	CT	7	AG	112
2	H45_(-62)-(-61)	TC	8	GA	113
2	H45_(-63)-(-62)	AT	9	AT	114
2	H45_(-64)-(-63)	AA	10	TT	115
2	H45_(-65)-(-64)	TA	11	TA	116
2	H45_(-66)-(-65)	TT	12	AA	117
2	H45_(-67)-(-66)	TT	13	AA	118
3	H45_(-61)-(-59)	CTT	14	AAG	119
3	H45_(-62)-(-60)	TCT	15	AGA	120
3	H45_(-63)-(-61)	ATC	16	GAT	121
3	H45_(-64)-(-62)	AAT	17	ATT	122
3	H45_(-65)-(-63)	TAA	18	TTA	123
3	H45_(-66)-(-64)	TTA	19	TAA	124
3	H45_(-67)-(-65)	TTT	20	AAA	125
3	H45_(-68)-(-66)	GTT	21	AAC	126
4	H45_(-61)-(-58)	CTTT	22	AAAG	127
4	H45_(-62)-(-59)	TCTT	23	AAGA	128
4	H45_(-63)-(-60)	ATCT	24	AGAT	129
4	H45_(-64)-(-61)	AATC	25	GATT	130

[Table 5-2]

4	H45_(-65)-(-62)	TAAT	26	ATTA	131
4	H45_(-66)-(-63)	TTAA	27	TTAA	132
4	H45_(-67)-(-64)	TTTA	28	TAAA	133
4	H45_(-68)-(-65)	GTTT	29	AAAC	134
4	H45_(-69)-(-66)	TGTT	30	AACA	135
5	H45_(-61)-(-57)	CTTTT	31	AAAAG	136
5	H45_(-62)-(-58)	TCTTT	32	AAAGA	137
5	H45_(-63)-(-59)	ATCTT	33	AAGAT	138
5	H45_(-64)-(-60)	AATCT	34	AGATT	139
5	H45_(-65)-(-61)	TAATC	35	GATTA	140
5	H45_(-66)-(-62)	TTAAT	36	ATTAA	141
5	H45_(-67)-(-63)	TTTAA	37	TTAAA	142
5	H45_(-68)-(-64)	GTTTA	38	TAAAC	143
5	H45_(-69)-(-65)	TGTTT	39	AAACA	144
5	H45_(-70)-(-66)	CTGTT	40	AACAG	145
6	H45_(-61)-(-56)	CTTTTC	41	GAAAAG	146
6	H45_(-62)-(-57)	TCTTTT	42	AAAAGA	147
6	H45_(-63)-(-58)	ATCTTT	43	AAAGAT	148
6	H45_(-64)-(-59)	AATCTT	44	AAGATT	149
6	H45_(-65)-(-60)	TAATCT	45	AGATTA	150
6	H45_(-66)-(-61)	TTAATC	46	GATTAA	151
6	H45_(-67)-(-62)	TTTAAT	47	ATTAAA	152
6	H45_(-68)-(-63)	GTTTAA	48	TTAAAC	153
6	H45_(-69)-(-64)	TGTTTA	49	TAAACA	154
6	H45_(-70)-(-65)	CTGTTT	50	AAACAG	155
6	H45_(-71)-(-66)	ACTGTT	51	AACAGT	156
7	H45_(-61)-(-55)	CTTTTCT	52	AGAAAAG	157
7	H45_(-62)-(-56)	TCTTTTC	53	GAAAAGA	158
7	H45_(-63)-(-57)	ATCTTTT	54	AAAAGAT	159
7	H45_(-64)-(-58)	AATCTTT	55	AAAGATT	160
7	H45_(-65)-(-59)	TAATCTT	56	AAGATTA	161
7	H45_(-66)-(-60)	TTAATCT	57	AGATTAA	162
7	H45_(-67)-(-61)	TTTAATC	58	GATTAAA	163
7	H45_(-68)-(-62)	GTTTAAT	59	ATTAAAC	164
7	H45_(-69)-(-63)	TGTTTAA	60	TTAAACA	165

[Table 5-3]

7	H45_(-70)-(-64)	CTGTTTA	61	TAAACAG	166
7	H45_(-71)-(-65)	ACTGTTT	62	AAACAGT	167
7	H45_(-72)-(-66)	CACTGTT	63	AACAGTG	168
8	H45_(-61)-(-54)	CTTTTCTC	64	GAGAAAAG	169
8	H45_(-62)-(-55)	TCTTTTCT	65	AGAAAAGA	170
8	H45_(-63)-(-56)	ATCTTTTC	66	GAAAAGAT	171
8	H45_(-64)-(-57)	AATCTTTT	67	AAAAGATT	172
8	H45_(-65)-(-58)	TAATCTTT	68	AAAGATTA	173
8	H45_(-66)-(-59)	TTAATCTT	69	AAGATTAA	174
8	H45_(-67)-(-60)	TTTAATCT	70	AGATTAAA	175
8	H45_(-68)-(-61)	GTTTAATC	71	GATTAAAC	176
8	H45_(-69)-(-62)	TGTTTAAT	72	ATTAAACA	177
8	H45_(-70)-(-63)	CTGTTTAA	73	TTAAACAG	178
8	H45_(-71)-(-64)	ACTGTTTA	74	TAAACAGT	179
8	H45_(-72)-(-65)	CACTGTTT	75	AAACAGTG	180
8	H45_(-73)-(-66)	ACACTGTT	76	AACAGTGT	181
9	H45_(-61)-(-53)	CTTTTCTCA	77	TGAGAAAAG	182
9	H45_(-62)-(-54)	TCTTTTCTC	78	GAGAAAAGA	183
9	H45_(-63)-(-55)	ATCTTTTCT	79	AGAAAAGAT	184
9	H45_(-64)-(-56)	AATCTTTTC	80	GAAAAGATT	185
9	H45_(-65)-(-57)	TAATCTTTT	81	AAAAGATTA	186
9	H45_(-66)-(-58)	TTAATCTTT	82	AAAGATTAA	187
9	H45_(-67)-(-59)	TTTAATCTT	83	AAGATTAAA	188
9	H45_(-68)-(-60)	GTTTAATCT	84	AGATTAAAC	189
9	H45_(-69)-(-61)	TGTTTAATC	85	GATTAAACA	190
9	H45_(-70)-(-62)	CTGTTTAAT	86	ATTAAACAG	191
9	H45_(-71)-(-63)	ACTGTTTAA	87	TTAAACAGT	192
9	H45_(-72)-(-64)	CACTGTTTA	88	TAAACAGTG	193
9	H45_(-73)-(-65)	ACACTGTTT	89	AAACAGTGT	194
9	H45_(-74)-(-66)	CACACTGTT	90	AACAGTGTG	195
10	H45_(-61)-(-52)	CTTTTCTCAA	91	TTGAGAAAAG	196
10	H45_(-62)-(-53)	TCTTTTCTCA	92	TGAGAAAAGA	197
10	H45_(-63)-(-54)	ATCTTTTCTC	93	GAGAAAAGAT	198
10	H45_(-64)-(-55)	AATCTTTTCT	94	AGAAAAGATT	199
10	H45_(-65)-(-56)	TAATCTTTTC	95	GAAAAGATTA	200

[Table 5-4]

10	H45_(-66)-(-57)	TTAATCTTTT	96	AAAAGATTAA	201
10	H45_(-67)-(-58)	TTTAATCTTT	97	AAAGATTAAA	202
10	H45_(-68)-(-59)	GTTTAATCTT	98	AAGATTAAAC	203
10	H45_(-69)-(-60)	TGTTTAATCT	99	AGATTAAACA	204
10	H45_(-70)-(-61)	CTGTTTAATC	100	GATTAAACAG	205
10	H45_(-71)-(-62)	ACTGTTTAAT	101	ATTAAACAGT	206
10	H45_(-72)-(-63)	CACTGTTTAA	102	TTAAACAGTG	207
10	H45_(-73)-(-64)	ACACTGTTTA	103	TAAACAGTGT	208
10	H45_(-74)-(-65)	CACACTGTTT	104	AAACAGTGTG	209
10	H45_(-75)-(-66)	GCACACTGTT	105	AACAGTGTGC	210

[0091]

In one embodiment, the second unit oligomer comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

[0092]

Herein, the base sequence (c) is a mutant type of the base sequence (a), and examples of such a mutant type also include:

(c-1) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±15% of the length of the any one base sequence selected,

(c-2) a base sequence that has at least 86% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±14% of the length of the any one base sequence selected,

(c-3) a base sequence that has at least 87% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±13% of the length of the any one base sequence selected,

(c-4) a base sequence that has at least 88% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±12% of the length of the any one base sequence selected,

(c-5) a base sequence that has at least 89% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length

within ±11% of the length of the any one base sequence selected,

(c-6) a base sequence that has at least 90% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±10% of the length of the any one base sequence selected,

(c-7) a base sequence that has at least 91% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±9% of the length of the any one base sequence selected,

(c-8) a base sequence that has at least 92% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±8% of the length of the any one base sequence selected,

(c-9) a base sequence that has at least 93% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±7% of the length of the any one base sequence selected,

(c-10) a base sequence that has at least 94% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±6% of the length of the any one base sequence selected,

(c-11) a base sequence that has at least 95% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±5% of the length of the any one base sequence selected,

(c-12) a base sequence that has at least 96% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±4% of the length of the any one base sequence selected,

(c-13) a base sequence that has at least 97% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±3% of the length of the any one base sequence selected,

(c-14) a base sequence that has at least 98% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±2% of the length of the any one base sequence selected,

(c-15) a base sequence that has at least 99% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±1% of the length of the any one base sequence selected, and

(c-16) a base sequence that has at least 99.5% identity with any one base sequence selected from the

group consisting of SEQ ID NOs: 1 to 105, and has a length within ±0.5% of the length of the any one base sequence selected.

[0093]

In one embodiment, the second unit oligomer comprises or consists of:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210; or

(b) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and has a length within ±15% of the length of the any one base sequence selected.

[0094]

Herein, the base sequence (b) is a mutant type of the base sequence (a), and examples of such a mutant type also include

(b-1) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and has a length within ±15% of the length of the any one base sequence selected,

(b-2) a base sequence that has at least 86% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and has a length within ±14% of the length of the any one base sequence selected,

(b-3) a base sequence that has at least 87% identity with any one base sequence selected from the group consisting

of SEQ ID NOs: 106 to 210, and has a length within ±13% of the length of the any one base sequence selected,

(b-4) a base sequence that has at least 88% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and has a length within ±12% of the length of the any one base sequence selected,

(b-5) a base sequence that has at least 89% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and has a length within ±11% of the length of the any one base sequence selected,

(b-6) a base sequence that has at least 90% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and has a length within ±10% of the length of the any one base sequence selected,

(b-7) a base sequence that has at least 91% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and has a length within ±9% of the length of the any one base sequence selected,

(b-8) a base sequence that has at least 92% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and has a length within ±8% of the length of the any one base sequence selected,

(b-9) a base sequence that has at least 93% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and has a length within ±7% of the length of the any one base sequence selected,

(b-10) a base sequence that has at least 94% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and has a length within ±6% of the length of the any one base sequence selected,

(b-11) a base sequence that has at least 95% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and has a length within ±5% of the length of the any one base sequence selected,

(b-12) a base sequence that has at least 96% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and has a length within ±4% of the length of the any one base sequence selected,

(b-13) a base sequence that has at least 97% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and has a length within ±3% of the length of the any one base sequence selected,

(b-14) a base sequence that has at least 98% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and has a length within ±2% of the length of the any one base sequence selected,

(b-15) a base sequence that has at least 99% identity with any one base sequence selected from the group

consisting of SEQ ID NOs: 106 to 210, and has a length within ±1% of the length of the any one base sequence selected, and

(b-16) a base sequence that has at least 99.5% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and has a length within ±0.5% of the length of the any one base sequence selected.

[0095]

In one embodiment, the second unit oligomer comprises or consists of any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210.

[0096]

In one embodiment, the second unit oligomer comprises or consists of any one base sequence selected from the group consisting of SEQ ID NOs: 114, 124, 151, 201, 203, and 205.

[0097]

In one embodiment, the first unit oligomer comprises or consists of any one base sequence selected from the group consisting of SEQ ID NOs: 907 to 1602, the second unit oligomer comprises or consists of any one base sequence selected from the group consisting of SEQ ID NOs: 106 to 210, and the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order.

[0098]

In one embodiment, the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, and

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, and the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, and the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 201,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, and the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 203,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, and the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 205,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1239, and the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 114,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1224, and the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 124,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1180, and the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1190, and the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1212, and the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, or

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1222, and the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151.

[0099]

Table 6 below shows examples of the target sequence of the second antisense oligomer of the present invention, and a complementary sequence (antisense sequence) thereof.

[Table 6-1]

Table 6

Length mer	Target site	Targe sequence	SEQ ID NO:	Antisense sequence (5' to 3')	SEQ ID NO:
15	H55_(-18)-(-4)	ACATTTGGTCCTTTG	3507	CAAAGGACCAAATGT	4299
15	H55_(-17)-(-3)	CATTTGGTCCTTTGC	3508	GCAAAGGACCAAATG	4300
15	H55_(-16)-(-2)	ATTTGGTCCTTTGCA	3509	TGCAAAGGACCAAAT	4301
15	H55_(-15)-(-1)	TTTGGTCCTTTGCAG	3510	CTGCAAAGGACCAAA	4302
15	H55_(-14)-1	TTGGTCCTTTGCAGG	3511	CCTGCAAAGGACCAA	4303
15	H55_(-13)-2	TGGTCCTTTGCAGGG	3512	CCCTGCAAAGGACCA	4304
15	H55_(-12)-3	GGTCCTTTGCAGGGT	3513	ACCCTGCAAAGGACC	4305
15	H55_(-11)-4	GTCCTTTGCAGGGTG	3514	CACCCTGCAAAGGAC	4306
15	H55_(-10)-5	TCCTTTGCAGGGTGA	3515	TCACCCTGCAAAGGA	4307
15	H55_(-9)-6	CCTTTGCAGGGTGAG	3516	CTCACCCTGCAAAGG	4308
15	H55_(-8)-7	CTTTGCAGGGTGAGT	3517	ACTCACCCTGCAAAG	4309
15	H55_(-7)-8	TTTGCAGGGTGAGTG	3518	CACTCACCCTGCAAA	4310
15	H55_(-6)-9	TTGCAGGGTGAGTGA	3519	TCACTCACCCTGCAA	4311
15	H55_(-5)-10	TGCAGGGTGAGTGAG	3520	CTCACTCACCCTGCA	4312
15	H55_(-4)-11	GCAGGGTGAGTGAGC	3521	GCTCACTCACCCTGC	4313
15	H55_(-3)-12	CAGGGTGAGTGAGCG	3522	CGCTCACTCACCCTG	4314
15	H55_(-2)-	AGGGTGAGTGAGCGA	3523	TCGCTCACTCACCCT	4315

[Table 6-2]

	13				
15	H55_(-1)-14	GGGTGAGTGAGCGAG	3524	CTCGCTCACTCACCC	4316
15	H55_1-15	GGTGAGTGAGCGAGA	3525	TCTCGCTCACTCACC	4317
15	H55_2-16	GTGAGTGAGCGAGAG	3526	CTCTCGCTCACTCAC	4318
15	H55_3-17	TGAGTGAGCGAGAGG	3527	CCTCTCGCTCACTCA	4319
15	H55_4-18	GAGTGAGCGAGAGGC	3528	GCCTCTCGCTCACTC	4320
15	H55_5-19	AGTGAGCGAGAGGCT	3529	AGCCTCTCGCTCACT	4321
15	H55_6-20	GTGAGCGAGAGGCTG	3530	CAGCCTCTCGCTCAC	4322
15	H55_7-21	TGAGCGAGAGGCTGC	3531	GCAGCCTCTCGCTCA	4323
15	H55_8-22	GAGCGAGAGGCTGCT	3532	AGCAGCCTCTCGCTC	4324
15	H55_9-23	AGCGAGAGGCTGCTT	3533	AAGCAGCCTCTCGCT	4325
15	H55_10-24	GCGAGAGGCTGCTTT	3534	AAAGCAGCCTCTCGC	4326
15	H55_11-25	CGAGAGGCTGCTTTG	3535	CAAAGCAGCCTCTCG	4327
15	H55_12-26	GAGAGGCTGCTTTGG	3536	CCAAAGCAGCCTCTC	4328
15	H55_13-27	AGAGGCTGCTTTGGA	3537	TCCAAAGCAGCCTCT	4329
15	H55_14-28	GAGGCTGCTTTGGAA	3538	TTCCAAAGCAGCCTC	4330
15	H55_15-29	AGGCTGCTTTGGAAG	3539	CTTCCAAAGCAGCCT	4331
15	H55_16-30	GGCTGCTTTGGAAGA	3540	TCTTCCAAAGCAGCC	4332
15	H55_17-31	GCTGCTTTGGAAGAA	3541	TTCTTCCAAAGCAGC	4333
15	H55_18-32	CTGCTTTGGAAGAAA	3542	TTTCTTCCAAAGCAG	4334
15	H55_19-33	TGCTTTGGAAGAAAC	3543	GTTTCTTCCAAAGCA	4335
15	H55_20-34	GCTTTGGAAGAAACT	3544	AGTTTCTTCCAAAGC	4336
15	H55_21-35	CTTTGGAAGAAACTC	3545	GAGTTTCTTCCAAAG	4337
15	H55_22-36	TTTGGAAGAAACTCA	3546	TGAGTTTCTTCCAAA	4338
15	H55_23-37	TTGGAAGAAACTCAT	3547	ATGAGTTTCTTCCAA	4339
15	H55_24-38	TGGAAGAAACTCATA	3548	TATGAGTTTCTTCCA	4340
16	H55_(-19)-(-4)	AACATTTGGTCCTTTG	3549	CAAAGGACCAAATGTT	4341
16	H55_(-18)-(-3)	ACATTTGGTCCTTTGC	3550	GCAAAGGACCAAATGT	4342
16	H55_(-17)-(-2)	CATTTGGTCCTTTGCA	3551	TGCAAAGGACCAAATG	4343
16	H55_(-16)-(-1)	ATTTGGTCCTTTGCAG	3552	CTGCAAAGGACCAAAT	4344

[Table 6-3]

16	H55_(-15)-1	TTTGGTCCTTTGCAGG	3553	CCTGCAAAGGACCAAA	4345
16	H55_(-14)-2	TTGGTCCTTTGCAGGG	3554	CCCTGCAAAGGACCAA	4346
16	H55_(-13)-3	TGGTCCTTTGCAGGGT	3555	ACCCTGCAAAGGACCA	4347
16	H55_(-12)-4	GGTCCTTTGCAGGGTG	3556	CACCCTGCAAAGGACC	4348
16	H55_(-11)-5	GTCCTTTGCAGGGTGA	3557	TCACCCTGCAAAGGAC	4349
16	H55_(-10)-6	TCCTTTGCAGGGTGAG	3558	CTCACCCTGCAAAGGA	4350
16	H55_(-9)-7	CCTTTGCAGGGTGAGT	3559	ACTCACCCTGCAAAGG	4351
16	H55_(-8)-8	CTTTGCAGGGTGAGTG	3560	CACTCACCCTGCAAAG	4352
16	H55_(-7)-9	TTTGCAGGGTGAGTGA	3561	TCACTCACCCTGCAAA	4353
16	H55_(-6)-10	TTGCAGGGTGAGTGAG	3562	CTCACTCACCCTGCAA	4354
16	H55_(-5)-11	TGCAGGGTGAGTGAGC	3563	GCTCACTCACCCTGCA	4355
16	H55_(-4)-12	GCAGGGTGAGTGAGCG	3564	CGCTCACTCACCCTGC	4356
16	H55_(-3)-13	CAGGGTGAGTGAGCGA	3565	TCGCTCACTCACCCTG	4357
16	H55_(-2)-14	AGGGTGAGTGAGCGAG	3566	CTCGCTCACTCACCCT	4358
16	H55_(-1)-15	GGGTGAGTGAGCGAGA	3567	TCTCGCTCACTCACCC	4359
16	H55_1-16	GGTGAGTGAGCGAGAG	3568	CTCTCGCTCACTCACC	4360
16	H55_2-17	GTGAGTGAGCGAGAGG	3569	CCTCTCGCTCACTCAC	4361
16	H55_3-18	TGAGTGAGCGAGAGGC	3570	GCCTCTCGCTCACTCA	4362
16	H55_4-19	GAGTGAGCGAGAGGCT	3571	AGCCTCTCGCTCACTC	4363
16	H55_5-20	AGTGAGCGAGAGGCTG	3572	CAGCCTCTCGCTCACT	4364

[Table 6-4]

16	H55_6-21	GTGAGCGAGAGGCTGC	3573	GCAGCCTCTCGCTCAC	4365
16	H55_7-22	TGAGCGAGAGGCTGCT	3574	AGCAGCCTCTCGCTCA	4366
16	H55_8-23	GAGCGAGAGGCTGCTT	3575	AAGCAGCCTCTCGCTC	4367
16	H55_9-24	AGCGAGAGGCTGCTTT	3576	AAAGCAGCCTCTCGCT	4368
16	H55_10-25	GCGAGAGGCTGCTTTG	3577	CAAAGCAGCCTCTCGC	4369
16	H55_11-26	CGAGAGGCTGCTTTGG	3578	CCAAAGCAGCCTCTCG	4370
16	H55_12-27	GAGAGGCTGCTTTGGA	3579	TCCAAAGCAGCCTCTC	4371
16	H55_13-28	AGAGGCTGCTTTCGAA	3580	TTCCAAAGCAGCCTCT	4372
16	H55_14-29	GAGGCTGCTTTGGAAG	3581	CTTCCAAAGCAGCCTC	4373
16	H55_15-30	AGGCTGCTTTGGAAGA	3582	TCTTCCAAAGCAGCCT	4374
16	H55_16-31	GGCTGCTTTGGAAGAA	3583	TTCTTCCAAAGCAGCC	4375
16	H55_17-32	GCTGCTTTGGAAGAAA	3584	TTTCTTCCAAAGCAGC	4376
16	H55_18-33	CTGCTTTGGAAGAAAC	3585	GTTTCTTCCAAAGCAG	4377
16	H55_19-34	TGCTTTGGAAGAAACT	3586	AGTTTCTTCCAAAGCA	4378
16	H55_20-35	GCTTTGGAAGAAACTC	3587	GAGTTTCTTCCAAAGC	4379
16	H55_21-36	CTTTGGAAGAAACTCA	3588	TGAGTTTCTTCCAAAG	4380
16	H55_22-37	TTTGGAAGAAACTCAT	3589	ATGAGTTTCTTCCAAA	4381
16	H55_23-38	TTGGAAGAAACTCATA	3590	TATGAGTTTCTTCCAA	4382
16	H55_24-39	TGGAAGAAACTCATAG	3591	CTATGAGTTTCTTCCA	4383
17	H55_(-20)-(-4)	GAACATTTGGTCCTTTG	3592	CAAAGGACCAAATGTTC	4384
17	H55_(-19)-(-3)	AACATTTGGTCCTTTGC	3593	GCAAAGGACCAAATGTT	4385
17	H55_(-18)-(-2)	ACATTTGGTCCTTTGCA	3594	TGCAAAGGACCAAATGT	4386
17	H55_(-17)-(-1)	CATTTGGTCCTTTGCAG	3595	CTGCAAAGGACCAAATG	4387
17	H55_(-16)-1	ATTTGGTCCTTTGCAGG	3596	CCTGCAAAGGACCAAAT	4388
17	H55_(-15)-2	TTTGGTCCTTTGCAGGG	3597	CCCTGCAAAGGACCAAA	4389
17	H55_(-14)-3	TTGGTCCTTTGCAGGGT	3598	ACCCTGCAAAGGACCAA	4390
17	H55_(-13)-4	TGGTCCTTTGCAGGGTG	3599	CACCCTGCAAAGGACCA	4391

[Table 6-5]

17	H55_(-12)-5	GGTCCTTTGCAGGGTGA	3600	TCACCCTGCAAAGGACC	4392
17	H55_(-11)-6	GTCCTTTGCAGGGTGAG	3601	CTCACCCTGCAAAGGAC	4393
17	H55_(-10)-7	TCCTTTGCAGGGTGAGT	3602	ACTCACCCTGCAAAGGA	4394
17	H55_(-9)-8	CCTTTGCAGGGTGAGTG	3603	CACTCACCCTGCAAAGG	4395
17	H55_(-8)-9	CTTTGCAGGGTGAGTGA	3604	TCACTCACCCTGCAAAG	4396
17	H55_(-7)-10	TTTGCAGGGTGAGTGAG	3605	CTCACTCACCCTGCAAA	4397
17	H55_(-6)-11	TTGCAGGGTGAGTGAGC	3606	GCTCACTCACCCTGCAA	4398
17	H55_(-5)-12	TGCAGGGTGAGTGAGCG	3607	CGCTCACTCACCCTGCA	4399
17	H55_(-4)-13	GCAGGGTGAGTGAGCGA	3608	TCGCTCACTCACCCTGC	4400
17	H55_(-3)-14	CAGGGTGAGTGAGCGAG	3609	CTCGCTCACTCACCCTG	4401
17	H55_(-2)-15	AGGGTGAGTGAGCGAGA	3610	TCTCGCTCACTCACCCT	4402
17	H55_(-1)-16	GGGTGAGTGAGCGAGAG	3611	CTCTCGCTCACTCACCC	4403
17	H55_1-17	GGTGAGTGAGCGAGAGG	3612	CCTCTCGCTCACTCACC	4404
17	H55_2-18	GTGAGTGAGCGAGAGGC	3613	GCCTCTCGCTCACTCAC	4405
17	H55_3-19	TGAGTGAGCGAGAGGCT	3614	AGCCTCTCGCTCACTCA	4406
17	H55_4-20	GAGTGAGCGAGAGGCTG	3615	CAGCCTCTCGCTCACTC	4407
17	H55_5-21	AGTGAGCGAGAGGCTGC	3616	GCAGCCTCTCGCTCACT	4408
17	H55_6-22	GTGAGCGAGAGGCTGCT	3617	AGCAGCCTCTCGCTCAC	4409
17	H55_7-23	TGAGCGAGAGGCTGCTT	3618	AAGCAGCCTCTCGCTCA	4410
17	H55_8-24	GAGCGAGAGGCTGCTTT	3619	AAAGCAGCCTCTCGCTC	4411
17	H55_9-25	AGCGAGAGGCTGCTTTG	3620	CAAAGCAGCCTCTCGCT	4412
17	H55_10-26	GCGAGAGGCTGCTTTGG	3621	CCAAAGCAGCCTCTCGC	4413
17	H55_11-27	CGAGAGGCTGCTTTGGA	3622	TCCAAAGCAGCCTCTCG	4414

[Table 6-6]

17	H55_12-28	GAGAGGCTGCTTTGGAA	3623	TTCCAAAGCAGCCTCTC	4415
17	H55_13-29	AGAGGCTGCTTTGGAAG	3624	CTTCCAAAGCAGCCTCT	4416
17	H55_14-30	GAGGCTGCTTTGGAAGA	3625	TCTTCCAAAGCAGCCTC	4417
17	H55_15-31	AGGCTGCTTTGGAAGAA	3626	TTCTTCCAAAGCAGCCT	4418
17	H55_16-32	GGCTGCTTTGGAAGAAA	3627	TTTCTTCCAAAGCAGCC	4419
17	H55_17-33	GCTGCTTTGGAAGAAAC	3628	GTTTCTTCCAAAGCAGC	4420
17	H55_18-34	CTGCTTTGGAAGAAACT	3629	AGTTTCTTCCAAAGCAG	4421
17	H55_19-35	TGCTTTGGAAGAAACTC	3630	GAGTTTCTTCCAAAGCA	4422
17	H55_20-36	GCTTTGGAAGAAACTCA	3631	TGAGTTTCTTCCAAAGC	4423
17	H55_21-37	CTTTGGAAGAAACTCAT	3632	ATGAGTTTCTTCCAAAG	4424
17	H55_22-38	TTTGGAAGAAACTCATA	3633	TATGAGTTTCTTCCAAA	4425
17	H55_23-39	TTGGAAGAAACTCATAG	3634	CTATGAGTTTCTTCCAA	4426
17	H55_24-40	TGGAAGAAACTCATAGA	3635	TCTATGAGTTTCTTCCA	4427
18	H55_(-21)-(-4)	TGAACATTTGGTCCTTTG	3636	CAAAGGACCAAATGTTCA	4428
18	H55_(-20)-(-3)	GAACATTTGGTCCTTTGC	3637	GCAAAGGACCAAATGTTC	4429
18	H55_(-19)-(-2)	AACATTTGGTCCTTTGCA	3638	TGCAAAGGACCAAATGTT	4430
18	H55_(-18)-(-1)	ACATTTGGTCCTTTGCAG	3639	CTGCAAAGGACCAAATGT	4431
18	H55_(-17)-1	CATTTGGTCCTTTGCAGG	3640	CCTGCAAAGGACCAAATG	4432
18	H55_(-16)-2	ATTTGGTCCTTTGCAGGG	3641	CCCTGCAAAGGACCAAAT	4433
18	H55_(-15)-3	TTTGGTCCTTTGCAGGGT	3642	ACCCTGCAAAGGACCAAA	4434
18	H55_(-14)-4	TTGGTCCTTTGCAGGGTG	3643	CACCCTGCAAAGGACCAA	4435
18	H55_(-13)-5	TGGTCCTTTGCAGGGTGA	3644	TCACCCTGCAAAGGACCA	4436
18	H55_(-12)-6	GGTCCTTTGCAGGGTGAG	3645	CTCACCCTGCAAAGGACC	4437
18	H55_(-11)-7	GTCCTTTGCAGGGTGAGT	3646	ACTCACCCTGCAAAGGAC	4438

[Table 6-7]

18	H55_(-10)-8	TCCTTTGCAGGGTGAGTG	3647	CACTCACCCTGCAAAGGA	4439
18	H55_(-9)-9	CCTTTGCAGGGTGAGTGA	3648	TCACTCACCCTGCAAAGG	4440
18	H55_(-8)-10	CTTTGCAGGGTGAGTGAG	3649	CTCACTCACCCTGCAAAG	4441
18	H55_(-7)-11	TTTGCAGGGTGAGTGAGC	3650	GCTCACTCACCCTGCAAA	4442
18	H55_(-6)-12	TTGCAGGGTGAGTGAGCG	3651	CGCTCACTCACCCTGCAA	4443
18	H55_(-5)-13	TGCAGGGTGAGTGAGCGA	3652	TCGCTCACTCACCCTGCA	4444
18	H55_(-4)-14	GCAGGGTGAGTGAGCGAG	3653	CTCGCTCACTCACCCTGC	4445
18	H55_(-3)-15	CAGGGTGAGTGAGCGAGA	3654	TCTCGCTCACTCACCCTG	4446
18	H55_(-2)-16	AGGGTGAGTGAGCGAGAG	3655	CTCTCGCTCACTCACCCT	4447
18	H55_(-1)-17	GGGTGAGTGAGCGAGAGG	3656	CCTCTCGCTCACTCACCC	4448
18	H55_1-18	GGTGAGTGAGCGAGAGGC	3657	GCCTCTCGCTCACTCACC	4449
18	H55_2-19	GTGAGTGAGCGAGAGGCT	3658	AGCCTCTCGCTCACTCAC	4450
18	H55_3-20	TGAGTGAGCGAGAGGCTG	3659	CAGCCTCTCGCTCACTCA	4451
18	H55_4-21	GAGTGAGCGAGAGGCTGC	3660	GCAGCCTCTCGCTCACTC	4452
18	H55_5-22	AGTGAGCGAGAGGCTGCT	3661	AGCAGCCTCTCGCTCACT	4453
18	H55_6-23	GTGAGCGAGAGGCTGCTT	3662	AAGCAGCCTCTCGCTCAC	4454
18	H55_7-24	TGAGCGAGAGGCTGCTTT	3663	AAAGCAGCCTCTCGCTCA	4455
18	H55_8-25	GAGCGAGAGGCTGCTTTG	3664	CAAAGCAGCCTCTCGCTC	4456
18	H55_9-26	AGCGAGAGGCTGCTTTGG	3665	CCAAAGCAGCCTCTCGCT	4457
18	H55_10-27	GCGAGAGGCTGCTTTGGA	3666	TCCAAAGCAGCCTCTCGC	4458
18	H55_11-28	CGAGAGGCTGCTTTGGAA	3667	TTCCAAAGCAGCCTCTCG	4459
18	H55_12-29	GAGAGGCTGCTTTGGAAG	3668	CTTCCAAAGCAGCCTCTC	4460
18	H55_13-30	AGAGGCTGCTTTGGAAGA	3669	TCTTCCAAAGCAGCCTCT	4461
18	H55_14-31	GAGGCTGCTTTGGAAGAA	3670	TTCTTCCAAAGCAGCCTC	4462
18	H55_15-32	AGGCTGCTTTGGAAGAAA	3671	TTTCTTCCAAAGCAGCCT	4463

[Table 6-8]

18	H55_16-33	GGCTGCTTTGGAAGAAAC	3672	GTTTCTTCCAAAGCAGCC	4464
18	H55_17-34	GCTGCTTTGGAAGAAACT	3673	AGTTTCTTCCAAAGCAGC	4465
18	H55_18-35	CTGCTTTGGAAGAAACTC	3674	GAGTTTCTTCCAAAGCAG	4466
18	H55_19-36	TGCTTTGGAAGAAACTCA	3675	TGAGTTTCTTCCAAAGCA	4467
18	H55_20-37	GCTTTGGAAGAAACTCAT	3676	ATGAGTTTCTTCCAAAGC	4468
18	H55_21-38	CTTTGGAAGAAACTCATA	3677	TATGAGTTTCTTCCAAAG	4469
18	H55_22-39	TTTGGAAGAAACTCATAG	3678	CTATGAGTTTCTTCCAAA	4470
18	H55_23-40	TTGGAAGAAACTCATAGA	3679	TCTATGAGTTTCTTCCAA	4471
18	H55_24-41	TGGAAGAAACTCATAGAT	3680	ATCTATGAGTTTCTTCCA	4472
19	H55_(-22)-(-4)	CTGAACATTTGGTCCTTTG	3681	CAAAGGACCAAATGTTCAG	4473
19	H55_(-21)-(-3)	TGAACATTTGGTCCTTTGC	3682	GCAAAGGACCAAATGTTCA	4474
19	H55_(-20)-(-2)	GAACATTTGGTCCTTTGCA	3683	TGCAAAGGACCAAATGTTC	4475
19	H55_(-19)-(-1)	AACATTTGGTCCTTTGCAG	3684	CTGCAAAGGACCAAATGTT	4476
19	H55_(-18)-1	ACATTTGGTCCTTTGCAGG	3685	CCTGCAAAGGACCAAATGT	4477
19	H55_(-17)-2	CATTTGGTCCTTTGCAGGG	3686	CCCTGCAAAGGACCAAATG	4478
19	H55_(-16)-3	ATTTGGTCCTTTGCAGGGT	3687	ACCCTGCAAAGGACCAAAT	4479
19	H55_(-15)-4	TTTGGTCCTTTGCAGGGTG	3688	CACCCTGCAAAGGACCAAA	4480
19	H55_(-14)-5	TTGGTCCTTTGCAGGGTGA	3689	TCACCCTGCAAAGGACCAA	4481
19	H55_(-13)-6	TGGTCCTTTGCAGGGTGAG	3690	CTCACCCTGCAAAGGACCA	4482
19	H55_(-12)-7	GGTCCTTTGCAGGGTGAGT	3691	ACTCACCCTGCAAAGGACC	4483
19	H55_(-11)-8	GTCCTTTGCAGGGTGAGTG	3692	CACTCACCCTGCAAAGGAC	4484
19	H55_(-10)-9	TCCTTTGCAGGGTGAGTGA	3693	TCACTCACCCTGCAAAGGA	4485

[Table 6-9]

19	H55_(-9)-10	CCTTTGCAGGGTGAGTGAG	3694	CTCACTCACCCTGCAAAGG	4486
19	H55_(-8)-11	CTTTGCAGGGTGAGTGAGC	3695	GCTCACTCACCCTGCAAAG	4487
19	H55_(-7)-12	TTTGCAGGGTGAGTGAGCG	3696	CGCTCACTCACCCTGCAAA	4488
19	H55_(-6)-13	TTGCAGGGTGAGTGAGCGA	3697	TCGCTCACTCACCCTGCAA	4489
19	H55_(-5)-14	TGCAGGGTGAGTGAGCGAG	3698	CTCGCTCACTCACCCTGCA	4490
19	H55_(-4)-15	GCAGGGTGAGTGAGCGAGA	3699	TCTCGCTCACTCACCCTGC	4491
19	H55_(-3)-16	CAGGGTGAGTGAGCGAGAG	3700	CTCTCGCTCACTCACCCTG	4492
19	H55_(-2)-17	AGGGTGAGTGAGCGAGAGG	3701	CCTCTCGCTCACTCACCCT	4493
19	H55_(-1)-18	GGGTGAGTGAGCGAGAGGC	3702	GCCTCTCGCTCACTCACCC	4494
19	H55_1-19	GGTGAGTGAGCGAGAGGCT	3703	AGCCTCTCGCTCACTCACC	4495
19	H55_2-20	GTGAGTGAGCGAGAGGCTG	3704	CAGCCTCTCGCTCACTCAC	4496
19	H55_3-21	TGAGTGAGCGAGAGGCTGC	3705	GCAGCCTCTCGCTCACTCA	4497
19	H55_4-22	GAGTGAGCGAGAGGCTGCT	3706	AGCAGCCTCTCGCTCACTC	4498
19	H55_5-23	AGTGAGCGAGAGGCTGCTT	3707	AAGCAGCCTCTCGCTCACT	4499
19	H55_6-24	GTGAGCGAGAGGCTGCTTT	3708	AAAGCAGCCTCTCGCTCAC	4500
19	H55_7-25	TGAGCGAGAGGCTGCTTTG	3709	CAAAGCAGCCTCTCGCTCA	4501
19	H55_8-26	GAGCGAGAGGCTGCTTTGG	3710	CCAAAGCAGCCTCTCGCTC	4502
19	H55_9-27	AGCGAGAGGCTGCTTTGGA	3711	TCCAAAGCAGCCTCTCGCT	4503
19	H55_10-28	GCGAGAGGCTGCTTTGGAA	3712	TTCCAAAGCAGCCTCTCGC	4504
19	H55_11-29	CGAGAGGCTGCTTTGGAAG	3713	CTTCCAAAGCAGCCTCTCG	4505
19	H55_12-30	GAGAGGCTGCTTTGGAAGA	3714	TCTTCCAAAGCAGCCTCTC	4506
19	H55_13-31	AGAGGCTGCTTTGGAAGAA	3715	TTCTTCCAAAGCAGCCTCT	4507
19	H55_14-32	GAGGCTGCTTTGGAAGAAA	3716	TTTCTTCCAAAGCAGCCTC	4508
19	H55_15-33	AGGCTGCTTTGGAAGAAAC	3717	GTTTCTTCCAAAGCAGCCT	4509
19	H55_16-34	GGCTGCTTTGGAAGAAACT	3718	AGTTTCTTCCAAAGCAGCC	4510
19	H55_17-35	GCTGCTTTGGAAGAAACTC	3719	GAGTTTCTTCCAAAGCAGC	4511

[Table 6-10]

19	H55_18-36	CTGCTTTGGAAGAAACTCA	3720	TGAGTTTCTTCCAAAGCAG	4512
19	H55_19-37	TGCTTTGGAAGAAACTCAT	3721	ATGAGTTTCTTCCAAAGCA	4513
19	H55_20-38	GCTTTGGAAGAAACTCATA	3722	TATGAGTTTCTTCCAAAGC	4514
19	H55_21-39	CTTTGGAAGAAACTCATAG	3723	CTATGAGTTTCTTCCAAAG	4515
19	H55_22-40	TTTGGAAGAAACTCATAGA	3724	TCTATGAGTTTCTTCCAAA	4516
19	H55_23-41	TTGGAAGAAACTCATAGAT	3725	ATCTATGAGTTTCTTCCAA	4517
19	H55_24-42	TGGAAGAAACTCATAGATT	3726	AATCTATGAGTTTCTTCCA	4518
20	H55_(-23)-(-4)	TCTGAACATTTGGTCCTTTG	3727	CAAAGGACCAAATGTTCAGA	4519
20	H55_(-22)-(-3)	CTGAACATTTGGTCCTTTGC	3728	GCAAAGGACCAAATGTTCAG	4520
20	H55_(-21)-(-2)	TGAACATTTGGTCCTTTGCA	3729	TGCAAAGGACCAAATGTTCA	4521
20	H55_(-20)-(-1)	GAACATTTGGTCCTTTGCAG	3730	CTGCAAAGGACCAAATGTTC	4522
20	H55_(-19)-1	AACATTTGGTCCTTTGCAGG	3731	CCTGCAAAGGACCAAATGTT	4523
20	H55_(-18)-2	ACATTTGGTCCTTTGCAGGG	3732	CCCTGCAAAGGACCAAATGT	4524
20	H55_(-17)-3	CATTTGGTCCTTTGCAGGGT	3733	ACCCTGCAAAGGACCAAATG	4525
20	H55_(-16)-4	ATTTGGTCCTTTGCAGGGTG	3734	CACCCTGCAAAGGACCAAAT	4526
20	H55_(-15)-5	TTTGGTCCTTTGCAGGGTGA	3735	TCACCCTGCAAAGGACCAAA	4527
20	H55_(-14)-6	TTGGTCCTTTGCAGGGTGAG	3736	CTCACCCTGCAAAGGACCAA	4528
20	H55_(-13)-7	TGGTCCTTTGCAGGGTGAGT	3737	ACTCACCCTGCAAAGGACCA	4529
20	H55_(-12)-8	GGTCCTTTGCAGGGTGAGTG	3738	CACTCACCCTGCAAAGGACC	4530
20	H55_(-11)-9	GTCCTTTGCAGGGTGAGTGA	3739	TCACTCACCCTGCAAAGGAC	4531
20	H55_(-10)-10	TCCTTTGCAGGGTGAGTGAG	3740	CTCACTCACCCTGCAAAGGA	4532

[Table 6-11]

20	H55_(-9)-11	CCTTTGCAGGGTGAGTGAGC	3741	GCTCACTCACCCTGCAAAGG	4533
20	H55_(-8)-12	CTTTGCAGGGTGAGTGAGCG	3742	CGCTCACTCACCCTGCAAAG	4534
20	H55_(-7)-13	TTTGCAGGGTGAGTGAGCGA	3743	TCGCTCACTCACCCTGCAAA	4535
20	H55_(-6)-14	TTGCAGGGTGAGTGAGCGAG	3744	CTCGCTCACTCACCCTGCAA	4536
20	H55_(-5)-15	TGCAGGGTGAGTGAGCGAGA	3745	TCTCGCTCACTCACCCTGCA	4537
20	H55_(-4)-16	GCAGGGTGAGTGAGCGAGAG	3746	CTCTCGCTCACTCACCCTGC	4538
20	H55_(-3)-17	CAGGGTGAGTGAGCGAGAGG	3747	CCTCTCGCTCACTCACCCTG	4539
20	H55_(-2)-18	AGGGTGAGTGAGCGAGAGGC	3748	GCCTCTCGCTCACTCACCCT	4540
20	H55_(-1)-19	GGGTGAGTGAGCGAGAGGCT	3749	AGCCTCTCGCTCACTCACCC	4541
20	H55_1-20	GGTGAGTGAGCGAGAGGCTG	3750	CAGCCTCTCGCTCACTCACC	4542
20	H55_2-21	GTGAGTGAGCGAGAGGCTGC	3751	GCAGCCTCTCGCTCACTCAC	4543
20	H55_3-22	TGAGTGAGCGAGAGGCTGCT	3752	AGCAGCCTCTCGCTCACTCA	4544
20	H55_4-23	GAGTGAGCGAGAGGCTGCTT	3753	AAGCAGCCTCTCGCTCACTC	4545
20	H55_5-24	AGTGAGCGAGAGGCTGCTTT	3754	AAAGCAGCCTCTCGCTCACT	4546
20	H55_6-25	GTGAGCGAGAGGCTGCTTTG	3755	CAAAGCAGCCTCTCGCTCAC	4547
20	H55_7-26	TGAGCGAGAGGCTGCTTTGG	3756	CCAAAGCAGCCTCTCGCTCA	4548
20	H55_8-27	GAGCGAGAGGCTGCTTTGGA	3757	TCCAAAGCAGCCTCTCGCTC	4549
20	H55_9-28	AGCGAGAGGCTGCTTTGGAA	3758	TTCCAAAGCAGCCTCTCGCT	4550
20	H55_10-29	GCGAGAGGCTGCTTTGGAAG	3759	CTTCCAAAGCAGCCTCTCGC	4551
20	H55_11-30	CGAGAGGCTGCTTTGGAAGA	3760	TCTTCCAAAGCAGCCTCTCG	4552
20	H55_12-31	GAGAGGCTGCTTTGGAAGAA	3761	TTCTTCCAAAGCAGCCTCTC	4553
20	H55_13-32	AGAGGCTGCTTTGGAAGAAA	3762	TTTCTTCCAAAGCAGCCTCT	4554
20	H55_14-33	GAGGCTGCTTTGGAAGAAAC	3763	GTTTCTTCCAAAGCAGCCTC	4555
20	H55_15-34	AGGCTGCTTTGGAAGAAACT	3764	AGTTTCTTCCAAAGCAGCCT	4556
20	H55_16-35	GGCTGCTTTGGAAGAAACTC	3765	GAGTTTCTTCCAAAGCAGCC	4557
20	H55_17-36	GCTGCTTTGGAAGAAACTCA	3766	TGAGTTTCTTCCAAAGCAGC	4558

[Table 6-12]

20	H55_18-37	CTGCTTTGGAAGAAACTCAT	3767	ATGAGTTTCTTCCAAAGCAG	4559
20	H55_19-38	TGCTTTGGAAGAAACTCATA	3768	TATGAGTTTCTTCCAAAGCA	4560
20	H55_20-39	GCTTTGGAAGAAACTCATAG	3769	CTATGAGTTTCTTCCAAAGC	4561
20	H55_21-40	CTTTGGAAGAAACTCATAGA	3770	TCTATGAGTTTCTTCCAAAG	4562
20	H55_22-41	TTTGGAAGAAACTCATAGAT	3771	ATCTATGAGTTTCTTCCAAA	4563
20	H55_23-42	TTGGAAGAAACTCATAGATT	3772	AATCTATGAGTTTCTTCCAA	4564
20	H55_24-43	TGGAAGAAACTCATAGATTA	3773	TAATCTATGAGTTTCTTCCA	4565
21	H55_(-24)-(-4)	ATCTGAACATTTGGTCCTTTG	3774	CAAAGGACCAAATGTTCAGAT	4566
21	H55_(-23)-(-3)	TCTGAACATTTGGTCCTTTGC	3775	GCAAAGGACCAAATGTTCAGA	4567
21	H55_(-22)-(-2)	CTGAACATTTGGTCCTTTGCA	3776	TGCAAAGGACCAAATGTTCAG	4568
21	H55_(-21)-(-1)	TGAACATTTGGTCCTTTGCAG	3777	CTGCAAAGGACCAAATGTTCA	4569
21	H55_(-20)-1	GAACATTTGGTCCTTTGCAGG	3778	CCTGCAAAGGACCAAATGTTC	4570
21	H55_(-19)-2	AACATTTGGTCCTTTGCAGGG	3779	CCCTGCAAAGGACCAAATGTT	4571
21	H55_(-18)-3	ACATTTGGTCCTTTGCAGGGT	3780	ACCCTGCAAAGGACCAAATGT	4572
21	H55_(-17)-4	CATTTGGTCCTTTGCAGGGTG	3781	CACCCTGCAAAGGACCAAATG	4573
21	H55_(-16)-5	ATTTGGTCCTTTGCAGGGTGA	3782	TCACCCTGCAAAGGACCAAAT	4574
21	H55_(-15)-6	TTTGGTCCTTTGCAGGGTGAG	3783	CTCACCCTGCAAAGGACCAAA	4575
21	H55_(-14)-7	TTGGTCCTTTGCAGGGTGAGT	3784	ACTCACCCTGCAAAGGACCAA	4576
21	H55_(-13)-8	TGGTCCTTTGCAGGGTGAGTG	3785	CACTCACCCTGCAAAGGACCA	4577
21	H55_(-12)-9	GGTCCTTTGCAGGGTGAGTGA	3786	TCACTCACCCTGCAAAGGACC	4578
21	H55_(-11)-10	GTCCTTTGCAGGGTGAGTGAG	3787	CTCACTCACCCTGCAAAGGAC	4579

[Table 6-13]

21	H55_(-10)-11	TCCTTTGCAGGGTGAGTGAGC	3788	GCTCACTCACCCTGCAAAGGA	4580
21	H55_(-9)-12	CCTTTGCAGGGTGAGTGAGCG	3789	CGCTCACTCACCCTGCAAAGG	4581
21	H55_(-8)-13	CTTTGCAGGGTGAGTGAGCGA	3790	TCGCTCACTCACCCTGCAAAG	4582
21	H55_(-7)-14	TTTGCAGGGTGAGTGAGCGAG	3791	CTCGCTCACTCACCCTGCAAA	4583
21	H55_(-6)-15	TTGCAGGGTGAGTGAGCGAGA	3792	TCTCGCTCACTCACCCTGCAA	4584
21	H55_(-5)-16	TGCAGGGTGAGTGAGCGAGAG	3793	CTCTCGCTCACTCACCCTGCA	4585
21	H55_(-4)-17	GCAGGGTGAGTGAGCGAGAGG	3794	CCTCTCGCTCACTCACCCTGC	4586
21	H55_(-3)-18	CAGGGTGAGTGAGCGAGAGGC	3795	GCCTCTCGCTCACTCACCCTG	4587
21	H55_(-2)-19	AGGGTGAGTGAGCGAGAGGCT	3796	AGCCTCTCGCTCACTCACCCT	4588
21	H55_(-1)-20	GGGTGAGTGAGCGAGAGGCTG	3797	CAGCCTCTCGCTCACTCACCC	4589
21	H55_1-21	GGTGAGTGAGCGAGAGGCTGC	3798	GCAGCCTCTCGCTCACTCACC	4590
21	H55_2-22	GTGAGTGAGCGAGAGGCTGCT	3799	AGCAGCCTCTCGCTCACTCAC	4591
21	H55_3-23	TGAGTGAGCGAGAGGCTGCTT	3800	AAGCAGCCTCTCGCTCACTCA	4592
21	H55_4-24	GAGTGAGCGAGAGGCTGCTTT	3801	AAAGCAGCCTCTCGCTCACTC	4593
21	H55_5-25	AGTGAGCGAGAGGCTGCTTTG	3802	CAAAGCAGCCTCTCGCTCACT	4594
21	H55_6-26	GTGAGCGAGAGGCTGCTTTGG	3803	CCAAAGCAGCCTCTCGCTCAC	4595
21	H55_7-27	TGAGCGAGAGGCTGCTTTGGA	3804	TCCAAAGCAGCCTCTCGCTCA	4596
21	H55_8-28	GAGCGAGAGGCTGCTTTGGAA	3805	TTCCAAAGCAGCCTCTCGCTC	4597
21	H55_9-29	AGCGAGAGGCTGCTTTGGAAG	3806	CTTCCAAAGCAGCCTCTCGCT	4598
21	H55_10-30	GCGAGAGGCTGCTTTGGAAGA	3807	TCTTCCAAAGCAGCCTCTCGC	4599
21	H55_11-31	CGAGAGGCTGCTTTGGAAGAA	3808	TTCTTCCAAAGCAGCCTCTCG	4600
21	H55_12-32	GAGAGGCTGCTTTGGAAGAAA	3809	TTTCTTCCAAAGCAGCCTCTC	4601
21	H55_13-33	AGAGGCTGCTTTGGAAGAAAC	3810	GTTTCTTCCAAAGCAGCCTCT	4602
21	H55_14-34	GAGGCTGCTTTGGAAGAAACT	3811	AGTTTCTTCCAAAGCAGCCTC	4603
21	H55_15-35	AGGCTGCTTTGGAAGAAACTC	3812	GAGTTTCTTCCAAAGCAGCCT	4604

[Table 6-14]

21	H55_16-36	GGCTGCTTTGGAAGAAACTCA	3813	TGAGTTTCTTCCAAAGCAGCC	4605
21	H55_17-37	GCTGCTTTGGAAGAAACTCAT	3814	ATGAGTTTCTTCCAAAGCAGC	4606
21	H55_18-38	CTGCTTTGGAAGAAACTCATA	3815	TATGAGTTTCTTCCAAAGCAG	4607
21	H55_19-39	TGCTTTGGAAGAAACTCATAG	3816	CTATGAGTTTCTTCCAAAGCA	4608
21	H55_20-40	GCTTTGGAAGAAACTCATAGA	3817	TCTATGAGTTTCTTCCAAAGC	4609
21	H55_21-41	CTTTGGAAGAAACTCATAGAT	3818	ATCTATGAGTTTCTTCCAAAG	4610
21	H55_22-42	TTTGGAAGAAACTCATAGATT	3819	AATCTATGAGTTTCTTCCAAA	4611
21	H55_23-43	TTGGAAGAAACTCATAGATTA	3820	TAATCTATGAGTTTCTTCCAA	4612
21	H55_24-44	TGGAAGAAACTCATAGATTAC	3821	GTAATCTATGAGTTTCTTCCA	4613
22	H55_(-25)-(-4)	CATCTGAACATTTGGTCCTTTG	3822	CAAAGGACCAAATGTTCAGAT G	4614
22	H55_(-24)-(-3)	ATCTGAACATTTGGTCCTTTGC	3823	GCAAAGGACCAAATGTTCAGA T	4615
22	H55_(-23)-(-2)	TCTGAACATTTGGTCCTTTGC A	3824	TGCAAAGGACCAAATGTTCAG A	4616
22	H55_(-22)-(-1)	CTGAACATTTGGTCCTTTGCA G	3825	CTGCAAAGGACCAAATGTTCA G	4617
22	H55_(-21)-1	TGAACATTTGGTCCTTTGCAG G	3826	CCTGCAAAGGACCAAATGTTC A	4618
22	H55_(-20)-2	GAACATTTGGTCCTTTGCAGG G	3827	CCCTGCAAAGGACCAAATGTT C	4619
22	H55_(-19)-3	AACATTTGGTCCTTTGCAGGG T	3828	ACCCTGCAAAGGACCAAATGT T	4620
22	H55_(-18)-4	ACATTTGGTCCTTTGCAGGGT G	3829	CACCCTGCAAAGGACCAAATG T	4621
22	H55_(-17)-5	CATTTGGTCCTTTGCAGGGTG A	3830	TCACCCTGCAAAGGACCAAAT G	4622
22	H55_(-16)-6	ATTTGGTCCTTTGCAGGGTGA G	3831	CTCACCCTGCAAAGGACCAAA T	4623
22	H55_(-15)-7	TTTGGTCCTTTGCAGGGTGAG T	3832	ACTCACCCTGCAAAGGACCAA A	4624
22	H55_(-14)-8	TTGGTCCTTTGCAGGGTGAGT G	3833	CACTCACCCTGCAAAGGACCA A	4625
22	H55_(-13)-9	TGGTCCTTTGCAGGGTGAGTG A	3834	TCACTCACCCTGCAAAGGACC A	4626

[Table 6-15]

22	H55_(-12)-10	GGTCCTTTGCAGGGTGAGTGAG	3835	CTCACTCACCCTGCAAAGGACC	4627
22	H55_(-11)-11	GTCCTTTGCAGGGTGAGTGAGC	3836	GCTCACTCACCCTGCAAAGGAC	4628
22	H55_(-10)-12	TCCTTTGCAGGGTGAGTGAGCG	3837	CGCTCACTCACCCTGCAAAGGA	4629
22	H55_(-9)-13	CCTTTGCAGGGTGAGTGAGCGA	3838	TCGCTCACTCACCCTGCAAAGG	4630
22	H55_(-8)-14	CTTTGCAGGGTGAGTGAGCGAG	3839	CTCGCTCACTCACCCTGCAAAG	4631
22	H55_(-7)-15	TTTGCAGGGTGAGTGAGCGAGA	3840	TCTCGCTCACTCACCCTGCAAA	4632
22	H55_(-6)-16	TTGCAGGGTGAGTGAGCGAGAG	3841	CTCTCGCTCACTCACCCTGCAA	4633
22	H55_(-5)-17	TGCAGGGTGAGTGAGCGAGAGG	3842	CCTCTCGCTCACTCACCCTGCA	4634
22	H55_(-4)-18	GCAGGGTGAGTGAGCGAGAGGC	3843	GCCTCTCGCTCACTCACCCTGC	4635
22	H55_(-3)-19	CAGGGTGAGTGAGCGAGAGGCT	3844	AGCCTCTCGCTCACTCACCCTG	4636
22	H55_(-2)-20	AGGGTGAGTGAGCGAGAGGCTG	3845	CAGCCTCTCGCTCACTCACCCT	4637
22	H55_(-1)-21	GGGTGAGTGAGCGAGAGGCTGC	3846	GCAGCCTCTCGCTCACTCACCC	4638
22	H55_1-22	GGTGAGTGAGCGAGAGGCTGCT	3847	AGCAGCCTCTCGCTCACTCACC	4639
22	H55_2-23	GTGAGTGAGCGAGAGGCTGCTT	3848	AAGCAGCCTCTCGCTCACTCAC	4640
22	H55_3-24	TGAGTGAGCGAGAGGCTGCTTT	3849	AAAGCAGCCTCTCGCTCACTCA	4641
22	H55_4-25	GAGTGAGCGAGAGGCTGCTTTG	3850	CAAAGCAGCCTCTCGCTCACTC	4642
22	H55_5-26	AGTGAGCGAGAGGCTGCTTTGG	3851	CCAAAGCAGCCTCTCGCTCACT	4643
22	H55_6-27	GTGAGCGAGAGGCTGCTTTGGA	3852	TCCAAAGCAGCCTCTCGCTCAC	4644

[Table 6-16]

22	H55_7-28	TGAGCGAGAGGCTGCTTTGGA A	3853	TTCCAAAGCAGCCTCTCGCTC A	4645
22	H55_8-29	GAGCGAGAGGCTGCTTTGGAA G	3854	CTTCCAAAGCAGCCTCTCGCT C	4646
22	H55_9-30	AGCGAGAGGCTGCTTTGGAAG A	3855	TCTTCCAAAGCAGCCTCTCGC T	4647
22	H55_10-31	GCGAGAGGCTGCTTTGGAAGA A	3856	TTCTTCCAAAGCAGCCTCTCG C	4648
22	H55_11-32	CGAGAGGCTGCTTTGGAAGAA A	3857	TTTCTTCCAAAGCAGCCTCTC G	4649
22	H55_12-33	GAGAGGCTGCTTTGGAAGAAA C	3858	GTTTCTTCCAAAGCAGCCTCT C	4650
22	H55_13-34	AGAGGCTGCTTTGGAAGAAAC T	3859	AGTTTCTTCCAAAGCAGCCTC T	4651
22	H55_14-35	GAGGCTGCTTTGGAAGAAACT C	3860	GAGTTTCTTCCAAAGCAGCCT C	4652
22	H55_15-36	AGGCTGCTTTGGAAGAAACTC A	3861	TGAGTTTCTTCCAAAGCAGCC T	4653
22	H55_16-37	GGCTGCTTTGGAAGAAACTCA T	3862	ATGAGTTTCTTCCAAAGCAGC C	4654
22	H55_17-38	GCTGCTTTGGAAGAAACTCAT A	3863	TATGAGTTTCTTCCAAAGCAG C	4655
22	H55_18-39	CTGCTTTGGAAGAAACTCATA G	3864	CTATGAGTTTCTTCCAAAGCA G	4656
22	H55_19-40	TGCTTTGGAAGAAACTCATAG A	3865	TCTATGAGTTTCTTCCAAAGC A	4657
22	H55_20-41	GCTTTGGAAGAAACTCATAGA T	3866	ATCTATGAGTTTCTTCCAAAG C	4658
22	H55_21-42	CTTTGGAAGAAACTCATAGAT T	3867	AATCTATGAGTTTCTTCCAAA G	4659
22	H55_22-43	TTTGGAAGAAACTCATAGATT A	3868	TAATCTATGAGTTTCTTCCAA A	4660
22	H55_23-44	TTGGAAGAAACTCATAGATTA C	3869	GTAATCTATGAGTTTCTTCCA A	4661
22	H55_24-45	TGGAAGAAACTCATAGATTAC T	3870	AGTAATCTATGAGTTTCTTCC A	4662

[Table 6-17]

23	H55_(-26)-(-4)	GCATCTGAACATTTGGTCCTTTG	3871	CAAAGGACCAAATGTTCAGATGC	4663
23	H55_(-25)-(-3)	CATCTGAACATTTGGTCCTTTGC	3872	GCAAAGGACCAAATGTTCAGATG	4664
23	H55_(-24)-(-2)	ATCTGAACATTTGGTCCTTTGCA	3873	TGCAAAGGACCAAATGTTCAGAT	4665
23	H55_(-23)-(-1)	TCTGAACATTTGGTCCTTTGCAG	3874	CTGCAAAGGACCAAATGTTCAGA	4666
23	H55_(-22)-1	CTGAACATTTGGTCCTTTGCAGG	3875	CCTGCAAAGGACCAAATGTTCAG	4667
23	H55_(-21)-2	TGAACATTTGGTCCTTTGCAGGG	3876	CCCTGCAAAGGACCAAATGTTCA	4668
23	H55_(-20)-3	GAACATTTGGTCCTTTGCAGGGT	3877	ACCCTGCAAAGGACCAAATGTTC	4669
23	H55_(-19)-4	AACATTTGGTCCTTTGCAGGGTG	3878	CACCCTGCAAAGGACCAAATGTT	4670
23	H55_(-18)-5	ACATTTGGTCCTTTGCAGGGTGA	3879	TCACCCTGCAAAGGACCAAATGT	4671
23	H55_(-17)-6	CATTTGGTCCTTTGCAGGGTGAG	3880	CTCACCCTGCAAAGGACCAAATG	4672
23	H55_(-16)-7	ATTTGGTCCTTTGCAGGGTGAGT	3881	ACTCACCCTGCAAAGGACCAAAT	4673
23	H55_(-15)-8	TTTGGTCCTTTGCAGGGTGAGTG	3882	CACTCACCCTGCAAAGGACCAAA	4674
23	H55_(-14)-9	TTGGTCCTTTGCAGGGTGAGTGA	3883	TCACTCACCCTGCAAAGGACCAA	4675
23	H55_(-13)-10	TGGTCCTTTGCAGGGTGAGTGAG	3884	CTCACTCACCCTGCAAAGGACCA	4676
23	H55_(-12)-11	GGTCCTTTGCAGGGTGAGTGAGC	3885	GCTCACTCACCCTGCAAAGGACC	4677
23	H55_(-11)-12	GTCCTTTGCAGGGTGAGTGAGCG	3886	CGCTCACTCACCCTGCAAAGGAC	4678
23	H55_(-10)-13	TCCTTTGCAGGGTGAGTGAGCGA	3887	TCGCTCACTCACCCTGCAAAGGA	4679
23	H55_(-9)-14	CCTTTGCAGGGTGAGTGAGCGAG	3888	CTCGCTCACTCACCCTGCAAAGG	4680

[Table 6-18]

23	H55_(-8)-15	CTTTGCAGGGTGAGTGAGCGAGA	3889	TCTCGCTCACTCACCCTGCAAAG	4681
23	H55_(-7)-16	TTTGCAGGGTGAGTGAGCGAGAG	3890	CTCTCGCTCACTCACCCTGCAAA	4682
23	H55_(-6)-17	TTGCAGGGTGAGTGAGCGAGAGG	3891	CCTCTCGCTCACTCACCCTGCAA	4683
23	H55_(-5)-18	TGCAGGGTGAGTGAGCGAGAGGC	3892	GCCTCTCGCTCACTCACCCTGCA	4684
23	H55_(-4)-19	GCAGGGTGAGTGAGCGAGAGGCT	3893	AGCCTCTCGCTCACTCACCCTGC	4685
23	H55_(-3)-20	CAGGGTGAGTGAGCGAGAGGCTG	3894	CAGCCTCTCGCTCACTCACCCTG	4686
23	H55_(-2)-21	AGGGTGAGTGAGCGAGAGGCTGC	3895	GCAGCCTCTCGCTCACTCACCCT	4687
23	H55_(-1)-22	GGGTGAGTGAGCGAGAGGCTGCT	3896	AGCAGCCTCTCGCTCACTCACCC	4688
23	H55_1-23	GGTGAGTGAGCGAGAGGCTGCTT	3897	AAGCAGCCTCTCGCTCACTCACC	4689
23	H55_2-24	GTGAGTGAGCGAGAGGCTGCTTT	3898	AAAGCAGCCTCTCGCTCACTCAC	4690
23	H55_3-25	TGAGTGAGCGAGAGGCTGCTTTG	3899	CAAAGCAGCCTCTCGCTCACTCA	4691
23	H55_4-26	GAGTGAGCGAGAGGCTGCTTTGG	3900	CCAAAGCAGCCTCTCGCTCACTC	4692
23	H55_5-27	AGTGAGCGAGAGGCTGCTTTGGA	3901	TCCAAAGCAGCCTCTCGCTCACT	4693
23	H55_6-28	GTGAGCGAGAGGCTGCTTTGGAA	3902	TTCCAAAGCAGCCTCTCGCTCAC	4694
23	H55_7-29	TGAGCGAGAGGCTGCTTTGGAAG	3903	CTTCCAAAGCAGCCTCTCGCTCA	4695
23	H55_8-30	GAGCGAGAGGCTGCTTTGGAAGA	3904	TCTTCCAAAGCAGCCTCTCGCTC	4696
23	H55_9-31	AGCGAGAGGCTGCTTTGGAAGAA	3905	TTCTTCCAAAGCAGCCTCTCGCT	4697
23	H55_10-32	GCGAGAGGCTGCTTTGGAAGAAA	3906	TTTCTTCCAAAGCAGCCTCTCGC	4698

[Table 6-19]

23	H55_11-33	CGAGAGGCTGCTTTGGAAGAAAC	3907	GTTTCTTCCAAAGCAGCCTCTCG	4699
23	H55_12-34	GAGAGGCTGCTTTGGAAGAAACT	3908	AGTTTCTTCCAAAGCAGCCTCTC	4700
23	H55_13-35	AGAGGCTGCTTTGGAAGAAACTC	3909	GAGTTTCTTCCAAAGCAGCCTCT	4701
23	H55_14-36	GAGGCTGCTTTGGAAGAAACTCA	3910	TGAGTTTCTTCCAAAGCAGCCTC	4702
23	H55_15-37	AGGCTGCTTTGGAAGAAACTCAT	3911	ATGAGTTTCTTCCAAAGCAGCCT	4703
23	H55_16-38	GGCTGCTTTGGAAGAAACTCATA	3912	TATGAGTTTCTTCCAAAGCAGCC	4704
23	H55_17-39	GCTGCTTTGGAAGAAACTCATAG	3913	CTATGAGTTTCTTCCAAAGCAGC	4705
23	H55_18-40	CTGCTTTGGAAGAAACTCATAGA	3914	TCTATGAGTTTCTTCCAAAGCAG	4706
23	H55_19-41	TGCTTTGGAAGAAACTCATAGAT	3915	ATCTATGAGTTTCTTCCAAAGCA	4707
23	H55_20-42	GCTTTGGAAGAAACTCATAGATT	3916	AATCTATGAGTTTCTTCCAAAGC	4708
23	H55_21-43	CTTTGGAAGAAACTCATAGATTA	3917	TAATCTATGAGTTTCTTCCAAAG	4709
23	H55_22-44	TTTGGAAGAAACTCATAGATTAC	3918	GTAATCTATGAGTTTCTTCCAAA	4710
23	H55_23-45	TTGGAAGAAACTCATAGATTACT	3919	AGTAATCTATGAGTTTCTTCCAA	4711
23	H55_24-46	TGGAAGAAACTCATAGATTACTG	3920	CAGTAATCTATGAGTTTCTTCCA	4712
24	H55_(-27)-(-4)	TGCATCTGAACATTTGGTCCTTTG	3921	CAAAGGACCAAATGTTCAGATGCA	4713
24	H55_(-26)-(-3)	GCATCTGAACATTTGGTCCTTTGC	3922	GCAAAGGACCAAATGTTCAGATGC	4714
24	H55_(-25)-(-2)	CATCTGAACATTTGGTCCTTTGCA	3923	TGCAAAGGACCAAATGTTCAGATG	4715
24	H55_(-24)-(-1)	ATCTGAACATTTGGTCCTTTGCAG	3924	CTGCAAAGGACCAAATGTTCAGAT	4716

[Table 6-20]

24	H55_(-23)-1	TCTGAACATTTGGTCCTTTGCAGG	3925	CCTGCAAAGGACCAAATGTTCAGA	4717
24	H55_(-22)-2	CTGAACATTTGGTCCTTTGCAGGG	3926	CCCTGCAAAGGACCAAATGTTCAG	4718
24	H55_(-21)-3	TGAACATTTGGTCCTTTGCAGGGT	3927	ACCCTGCAAAGGACCAAATGTTCA	4719
24	H55_(-20)-4	GAACATTTGGTCCTTTGCAGGGTG	3928	CACCCTGCAAAGGACCAAATGTTC	4720
24	H55_(-19)-5	AACATTTGGTCCTTTGCAGGGTGA	3929	TCACCCTGCAAAGGACCAAATGTT	4721
24	H55_(-18)-6	ACATTTGGTCCTTTGCAGGGTGAG	3930	CTCACCCTGCAAAGGACCAAATGT	4722
24	H55_(-17)-7	CATTTGGTCCTTTGCAGGGTGAGT	3931	ACTCACCCTGCAAAGGACCAAATG	4723
24	H55_(-16)-8	ATTTGGTCCTTTGCAGGGTGAGTG	3932	CACTCACCCTGCAAAGGACCAAAT	4724
24	H55_(-15)-9	TTTGGTCCTTTGCAGGGTGAGTGA	3933	TCACTCACCCTGCAAAGGACCAAA	4725
24	H55_(-14)-10	TTGGTCCTTTGCAGGGTGAGTGAG	3934	CTCACTCACCCTGCAAAGGACCAA	4726
24	H55_(-13)-11	TGGTCCTTTGCAGGGTGAGTGAGC	3935	GCTCACTCACCCTGCAAAGGACCA	4727
24	H55_(-12)-12	GGTCCTTTGCAGGGTGAGTGAGCG	3936	CGCTCACTCACCCTGCAAAGGACC	4728
24	H55_(-11)-13	GTCCTTTGCAGGGTGAGTGAGCGA	3937	TCGCTCACTCACCCTGCAAAGGAC	4729
24	H55_(-10)-14	TCCTTTGCAGGGTGAGTGAGCGAG	3938	CTCGCTCACTCACCCTGCAAAGGA	4730
24	H55_(-9)-15	CCTTTGCAGGGTGAGTGAGCGAGA	3939	TCTCGCTCACTCACCCTGCAAAGG	4731
24	H55_(-8)-16	CTTTGCAGGGTGAGTGAGCGAGAG	3940	CTCTCGCTCACTCACCCTGCAAAG	4732
24	H55_(-7)-17	TTTGCAGGGTGAGTGAGCGAGAGG	3941	CCTCTCGCTCACTCACCCTGCAAA	4733
24	H55_(-6)-18	TTGCAGGGTGAGTGAGCGAGAGGC	3942	GCCTCTCGCTCACTCACCCTGCAA	4734

[Table 6-21]

24	H55_(-5)-19	TGCAGGGTGAGTGAGCGAGAGGCT	3943	AGCCTCTCGCTCACTCACCCTGCA	4735
24	H55_(-4)-20	GCAGGGTGAGTGAGCGAGAGGCTG	3944	CAGCCTCTCGCTCACTCACCCTGC	4736
24	H55_(-3)-21	CAGGGTGAGTGAGCGAGAGGCTGC	3945	GCAGCCTCTCGCTCACTCACCCTG	4737
24	H55_(-2)-22	AGGGTGAGTGAGCGAGAGGCTGCT	3946	AGCAGCCTCTCGCTCACTCACCCT	4738
24	H55_(-1)-23	GGGTGAGTGAGCGAGAGGCTGCTT	3947	AAGCAGCCTCTCGCTCACTCACCC	4739
24	H55_1-24	GGTGAGTGAGCGAGAGGCTGCTTT	3948	AAAGCAGCCTCTCGCTCACTCACC	4740
24	H55_2-25	GTGAGTGAGCGAGAGGCTGCTTTG	3949	CAAAGCAGCCTCTCGCTCACTCAC	4741
24	H55_3-26	TGAGTGAGCGAGAGGCTGCTTTGG	3950	CCAAAGCAGCCTCTCGCTCACTCA	4742
24	H55_4-27	GAGTGAGCGAGAGGCTGCTTTGGA	3951	TCCAAAGCAGCCTCTCGCTCACTC	4743
24	H55_5-28	AGTGAGCGAGAGGCTGCTTTGGAA	3952	TTCCAAAGCAGCCTCTCGCTCACT	4744
24	H55_6-29	GTGAGCGAGAGGCTGCTTTGGAAG	3953	CTTCCAAAGCAGCCTCTCGCTCAC	4745
24	H55_7-30	TGAGCGAGAGGCTGCTTTGGAAGA	3954	TCTTCCAAAGCAGCCTCTCGCTCA	4746
24	H55_8-31	GAGCGAGAGGCTGCTTTGGAAGAA	3955	TTCTTCCAAAGCAGCCTCTCGCTC	4747
24	H55_9-32	AGCGAGAGGCTGCTTTGGAAGAAA	3956	TTTCTTCCAAAGCAGCCTCTCGCT	4748
24	H55_10-33	GCGAGAGGCTGCTTTGGAAGAAAC	3957	GTTTCTTCCAAAGCAGCCTCTCGC	4749
24	H55_11-34	CGAGAGGCTGCTTTGGAAGAAACT	3958	AGTTTCTTCCAAAGCAGCCTCTCG	4750
24	H55_12-35	GAGAGGCTGCTTTGGAAGAAACTC	3959	GAGTTTCTTCCAAAGCAGCCTCTC	4751
24	H55_13-36	AGAGGCTGCTTTGGAAGAAACTCA	3960	TGAGTTTCTTCCAAAGCAGCCTCT	4752

[Table 6-22]

24	H55_14-37	GAGGCTGCTTTGGAAGAAACT CAT	3961	ATGAGTTTCTTCCAAAGCAGC CTC	4753
24	H55_15-38	AGGCTGCTTTGGAAGAAACTC ATA	3962	TATGAGTTTCTTCCAAAGCAG CCT	4754
24	H55_16-39	GGCTGCTTTGGAAGAAACTCA TAG	3963	CTATGAGTTTCTTCCAAAGCA GCC	4755
24	H55_17-40	GCTGCTTTGGAAGAAACTCAT AGA	3964	TCTATGAGTTTCTTCCAAAGC AGC	4756
24	H55_18-41	CTGCTTTGGAAGAAACTCATA GAT	3965	ATCTATGAGTTTCTTCCAAAG CAG	4757
24	H55_19-42	TGCTTTGGAAGAAACTCATAG ATT	3966	AATCTATGAGTTTCTTCCAAA GCA	4758
24	H55_20-43	GCTTTGGAAGAAACTCATAGA TTA	3967	TAATCTATGAGTTTCTTCCAA AGC	4759
24	H55_21-44	CTTTGGAAGAAACTCATAGAT TAC	3968	GTAATCTATGAGTTTCTTCCA AAG	4760
24	H55_22-45	TTTGGAAGAAACTCATAGATT ACT	3969	AGTAATCTATGAGTTTCTTCC AAA	4761
24	H55_23-46	TTGGAAGAAACTCATAGATTA CTG	3970	CAGTAATCTATGAGTTTCTTC CAA	4762
24	H55_24-47	TGGAAGAAACTCATAGATTAC TGC	3971	GCAGTAATCTATGAGTTTCTT CCA	4763
25	H55_(-28)-(-4)	TTGCATCTGAACATTTGGTCC TTTG	3972	CAAAGGACCAAATGTTCAGAT GCAA	4764
25	H55_(-27)-(-3)	TGCATCTGAACATTTGGTCCT TTGC	3973	GCAAAGGACCAAATGTTCAGA TGCA	4765
25	H55_(-26)-(-2)	GCATCTGAACATTTGGTCCTT TGCA	3974	TGCAAAGGACCAAATGTTCAG ATGC	4766
25	H55_(-25)-(-1)	CATCTGAACATTTGGTCCTTT GCAG	3975	CTGCAAAGGACCAAATGTTCA GATG	4767
25	H55_(-24)-1	ATCTGAACATTTGGTCCTTTG CAGG	3976	CCTGCAAAGGACCAAATGTTC AGAT	4768
25	H55_(-23)-2	TCTGAACATTTGGTCCTTTGC AGGG	3977	CCCTGCAAAGGACCAAATGTT CAGA	4769
25	H55_(-22)-3	CTGAACATTTGGTCCTTTGCA GGGT	3978	ACCCTGCAAAGGACCAAATGT TCAG	4770

[Table 6-23]

25	H55_(-21)-4	TGAACATTTGGTCCTTTGCAGGGTG	3979	CACCCTGCAAAGGACCAAATGTTCA	4771
25	H55_(-20)-5	GAACATTTGGTCCTTTGCAGGGTGA	3980	TCACCCTGCAAAGGACCAAATGTTC	4772
25	H55_(-19)-6	AACATTTGGTCCTTTGCAGGGTGAG	3981	CTCACCCTGCAAAGGACCAAATGTT	4773
25	H55_(-18)-7	ACATTTGGTCCTTTGCAGGGTGAGT	3982	ACTCACCCTGCAAAGGACCAAATGT	4774
25	H55_(-17)-8	CATTTGGTCCTTTGCAGGGTGAGTG	3983	CACTCACCCTGCAAAGGACCAAATG	4775
25	H55_(-16)-9	ATTTGGTCCTTTGCAGGGTGAGTGA	3984	TCACTCACCCTGCAAAGGACCAAAT	4776
25	H55_(-15)-10	TTTGGTCCTTTGCAGGGTGAGTGAG	3985	CTCACTCACCCTGCAAAGGACCAAA	4777
25	H55_(-14)-11	TTGGTCCTTTGCAGGGTGAGTGAGC	3986	GCTCACTCACCCTGCAAAGGACCAA	4778
25	H55_(-13)-12	TGGTCCTTTGCAGGGTGAGTGAGCG	3987	CGCTCACTCACCCTGCAAAGGACCA	4779
25	H55_(-12)-13	GGTCCTTTGCAGGGTGAGTGAGCGA	3988	TCGCTCACTCACCCTGCAAAGGACC	4780
25	H55_(-11)-14	GTCCTTTGCAGGGTGAGTGAGCGAG	3989	CTCGCTCACTCACCCTGCAAAGGAC	4781
25	H55_(-10)-15	TCCTTTGCAGGGTGAGTGAGCGAGA	3990	TCTCGCTCACTCACCCTGCAAAGGA	4782
25	H55_(-9)-16	CCTTTGCAGGGTGAGTGAGCGAGAG	3991	CTCTCGCTCACTCACCCTGCAAAGG	4783
25	H55_(-8)-17	CTTTGCAGGGTGAGTGAGCGAGAGG	3992	CCTCTCGCTCACTCACCCTGCAAAG	4784
25	H55_(-7)-18	TTTGCAGGGTGAGTGAGCGAGAGGC	3993	GCCTCTCGCTCACTCACCCTGCAAA	4785
25	H55_(-6)-19	TTGCAGGGTGAGTGAGCGAGAGGCT	3994	AGCCTCTCGCTCACTCACCCTGCAA	4786
25	H55_(-5)-20	TGCAGGGTGAGTGAGCGAGAGGCTG	3995	CAGCCTCTCGCTCACTCACCCTGCA	4787
25	H55_(-4)-21	GCAGGGTGAGTGAGCGAGAGGCTGC	3996	GCAGCCTCTCGCTCACTCACCCTGC	4788

[Table 6-24]

25	H55_(-3)-22	CAGGGTGAGTGAGCGAGAGGCTGCT	3997	AGCAGCCTCTCGCTCACTCACCCTG	4789
25	H55_(-2)-23	AGGGTGAGTGAGCGAGAGGCTGCTT	3998	AAGCAGCCTCTCGCTCACTCACCCT	4790
25	H55_(-1)-24	GGGTGAGTGAGCGAGAGGCTGCTTT	3999	AAAGCAGCCTCTCGCTCACTCACCC	4791
25	H55_1-25	GGTGAGTGAGCGAGAGGCTGCTTTG	4000	CAAAGCAGCCTCTCGCTCACTCACC	4792
25	H55_2-26	GTGAGTGAGCGAGAGGCTGCTTTGG	4001	CCAAAGCAGCCTCTCGCTCACTCAC	4793
25	H55_3-27	TGAGTGAGCGAGAGGCTGCTTTGGA	4002	TCCAAAGCAGCCTCTCGCTCACTCA	4794
25	H55_4-28	GAGTGAGCGAGAGGCTGCTTTGGAA	4003	TTCCAAAGCAGCCTCTCGCTCACTC	4795
25	H55_5-29	AGTGAGCGAGAGGCTGCTTTGGAAG	4004	CTTCCAAAGCAGCCTCTCGCTCACT	4796
25	H55_6-30	GTGAGCGAGAGGCTGCTTTGGAAGA	4005	TCTTCCAAAGCAGCCTCTCGCTCAC	4797
25	H55_7-31	TGAGCGAGAGGCTGCTTTGGAAGAA	4006	TTCTTCCAAAGCAGCCTCTCGCTCA	4798
25	H55_8-32	GAGCGAGAGGCTGCTTTGGAAGAAA	4007	TTTCTTCCAAAGCAGCCTCTCGCTC	4799
25	H55_9-33	AGCGAGAGGCTGCTTTGGAAGAAAC	4008	GTTTCTTCCAAAGCAGCCTCTCGCT	4800
25	H55_10-34	GCGAGAGGCTGCTTTGGAAGAAACT	4009	AGTTTCTTCCAAAGCAGCCTCTCGC	4801
25	H55_11-35	CGAGAGGCTGCTTTGGAAGAAACTC	4010	GAGTTTCTTCCAAAGCAGCCTCTCG	4802
25	H55_12-36	GAGAGGCTGCTTTGGAAGAAACTCA	4011	TGAGTTTCTTCCAAAGCAGCCTCTC	4803
25	H55_13-37	AGAGGCTGCTTTGGAAGAAACTCAT	4012	ATGAGTTTCTTCCAAAGCAGCCTCT	4804
25	H55_14-38	GAGGCTGCTTTGGAAGAAACTCATA	4013	TATGAGTTTCTTCCAAAGCAGCCTC	4805
25	H55_15-39	AGGCTGCTTTGGAAGAAACTCATAG	4014	CTATGAGTTTCTTCCAAAGCAGCCT	4806

[Table 6-25]

25	H55_16-40	GGCTGCTTTGGAAGAAACTCATAGA	4015	TCTATGAGTTTCTTCCAAAGCAGCC	4807
25	H55_17-41	GCTGCTTTGGAAGAAACTCATAGAT	4016	ATCTATGAGTTTCTTCCAAAGCAGC	4808
25	H55_18-42	CTGCTTTGGAAGAAACTCATAGATT	4017	AATCTATGAGTTTCTTCCAAAGCAG	4809
25	H55_19-43	TGCTTTGGAAGAAACTCATAGATTA	4018	TAATCTATGAGTTTCTTCCAAAGCA	4810
25	H55_20-44	GCTTTGGAAGAAACTCATAGATTAC	4019	GTAATCTATGAGTTTCTTCCAAAGC	4811
25	H55_21-45	CTTTGGAAGAAACTCATAGATTACT	4020	AGTAATCTATGAGTTTCTTCCAAAG	4812
25	H55_22-46	TTTGGAAGAAACTCATAGATTACTG	4021	CAGTAATCTATGAGTTTCTTCCAAA	4813
25	H55_23-47	TTGGAAGAAACTCATAGATTACTGC	4022	GCAGTAATCTATGAGTTTCTTCCAA	4814
25	H55_24-48	TGGAAGAAACTCATAGATTACTGCA	4023	TGCAGTAATCTATGAGTTTCTTCCA	4815
26	H55_(-29)-(-4)	ATTGCATCTGAACATTTGGTCCTTTG	4024	CAAAGGACCAAATGTTCAGATGCAAT	4816
26	H55_(-28)-(-3)	TTGCATCTGAACATTTGGTCCTTTGC	4025	GCAAAGGACCAAATGTTCAGATGCAA	4817
26	H55_(-27)-(-2)	TGCATCTGAACATTTGGTCCTTTGCA	4026	TGCAAAGGACCAAATGTTCAGATGCA	4818
26	H55_(-26)-(-1)	GCATCTGAACATTTGGTCCTTTGCAG	4027	CTGCAAAGGACCAAATGTTCAGATGC	4819
26	H55_(-25)-1	CATCTGAACATTTGGTCCTTTGCAGG	4028	CCTGCAAAGGACCAAATGTTCAGATG	4820
26	H55_(-24)-2	ATCTGAACATTTGGTCCTTTGCAGGG	4029	CCCTGCAAAGGACCAAATGTTCAGAT	4821
26	H55_(-23)-3	TCTGAACATTTGGTCCTTTGCAGGGT	4030	ACCCTGCAAAGGACCAAATGTTCAGA	4822
26	H55_(-22)-4	CTGAACATTTGGTCCTTTGCAGGGTG	4031	CACCCTGCAAAGGACCAAATGTTCAG	4823
26	H55_(-21)-5	TGAACATTTGGTCCTTTGCAGGGTGA	4032	TCACCCTGCAAAGGACCAAATGTTCA	4824

[Table 6-26]

26	H55_(-20)-6	GAACATTTGGTCCTTTGCAGGGTGAG	4033	CTCACCCTGCAAAGGACCAAATGTTC	4825
26	H55_(-19)-7	AACATTTGGTCCTTTGCAGGGTGAGT	4034	ACTCACCCTGCAAAGGACCAAATGTT	4826
26	H55_(-18)-8	ACATTTGGTCCTTTGCAGGGTGAGTG	4035	CACTCACCCTGCAAAGGACCAAATGT	4827
26	H55_(-17)-9	CATTTGGTCCTTTGCAGGGTGAGTGA	4036	TCACTCACCCTGCAAAGGACCAAATG	4828
26	H55_(-16)-10	ATTTGGTCCTTTGCAGGGTGAGTGAG	4037	CTCACTCACCCTGCAAAGGACCAAAT	4829
26	H55_(-15)-11	TTTGGTCCTTTGCAGGGTGAGTGAGC	4038	GCTCACTCACCCTGCAAAGGACCAAA	4830
26	H55_(-14)-12	TTGGTCCTTTGCAGGGTGAGTGAGCG	4039	CGCTCACTCACCCTGCAAAGGACCAA	4831
26	H55_(-13)-13	TGGTCCTTTGCAGGGTGAGTGAGCGA	4040	TCGCTCACTCACCCTGCAAAGGACCA	4832
26	H55_(-12)-14	GGTCCTTTGCAGGGTGAGTGAGCGAG	4041	CTCGCTCACTCACCCTGCAAAGGACC	4833
26	H55_(-11)-15	GTCCTTTGCAGGGTGAGTGAGCGAGA	4042	TCTCGCTCACTCACCCTGCAAAGGAC	4834
26	H55_(-10)-16	TCCTTTGCAGGGTGAGTGAGCGAGAG	4043	CTCTCGCTCACTCACCCTGCAAAGGA	4835
26	H55_(-9)-17	CCTTTGCAGGGTGAGTGAGCGAGAGG	4044	CCTCTCGCTCACTCACCCTGCAAAGG	4836
26	H55_(-8)-18	CTTTGCAGGGTGAGTGAGCGAGAGGC	4045	GCCTCTCGCTCACTCACCCTGCAAAG	4837
26	H55_(-7)-19	TTTGCAGGGTGAGTGAGCGAGAGGCT	4046	AGCCTCTCGCTCACTCACCCTGCAAA	4838
26	H55_(-6)-20	TTGCAGGGTGAGTGAGCGAGAGGCTG	4047	CAGCCTCTCGCTCACTCACCCTGCAA	4839
26	H55_(-5)-21	TGCAGGGTGAGTGAGCGAGAGGCTGC	4048	GCAGCCTCTCGCTCACTCACCCTGCA	4840
26	H55_(-4)-22	GCAGGGTGAGTGAGCGAGAGGCTGCT	4049	AGCAGCCTCTCGCTCACTCACCCTGC	4841
26	H55_(-3)-23	CAGGGTGAGTGAGCGAGAGGCTGCTT	4050	AAGCAGCCTCTCGCTCACTCACCCTG	4842

[Table 6-27]

26	H55_(-2)-24	AGGGTGAGTGAGCGAGAGGCTGCTTT	4051	AAAGCAGCCTCTCGCTCACTCACCCT	4843
26	H55_(-1)-25	GGGTGAGTGAGCGAGAGGCTGCTTTG	4052	CAAAGCAGCCTCTCGCTCACTCACCC	4844
26	H55_1-26	GGTGAGTGAGCGAGAGGCTGCTTTGG	4053	CCAAAGCAGCCTCTCGCTCACTCACC	4845
26	H55_2-27	GTGAGTGAGCGAGAGGCTGCTTTGGA	4054	TCCAAAGCAGCCTCTCGCTCACTCAC	4846
26	H55_3-28	TGAGTGAGCGAGAGGCTGCTTTGGAA	4055	TTCCAAAGCAGCCTCTCGCTCACTCA	4847
26	H55_4-29	GAGTGAGCGAGAGGCTGCTTTGGAAG	4056	CTTCCAAAGCAGCCTCTCGCTCACTC	4848
26	H55_5-30	AGTGAGCGAGAGGCTGCTTTGGAAGA	4057	TCTTCCAAAGCAGCCTCTCGCTCACT	4849
26	H55_6-31	GTGAGCGAGAGGCTGCTTTGGAAGAA	4058	TTCTTCCAAAGCAGCCTCTCGCTCAC	4850
26	H55_7-32	TGAGCGAGAGGCTGCTTTGGAAGAAA	4059	TTTCTTCCAAAGCAGCCTCTCGCTCA	4851
26	H55_8-33	GAGCGAGAGGCTGCTTTGGAAGAAAC	4060	GTTTCTTCCAAAGCAGCCTCTCGCTC	4852
26	H55_9-34	AGCGAGAGGCTGCTTTGGAAGAAACT	4061	AGTTTCTTCCAAAGCAGCCTCTCGCT	4853
26	H55_10-35	GCGAGAGGCTGCTTTGGAAGAAACTC	4062	GAGTTTCTTCCAAAGCAGCCTCTCGC	4854
26	H55_11-36	CGAGAGGCTGCTTTGGAAGAAACTCA	4063	TGAGTTTCTTCCAAAGCAGCCTCTCG	4855
26	H55_12-37	GAGAGGCTGCTTTGGAAGAAACTCAT	4064	ATGAGTTTCTTCCAAAGCAGCCTCTC	4856
26	H55_13-38	AGAGGCTGCTTTGGAAGAAACTCATA	4065	TATGAGTTTCTTCCAAAGCAGCCTCT	4857
26	H55_14-39	GAGGCTGCTTTGGAAGAAACTCATAG	4066	CTATGAGTTTCTTCCAAAGCAGCCTC	4858
26	H55_15-40	AGGCTGCTTTGGAAGAAACTCATAGA	4067	TCTATGAGTTTCTTCCAAAGCAGCCT	4859
26	H55_16-41	GGCTGCTTTGGAAGAAACTCATAGAT	4068	ATCTATGAGTTTCTTCCAAAGCAGCC	4860

[Table 6-28]

26	H55_17-42	GCTGCTTTGGAAGAAACTCATAGATT	4069	AATCTATGAGTTTCTTCCAAAGCAGC	4861
26	H55_18-43	CTGCTTTGGAAGAAACTCATAGATTA	4070	TAATCTATGAGTTTCTTCCAAAGCAG	4862
26	H55_19-44	TGCTTTGGAAGAAACTCATAGATTAC	4071	GTAATCTATGAGTTTCTTCCAAAGCA	4863
26	H55_20-45	GCTTTGGAAGAAACTCATAGATTACT	4072	AGTAATCTATGAGTTTCTTCCAAAGC	4864
26	H55_21-46	CTTTGGAAGAAACTCATAGATTACTG	4073	CAGTAATCTATGAGTTTCTTCCAAAG	4865
26	H55_22-47	TTTGGAAGAAACTCATAGATTACTGC	4074	GCAGTAATCTATGAGTTTCTTCCAAA	4866
26	H55_23-48	TTGGAAGAAACTCATAGATTACTGCA	4075	TGCAGTAATCTATGAGTTTCTTCCAA	4867
26	H55_24-49	TGGAAGAAACTCATAGATTACTGCAA	4076	TTGCAGTAATCTATGAGTTTCTTCCA	4868
27	H55_(-30)-(-4)	AATTGCATCTGAACATTTGGTCCTTTG	4077	CAAAGGACCAAATGTTCAGATGCAATT	4869
27	H55_(-29)-(-3)	ATTGCATCTGAACATTTGGTCCTTTGC	4078	GCAAAGGACCAAATGTTCAGATGCAAT	4870
27	H55_(-28)-(-2)	TTGCATCTGAACATTTGGTCCTTTGCA	4079	TGCAAAGGACCAAATGTTCAGATGCAA	4871
27	H55_(-27)-(-1)	TGCATCTGAACATTTGGTCCTTTGCAG	4080	CTGCAAAGGACCAAATGTTCAGATGCA	4872
27	H55_(-26)-1	GCATCTGAACATTTGGTCCTTTGCAGG	4081	CCTGCAAAGGACCAAATGTTCAGATGC	4873
27	H55_(-25)-2	CATCTGAACATTTGGTCCTTTGCAGGG	4082	CCCTGCAAAGGACCAAATGTTCAGATG	4874
27	H55_(-24)-3	ATCTGAACATTTGGTCCTTTGCAGGGT	4083	ACCCTGCAAAGGACCAAATGTTCAGAT	4875
27	H55_(-23)-4	TCTGAACATTTGGTCCTTTGCAGGGTG	4084	CACCCTGCAAAGGACCAAATGTTCAGA	4876
27	H55_(-22)-5	CTGAACATTTGGTCCTTTGCAGGGTGA	4085	TCACCCTGCAAAGGACCAAATGTTCAG	4877
27	H55_(-21)-6	TGAACATTTGGTCCTTTGCAGGGTGAG	4086	CTCACCCTGCAAAGGACCAAATGTTCA	4878

[Table 6-29]

27	H55_(-20)-7	GAACATTTGGTCCTTTGCAGGGTGAGT	4087	ACTCACCCTGCAAAGGACCAAATGTTC	4879
27	H55_(-19)-8	AACATTTGGTCCTTTGCAGGGTGAGTG	4088	CACTCACCCTGCAAAGGACCAAATGTT	4880
27	H55_(-18)-9	ACATTTGGTCCTTTGCAGGGTGAGTGA	4089	TCACTCACCCTGCAAAGGACCAAATGT	4881
27	H55_(-17)-10	CATTTGGTCCTTTGCAGGGTGAGTGAG	4090	CTCACTCACCCTGCAAAGGACCAAATG	4882
27	H55_(-16)-11	ATTTGGTCCTTTGCAGGGTGAGTGAGC	4091	GCTCACTCACCCTGCAAAGGACCAAAT	4883
27	H55_(-15)-12	TTTGGTCCTTTGCAGGGTGAGTGAGCG	4092	CGCTCACTCACCCTGCAAAGGACCAAA	4884
27	H55_(-14)-13	TTGGTCCTTTGCAGGGTGAGTGAGCGA	4093	TCGCTCACTCACCCTGCAAAGGACCAA	4885
27	H55_(-13)-14	TGGTCCTTTGCAGGGTGAGTGAGCGAG	4094	CTCGCTCACTCACCCTGCAAAGGACCA	4886
27	H55_(-12)-15	GGTCCTTTGCAGGGTGAGTGAGCGAGA	4095	TCTCGCTCACTCACCCTGCAAAGGACC	4887
27	H55_(-11)-16	GTCCTTTGCAGGGTGAGTGAGCGAGAG	4096	CTCTCGCTCACTCACCCTGCAAAGGAC	4888
27	H55_(-10)-17	TCCTTTGCAGGGTGAGTGAGCGAGAGG	4097	CCTCTCGCTCACTCACCCTGCAAAGGA	4889
27	H55_(-9)-18	CCTTTGCAGGGTGAGTGAGCGAGAGGC	4098	GCCTCTCGCTCACTCACCCTGCAAAGG	4890
27	H55_(-8)-19	CTTTGCAGGGTGAGTGAGCGAGAGGCT	4099	AGCCTCTCGCTCACTCACCCTGCAAAG	4891
27	H55_(-7)-20	TTTGCAGGGTGAGTGAGCGAGAGGCTG	4100	CAGCCTCTCGCTCACTCACCCTGCAAA	4892
27	H55_(-6)-21	TTGCAGGGTGAGTGAGCGAGAGGCTGC	4101	GCAGCCTCTCGCTCACTCACCCTGCAA	4893
27	H55_(-5)-22	TGCAGGGTGAGTGAGCGAGAGGCTGCT	4102	AGCAGCCTCTCGCTCACTCACCCTGCA	4894
27	H55_(-4)-23	GCAGGGTGAGTGAGCGAGAGGCTGCTT	4103	AAGCAGCCTCTCGCTCACTCACCCTGC	4895
27	H55_(-3)-24	CAGGGTGAGTGAGCGAGAGGCTGCTTT	4104	AAAGCAGCCTCTCGCTCACTCACCCTG	4896

[Table 6-30]

27	H55_(-2)-25	AGGGTGAGTGAGCGAGAGGCTGCTTTG	4105	CAAAGCAGCCTCTCGCTCACTCACCCT	4897
27	H55_(-1)-26	GGGTGAGTGAGCGAGAGGCTGCTTTGG	4106	CCAAAGCAGCCTCTCGCTCACTCACCC	4898
27	H55_1-27	GGTGAGTGAGCGAGAGGCTGCTTTGGA	4107	TCCAAAGCAGCCTCTCGCTCACTCACC	4899
27	H55_2-28	GTGAGTGAGCGAGAGGCTGCTTTGGAA	4108	TTCCAAAGCAGCCTCTCGCTCACTCAC	4900
27	H55_3-29	TGAGTGAGCGAGAGGCTGCTTTGGAAG	4109	CTTCCAAAGCAGCCTCTCGCTCACTCA	4901
27	H55_4-30	GAGTGAGCGAGAGGCTGCTTTGGAAGA	4110	TCTTCCAAAGCAGCCTCTCGCTCACTC	4902
27	H55_5-31	AGTGAGCGAGAGGCTGCTTTGGAAGAA	4111	TTCTTCCAAAGCAGCCTCTCGCTCACT	4903
27	H55_6-32	GTGAGCGAGAGGCTGCTTTGGAAGAAA	4112	TTTCTTCCAAAGCAGCCTCTCGCTCAC	4904
27	H55_7-33	TGAGCGAGAGGCTGCTTTGGAAGAAAC	4113	GTTTCTTCCAAAGCAGCCTCTCGCTCA	4905
27	H55_8-34	GAGCGAGAGGCTGCTTTGGAAGAAACT	4114	AGTTTCTTCCAAAGCAGCCTCTCGCTC	4906
27	H55_9-35	AGCGAGAGGCTGCTTTGGAAGAAACTC	4115	GAGTTTCTTCCAAAGCAGCCTCTCGCT	4907
27	H55_10-36	GCGAGAGGCTGCTTTGGAAGAAACTCA	4116	TGAGTTTCTTCCAAAGCAGCCTCTCGC	4908
27	H55_11-37	CGAGAGGCTGCTTTGGAAGAAACTCAT	4117	ATGAGTTTCTTCCAAAGCAGCCTCTCG	4909
27	H55_12-38	GAGAGGCTGCTTTGGAAGAAACTCATA	4118	TATGAGTTTCTTCCAAAGCAGCCTCTC	4910
27	H55_13-39	AGAGGCTGCTTTGGAAGAAACTCATAG	4119	CTATGAGTTTCTTCCAAAGCAGCCTCT	4911
27	H55_14-40	GAGGCTGCTTTGGAAGAAACTCATAGA	4120	TCTATGAGTTTCTTCCAAAGCAGCCTC	4912
27	H55_15-41	AGGCTGCTTTGGAAGAAACTCATAGAT	4121	ATCTATGAGTTTCTTCCAAAGCAGCCT	4913
27	H55_16-42	GGCTGCTTTGGAAGAAACTCATAGATT	4122	AATCTATGAGTTTCTTCCAAAGCAGCC	4914

[Table 6-31]

27	H55_17-43	GCTGCTTTGGAAGAAACTCAT AGATTA	4123	TAATCTATGAGTTTCTTCCAA AGCAGC	4915
27	H55_18-44	CTGCTTTGGAAGAAACTCATA GATTAC	4124	GTAATCTATGAGTTTCTTCCA AAGCAG	4916
27	H55_19-45	TGCTTTGGAAGAAACTCATAG ATTACT	4125	AGTAATCTATGAGTTTCTTCC AAAGCA	4917
27	H55_20-46	GCTTTGGAAGAAACTCATAGA TTACTG	4126	CAGTAATCTATGAGTTTCTTC CAAAGC	4918
27	H55_21-47	CTTTGGAAGAAACTCATAGAT TACTGC	4127	GCAGTAATCTATGAGTTTCTT CCAAAG	4919
27	H55_22-48	TTTGGAAGAAACTCATAGATT ACTGCA	4128	TGCAGTAATCTATGAGTTTCT TCCAAA	4920
27	H55_23-49	TTGGAAGAAACTCATAGATTA CTGCAA	4129	TTGCAGTAATCTATGAGTTTC TTCCAA	4921
27	H55_24-50	TGGAAGAAACTCATAGATTAC TGCAAC	4130	GTTGCAGTAATCTATGAGTTT CTTCCA	4922
28	H55_(-31)-(-4)	TAATTGCATCTGAACATTTGG TCCTTTG	4131	CAAAGGACCAAATGTTCAGAT GCAATTA	4923
28	H55_(-30)-(-3)	AATTGCATCTGAACATTTGGT CCTTTGC	4132	GCAAAGGACCAAATGTTCAGA TGCAATT	4924
28	H55_(-29)-(-2)	ATTGCATCTGAACATTTGGTC CTTTGCA	4133	TGCAAAGGACCAAATGTTCAG ATGCAAT	4925
28	H55_(-28)-(-1)	TTGCATCTGAACATTTGGTCC TTTGCAG	4134	CTGCAAAGGACCAAATGTTCA GATGCAA	4926
28	H55_(-27)-1	TGCATCTGAACATTTGGTCCT TTGCAGG	4135	CCTGCAAAGGACCAAATGTTC AGATGCA	4927
28	H55_(-26)-2	GCATCTGAACATTTGGTCCTT TGCAGGG	4136	CCCTGCAAAGGACCAAATGTT CAGATGC	4928
28	H55_(-25)-3	CATCTGAACATTTGGTCCTTT GCAGGGT	4137	ACCCTGCAAAGGACCAAATGT TCAGATG	4929
28	H55_(-24)-4	ATCTGAACATTTGGTCCTTTG CAGGGTG	4138	CACCCTGCAAAGGACCAAATG TTCAGAT	4930
28	H55_(-23)-5	TCTGAACATTTGGTCCTTTGC AGGGTGA	4139	TCACCCTGCAAAGGACCAAAT GTTCAGA	4931
28	H55_(-22)-6	CTGAACATTTGGTCCTTTGCA GGGTGAG	4140	CTCACCCTGCAAAGGACCAAA TGTTCAG	4932

[Table 6-32]

28	H55_(-21)-7	TGAACATTTGGTCCTTTGCAGGGTGAGT	4141	ACTCACCCTGCAAAGGACCAAATGTTCA	4933
28	H55_(-20)-8	GAACATTTGGTCCTTTGCAGGGTGAGTG	4142	CACTCACCCTGCAAAGGACCAAATGTTC	4934
28	H55_(-19)-9	AACATTTGGTCCTTTGCAGGGTGAGTGA	4143	TCACTCACCCTGCAAAGGACCAAATGTT	4935
28	H55_(-18)-10	ACATTTGGTCCTTTGCAGGGTGAGTGAG	4144	CTCACTCACCCTGCAAAGGACCAAATGT	4936
28	H55_(-17)-11	CATTTGGTCCTTTGCAGGGTGAGTGAGC	4145	GCTCACTCACCCTGCAAAGGACCAAATG	4937
28	H55_(-16)-12	ATTTGGTCCTTTGCAGGGTGAGTGAGCG	4146	CGCTCACTCACCCTGCAAAGGACCAAAT	4938
28	H55_(-15)-13	TTTGGTCCTTTGCAGGGTGAGTGAGCGA	4147	TCGCTCACTCACCCTGCAAAGGACCAAA	4939
28	H55_(-14)-14	TTGGTCCTTTGCAGGGTGAGTGAGCGAG	4148	CTCGCTCACTCACCCTGCAAAGGACCAA	4940
28	H55_(-13)-15	TGGTCCTTTGCAGGGTGAGTGAGCGAGA	4149	TCTCGCTCACTCACCCTGCAAAGGACCA	4941
28	H55_(-12)-16	GGTCCTTTGCAGGGTGAGTGAGCGAGAG	4150	CTCTCGCTCACTCACCCTGCAAAGGACC	4942
28	H55_(-11)-17	GTCCTTTGCAGGGTGAGTGAGCGAGAGG	4151	CCTCTCGCTCACTCACCCTGCAAAGGAC	4943
28	H55_(-10)-18	TCCTTTGCAGGGTGAGTGAGCGAGAGGC	4152	GCCTCTCGCTCACTCACCCTGCAAAGGA	4944
28	H55_(-9)-19	CCTTTGCAGGGTGAGTGAGCGAGAGGCT	4153	AGCCTCTCGCTCACTCACCCTGCAAAGG	4945
28	H55_(-8)-20	CTTTGCAGGGTGAGTGAGCGAGAGGCTG	4154	CAGCCTCTCGCTCACTCACCCTGCAAAG	4946
28	H55_(-7)-21	TTTGCAGGGTGAGTGAGCGAGAGGCTGC	4155	GCAGCCTCTCGCTCACTCACCCTGCAAA	4947
28	H55_(-6)-22	TTGCAGGGTGAGTGAGCGAGAGGCTGCT	4156	AGCAGCCTCTCGCTCACTCACCCTGCAA	4948
28	H55_(-5)-23	TGCAGGGTGAGTGAGCGAGAGGCTGCTT	4157	AAGCAGCCTCTCGCTCACTCACCCTGCA	4949
28	H55_(-4)-24	GCAGGGTGAGTGAGCGAGAGGCTGCTTT	4158	AAAGCAGCCTCTCGCTCACTCACCCTGC	4950

[Table 6-33]

28	H55_(-3)-25	CAGGGTGAGTGAGCGAGAGGCTGCTTTG	4159	CAAAGCAGCCTCTCGCTCACTCACCCTG	4951
28	H55_(-2)-26	AGGGTGAGTGAGCGAGAGGCTGCTTTGG	4160	CCAAAGCAGCCTCTCGCTCACTCACCCT	4952
28	H55_(-1)-27	GGGTGAGTGAGCGAGAGGCTGCTTTGGA	4161	TCCAAAGCAGCCTCTCGCTCACTCACCC	4953
28	H55_1-28	GGTGAGTGAGCGAGAGGCTGCTTTGGAA	4162	TTCCAAAGCAGCCTCTCGCTCACTCACC	4954
28	H55_2-29	GTGAGTGAGCGAGAGGCTGCTTTGGAAG	4163	CTTCCAAAGCAGCCTCTCGCTCACTCAC	4955
28	H55_3-30	TGAGTGAGCGAGAGGCTGCTTTGGAAGA	4164	TCTTCCAAAGCAGCCTCTCGCTCACTCA	4956
28	H55_4-31	GAGTGAGCGAGAGGCTGCTTTGGAAGAA	4165	TTCTTCCAAAGCAGCCTCTCGCTCACTC	4957
28	H55_5-32	AGTGAGCGAGAGGCTGCTTTGGAAGAAA	4166	TTTCTTCCAAAGCAGCCTCTCGCTCACT	4958
28	H55_6-33	GTGAGCGAGAGGCTGCTTTGGAAGAAAC	4167	GTTTCTTCCAAAGCAGCCTCTCGCTCAC	4959
28	H55_7-34	TGAGCGAGAGGCTGCTTTGGAAGAAACT	4168	AGTTTCTTCCAAAGCAGCCTCTCGCTCA	4960
28	H55_8-35	GAGCGAGAGGCTGCTTTGGAAGAAACTC	4169	GAGTTTCTTCCAAAGCAGCCTCTCGCTC	4961
28	H55_9-36	AGCGAGAGGCTGCTTTGGAAGAAACTCA	4170	TGAGTTTCTTCCAAAGCAGCCTCTCGCT	4962
28	H55_10-37	GCGAGAGGCTGCTTTGGAAGAAACTCAT	4171	ATGAGTTTCTTCCAAAGCAGCCTCTCGC	4963
28	H55_11-38	CGAGAGGCTGCTTTGGAAGAAACTCATA	4172	TATGAGTTTCTTCCAAAGCAGCCTCTCG	4964
28	H55_12-39	GAGAGGCTGCTTTGGAAGAAACTCATAG	4173	CTATGAGTTTCTTCCAAAGCAGCCTCTC	4965
28	H55_13-40	AGAGGCTGCTTTGGAAGAAACTCATAGA	4174	TCTATGAGTTTCTTCCAAAGCAGCCTCT	4966
28	H55_14-41	GAGGCTGCTTTGGAAGAAACTCATAGAT	4175	ATCTATGAGTTTCTTCCAAAGCAGCCTC	4967
28	H55_15-42	AGGCTGCTTTGGAAGAAACTCATAGATT	4176	AATCTATGAGTTTCTTCCAAAGCAGCCT	4968

[Table 6-34]

28	H55_16-43	GGCTGCTTTGGAAGAAACTCA TAGATTA	4177	TAATCTATGAGTTTCTTCCAA AGCAGCC	4969
28	H55_17-44	GCTGCTTTGGAAGAAACTCAT AGATTAC	4178	GTAATCTATGAGTTTCTTCCA AAGCAGC	4970
28	H55_18-45	CTGCTTTGGAAGAAACTCATA GATTACT	4179	AGTAATCTATGAGTTTCTTCC AAAGCAG	4971
28	H55_19-46	TGCTTTGGAAGAAACTCATAG ATTACTG	4180	CAGTAATCTATGAGTTTCTTC CAAAGCA	4972
28	H55_20-47	GCTTTGGAAGAAACTCATAGA TTACTGC	4181	GCAGTAATCTATGAGTTTCTT CCAAAGC	4973
28	H55_21-48	CTTTGGAAGAAACTCATAGAT TACTGCA	4182	TGCAGTAATCTATGAGTTTCT TCCAAAG	4974
28	H55_22-49	TTTGGAAGAAACTCATAGATT ACTGCAA	4183	TTGCAGTAATCTATGAGTTTC TTCCAAA	4975
28	H55_23-50	TTGGAAGAAACTCATAGATTA CTGCAAC	4184	GTTGCAGTAATCTATGAGTTT CTTCCAA	4976
28	H55_24-51	TGGAAGAAACTCATAGATTAC TGCAACA	4185	TGTTGCAGTAATCTATGAGTT TCTTCCA	4977
29	H55_(-32)-(-4)	ATAATTGCATCTGAACATTTG GTCCTTTG	4186	CAAAGGACCAAATGTTCAGAT GCAATTAT	4978
29	H55_(-31)-(-3)	TAATTGCATCTGAACATTTGG TCCTTTGC	4187	GCAAAGGACCAAATGTTCAGA TGCAATTA	4979
29	H55_(-30)-(-2)	AATTGCATCTGAACATTTGGT CCTTTGCA	4188	TGCAAAGGACCAAATGTTCAG ATGCAATT	4980
29	H55_(-29)-(-1)	ATTGCATCTGAACATTTGGTC CTTTGCAG	4189	CTGCAAAGGACCAAATGTTCA GATGCAAT	4981
29	H55_(-28)-1	TTGCATCTGAACATTTGGTCC TTTGCAGG	4190	CCTGCAAAGGACCAAATGTTC AGATGCAA	4982
29	H55_(-27)-2	TGCATCTGAACATTTGGTCCT TTGCAGGG	4191	CCCTGCAAAGGACCAAATGTT CAGATGCA	4983
29	H55_(-26)-3	GCATCTGAACATTTGGTCCTT TGCAGGGT	4192	ACCCTGCAAAGGACCAAATGT TCAGATGC	4984
29	H55_(-25)-4	CATCTGAACATTTGGTCCTTT GCAGGGTG	4193	CACCCTGCAAAGGACCAAATG TTCAGATG	4985
29	H55_(-24)-5	ATCTGAACATTTGGTCCTTTG CAGGGTGA	4194	TCACCCTGCAAAGGACCAAAT GTTCAGAT	4986

[Table 6-35]

29	H55_(-23)-6	TCTGAACATTTGGTCCTTTGCAGGGTGAG	4195	CTCACCCTGCAAAGGACCAAATGTTCAGA	4987
29	H55_(-22)-7	CTGAACATTTGGTCCTTTGCAGGGTGAGT	4196	ACTCACCCTGCAAAGGACCAAATGTTCAG	4988
29	H55_(-21)-8	TGAACATTTGGTCCTTTGCAGGGTGAGTG	4197	CACTCACCCTGCAAAGGACCAAATGTTCA	4989
29	H55_(-20)-9	GAACATTTGGTCCTTTGCAGGGTGAGTGA	4198	TCACTCACCCTGCAAAGGACCAAATGTTC	4990
29	H55_(-19)-10	AACATTTGGTCCTTTGCAGGGTGAGTGAG	4199	CTCACTCACCCTGCAAAGGACCAAATGTT	4991
29	H55_(-18)-11	ACATTTGGTCCTTTGCAGGGTGAGTGAGC	4200	GCTCACTCACCCTGCAAAGGACCAAATGT	4992
29	H55_(-17)-12	CATTTGGTCCTTTGCAGGGTGAGTGAGCG	4201	CGCTCACTCACCCTGCAAAGGACCAAATG	4993
29	H55_(-16)-13	ATTTGGTCCTTTGCAGGGTGAGTGAGCGA	4202	TCGCTCACTCACCCTGCAAAGGACCAAAT	4994
29	H55_(-15)-14	TTTGGTCCTTTGCAGGGTGAGTGAGCGAG	4203	CTCGCTCACTCACCCTGCAAAGGACCAAA	4995
29	H55_(-14)-15	TTGGTCCTTTGCAGGGTGAGTGAGCGAGA	4204	TCTCGCTCACTCACCCTGCAAAGGACCAA	4996
29	H55_(-13)-16	TGGTCCTTTGCAGGGTGAGTGAGCGAGAG	4205	CTCTCGCTCACTCACCCTGCAAAGGACCA	4997
29	H55_(-12)-17	GGTCCTTTGCAGGGTGAGTGAGCGAGAGG	4206	CCTCTCGCTCACTCACCCTGCAAAGGACC	4998
29	H55_(-11)-18	GTCCTTTGCAGGGTGAGTGAGCGAGAGGC	4207	GCCTCTCGCTCACTCACCCTGCAAAGGAC	4999
29	H55_(-10)-19	TCCTTTGCAGGGTGAGTGAGCGAGAGGCT	4208	AGCCTCTCGCTCACTCACCCTGCAAAGGA	5000
29	H55_(-9)-20	CCTTTGCAGGGTGAGTGAGCGAGAGGCTG	4209	CAGCCTCTCGCTCACTCACCCTGCAAAGG	5001
29	H55_(-8)-21	CTTTGCAGGGTGAGTGAGCGAGAGGCTGC	4210	GCAGCCTCTCGCTCACTCACCCTGCAAAG	5002
29	H55_(-7)-22	TTTGCAGGGTGAGTGAGCGAGAGGCTGCT	4211	AGCAGCCTCTCGCTCACTCACCCTGCAAA	5003
29	H55_(-6)-23	TTGCAGGGTGAGTGAGCGAGAGGCTGCTT	4212	AAGCAGCCTCTCGCTCACTCACCCTGCAA	5004

[Table 6-36]

29	H55_(-5)-24	TGCAGGGTGAGTGAGCGAGAGGCTGCTTT	4213	AAAGCAGCCTCTCGCTCACTCACCCTGCA	5005
29	H55_(-4)-25	GCAGGGTGAGTGAGCGAGAGGCTGCTTTG	4214	CAAAGCAGCCTCTCGCTCACTCACCCTGC	5006
29	H55_(-3)-26	CAGGGTGAGTGAGCGAGAGGCTGCTTTGG	4215	CCAAAGCAGCCTCTCGCTCACTCACCCTG	5007
29	H55_(-2)-27	AGGGTGAGTGAGCGAGAGGCTGCTTTGGA	4216	TCCAAAGCAGCCTCTCGCTCACTCACCCT	5008
29	H55_(-1)-28	GGGTGAGTGAGCGAGAGGCTGCTTTGGAA	4217	TTCCAAAGCAGCCTCTCGCTCACTCACCC	5009
29	H55_1-29	GGTGAGTGAGCGAGAGGCTGCTTTGGAAG	4218	CTTCCAAAGCAGCCTCTCGCTCACTCACC	5010
29	H55_2-30	GTGAGTGAGCGAGAGGCTGCTTTGGAAGA	4219	TCTTCCAAAGCAGCCTCTCGCTCACTCAC	5011
29	H55_3-31	TGAGTGAGCGAGAGGCTGCTTTGGAAGAA	4220	TTCTTCCAAAGCAGCCTCTCGCTCACTCA	5012
29	H55_4-32	GAGTGAGCGAGAGGCTGCTTTGGAAGAAA	4221	TTTCTTCCAAAGCAGCCTCTCGCTCACTC	5013
29	H55_5-33	AGTGAGCGAGAGGCTGCTTTGGAAGAAAC	4222	GTTTCTTCCAAAGCAGCCTCTCGCTCACT	5014
29	H55_6-34	GTGAGCGAGAGGCTGCTTTGGAAGAAACT	4223	AGTTTCTTCCAAAGCAGCCTCTCGCTCAC	5015
29	H55_7-35	TGAGCGAGAGGCTGCTTTGGAAGAAACTC	4224	GAGTTTCTTCCAAAGCAGCCTCTCGCTCA	5016
29	H55_8-36	GAGCGAGAGGCTGCTTTGGAAGAAACTCA	4225	TGAGTTTCTTCCAAAGCAGCCTCTCGCTC	5017
29	H55_9-37	AGCGAGAGGCTGCTTTGGAAGAAACTCAT	4226	ATGAGTTTCTTCCAAAGCAGCCTCTCGCT	5018
29	H55_10-38	GCGAGAGGCTGCTTTGGAAGAAACTCATA	4227	TATGAGTTTCTTCCAAAGCAGCCTCTCGC	5019
29	H55_11-39	CGAGAGGCTGCTTTGGAAGAAACTCATAG	4228	CTATGAGTTTCTTCCAAAGCAGCCTCTCG	5020
29	H55_12-40	GAGAGGCTGCTTTGGAAGAAACTCATAGA	4229	TCTATGAGTTTCTTCCAAAGCAGCCTCTC	5021
29	H55_13-41	AGAGGCTGCTTTGGAAGAAACTCATAGAT	4230	ATCTATGAGTTTCTTCCAAAGCAGCCTCT	5022

[Table 6-37]

29	H55_14-42	GAGGCTGCTTTGGAAGAAACT CATAGATT	4231	AATCTATGAGTTTCTTCCAAA GCAGCCTC	5023
29	H55_15-43	AGGCTGCTTTGGAAGAAACTC ATAGATTA	4232	TAATCTATGAGTTTCTTCCAA AGCAGCCT	5024
29	H55_16-44	GGCTGCTTTGGAAGAAACTCA TAGATTAC	4233	GTAATCTATGAGTTTCTTCCA AAGCAGCC	5025
29	H55_17-45	GCTGCTTTGGAAGAAACTCAT AGATTACT	4234	AGTAATCTATGAGTTTCTTCC AAAGCAGC	5026
29	H55_18-46	CTGCTTTGGAAGAAACTCATA GATTACTG	4235	CAGTAATCTATGAGTTTCTTC CAAAGCAG	5027
29	H55_19-47	TGCTTTGGAAGAAACTCATAG ATTACTGC	4236	GCAGTAATCTATGAGTTTCTT CCAAAGCA	5028
29	H55_20-48	GCTTTGGAAGAAACTCATAGA TTACTGCA	4237	TGCAGTAATCTATGAGTTTCT TCCAAAGC	5029
29	H55_21-49	CTTTGGAAGAAACTCATAGAT TACTGCAA	4238	TTGCAGTAATCTATGAGTTTC TTCCAAAG	5030
29	H55_22-50	TTTGGAAGAAACTCATAGATT ACTGCAAC	4239	GTTGCAGTAATCTATGAGTTT CTTCCAAA	5031
29	H55_23-51	TTGGAAGAAACTCATAGATTA CTGCAACA	4240	TGTTGCAGTAATCTATGAGTT TCTTCCAA	5032
29	H55_24-52	TGGAAGAAACTCATAGATTAC TGCAACAG	4241	CTGTTGCAGTAATCTATGAGT TTCTTCCA	5033
30	H55_(-33)-(-4)	AATAATTGCATCTGAACATTT GGTCCTTTG	4242	CAAAGGACCAAATGTTCAGAT GCAATTATT	5034
30	H55_(-32)-(-3)	ATAATTGCATCTGAACATTTG GTCCTTTGC	4243	GCAAAGGACCAAATGTTCAGA TGCAATTAT	5035
30	H55_(-31)-(-2)	TAATTGCATCTGAACATTTGG TCCTTTGCA	4244	TGCAAAGGACCAAATGTTCAG ATGCAATTA	5036
30	H55_(-30)-(-1)	AATTGCATCTGAACATTTGGT CCTTTGCAG	4245	CTGCAAAGGACCAAATGTTCA GATGCAATT	5037
30	H55_(-29)-1	ATTGCATCTGAACATTTGGTC CTTTGCAGG	4246	CCTGCAAAGGACCAAATGTTC AGATGCAAT	5038
30	H55_(-28)-2	TTGCATCTGAACATTTGGTCC TTTGCAGGG	4247	CCCTGCAAAGGACCAAATGTT CAGATGCAA	5039
30	H55_(-27)-3	TGCATCTGAACATTTGGTCCT TTGCAGGGT	4248	ACCCTGCAAAGGACCAAATGT TCAGATGCA	5040

[Table 6-38]

30	H55_(-26)-4	GCATCTGAACATTTGGTCCTTTGCAGGGTG	4249	CACCCTGCAAAGGACCAAATGTTCAGATGC	5041
30	H55_(-25)-5	CATCTGAACATTTGGTCCTTTGCAGGGTGA	4250	TCACCCTGCAAAGGACCAAATGTTCAGATG	5042
30	H55_(-24)-6	ATCTGAACATTTGGTCCTTTGCAGGGTGAG	4251	CTCACCCTGCAAAGGACCAAATGTTCAGAT	5043
30	H55_(-23)-7	TCTGAACATTTGGTCCTTTGCAGGGTGAGT	4252	ACTCACCCTGCAAAGGACCAAATGTTCAGA	5044
30	H55_(-22)-8	CTGAACATTTGGTCCTTTGCAGGGTGAGTG	4253	CACTCACCCTGCAAAGGACCAAATGTTCAG	5045
30	H55_(-21)-9	TGAACATTTGGTCCTTTGCAGGGTGAGTGA	4254	TCACTCACCCTGCAAAGGACCAAATGTTCA	5046
30	H55_(-20)-10	GAACATTTGGTCCTTTGCAGGGTGAGTGAG	4255	CTCACTCACCCTGCAAAGGACCAAATGTTC	5047
30	H55_(-19)-11	AACATTTGGTCCTTTGCAGGGTGAGTGAGC	4256	GCTCACTCACCCTGCAAAGGACCAAATGTT	5048
30	H55_(-18)-12	ACATTTGGTCCTTTGCAGGGTGAGTGAGCG	4257	CGCTCACTCACCCTGCAAAGGACCAAATGT	5049
30	H55_(-17)-13	CATTTGGTCCTTTGCAGGGTGAGTGAGCGA	4258	TCGCTCACTCACCCTGCAAAGGACCAAATG	5050
30	H55_(-16)-14	ATTTGGTCCTTTGCAGGGTGAGTGAGCGAG	4259	CTCGCTCACTCACCCTGCAAAGGACCAAAT	5051
30	H55_(-15)-15	TTTGGTCCTTTGCAGGGTGAGTGAGCGAGA	4260	TCTCGCTCACTCACCCTGCAAAGGACCAAA	5052
30	H55_(-14)-16	TTGGTCCTTTGCAGGGTGAGTGAGCGAGAG	4261	CTCTCGCTCACTCACCCTGCAAAGGACCAA	5053
30	H55_(-13)-17	TGGTCCTTTGCAGGGTGAGTGAGCGAGAGG	4262	CCTCTCGCTCACTCACCCTGCAAAGGACCA	5054
30	H55_(-12)-18	GGTCCTTTGCAGGGTGAGTGAGCGAGAGGC	4263	GCCTCTCGCTCACTCACCCTGCAAAGGACC	5055
30	H55_(-11)-19	GTCCTTTGCAGGGTGAGTGAGCGAGAGGCT	4264	AGCCTCTCGCTCACTCACCCTGCAAAGGAC	5056
30	H55_(-10)-20	TCCTTTGCAGGGTGAGTGAGCGAGAGGCTG	4265	CAGCCTCTCGCTCACTCACCCTGCAAAGGA	5057
30	H55_(-9)-21	CCTTTGCAGGGTGAGTGAGCGAGAGGCTGC	4266	GCAGCCTCTCGCTCACTCACCCTGCAAAGG	5058

[Table 6-39]

30	H55_(-8)-22	CTTTGCAGGGTGAGTGAGCGAGAGGCTGCT	4267	AGCAGCCTCTCGCTCACTCACCCTGCAAAG	5059
30	H55_(-7)-23	TTTGCAGGGTGAGTGAGCGAGAGGCTGCTT	4268	AAGCAGCCTCTCGCTCACTCACCCTGCAAA	5060
30	H55_(-6)-24	TTGCAGGGTGAGTGAGCGAGAGGCTGCTTT	4269	AAAGCAGCCTCTCGCTCACTCACCCTGCAA	5061
30	H55_(-5)-25	TGCAGGGTGAGTGAGCGAGAGGCTGCTTTG	4270	CAAAGCAGCCTCTCGCTCACTCACCCTGCA	5062
30	H55_(-4)-26	GCAGGGTGAGTGAGCGAGAGGCTGCTTTGG	4271	CCAAAGCAGCCTCTCGCTCACTCACCCTGC	5063
30	H55_(-3)-27	CAGGGTGAGTGAGCGAGAGGCTGCTTTGGA	4272	TCCAAAGCAGCCTCTCGCTCACTCACCCTG	5064
30	H55_(-2)-28	AGGGTGAGTGAGCGAGAGGCTGCTTTGGAA	4273	TTCCAAAGCAGCCTCTCGCTCACTCACCCT	5065
30	H55_(-1)-29	GGGTGAGTGAGCGAGAGGCTGCTTTGGAAG	4274	CTTCCAAAGCAGCCTCTCGCTCACTCACCC	5066
30	H55_1-30	GGTGAGTGAGCGAGAGGCTGCTTTGGAAGA	4275	TCTTCCAAAGCAGCCTCTCGCTCACTCACC	5067
30	H55_2-31	GTGAGTGAGCGAGAGGCTGCTTTGGAAGAA	4276	TTCTTCCAAAGCAGCCTCTCGCTCACTCAC	5068
30	H55_3-32	TGAGTGAGCGAGAGGCTGCTTTGGAAGAAA	4277	TTTCTTCCAAAGCAGCCTCTCGCTCACTCA	5069
30	H55_4-33	GAGTGAGCGAGAGGCTGCTTTGGAAGAAAC	4278	GTTTCTTCCAAAGCAGCCTCTCGCTCACTC	5070
30	H55_5-34	AGTGAGCGAGAGGCTGCTTTGGAAGAAACT	4279	AGTTTCTTCCAAAGCAGCCTCTCGCTCACT	5071
30	H55_6-35	GTGAGCGAGAGGCTGCTTTGGAAGAAACTC	4280	GAGTTTCTTCCAAAGCAGCCTCTCGCTCAC	5072
30	H55_7-36	TGAGCGAGAGGCTGCTTTGGAAGAAACTCA	4281	TGAGTTTCTTCCAAAGCAGCCTCTCGCTCA	5073
30	H55_8-37	GAGCGAGAGGCTGCTTTGGAAGAAACTCAT	4282	ATGAGTTTCTTCCAAAGCAGCCTCTCGCTC	5074
30	H55_9-38	AGCGAGAGGCTGCTTTGGAAGAAACTCATA	4283	TATGAGTTTCTTCCAAAGCAGCCTCTCGCT	5075
30	H55_10-39	GCGAGAGGCTGCTTTGGAAGAAACTCATAG	4284	CTATGAGTTTCTTCCAAAGCAGCCTCTCGC	5076

[Table 6-40]

30	H55_11-40	CGAGAGGCTGCTTTGGAAGAA ACTCATAGA	4285	TCTATGAGTTTCTTCCAAAGC AGCCTCTCG	5077
30	H55_12-41	GAGAGGCTGCTTTGGAAGAAA CTCATAGAT	4286	ATCTATGAGTTTCTTCCAAAG CAGCCTCTC	5078
30	H55_13-42	AGAGGCTGCTTTGGAAGAAAC TCATAGATT	4287	AATCTATGAGTTTCTTCCAAA GCAGCCTCT	5079
30	H55_14-43	GAGGCTGCTTTGGAAGAAACT CATAGATTA	4288	TAATCTATGAGTTTCTTCCAA AGCAGCCTC	5080
30	H55_15-44	AGGCTGCTTTGGAAGAAACTC ATAGATTAC	4289	GTAATCTATGAGTTTCTTCCA AAGCAGCCT	5081
30	H55_16-45	GGCTGCTTTGGAAGAAACTCA TAGATTACT	4290	AGTAATCTATGAGTTTCTTCC AAAGCAGCC	5082
30	H55_17-46	GCTGCTTTGGAAGAAACTCAT AGATTACTG	4291	CAGTAATCTATGAGTTTCTTC CAAAGCAGC	5083
30	H55_18-47	CTGCTTTGGAAGAAACTCATA GATTACTGC	4292	GCAGTAATCTATGAGTTTCTT CCAAAGCAG	5084
30	H55_19-48	TGCTTTGGAAGAAACTCATAG ATTACTGCA	4293	TGCAGTAATCTATGAGTTTCT TCCAAAGCA	5085
30	H55_20-49	GCTTTGGAAGAAACTCATAGA TTACTGCAA	4294	TTGCAGTAATCTATGAGTTTC TTCCAAAGC	5086
30	H55_21-50	CTTTGGAAGAAACTCATAGAT TACTGCAAC	4295	GTTGCAGTAATCTATGAGTTT CTTCCAAAG	5087
30	H55_22-51	TTTGGAAGAAACTCATAGATT ACTGCAACA	4296	TGTTGCAGTAATCTATGAGTT TCTTCCAAA	5088
30	H55_23-52	TTGGAAGAAACTCATAGATTA CTGCAACAG	4297	CTGTTGCAGTAATCTATGAGT TTCTTCCAA	5089
30	H55_24-53	TGGAAGAAACTCATAGATTAC TGCAACAGT	4298	ACTGTTGCAGTAATCTATGAG TTTCTTCCA	5090

[0100]

In one embodiment, the second antisense oligomer of the present invention comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

[0101]

Herein, the base sequence (c) is a mutant type of the base sequence (a), and examples of such a mutant type also include:

(c-1) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±15% of the length of the any one base sequence selected,

(c-2) a base sequence that has at least 86% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±14% of the length of the any one base sequence selected,

(c-3) a base sequence that has at least 87% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±13% of the length of the any one base sequence selected,

(c-4) a base sequence that has at least 88% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±12% of the length of the any one base sequence selected,

(c-5) a base sequence that has at least 89% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±11% of the length of the any one base sequence selected,

(c-6) a base sequence that has at least 90% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±10% of the length of the any one base sequence selected,

(c-7) a base sequence that has at least 91% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±9% of the length of the any one base sequence selected,

(c-8) a base sequence that has at least 92% identity with any one base sequence selected from the group

consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±8% of the length of the any one base sequence selected,

(c-9) a base sequence that has at least 93% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±7% of the length of the any one base sequence selected,

(c-10) a base sequence that has at least 94% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±6% of the length of the any one base sequence selected,

(c-11) a base sequence that has at least 95% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±5% of the length of the any one base sequence selected,

(c-12) a base sequence that has at least 96% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±4% of the length of the any one base sequence selected,

(c-13) a base sequence that has at least 97% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a

length within ±3% of the length of the any one base sequence selected,

(c-14) a base sequence that has at least 98% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±2% of the length of the any one base sequence selected,

(c-15) a base sequence that has at least 99% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±1% of the length of the any one base sequence selected, and

(c-16) a base sequence that has at least 99.5% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±0.5% of the length of the any one base sequence selected.

[0102]

In one embodiment, the second antisense oligomer of the present invention comprises or consists of:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090; or

(b) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±15% of the length of the any one base sequence selected.

[0103]

Herein, the base sequence (b) is a mutant type of the base sequence (a), and examples of such a mutant type also include:

(b-1) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±15% of the length of the any one base sequence selected,

(b-2) a base sequence that has at least 86% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±14% of the length of the any one base sequence selected,

(b-3) a base sequence that has at least 87% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±13% of the length of the any one base sequence selected,

(b-4) a base sequence that has at least 88% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±12% of the length of the any one base sequence selected,

(b-5) a base sequence that has at least 89% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length

within ±11% of the length of the any one base sequence selected,

(b-6) a base sequence that has at least 90% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±10% of the length of the any one base sequence selected,

(b-7) a base sequence that has at least 91% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±9% of the length of the any one base sequence selected,

(b-8) a base sequence that has at least 92% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±8% of the length of the any one base sequence selected,

(b-9) a base sequence that has at least 93% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±7% of the length of the any one base sequence selected,

(b-10) a base sequence that has at least 94% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±6% of the length of the any one base sequence selected,

(b-11) a base sequence that has at least 95% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±5% of the length of the any one base sequence selected,

(b-12) a base sequence that has at least 96% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±4% of the length of the any one base sequence selected,

(b-13) a base sequence that has at least 97% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±3% of the length of the any one base sequence selected,

(b-14) a base sequence that has at least 98% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±2% of the length of the any one base sequence selected,

(b-15) a base sequence that has at least 99% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±1% of the length of the any one base sequence selected, and

(b-16) a base sequence that has at least 99.5% identity with any one base sequence selected from the

group consisting of SEQ ID NOs: 4299 to 5090, and has a length within ±0.5% of the length of the any one base sequence selected.

[0104]

In one embodiment, the second antisense oligomer of the present invention comprises or consists of any one base sequence selected from the group consisting of SEQ ID Nos: 4299 to 5090.

[0105]

In one embodiment, the second antisense oligomer comprises or consists of any one base sequence selected from the group consisting of SEQ ID NOs: 4698, 4702, 4752, 4923, 4926, 4936, 4950, and 4977.

[0106]

Table 7 below shows examples of the target sequence of the third antisense oligomer of the present invention, and a complementary sequence (antisense sequence) thereof.

[Table 7-1]

Table 7

Length mer	Target site	Targe sequence	SEQ ID NO:	Antisense sequence (5' to 3')	SEQ ID NO:
15	H45_169-183	AAAAAGAGGTAGGGC	1603	GCCCTACCTCTTTTT	2555
15	H45_170-184	AAAAGAGGTAGGGCG	1604	CGCCCTACCTCTTTT	2556
15	H45_171-185	AAAGAGGTAGGGCGA	1605	TCGCCCTACCTCTTT	2557
15	H45_172-186	AAGAGGTAGGGCGAC	1606	GTCGCCCTACCTCTT	2558
15	H45_173-187	AGAGGTAGGGCGACA	1607	TGTCGCCCTACCTCT	2559
15	H45_174-188	GAGGTAGGGCGACAG	1608	CTGTCGCCCTACCTC	2560

[Table 7-2]

15	H45_175-189	AGGTAGGGCGACAGA	1609	TCTGTCGCCCTACCT	2561
15	H45_176-190	GGTAGGGCGACAGAT	1610	ATCTGTCGCCCTACC	2562
15	H45_177-191	GTAGGGCGACAGATC	1611	GATCTGTCGCCCTAC	2563
15	H45_178-192	TAGGGCGACAGATCT	1612	AGATCTGTCGCCCTA	2564
15	H45_179-193	AGGGCGACAGATCTA	1613	TAGATCTGTCGCCCT	2565
15	H45_180-194	GGGCGACAGATCTAA	1614	TTAGATCTGTCGCCC	2566
15	H45_181-195	GGCGACAGATCTAAT	1615	ATTAGATCTGTCGCC	2567
15	H45_182-196	GCGACAGATCTAATA	1616	TATTAGATCTGTCGC	2568
15	H45_183-197	CGACAGATCTAATAG	1617	CTATTAGATCTGTCG	2569
15	H45_184-198	GACAGATCTAATAGG	1618	CCTATTAGATCTGTC	2570
15	H45_185-199	ACAGATCTAATAGGA	1619	TCCTATTAGATCTGT	2571
15	H45_186-200	CAGATCTAATAGGAA	1620	TTCCTATTAGATCTG	2572
15	H45_187-201	AGATCTAATAGGAAT	1621	ATTCCTATTAGATCT	2573
15	H45_188-202	GATCTAATAGGAATG	1622	CATTCCTATTAGATC	2574
15	H45_189-203	ATCTAATAGGAATGA	1623	TCATTCCTATTAGAT	2575
15	H45_190-204	TCTAATAGGAATGAA	1624	TTCATTCCTATTAGA	2576
15	H45_191-205	CTAATAGGAATGAAA	1625	TTTCATTCCTATTAG	2577
15	H45_192-206	TAATAGGAATGAAAA	1626	TTTTCATTCCTATTA	2578

[Table 7-3]

15	H45_193-207	AATAGGAATGAAAAC	1627	GTTTTCATTCCTATT	2579
15	H45_194-208	ATAGGAATGAAAACA	1628	TGTTTTCATTCCTAT	2580
15	H45_195-209	TAGGAATGAAAACAT	1629	ATGTTTTCATTCCTA	2581
15	H45_196-210	AGGAATGAAAACATT	1630	AATGTTTTCATTCCT	2582
15	H45_197-211	GGAATGAAAACATTT	1631	AAATGTTTTCATTCC	2583
15	H45_198-212	GAATGAAAACATTTT	1632	AAAATGTTTTCATTC	2584
15	H45_199-213	AATGAAAACATTTTA	1633	TAAAATGTTTTCATT	2585
15	H45_200-214	ATGAAAACATTTTAG	1634	CTAAAATGTTTTCAT	2586
15	H45_201-215	TGAAAACATTTTAGC	1635	GCTAAAATGTTTTCA	2587
15	H45_202-216	GAAAACATTTTAGCA	1636	TGCTAAAATGTTTTC	2588
15	H45_203-217	AAAACATTTTAGCAG	1637	CTGCTAAAATGTTTT	2589
15	H45_204-218	AAACATTTTAGCAGA	1638	TCTGCTAAAATGTTT	2590
15	H45_205-219	AACATTTTAGCAGAC	1639	GTCTGCTAAAATGTT	2591
15	H45_206-220	ACATTTTAGCAGACT	1640	AGTCTGCTAAAATGT	2592
15	H45_207-221	CATTTTAGCAGACTT	1641	AAGTCTGCTAAAATG	2593
15	H45_208-222	ATTTTAGCAGACTTT	1642	AAAGTCTGCTAAAAT	2594
15	H45_209-223	TTTTAGCAGACTTTT	1643	AAAAGTCTGCTAAAA	2595
15	H45_210-224	TTTAGCAGACTTTTT	1644	AAAAAGTCTGCTAAA	2596

[Table 7-4]

15	H45_211-225	TTAGCAGACTTTTTA	1645	TAAAAAGTCTGCTAA	2597
15	H45_212-226	TAGCAGACTTTTTAA	1646	TTAAAAAGTCTGCTA	2598
15	H45_213-227	AGCAGACTTTTTAAG	1647	CTTAAAAAGTCTGCT	2599
15	H45_214-228	GCAGACTTTTTAAGC	1648	GCTTAAAAAGTCTGC	2600
15	H45_215-229	CAGACTTTTTAAGCT	1649	AGCTTAAAAAGTCTG	2601
15	H45_216-230	AGACTTTTTAAGCTT	1650	AAGCTTAAAAAGTCT	2602
15	H45_217-231	GACTTTTTAAGCTTT	1651	AAAGCTTAAAAAGTC	2603
15	H45_218-232	ACTTTTTAAGCTTTC	1652	GAAAGCTTAAAAAGT	2604
15	H45_219-233	CTTTTTAAGCTTTCT	1653	AGAAAGCTTAAAAAG	2605
15	H45_220-234	TTTTTAAGCTTTCTT	1654	AAGAAAGCTTAAAAA	2606
16	H45_168-183	AAAAAAGAGGTAGGGC	1655	GCCCTACCTCTTTTTT	2607
16	H45_169-184	AAAAAGAGGTAGGGCG	1656	CGCCCTACCTCTTTTT	2608
16	H45_170-185	AAAAGAGGTAGGGCGA	1657	TCGCCCTACCTCTTTT	2609
16	H45_171-186	AAAGAGGTAGGGCGAC	1658	GTCGCCCTACCTCTTT	2610
16	H45_172-187	AAGAGGTAGGGCGACA	1659	TGTCGCCCTACCTCTT	2611
16	H45_173-188	AGAGGTAGGGCGACAG	1660	CTGTCGCCCTACCTCT	2612
16	H45_174-189	GAGGTAGGGCGACAGA	1661	TCTGTCGCCCTACCTC	2613
16	H45_175-190	AGGTAGGGCGACAGAT	1662	ATCTGTCGCCCTACCT	2614

[Table 7-5]

16	H45_176-191	GGTAGGGCGACAGATC	1663	GATCTGTCGCCCTACC	2615
16	H45_177-192	GTAGGGCGACAGATCT	1664	AGATCTGTCGCCCTAC	2616
16	H45_178-193	TAGGGCGACAGATCTA	1665	TAGATCTGTCGCCCTA	2617
16	H45_179-194	AGGGCGACAGATCTAA	1666	TTAGATCTGTCGCCCT	2618
16	H45_180-195	GGGCGACAGATCTAAT	1667	ATTAGATCTGTCGCCC	2619
16	H45_181-196	GGCGACAGATCTAATA	1668	TATTAGATCTGTCGCC	2620
16	H45_182-197	GCGACAGATCTAATAG	1669	CTATTAGATCTGTCGC	2621
16	H45_183-198	CGACAGATCTAATAGG	1670	CCTATTAGATCTGTCG	2622
16	H45_184-199	GACAGATCTAATAGGA	1671	TCCTATTAGATCTGTC	2623
16	H45_185-200	ACAGATCTAATAGGAA	1672	TTCCTATTAGATCTGT	2624
16	H45_186-201	CAGATCTAATAGGAAT	1673	ATTCCTATTAGATCTG	2625
16	H45_187-202	AGATCTAATAGGAATG	1674	CATTCCTATTAGATCT	2626
16	H45_188-203	GATCTAATAGGAATGA	1675	TCATTCCTATTAGATC	2627
16	H45_189-204	ATCTAATAGGAATGAA	1676	TTCATTCCTATTAGAT	2628
16	H45_190-205	TCTAATAGGAATGAAA	1677	TTTCATTCCTATTAGA	2629
16	H45_191-206	CTAATAGGAATGAAAA	1678	TTTTCATTCCTATTAG	2630
16	H45_192-207	TAATAGGAATGAAAAC	1679	GTTTTCATTCCTATTA	2631
16	H45_193-208	AATAGGAATGAAAACA	1680	TGTTTTCATTCCTATT	2632

[Table 7-6]

16	H45_194-209	ATAGGAATGAAAACAT	1681	ATGTTTTCATTCCTAT	2633
16	H45_195-210	TAGGAATGAAAACATT	1682	AATGTTTTCATTCCTA	2634
16	H45_196-211	AGGAATGAAAACATTT	1683	AAATGTTTTCATTCCT	2635
16	H45_197-212	GGAATGAAAACATTTT	1684	AAAATGTTTTCATTCC	2636
16	H45_198-213	GAATGAAAACATTTTA	1685	TAAAATGTTTTCATTC	2637
16	H45_199-214	AATGAAAACATTTTAG	1686	CTAAAATGTTTTCATT	2638
16	H45_200-215	ATGAAAACATTTTAGC	1687	GCTAAAATGTTTTCAT	2639
16	H45_201-216	TGAAAACATTTTAGCA	1688	TGCTAAAATGTTTTCA	2640
16	H45_202-217	GAAAACATTTTAGCAG	1689	CTGCTAAAATGTTTTC	2641
16	H45_203-218	AAAACATTTTAGCAGA	1690	TCTGCTAAAATGTTTT	2642
16	H45_204-219	AAACATTTTAGCAGAC	1691	GTCTGCTAAAATGTTT	2643
16	H45_205-220	AACATTTTAGCAGACT	1692	AGTCTGCTAAAATGTT	2644
16	H45_206-221	ACATTTTAGCAGACTT	1693	AAGTCTGCTAAAATGT	2645
16	H45_207-222	CATTTTAGCAGACTTT	1694	AAAGTCTGCTAAAATG	2646
16	H45_208-223	ATTTTAGCAGACTTTT	1695	AAAAGTCTGCTAAAAT	2647
16	H45_209-224	TTTTAGCAGACTTTTT	1696	AAAAAGTCTGCTAAAA	2648
16	H45_210-225	TTTAGCAGACTTTTTA	1697	TAAAAAGTCTGCTAAA	2649
16	H45_211-226	TTAGCAGACTTTTTAA	1698	TTAAAAAGTCTGCTAA	2650

[Table 7-7]

16	H45_212-227	TAGCAGACTTTTTAAG	1699	CTTAAAAAGTCTGCTA	2651
16	H45_213-228	AGCAGACTTTTTAAGC	1700	GCTTAAAAAGTCTGCT	2652
16	H45_214-229	GCAGACTTTTTAAGCT	1701	AGCTTAAAAAGTCTGC	2653
16	H45_215-230	CAGACTTTTTAAGCTT	1702	AAGCTTAAAAAGTCTG	2654
16	H45_216-231	AGACTTTTTAAGCTTT	1703	AAAGCTTAAAAAGTCT	2655
16	H45_217-232	GACTTTTTAAGCTTTC	1704	GAAAGCTTAAAAAGTC	2656
16	H45_218-233	ACTTTTTAAGCTTTCT	1705	AGAAAGCTTAAAAAGT	2657
16	H45_219-234	CTTTTTAAGCTTTCTT	1706	AAGAAAGCTTAAAAAG	2658
16	H45_220-235	TTTTTAAGCTTTCTTT	1707	AAAGAAAGCTTAAAAA	2659
17	H45_167-183	GAAAAAAGAGGTAGGGC	1708	GCCCTACCTCTTTTTTC	2660
17	H45_168-184	AAAAAAGAGGTAGGGCG	1709	CGCCCTACCTCTTTTTT	2661
17	H45_169-185	AAAAAGAGGTAGGGCGA	1710	TCGCCCTACCTCTTTTT	2662
17	H45_170-186	AAAAGAGGTAGGGCGAC	1711	GTCGCCCTACCTCTTTT	2663
17	H45_171-187	AAAGAGGTAGGGCGACA	1712	TGTCGCCCTACCTCTTT	2664
17	H45_172-188	AAGAGGTAGGGCGACAG	1713	CTGTCGCCCTACCTCTT	2665
17	H45_173-189	AGAGGTAGGGCGACAGA	1714	TCTGTCGCCCTACCTCT	2666
17	H45_174-190	GAGGTAGGGCGACAGAT	1715	ATCTGTCGCCCTACCTC	2667
17	H45_175-191	AGGTAGGGCGACAGATC	1716	GATCTGTCGCCCTACCT	2668

[Table 7-8]

17	H45_176-192	GGTAGGGCGACAGATCT	1717	AGATCTGTCGCCCTACC	2669
17	H45_177-193	GTAGGGCGACAGATCTA	1718	TAGATCTGTCGCCCTAC	2670
17	H45_178-194	TAGGGCGACAGATCTAA	1719	TTAGATCTGTCGCCCTA	2671
17	H45_179-195	AGGGCGACAGATCTAAT	1720	ATTAGATCTGTCGCCCT	2672
17	H45_180-196	GGGCGACAGATCTAATA	1721	TATTAGATCTGTCGCCC	2673
17	H45_181-197	GGCGACAGATCTAATAG	1722	CTATTAGATCTGTCGCC	2674
17	H45_182-198	GCGACAGATCTAATAGG	1723	CCTATTAGATCTGTCGC	2675
17	H45_183-199	CGACAGATCTAATAGGA	1724	TCCTATTAGATCTGTCG	2676
17	H45_184-200	GACAGATCTAATAGGAA	1725	TTCCTATTAGATCTGTC	2677
17	H45_185-201	ACAGATCTAATAGGAAT	1726	ATTCCTATTAGATCTGT	2678
17	H45_186-202	CAGATCTAATAGGAATG	1727	CATTCCTATTAGATCTG	2679
17	H45_187-203	AGATCTAATAGGAATGA	1728	TCATTCCTATTAGATCT	2680
17	H45_188-204	GATCTAATAGGAATGAA	1729	TTCATTCCTATTAGATC	2681
17	H45_189-205	ATCTAATAGGAATGAAA	1730	TTTCATTCCTATTAGAT	2682
17	H45_190-206	TCTAATAGGAATGAAAA	1731	TTTTCATTCCTATTAGA	2683
17	H45_191-207	CTAATAGGAATGAAAAC	1732	GTTTTCATTCCTATTAG	2684
17	H45_192-208	TAATAGGAATGAAAACA	1733	TGTTTTCATTCCTATTA	2685
17	H45_193-209	AATAGGAATGAAAACAT	1734	ATGTTTTCATTCCTATT	2686

[Table 7-9]

17	H45_194-210	ATAGGAATGAAAACATT	1735	AATGTTTTCATTCCTAT	2687
17	H45_195-211	TAGGAATGAAAACATTT	1736	AAATGTTTTCATTCCTA	2688
17	H45_196-212	AGGAATGAAAACATTTT	1737	AAAATGTTTTCATTCCT	2689
17	H45_197-213	GGAATGAAAACATTTTA	1738	TAAAATGTTTTCATTCC	2690
17	H45_198-214	GAATGAAAACATTTTAG	1739	CTAAAATGTTTTCATTC	2691
17	H45_199-215	AATGAAAACATTTTAGC	1740	GCTAAAATGTTTTCATT	2692
17	H45_200-216	ATGAAAACATTTTAGCA	1741	TGCTAAAATGTTTTCAT	2693
17	H45_201-217	TGAAAACATTTTAGCAG	1742	CTGCTAAAATGTTTTCA	2694
17	H45_202-218	GAAAACATTTTAGCAGA	1743	TCTGCTAAAATGTTTTC	2695
17	H45_203-219	AAAACATTTTAGCAGAC	1744	GTCTGCTAAAATGTTTT	2696
17	H45_204-220	AAACATTTTAGCAGACT	1745	AGTCTGCTAAAATGTTT	2697
17	H45_205-221	AACATTTTAGCAGACTT	1746	AAGTCTGCTAAAATGTT	2698
17	H45_206-222	ACATTTTAGCAGACTTT	1747	AAAGTCTGCTAAAATGT	2699
17	H45_207-223	CATTTTAGCAGACTTTT	1748	AAAAGTCTGCTAAAATG	2700
17	H45_208-224	ATTTTAGCAGACTTTTT	1749	AAAAAGTCTGCTAAAAT	2701
17	H45_209-225	TTTTAGCAGACTTTTTA	1750	TAAAAAGTCTGCTAAAA	2702
17	H45_210-226	TTTAGCAGACTTTTTAA	1751	TTAAAAAGTCTGCTAAA	2703
17	H45_211-227	TTAGCAGACTTTTTAAG	1752	CTTAAAAAGTCTGCTAA	2704

[Table 7-10]

17	H45_212-228	TAGCAGACTTTTTAAGC	1753	GCTTAAAAAGTCTGCTA	2705
17	H45_213-229	AGCAGACTTTTTAAGCT	1754	AGCTTAAAAAGTCTGCT	2706
17	H45_214-230	GCAGACTTTTTAAGCTT	1755	AAGCTTAAAAAGTCTGC	2707
17	H45_215-231	CAGACTTTTTAAGCTTT	1756	AAAGCTTAAAAAGTCTG	2708
17	H45_216-232	AGACTTTTTAAGCTTTC	1757	GAAAGCTTAAAAAGTCT	2709
17	H45_217-233	GACTTTTTAAGCTTTCT	1758	AGAAAGCTTAAAAAGTC	2710
17	H45_218-234	ACTTTTTAAGCTTTCTT	1759	AAGAAAGCTTAAAAAGT	2711
17	H45_219-235	CTTTTTAAGCTTTCTTT	1760	AAAGAAAGCTTAAAAAG	2712
17	H45_220-236	TTTTTAAGCTTTCTTTA	1761	TAAAGAAAGCTTAAAAA	2713
18	H45_166-183	AGAAAAAAGAGGTAGGGC	1762	GCCCTACCTCTTTTTTCT	2714
18	H45_167-184	GAAAAAAGAGGTAGGGCG	1763	CGCCCTACCTCTTTTTTC	2715
18	H45_168-185	AAAAAAGAGGTAGGGCGA	1764	TCGCCCTACCTCTTTTTT	2716
18	H45_169-186	AAAAAGAGGTAGGGCGAC	1765	GTCGCCCTACCTCTTTTT	2717
18	H45_170-187	AAAAGAGGTAGGGCGACA	1766	TGTCGCCCTACCTCTTTT	2718
18	H45_171-188	AAAGAGGTAGGGCGACAG	1767	CTGTCGCCCTACCTCTTT	2719
18	H45_172-189	AAGAGGTAGGGCGACAGA	1768	TCTGTCGCCCTACCTCTT	2720
18	H45_173-190	AGAGGTAGGGCGACAGAT	1769	ATCTGTCGCCCTACCTCT	2721
18	H45_174-191	GAGGTAGGGCGACAGATC	1770	GATCTGTCGCCCTACCTC	2722

[Table 7-11]

18	H45_175-192	AGGTAGGGCGACAGATCT	1771	AGATCTGTCGCCCTACCT	2723
18	H45_176-193	GGTAGGGCGACAGATCTA	1772	TAGATCTGTCGCCCTACC	2724
18	H45_177-194	GTAGGGCGACAGATCTAA	1773	TTAGATCTGTCGCCCTAC	2725
18	H45_178-195	TAGGGCGACAGATCTAAT	1774	ATTAGATCTGTCGCCCTA	2726
18	H45_179-196	AGGGCGACAGATCTAATA	1775	TATTAGATCTGTCGCCCT	2727
18	H45_180-197	GGGCGACAGATCTAATAG	1776	CTATTAGATCTGTCGCCC	2728
18	H45_181-198	GGCGACAGATCTAATAGG	1777	CCTATTAGATCTGTCGCC	2729
18	H45_182-199	GCGACAGATCTAATAGGA	1778	TCCTATTAGATCTGTCGC	2730
18	H45_183-200	CGACAGATCTAATAGGAA	1779	TTCCTATTAGATCTGTCG	2731
18	H45_184-201	GACAGATCTAATAGGAAT	1780	ATTCCTATTAGATCTGTC	2732
18	H45_185-202	ACAGATCTAATAGGAATG	1781	CATTCCTATTAGATCTGT	2733
18	H45_186-203	CAGATCTAATAGGAATGA	1782	TCATTCCTATTAGATCTG	2734
18	H45_187-204	AGATCTAATAGGAATGAA	1783	TTCATTCCTATTAGATCT	2735
18	H45_188-205	GATCTAATAGGAATGAAA	1784	TTTCATTCCTATTAGATC	2736
18	H45_189-206	ATCTAATAGGAATGAAAA	1785	TTTTCATTCCTATTAGAT	2737
18	H45_190-207	TCTAATAGGAATGAAAAC	1786	GTTTTCATTCCTATTAGA	2738
18	H45_191-208	CTAATAGGAATGAAAACA	1787	TGTTTTCATTCCTATTAG	2739
18	H45_192-209	TAATAGGAATGAAAACAT	1788	ATGTTTTCATTCCTATTA	2740

[Table 7-12]

18	H45_193-210	AATAGGAATGAAAACATT	1789	AATGTTTTCATTCCTATT	2741
18	H45_194-211	ATAGGAATGAAAACATTT	1790	AAATGTTTTCATTCCTAT	2742
18	H45_195-212	TAGGAATGAAAACATTTT	1791	AAAATGTTTTCATTCCTA	2743
18	H45_196-213	AGGAATGAAAACATTTTA	1792	TAAAATGTTTTCATTCCT	2744
18	H45_197-214	GGAATGAAAACATTTTAG	1793	CTAAAATGTTTTCATTCC	2745
18	H45_198-215	GAATGAAAACATTTTAGC	1794	GCTAAAATGTTTTCATTC	2746
18	H45_199-216	AATGAAAACATTTTAGCA	1795	TGCTAAAATGTTTTCATT	2747
18	H45_200-217	ATGAAAACATTTTAGCAG	1796	CTGCTAAAATGTTTTCAT	2748
18	H45_201-218	TGAAAACATTTTAGCAGA	1797	TCTGCTAAAATGTTTTCA	2749
18	H45_202-219	GAAAACATTTTAGCAGAC	1798	GTCTGCTAAAATGTTTTC	2750
18	H45_203-220	AAAACATTTTAGCAGACT	1799	AGTCTGCTAAAATGTTTT	2751
18	H45_204-221	AAACATTTTAGCAGACTT	1800	AAGTCTGCTAAAATGTTT	2752
18	H45_205-222	AACATTTTAGCAGACTTT	1801	AAAGTCTGCTAAAATGTT	2753
18	H45_206-223	ACATTTTAGCAGACTTTT	1802	AAAAGTCTGCTAAAATGT	2754
18	H45_207-224	CATTTTAGCAGACTTTTT	1803	AAAAAGTCTGCTAAAATG	2755
18	H45_208-225	ATTTTAGCAGACTTTTTA	1804	TAAAAAGTCTGCTAAAAT	2756
18	H45_209-226	TTTTAGCAGACTTTTTAA	1805	TTAAAAAGTCTGCTAAAA	2757
18	H45_210-227	TTTAGCAGACTTTTTAAG	1806	CTTAAAAAGTCTGCTAAA	2758

[Table 7-13]

18	H45_211-228	TTAGCAGACTTTTTAAGC	1807	GCTTAAAAAGTCTGCTAA	2759
18	H45_212-229	TAGCAGACTTTTTAAGCT	1808	AGCTTAAAAAGTCTGCTA	2760
18	H45_213-230	AGCAGACTTTTTAAGCTT	1809	AAGCTTAAAAAGTCTGCT	2761
18	H45_214-231	GCAGACTTTTTAAGCTTT	1810	AAAGCTTAAAAAGTCTGC	2762
18	H45_215-232	CAGACTTTTTAAGCTTTC	1811	GAAAGCTTAAAAAGTCTG	2763
18	H45_216-233	AGACTTTTTAAGCTTTCT	1812	AGAAAGCTTAAAAAGTCT	2764
18	H45_217-234	GACTTTTTAAGCTTTCTT	1813	AAGAAAGCTTAAAAAGTC	2765
18	H45_218-235	ACTTTTTAAGCTTTCTTT	1814	AAAGAAAGCTTAAAAAGT	2766
18	H45_219-236	CTTTTTAAGCTTTCTTTA	1815	TAAAGAAAGCTTAAAAAG	2767
18	H45_220-237	TTTTTAAGCTTTCTTTAG	1816	CTAAAGAAAGCTTAAAAA	2768
19	H45_165-183	CAGAAAAAAGAGGTAGGGC	1817	GCCCTACCTCTTTTTTCTG	2769
19	H45_166-184	AGAAAAAAGAGGTAGGGCG	1818	CGCCCTACCTCTTTTTTCT	2770
19	H45_167-185	GAAAAAAGAGGTAGGGCGA	1819	TCGCCCTACCTCTTTTTTC	2771
19	H45_168-186	AAAAAAGAGGTAGGGCGAC	1820	GTCGCCCTACCTCTTTTTT	2772
19	H45_169-187	AAAAAGAGGTAGGGCGACA	1821	TGTCGCCCTACCTCTTTTT	2773
19	H45_170-188	AAAAGAGGTAGGGCGACAG	1822	CTGTCGCCCTACCTCTTTT	2774
19	H45_171-189	AAAGAGGTAGGGCGACAGA	1823	TCTGTCGCCCTACCTCTTT	2775
19	H45_172-190	AAGAGGTAGGGCGACAGAT	1824	ATCTGTCGCCCTACCTCTT	2776

[Table 7-14]

19	H45_173-191	AGAGGTAGGGCGACAGATC	1825	GATCTGTCGCCCTACCTCT	2777
19	H45_174-192	GAGGTAGGGCGACAGATCT	1826	AGATCTGTCGCCCTACCTC	2778
19	H45_175-193	AGGTAGGGCGACAGATCTA	1827	TAGATCTGTCGCCCTACCT	2779
19	H45_176-194	GGTAGGGCGACAGATCTAA	1828	TTAGATCTGTCGCCCTACC	2780
19	H45_177-195	GTAGGGCGACAGATCTAAT	1829	ATTAGATCTGTCGCCCTAC	2781
19	H45_178-196	TAGGGCGACAGATCTAATA	1830	TATTAGATCTGTCGCCCTA	2782
19	H45_179-197	AGGGCGACAGATCTAATAG	1831	CTATTAGATCTGTCGCCCT	2783
19	H45_180-198	GGGCGACAGATCTAATAGG	1832	CCTATTAGATCTGTCGCCC	2784
19	H45_181-199	GGCGACAGATCTAATAGGA	1833	TCCTATTAGATCTGTCGCC	2785
19	H45_182-200	GCGACAGATCTAATAGGAA	1834	TTCCTATTAGATCTGTCGC	2786
19	H45_183-201	CGACAGATCTAATAGGAAT	1835	ATTCCTATTAGATCTGTCG	2787
19	H45_184-202	GACAGATCTAATAGGAATG	1836	CATTCCTATTAGATCTGTC	2788
19	H45_185-203	ACAGATCTAATAGGAATGA	1837	TCATTCCTATTAGATCTGT	2789
19	H45_186-204	CAGATCTAATAGGAATGAA	1838	TTCATTCCTATTAGATCTG	2790
19	H45_187-205	AGATCTAATAGGAATGAAA	1839	TTTCATTCCTATTAGATCT	2791
19	H45_188-206	GATCTAATAGGAATGAAAA	1840	TTTTCATTCCTATTAGATC	2792
19	H45_189-207	ATCTAATAGGAATGAAAAC	1841	GTTTTCATTCCTATTAGAT	2793
19	H45_190-208	TCTAATAGGAATGAAAACA	1842	TGTTTTCATTCCTATTAGA	2794

[Table 7-15]

19	H45_191-209	CTAATAGGAATGAAAACAT	1843	ATGTTTTCATTCCTATTAG	2795
19	H45_192-210	TAATAGGAATGAAAACATT	1844	AATGTTTTCATTCCTATTA	2796
19	H45_193-211	AATAGGAATGAAAACATTT	1845	AAATGTTTTCATTCCTATT	2797
19	H45_194-212	ATAGGAATGAAAACATTTT	1846	AAAATGTTTTCATTCCTAT	2798
19	H45_195-213	TAGGAATGAAAACATTTTA	1847	TAAAATGTTTTCATTCCTA	2799
19	H45_196-214	AGGAATGAAAACATTTTAG	1848	CTAAAATGTTTTCATTCCT	2800
19	H45_197-215	GGAATGAAAACATTTTAGC	1849	GCTAAAATGTTTTCATTCC	2801
19	H45_198-216	GAATGAAAACATTTTAGCA	1850	TGCTAAAATGTTTTCATTC	2802
19	H45_199-217	AATGAAAACATTTTAGCAG	1851	CTGCTAAAATGTTTTCATT	2803
19	H45_200-218	ATGAAAACATTTTAGCAGA	1852	TCTGCTAAAATGTTTTCAT	2804
19	H45_201-219	TGAAAACATTTTAGCAGAC	1853	GTCTGCTAAAATGTTTTCA	2805
19	H45_202-220	GAAAACATTTTAGCAGACT	1854	AGTCTGCTAAAATGTTTTC	2806
19	H45_203-221	AAAACATTTTAGCAGACTT	1855	AAGTCTGCTAAAATGTTTT	2807
19	H45_204-222	AAACATTTTAGCAGACTTT	1856	AAAGTCTGCTAAAATGTTT	2808
19	H45_205-223	AACATTTTAGCAGACTTTT	1857	AAAAGTCTGCTAAAATGTT	2809
19	H45_206-224	ACATTTTAGCAGACTTTTT	1858	AAAAAGTCTGCTAAAATGT	2810
19	H45_207-225	CATTTTAGCAGACTTTTTA	1859	TAAAAAGTCTGCTAAAATG	2811
19	H45_208-226	ATTTTAGCAGACTTTTTAA	1860	TTAAAAAGTCTGCTAAAAT	2812

[Table 7-16]

19	H45_209-227	TTTTAGCAGACTTTTTAAG	1861	CTTAAAAAGTCTGCTAAAA	2813
19	H45_210-228	TTTAGCAGACTTTTTAAGC	1862	GCTTAAAAAGTCTGCTAAA	2814
19	H45_211-229	TTAGCAGACTTTTTAAGCT	1863	AGCTTAAAAAGTCTGCTAA	2815
19	H45_212-230	TAGCAGACTTTTTAAGCTT	1864	AAGCTTAAAAAGTCTGCTA	2816
19	H45_213-231	AGCAGACTTTTTAAGCTTT	1865	AAAGCTTAAAAAGTCTGCT	2817
19	H45_214-232	GCAGACTTTTTAAGCTTTC	1866	GAAAGCTTAAAAAGTCTGC	2818
19	H45_215-233	CAGACTTTTTAAGCTTTCT	1867	AGAAAGCTTAAAAAGTCTG	2819
19	H45_216-234	AGACTTTTTAAGCTTTCTT	1868	AAGAAAGCTTAAAAAGTCT	2820
19	H45_217-235	GACTTTTTAAGCTTTCTTT	1869	AAAGAAAGCTTAAAAAGTC	2821
19	H45_218-236	ACTTTTTAAGCTTTCTTTA	1870	TAAAGAAAGCTTAAAAAGT	2822
19	H45_219-237	CTTTTTAAGCTTTCTTTAG	1871	CTAAAGAAAGCTTAAAAAG	2823
19	H45_220-238	TTTTTAAGCTTTCTTTAGA	1872	TCTAAAGAAAGCTTAAAAA	2824
20	H45_164-183	ACAGAAAAAAGAGGTAGGGC	1873	GCCCTACCTCTTTTTTCTGT	2825
20	H45_165-184	CAGAAAAAAGAGGTAGGGCG	1874	CGCCCTACCTCTTTTTTCTG	2826
20	H45_166-185	AGAAAAAAGAGGTAGGGCGA	1875	TCGCCCTACCTCTTTTTTCT	2827
20	H45_167-186	GAAAAAAGAGGTAGGGCGAC	1876	GTCGCCCTACCTCTTTTTTC	2828
20	H45_168-187	AAAAAAGAGGTAGGGCGACA	1877	TGTCGCCCTACCTCTTTTTT	2829
20	H45_169-188	AAAAAGAGGTAGGGCGACAG	1878	CTGTCGCCCTACCTCTTTTT	2830

[Table 7-17]

20	H45_170-189	AAAAGAGGTAGGGCGACAGA	1879	TCTGTCGCCCTACCTCTTTT	2831
20	H45_171-190	AAAGAGGTAGGGCGACAGAT	1880	ATCTGTCGCCCTACCTCTTT	2832
20	H45_172-191	AAGAGGTAGGGCGACAGATC	1881	GATCTGTCGCCCTACCTCTT	2833
20	H45_173-192	AGAGGTAGGGCGACAGATCT	1882	AGATCTGTCGCCCTACCTCT	2834
20	H45_174-193	GAGGTAGGGCGACAGATCTA	1883	TAGATCTGTCGCCCTACCTC	2835
20	H45_175-194	AGGTAGGGCGACAGATCTAA	1884	TTAGATCTGTCGCCCTACCT	2836
20	H45_176-195	GGTAGGGCGACAGATCTAAT	1885	ATTAGATCTGTCGCCCTACC	2837
20	H45_177-196	GTAGGGCGACAGATCTAATA	1886	TATTAGATCTGTCGCCCTAC	2838
20	H45_178-197	TAGGGCGACAGATCTAATAG	1887	CTATTAGATCTGTCGCCCTA	2839
20	H45_179-198	AGGGCGACAGATCTAATAGG	1888	CCTATTAGATCTGTCGCCCT	2840
20	H45_180-199	GGGCGACAGATCTAATAGGA	1889	TCCTATTAGATCTGTCGCCC	2841
20	H45_181-200	GGCGACAGATCTAATAGGAA	1890	TTCCTATTAGATCTGTCGCC	2842
20	H45_182-201	GCGACAGATCTAATAGGAAT	1891	ATTCCTATTAGATCTGTCGC	2843
20	H45_183-202	CGACAGATCTAATAGGAATG	1892	CATTCCTATTAGATCTGTCG	2844
20	H45_184-203	GACAGATCTAATAGGAATGA	1893	TCATTCCTATTAGATCTGTC	2845
20	H45_185-204	ACAGATCTAATAGGAATGAA	1894	TTCATTCCTATTAGATCTGT	2846
20	H45_186-205	CAGATCTAATAGGAATGAAA	1895	TTTCATTCCTATTAGATCTG	2847
20	H45_187-206	AGATCTAATAGGAATGAAAA	1896	TTTTCATTCCTATTAGATCT	2848

[Table 7-18]

20	H45_188-207	GATCTAATAGGAATGAAAAC	1897	GTTTTCATTCCTATTAGATC	2849
20	H45_189-208	ATCTAATAGGAATGAAAACA	1898	TGTTTTCATTCCTATTAGAT	2850
20	H45_190-209	TCTAATAGGAATGAAAACAT	1899	ATGTTTTCATTCCTATTAGA	2851
20	H45_191-210	CTAATAGGAATGAAAACATT	1900	AATGTTTTCATTCCTATTAG	2852
20	H45_192-211	TAATAGGAATGAAAACATTT	1901	AAATGTTTTCATTCCTATTA	2853
20	H45_193-212	AATAGGAATGAAAACATTTT	1902	AAAATGTTTTCATTCCTATT	2854
20	H45_194-213	ATAGGAATGAAAACATTTTA	1903	TAAAATGTTTTCATTCCTAT	2855
20	H45_195-214	TAGGAATGAAAACATTTTAG	1904	CTAAAATGTTTTCATTCCTA	2856
20	H45_196-215	AGGAATGAAAACATTTTAGC	1905	GCTAAAATGTTTTCATTCCT	2857
20	H45_197-216	GGAATGAAAACATTTTAGCA	1906	TGCTAAAATGTTTTCATTCC	2858
20	H45_198-217	GAATGAAAACATTTTAGCAG	1907	CTGCTAAAATGTTTTCATTC	2859
20	H45_199-218	AATGAAAACATTTTAGCAGA	1908	TCTGCTAAAATGTTTTCATT	2860
20	H45_200-219	ATGAAAACATTTTAGCAGAC	1909	GTCTGCTAAAATGTTTTCAT	2861
20	H45_201-220	TGAAAACATTTTAGCAGACT	1910	AGTCTGCTAAAATGTTTTCA	2862
20	H45_202-221	GAAAACATTTTAGCAGACTT	1911	AAGTCTGCTAAAATGTTTTC	2863
20	H45_203-222	AAAACATTTTAGCAGACTTT	1912	AAAGTCTGCTAAAATGTTTT	2864
20	H45_204-223	AAACATTTTAGCAGACTTTT	1913	AAAAGTCTGCTAAAATGTTT	2865
20	H45_205-224	AACATTTTAGCAGACTTTTT	1914	AAAAAGTCTGCTAAAATGTT	2866

[Table 7-19]

20	H45_206-225	ACATTTTAGCAGACTTTTTA	1915	TAAAAAGTCTGCTAAAATGT	2867
20	H45_207-226	CATTTTAGCAGACTTTTTAA	1916	TTAAAAAGTCTGCTAAAATG	2868
20	H45_208-227	ATTTTAGCAGACTTTTTAAG	1917	CTTAAAAAGTCTGCTAAAAT	2869
20	H45_209-228	TTTTAGCAGACTTTTTAAGC	1918	GCTTAAAAAGTCTGCTAAAA	2870
20	H45_210-229	TTTAGCAGACTTTTTAAGCT	1919	AGCTTAAAAAGTCTGCTAAA	2871
20	H45_211-230	TTAGCAGACTTTTTAAGCTT	1920	AAGCTTAAAAAGTCTGCTAA	2872
20	H45_212-231	TAGCAGACTTTTTAAGCTTT	1921	AAAGCTTAAAAAGTCTGCTA	2873
20	H45_213-232	AGCAGACTTTTTAAGCTTTC	1922	GAAAGCTTAAAAAGTCTGCT	2874
20	H45_214-233	GCAGACTTTTTAAGCTTTCT	1923	AGAAAGCTTAAAAAGTCTGC	2875
20	H45_215-234	CAGACTTTTTAAGCTTTCTT	1924	AAGAAAGCTTAAAAAGTCTG	2876
20	H45_216-235	AGACTTTTTAAGCTTTCTTT	1925	AAAGAAAGCTTAAAAAGTCT	2877
20	H45_217-236	GACTTTTTAAGCTTTCTTTA	1926	TAAAGAAAGCTTAAAAAGTC	2878
20	H45_218-237	ACTTTTTAAGCTTTCTTTAG	1927	CTAAAGAAAGCTTAAAAAGT	2879
20	H45_219-238	CTTTTTAAGCTTTCTTTAGA	1928	TCTAAAGAAAGCTTAAAAAG	2880
20	H45_220-239	TTTTTAAGCTTTCTTTAGAA	1929	TTCTAAAGAAAGCTTAAAAA	2881
21	H45_163-183	GACAGAAAAAAGAGGTAGGGC	1930	GCCCTACCTCTTTTTTCTGTC	2882
21	H45_164-184	ACAGAAAAAAGAGGTAGGGCG	1931	CGCCCTACCTCTTTTTTCTGT	2883
21	H45_165-185	CAGAAAAAAGAGGTAGGGCGA	1932	TCGCCCTACCTCTTTTTTCTG	2884

[Table 7-20]

21	H45_166-186	AGAAAAAAGAGGTAGGGCGAC	1933	GTCGCCCTACCTCTTTTTTCT	2885
21	H45_167-187	GAAAAAAGAGGTAGGGCGACA	1934	TGTCGCCCTACCTCTTTTTTC	2886
21	H45_168-188	AAAAAAGAGGTAGGGCGACAG	1935	CTGTCGCCCTACCTCTTTTTT	2887
21	H45_169-189	AAAAAGAGGTAGGGCGACAGA	1936	TCTGTCGCCCTACCTCTTTTT	2888
21	H45_170-190	AAAAGAGGTAGGGCGACAGAT	1937	ATCTGTCGCCCTACCTCTTTT	2889
21	H45_171-191	AAAGAGGTAGGGCGACAGATC	1938	GATCTGTCGCCCTACCTCTTT	2890
21	H45_172-192	AAGAGGTAGGGCGACAGATCT	1939	AGATCTGTCGCCCTACCTCTT	2891
21	H45_173-193	AGAGGTAGGGCGACAGATCTA	1940	TAGATCTGTCGCCCTACCTCT	2892
21	H45_174-194	GAGGTAGGGCGACAGATCTAA	1941	TTAGATCTGTCGCCCTACCTC	2893
21	H45_175-195	AGGTAGGGCGACAGATCTAAT	1942	ATTAGATCTGTCGCCCTACCT	2894
21	H45_176-196	GGTAGGGCGACAGATCTAATA	1943	TATTAGATCTGTCGCCCTACC	2895
21	H45_177-197	GTAGGGCGACAGATCTAATAG	1944	CTATTAGATCTGTCGCCCTAC	2896
21	H45_178-198	TAGGGCGACAGATCTAATAGG	1945	CCTATTAGATCTGTCGCCCTA	2897
21	H45_179-199	AGGGCGACAGATCTAATAGGA	1946	TCCTATTAGATCTGTCGCCCT	2898
21	H45_180-200	GGGCGACAGATCTAATAGGAA	1947	TTCCTATTAGATCTGTCGCCC	2899
21	H45_181-201	GGCGACAGATCTAATAGGAAT	1948	ATTCCTATTAGATCTGTCGCC	2900
21	H45_182-202	GCGACAGATCTAATAGGAATG	1949	CATTCCTATTAGATCTGTCGC	2901
21	H45_183-203	CGACAGATCTAATAGGAATGA	1950	TCATTCCTATTAGATCTGTCG	2902

[Table 7-21]

21	H45_184-204	GACAGATCTAATAGGAATGAA	1951	TTCATTCCTATTAGATCTGTC	2903
21	H45_185-205	ACAGATCTAATAGGAATGAAA	1952	TTTCATTCCTATTAGATCTGT	2904
21	H45_186-206	CAGATCTAATAGGAATGAAAA	1953	TTTTCATTCCTATTAGATCTG	2905
21	H45_187-207	AGATCTAATAGGAATGAAAAC	1954	GTTTTCATTCCTATTAGATCT	2906
21	H45_188-208	GATCTAATAGGAATGAAAACA	1955	TGTTTTCATTCCTATTAGATC	2907
21	H45_189-209	ATCTAATAGGAATGAAAACAT	1956	ATGTTTTCATTCCTATTAGAT	2908
21	H45_190-210	TCTAATAGGAATGAAAACATT	1957	AATGTTTTCATTCCTATTAGA	2909
21	H45_191-211	CTAATAGGAATGAAAACATTT	1958	AAATGTTTTCATTCCTATTAG	2910
21	H45_192-212	TAATAGGAATGAAAACATTTT	1959	AAAATGTTTTCATTCCTATTA	2911
21	H45_193-213	AATAGGAATGAAAACATTTTA	1960	TAAAATGTTTTCATTCCTATT	2912
21	H45_194-214	ATAGGAATGAAAACATTTTAG	1961	CTAAAATGTTTTCATTCCTAT	2913
21	H45_195-215	TAGGAATGAAAACATTTTAGC	1962	GCTAAAATGTTTTCATTCCTA	2914
21	H45_196-216	AGGAATGAAAACATTTTAGCA	1963	TGCTAAAATGTTTTCATTCCT	2915
21	H45_197-217	GGAATGAAAACATTTTAGCAG	1964	CTGCTAAAATGTTTTCATTCC	2916
21	H45_198-218	GAATGAAAACATTTTAGCAGA	1965	TCTGCTAAAATGTTTTCATTC	2917
21	H45_199-219	AATGAAAACATTTTAGCAGAC	1966	GTCTGCTAAAATGTTTTCATT	2918
21	H45_200-220	ATGAAAACATTTTAGCAGACT	1967	AGTCTGCTAAAATGTTTTCAT	2919
21	H45_201-221	TGAAAACATTTTAGCAGACTT	1968	AAGTCTGCTAAAATGTTTTCA	2920

[Table 7-22]

21	H45_202-222	GAAAACATTTTAGCAGACTTT	1969	AAAGTCTGCTAAAATGTTTTC	2921
21	H45_203-223	AAAACATTTTAGCAGACTTTT	1970	AAAAGTCTGCTAAAATGTTTT	2922
21	H45_204-224	AAACATTTTAGCAGACTTTTT	1971	AAAAAGTCTGCTAAAATGTTT	2923
21	H45_205-225	AACATTTTAGCAGACTTTTTA	1972	TAAAAAGTCTGCTAAAATGTT	2924
21	H45_206-226	ACATTTTAGCAGACTTTTTAA	1973	TTAAAAAGTCTGCTAAAATGT	2925
21	H45_207-227	CATTTTAGCAGACTTTTTAAG	1974	CTTAAAAAGTCTGCTAAAATG	2926
21	H45_208-228	ATTTTAGCAGACTTTTTAAGC	1975	GCTTAAAAAGTCTGCTAAAAT	2927
21	H45_209-229	TTTTAGCAGACTTTTTAAGCT	1976	AGCTTAAAAAGTCTGCTAAAA	2928
21	H45_210-230	TTTAGCAGACTTTTTAAGCTT	1977	AAGCTTAAAAAGTCTGCTAAA	2929
21	H45_211-231	TTAGCAGACTTTTTAAGCTTT	1978	AAAGCTTAAAAAGTCTGCTAA	2930
21	H45_212-232	TAGCAGACTTTTTAAGCTTTC	1979	GAAAGCTTAAAAAGTCTGCTA	2931
21	H45_213-233	AGCAGACTTTTTAAGCTTTCT	1980	AGAAAGCTTAAAAAGTCTGCT	2932
21	H45_214-234	GCAGACTTTTTAAGCTTTCTT	1981	AAGAAAGCTTAAAAAGTCTGC	2933
21	H45_215-235	CAGACTTTTTAAGCTTTCTTT	1982	AAAGAAAGCTTAAAAAGTCTG	2934
21	H45_216-236	AGACTTTTTAAGCTTTCTTTA	1983	TAAAGAAAGCTTAAAAAGTCT	2935
21	H45_217-237	GACTTTTTAAGCTTTCTTTAG	1984	CTAAAGAAAGCTTAAAAAGTC	2936
21	H45_218-238	ACTTTTTAAGCTTTCTTTAGA	1985	TCTAAAGAAAGCTTAAAAAGT	2937
21	H45_219-239	CTTTTTAAGCTTTCTTTAGAA	1986	TTCTAAAGAAAGCTTAAAAAG	2938

[Table 7-23]

21	H45_220-240	TTTTTAAGCTTTCTTTAGAAG	1987	CTTCTAAAGAAAGCTTAAAAA	2939
22	H45_162-183	AGACAGAAAAAAGAGGTAGGGC	1988	GCCCTACCTCTTTTTTCTGTCT	2940
22	H45_163-184	GACAGAAAAAAGAGGTAGGGCG	1989	CGCCCTACCTCTTTTTTCTGTC	2941
22	H45_164-185	ACAGAAAAAAGAGGTAGGGCGA	1990	TCGCCCTACCTCTTTTTTCTGT	2942
22	H45_165-186	CAGAAAAAAGAGGTAGGGCGAC	1991	GTCGCCCTACCTCTTTTTTCTG	2943
22	H45_166-187	AGAAAAAAGAGGTAGGGCGACA	1992	TGTCGCCCTACCTCTTTTTTCT	2944
22	H45_167-188	GAAAAAAGAGGTAGGGCGACAG	1993	CTGTCGCCCTACCTCTTTTTTC	2945
22	H45_168-189	AAAAAAGAGGTAGGGCGACAGA	1994	TCTGTCGCCCTACCTCTTTTTT	2946
22	H45_169-190	AAAAAGAGGTAGGGCGACAGAT	1995	ATCTGTCGCCCTACCTCTTTTT	2947
22	H45_170-191	AAAAGAGGTAGGGCGACAGATC	1996	GATCTGTCGCCCTACCTCTTTT	2948
22	H45_171-192	AAAGAGGTAGGGCGACAGATCT	1997	AGATCTGTCGCCCTACCTCTTT	2949
22	H45_172-193	AAGAGGTAGGGCGACAGATCTA	1998	TAGATCTGTCGCCCTACCTCTT	2950
22	H45_173-194	AGAGGTAGGGCGACAGATCTAA	1999	TTAGATCTGTCGCCCTACCTCT	2951
22	H45_174-195	GAGGTAGGGCGACAGATCTAAT	2000	ATTAGATCTGTCGCCCTACCTC	2952
22	H45_175-196	AGGTAGGGCGACAGATCTAATA	2001	TATTAGATCTGTCGCCCTACCT	2953
22	H45_176-197	GGTAGGGCGACAGATCTAATAG	2002	CTATTAGATCTGTCGCCCTACC	2954
22	H45_177-198	GTAGGGCGACAGATCTAATAGG	2003	CCTATTAGATCTGTCGCCCTAC	2955
22	H45_178-199	TAGGGCGACAGATCTAATAGGA	2004	TCCTATTAGATCTGTCGCCCTA	2956

[Table 7-24]

22	H45_179-200	AGGGCGACAGATCTAATAGGAA	2005	TTCCTATTAGATCTGTCGCCCT	2957
22	H45_180-201	GGGCGACAGATCTAATAGGAAT	2006	ATTCCTATTAGATCTGTCGCCC	2958
22	H45_181-202	GGCGACAGATCTAATAGGAATG	2007	CATTCCTATTAGATCTGTCGCC	2959
22	H45_182-203	GCGACAGATCTAATAGGAATGA	2008	TCATTCCTATTAGATCTGTCGC	2960
22	H45_183-204	CGACAGATCTAATAGGAATGAA	2009	TTCATTCCTATTAGATCTGTCG	2961
22	H45_184-205	GACAGATCTAATAGGAATGAAA	2010	TTTCATTCCTATTAGATCTGTC	2962
22	H45_185-206	ACAGATCTAATAGGAATGAAAA	2011	TTTTCATTCCTATTAGATCTGT	2963
22	H45_186-207	CAGATCTAATAGGAATGAAAAC	2012	GTTTTCATTCCTATTAGATCTG	2964
22	H45_187-208	AGATCTAATAGGAATGAAAACA	2013	TGTTTTCATTCCTATTAGATCT	2965
22	H45_188-209	GATCTAATAGGAATGAAAACAT	2014	ATGTTTTCATTCCTATTAGATC	2966
22	H45_189-210	ATCTAATAGGAATGAAAACATT	2015	AATGTTTTCATTCCTATTAGAT	2967
22	H45_190-211	TCTAATAGGAATGAAAACATTT	2016	AAATGTTTTCATTCCTATTAGA	2968
22	H45_191-212	CTAATAGGAATGAAAACATTTT	2017	AAAATGTTTTCATTCCTATTAG	2969
22	H45_192-213	TAATAGGAATGAAAACATTTTA	2018	TAAAATGTTTTCATTCCTATTA	2970
22	H45_193-214	AATAGGAATGAAAACATTTTAG	2019	CTAAAATGTTTTCATTCCTATT	2971
22	H45_194-215	ATAGGAATGAAAACATTTTAGC	2020	GCTAAAATGTTTTCATTCCTAT	2972
22	H45_195-216	TAGGAATGAAAACATTTTAGCA	2021	TGCTAAAATGTTTTCATTCCTA	2973
22	H45_196-217	AGGAATGAAAACATTTTAGCAG	2022	CTGCTAAAATGTTTTCATTCCT	2974

[Table 7-25]

22	H45_197-218	GGAATGAAAACATTTTAGCAGA	2023	TCTGCTAAAATGTTTTCATTCC	2975
22	H45_198-219	GAATGAAAACATTTTAGCAGAC	2024	GTCTGCTAAAATGTTTTCATTC	2976
22	H45_199-220	AATGAAAACATTTTAGCAGACT	2025	AGTCTGCTAAAATGTTTTCATT	2977
22	H45_200-221	ATGAAAACATTTTAGCAGACTT	2026	AAGTCTGCTAAAATGTTTTCAT	2978
22	H45_201-222	TGAAAACATTTTAGCAGACTTT	2027	AAAGTCTGCTAAAATGTTTTCA	2979
22	H45_202-223	GAAAACATTTTAGCAGACTTTT	2028	AAAAGTCTGCTAAAATGTTTTC	2980
22	H45_203-224	AAAACATTTTAGCAGACTTTTT	2029	AAAAAGTCTGCTAAAATGTTTT	2981
22	H45_204-225	AAACATTTTAGCAGACTTTTTA	2030	TAAAAAGTCTGCTAAAATGTTT	2982
22	H45_205-226	AACATTTTAGCAGACTTTTTAA	2031	TTAAAAAGTCTGCTAAAATGTT	2983
22	H45_206-227	ACATTTTAGCAGACTTTTTAAG	2032	CTTAAAAAGTCTGCTAAAATGT	2984
22	H45_207-228	CATTTTAGCAGACTTTTTAAGC	2033	GCTTAAAAAGTCTGCTAAAATG	2985
22	H45_208-229	ATTTTAGCAGACTTTTTAAGCT	2034	AGCTTAAAAAGTCTGCTAAAAT	2986
22	H45_209-230	TTTTAGCAGACTTTTTAAGCTT	2035	AAGCTTAAAAAGTCTGCTAAAA	2987
22	H45_210-231	TTTAGCAGACTTTTTAAGCTTT	2036	AAAGCTTAAAAAGTCTGCTAAA	2988
22	H45_211-232	TTAGCAGACTTTTTAAGCTTTC	2037	GAAAGCTTAAAAAGTCTGCTAA	2989
22	H45_212-233	TAGCAGACTTTTTAAGCTTTCT	2038	AGAAAGCTTAAAAAGTCTGCTA	2990
22	H45_213-234	AGCAGACTTTTTAAGCTTTCTT	2039	AAGAAAGCTTAAAAAGTCTGCT	2991
22	H45_214-235	GCAGACTTTTTAAGCTTTCTTT	2040	AAAGAAAGCTTAAAAAGTCTGC	2992

[Table 7-26]

22	H45_215-236	CAGACTTTTTAAGCTTTCTTTA	2041	TAAAGAAAGCTTAAAAAGTCTG	2993
22	H45_216-237	AGACTTTTTAAGCTTTCTTTAG	2042	CTAAAGAAAGCTTAAAAAGTCT	2994
22	H45_217-238	GACTTTTTAAGCTTTCTTTAGA	2043	TCTAAAGAAAGCTTAAAAAGTC	2995
22	H45_218-239	ACTTTTTAAGCTTTCTTTAGAA	2044	TTCTAAAGAAAGCTTAAAAAGT	2996
22	H45_219-240	CTTTTTAAGCTTTCTTTAGAAG	2045	CTTCTAAAGAAAGCTTAAAAAG	2997
22	H45_220-241	TTTTTAAGCTTTCTTTAGAAGA	2046	TCTTCTAAAGAAAGCTTAAAAA	2998
23	H45_161-183	CAGACAGAAAAAAGAGGTAGGGC	2047	GCCCTACCTCTTTTTTCTGTCTG	2999
23	H45_162-184	AGACAGAAAAAAGAGGTAGGGCG	2048	CGCCCTACCTCTTTTTTCTGTCT	3000
23	H45_163-185	GACAGAAAAAAGAGGTAGGGCGA	2049	TCGCCCTACCTCTTTTTTCTGTC	3001
23	H45_164-186	ACAGAAAAAAGAGGTAGGGCGAC	2050	GTCGCCCTACCTCTTTTTTCTGT	3002
23	H45_165-187	CAGAAAAAAGAGGTAGGGCGACA	2051	TGTCGCCCTACCTCTTTTTTCTG	3003
23	H45_166-188	AGAAAAAAGAGGTAGGGCGACAG	2052	CTGTCGCCCTACCTCTTTTTTCT	3004
23	H45_167-189	GAAAAAAGAGGTAGGGCGACAGA	2053	TCTGTCGCCCTACCTCTTTTTTC	3005
23	H45_168-190	AAAAAAGAGGTAGGGCGACAGAT	2054	ATCTGTCGCCCTACCTCTTTTTT	3006
23	H45_169-191	AAAAAGAGGTAGGGCGACAGATC	2055	GATCTGTCGCCCTACCTCTTTTT	3007
23	H45_170-192	AAAAGAGGTAGGGCGACAGATCT	2056	AGATCTGTCGCCCTACCTCTTTT	3008
23	H45_171-193	AAAGAGGTAGGGCGACAGATCTA	2057	TAGATCTGTCGCCCTACCTCTTT	3009
23	H45_172-194	AAGAGGTAGGGCGACAGATCTAA	2058	TTAGATCTGTCGCCCTACCTCTT	3010

[Table 7-27]

23	H45_173-195	AGAGGTAGGGCGACAGATCTAAT	2059	ATTAGATCTGTCGCCCTACCTCT	3011
23	H45_174-196	GAGGTAGGGCGACAGATCTAATA	2060	TATTAGATCTGTCGCCCTACCTC	3012
23	H45_175-197	AGGTAGGGCGACAGATCTAATAG	2061	CTATTAGATCTGTCGCCCTACCT	3013
23	H45_176-198	GGTAGGGCGACAGATCTAATAGG	2062	CCTATTAGATCTGTCGCCCTACC	3014
23	H45_177-199	GTAGGGCGACAGATCTAATAGGA	2063	TCCTATTAGATCTGTCGCCCTAC	3015
23	H45_178-200	TAGGGCGACAGATCTAATAGGAA	2064	TTCCTATTAGATCTGTCGCCCTA	3016
23	H45_179-201	AGGGCGACAGATCTAATAGGAAT	2065	ATTCCTATTAGATCTGTCGCCCT	3017
23	H45_180-202	GGGCGACAGATCTAATAGGAATG	2066	CATTCCTATTAGATCTGTCGCCC	3018
23	H45_181-203	GGCGACAGATCTAATAGGAATGA	2067	TCATTCCTATTAGATCTGTCGCC	3019
23	H45_182-204	GCGACAGATCTAATAGGAATGAA	2068	TTCATTCCTATTAGATCTGTCGC	3020
23	H45_183-205	CGACAGATCTAATAGGAATGAAA	2069	TTTCATTCCTATTAGATCTGTCG	3021
23	H45_184-206	GACAGATCTAATAGGAATGAAAA	2070	TTTTCATTCCTATTAGATCTGTC	3022
23	H45_185-207	ACAGATCTAATAGGAATGAAAAC	2071	GTTTTCATTCCTATTAGATCTGT	3023
23	H45_186-208	CAGATCTAATAGGAATGAAAACA	2072	TGTTTTCATTCCTATTAGATCTG	3024
23	H45_187-209	AGATCTAATAGGAATGAAAACAT	2073	ATGTTTTCATTCCTATTAGATCT	3025
23	H45_188-210	GATCTAATAGGAATGAAAACATT	2074	AATGTTTTCATTCCTATTAGATC	3026
23	H45_189-211	ATCTAATAGGAATGAAAACATTT	2075	AAATGTTTTCATTCCTATTAGAT	3027
23	H45_190-212	TCTAATAGGAATGAAAACATTTT	2076	AAAATGTTTTCATTCCTATTAGA	3028

[Table 7-28]

23	H45_191-213	CTAATAGGAATGAAAACATTTTA	2077	TAAAATGTTTTCATTCCTATTAG	3029
23	H45_192-214	TAATAGGAATGAAAACATTTTAG	2078	CTAAAATGTTTTCATTCCTATTA	3030
23	H45_193-215	AATAGGAATGAAAACATTTTAGC	2079	GCTAAAATGTTTTCATTCCTATT	3031
23	H45_194-216	ATAGGAATGAAAACATTTTAGCA	2080	TGCTAAAATGTTTTCATTCCTAT	3032
23	H45_195-217	TAGGAATGAAAACATTTTAGCAG	2081	CTGCTAAAATGTTTTCATTCCTA	3033
23	H45_196-218	AGGAATGAAAACATTTTAGCAGA	2082	TCTGCTAAAATGTTTTCATTCCT	3034
23	H45_197-219	GGAATGAAAACATTTTAGCAGAC	2083	GTCTGCTAAAATGTTTTCATTCC	3035
23	H45_198-220	GAATGAAAACATTTTAGCAGACT	2084	AGTCTGCTAAAATGTTTTCATTC	3036
23	H45_199-221	AATGAAAACATTTTAGCAGACTT	2085	AAGTCTGCTAAAATGTTTTCATT	3037
23	H45_200-222	ATGAAAACATTTTAGCAGACTTT	2086	AAAGTCTGCTAAAATGTTTTCAT	3038
23	H45_201-223	TGAAAACATTTTAGCAGACTTTT	2087	AAAAGTCTGCTAAAATGTTTTCA	3039
23	H45_202-224	GAAAACATTTTAGCAGACTTTTT	2088	AAAAAGTCTGCTAAAATGTTTTC	3040
23	H45_203-225	AAAACATTTTAGCAGACTTTTTA	2089	TAAAAAGTCTGCTAAAATGTTTT	3041
23	H45_204-226	AAACATTTTAGCAGACTTTTTAA	2090	TTAAAAAGTCTGCTAAAATGTTT	3042
23	H45_205-227	AACATTTTAGCAGACTTTTTAAG	2091	CTTAAAAAGTCTGCTAAAATGTT	3043
23	H45_206-228	ACATTTTAGCAGACTTTTTAAGC	2092	GCTTAAAAAGTCTGCTAAAATGT	3044
23	H45_207-229	CATTTTAGCAGACTTTTTAAGCT	2093	AGCTTAAAAAGTCTGCTAAAATG	3045
23	H45_208-230	ATTTTAGCAGACTTTTTAAGCTT	2094	AAGCTTAAAAAGTCTGCTAAAAT	3046

[Table 7-29]

23	H45_209-231	TTTTAGCAGACTTTTTAAGCTTT	2095	AAAGCTTAAAAAGTCTGCTAAAA	3047
23	H45_210-232	TTTAGCAGACTTTTTAAGCTTTC	2096	GAAAGCTTAAAAAGTCTGCTAAA	3048
23	H45_211-233	TTAGCAGACTTTTTAAGCTTTCT	2097	AGAAAGCTTAAAAAGTCTGCTAA	3049
23	H45_212-234	TAGCAGACTTTTTAAGCTTTCTT	2098	AAGAAAGCTTAAAAAGTCTGCTA	3050
23	H45_213-235	AGCAGACTTTTTAAGCTTTCTTT	2099	AAAGAAAGCTTAAAAAGTCTGCT	3051
23	H45_214-236	GCAGACTTTTTAAGCTTTCTTTA	2100	TAAAGAAAGCTTAAAAAGTCTGC	3052
23	H45_215-237	CAGACTTTTTAAGCTTTCTTTAG	2101	CTAAAGAAAGCTTAAAAAGTCTG	3053
23	H45_216-238	AGACTTTTTAAGCTTTCTTTAGA	2102	TCTAAAGAAAGCTTAAAAAGTCT	3054
23	H45_217-239	GACTTTTTAAGCTTTCTTTAGAA	2103	TTCTAAAGAAAGCTTAAAAAGTC	3055
23	H45_218-240	ACTTTTTAAGCTTTCTTTAGAAG	2104	CTTCTAAAGAAAGCTTAAAAAGT	3056
23	H45_219-241	CTTTTTAAGCTTTCTTTAGAAGA	2105	TCTTCTAAAGAAAGCTTAAAAAG	3057
23	H45_220-242	TTTTTAAGCTTTCTTTAGAAGAA	2106	TTCTTCTAAAGAAAGCTTAAAAA	3058
24	H45_160-183	TCAGACAGAAAAAAGAGGTAGGGC	2107	GCCCTACCTCTTTTTTCTGTCTGA	3059
24	H45_161-184	CAGACAGAAAAAAGAGGTAGGGCG	2108	CGCCCTACCTCTTTTTTCTGTCTG	3060
24	H45_162-185	AGACAGAAAAAAGAGGTAGGGCGA	2109	TCGCCCTACCTCTTTTTTCTGTCT	3061
24	H45_163-186	GACAGAAAAAAGAGGTAGGGCGAC	2110	GTCGCCCTACCTCTTTTTTCTGTC	3062
24	H45_164-187	ACAGAAAAAAGAGGTAGGGCGACA	2111	TGTCGCCCTACCTCTTTTTTCTGT	3063
24	H45_165-188	CAGAAAAAAGAGGTAGGGCGACAG	2112	CTGTCGCCCTACCTCTTTTTTCTG	3064

[Table 7-30]

24	H45_166-189	AGAAAAAAGAGGTAGGGCGACAGA	2113	TCTGTCGCCCTACCTCTTTTTTC T	3065
24	H45_167-190	GAAAAAAGAGGTAGGGCGACAGAT	2114	ATCTGTCGCCCTACCTCTTTTTT C	3066
24	H45_168-191	AAAAAAGAGGTAGGGCGACAGATC	2115	GATCTGTCGCCCTACCTCTTTTT T	3067
24	H45_169-192	AAAAAGAGGTAGGGCGACAGATCT	2116	AGATCTGTCGCCCTACCTCTTTT T	3068
24	H45_170-193	AAAAGAGGTAGGGCGACAGATCTA	2117	TAGATCTGTCGCCCTACCTCTTT T	3069
24	H45_171-194	AAAGAGGTAGGGCGACAGATCTAA	2118	TTAGATCTGTCGCCCTACCTCTT T	3070
24	H45_172-195	AAGAGGTAGGGCGACAGATCTAAT	2119	ATTAGATCTGTCGCCCTACCTCT T	3071
24	H45_173-196	AGAGGTAGGGCGACAGATCTAATA	2120	TATTAGATCTGTCGCCCTACCTC T	3072
24	H45_174-197	GAGGTAGGGCGACAGATCTAATAG	2121	CTATTAGATCTGTCGCCCTACCT C	3073
24	H45_175-198	AGGTAGGGCGACAGATCTAATAGG	2122	CCTATTAGATCTGTCGCCCTACC T	3074
24	H45_176-199	GGTAGGGCGACAGATCTAATAGGA	2123	TCCTATTAGATCTGTCGCCCTAC C	3075
24	H45_177-200	GTAGGGCGACAGATCTAATAGGAA	2124	TTCCTATTAGATCTGTCGCCCTA C	3076
24	H45_178-201	TAGGGCGACAGATCTAATAGGAAT	2125	ATTCCTATTAGATCTGTCGCCCT A	3077
24	H45_179-202	AGGGCGACAGATCTAATAGGAATG	2126	CATTCCTATTAGATCTGTCGCCC T	3078
24	H45_180-203	GGGCGACAGATCTAATAGGAATGA	2127	TCATTCCTATTAGATCTGTCGCC C	3079
24	H45_181-204	GGCGACAGATCTAATAGGAATGAA	2128	TTCATTCCTATTAGATCTGTCGC C	3080
24	H45_182-205	GCGACAGATCTAATAGGAATGAAA	2129	TTTCATTCCTATTAGATCTGTCG C	3081
24	H45_183-206	CGACAGATCTAATAGGAATGAAAA	2130	TTTTCATTCCTATTAGATCTGTC G	3082

[Table 7-31]

24	H45_184-207	GACAGATCTAATAGGAATGAAAAC	2131	GTTTTCATTCCTATTAGATCTGTC	3083
24	H45_185-208	ACAGATCTAATAGGAATGAAAACA	2132	TGTTTTCATTCCTATTAGATCTGT	3084
24	H45_186-209	CAGATCTAATAGGAATGAAAACAT	2133	ATGTTTTCATTCCTATTAGATCTG	3085
24	H45_187-210	AGATCTAATAGGAATGAAAACATT	2134	AATGTTTTCATTCCTATTAGATCT	3086
24	H45_188-211	GATCTAATAGGAATGAAAACATTT	2135	AAATGTTTTCATTCCTATTAGATC	3087
24	H45_189-212	ATCTAATAGGAATGAAAACATTTT	2136	AAAATGTTTTCATTCCTATTAGAT	3088
24	H45_190-213	TCTAATAGGAATGAAAACATTTTA	2137	TAAAATGTTTTCATTCCTATTAGA	3089
24	H45_191-214	CTAATAGGAATGAAAACATTTTAG	2138	CTAAAATGTTTTCATTCCTATTAG	3090
24	H45_192-215	TAATAGGAATGAAAACATTTTAGC	2139	GCTAAAATGTTTTCATTCCTATTA	3091
24	H45_193-216	AATAGGAATGAAAACATTTTAGCA	2140	TGCTAAAATGTTTTCATTCCTATT	3092
24	H45_194-217	ATAGGAATGAAAACATTTTAGCAG	2141	CTGCTAAAATGTTTTCATTCCTAT	3093
24	H45_195-218	TAGGAATGAAAACATTTTAGCAGA	2142	TCTGCTAAAATGTTTTCATTCCTA	3094
24	H45_196-219	AGGAATGAAAACATTTTAGCAGAC	2143	GTCTGCTAAAATGTTTTCATTCCT	3095
24	H45_197-220	GGAATGAAAACATTTTAGCAGACT	2144	AGTCTGCTAAAATGTTTTCATTCC	3096
24	H45_198-221	GAATGAAAACATTTTAGCAGACTT	2145	AAGTCTGCTAAAATGTTTTCATTC	3097
24	H45_199-222	AATGAAAACATTTTAGCAGACTTT	2146	AAAGTCTGCTAAAATGTTTTCATT	3098
24	H45_200-223	ATGAAAACATTTTAGCAGACTTTT	2147	AAAAGTCTGCTAAAATGTTTTCAT	3099
24	H45_201-224	TGAAAACATTTTAGCAGACTTTTT	2148	AAAAAGTCTGCTAAAATGTTTTCA	3100

[Table 7-32]

24	H45_202-225	GAAAACATTTTAGCAGACTTTTTA	2149	TAAAAAGTCTGCTAAAATGTTTTC	3101
24	H45_203-226	AAAACATTTTAGCAGACTTTTTAA	2150	TTAAAAAGTCTGCTAAAATGTTTT	3102
24	H45_204-227	AAACATTTTAGCAGACTTTTTAAG	2151	CTTAAAAAGTCTGCTAAAATGTTT	3103
24	H45_205-228	AACATTTTAGCAGACTTTTTAAGC	2152	GCTTAAAAAGTCTGCTAAAATGT	3104
24	H45_206-229	ACATTTTAGCAGACTTTTTAAGCT	2153	AGCTTAAAAAGTCTGCTAAAATG	3105
24	H45_207-230	CATTTTAGCAGACTTTTTAAGCTT	2154	AAGCTTAAAAAGTCTGCTAAAAT	3106
24	H45_208-231	ATTTTAGCAGACTTTTTAAGCTTT	2155	AAAGCTTAAAAAGTCTGCTAAAA	3107
24	H45_209-232	TTTTAGCAGACTTTTTAAGCTTTC	2156	GAAAGCTTAAAAAGTCTGCTAAA	3108
24	H45_210-233	TTTAGCAGACTTTTTAAGCTTTCT	2157	AGAAAGCTTAAAAAGTCTGCTAA	3109
24	H45_211-234	TTAGCAGACTTTTTAAGCTTTCTT	2158	AAGAAAGCTTAAAAAGTCTGCTA	3110
24	H45_212-235	TAGCAGACTTTTTAAGCTTTCTTT	2159	AAAGAAAGCTTAAAAAGTCTGCT	3111
24	H45_213-236	AGCAGACTTTTTAAGCTTTCTTTA	2160	TAAAGAAAGCTTAAAAAGTCTGC	3112
24	H45_214-237	GCAGACTTTTTAAGCTTTCTTTAG	2161	CTAAAGAAAGCTTAAAAAGTCTG	3113
24	H45_215-238	CAGACTTTTTAAGCTTTCTTTAGA	2162	TCTAAAGAAAGCTTAAAAAGTCT	3114
24	H45_216-239	AGACTTTTTAAGCTTTCTTTAGAA	2163	TTCTAAAGAAAGCTTAAAAAGTC	3115
24	H45_217-240	GACTTTTTAAGCTTTCTTTAGAAG	2164	CTTCTAAAGAAAGCTTAAAAAGT	3116
24	H45_218-241	ACTTTTTAAGCTTTCTTTAGAAGA	2165	TCTTCTAAAGAAAGCTTAAAAAG	3117
24	H45_219-242	CTTTTTAAGCTTTCTTTAGAAGAA	2166	TTCTTCTAAAGAAAGCTTAAAAA	3118

[Table 7-33]

24	H45_220-243	TTTTTAAGCTTTCTTTAGAAGAAT	2167	ATTCTTCTAAAGAAAGCTTAAAAA	3119
25	H45_159-183	GTCAGACAGAAAAAAGAGGTAGGGC	2168	GCCCTACCTCTTTTTTCTGTCTGAC	3120
25	H45_160-184	TCAGACAGAAAAAAGAGGTAGGGCG	2169	CGCCCTACCTCTTTTTTCTGTCTGA	3121
25	H45_161-185	CAGACAGAAAAAAGAGGTAGGGCGA	2170	TCGCCCTACCTCTTTTTTCTGTCTG	3122
25	H45_162-186	AGACAGAAAAAAGAGGTAGGGCGAC	2171	GTCGCCCTACCTCTTTTTTCTGTCT	3123
25	H45_163-187	GACAGAAAAAAGAGGTAGGGCGACA	2172	TGTCGCCCTACCTCTTTTTTCTGTC	3124
25	H45_164-188	ACAGAAAAAAGAGGTAGGGCGACAG	2173	CTGTCGCCCTACCTCTTTTTTCTGT	3125
25	H45_165-189	CAGAAAAAAGAGGTAGGGCGACAGA	2174	TCTGTCGCCCTACCTCTTTTTTCTG	3126
25	H45_166-190	AGAAAAAAGAGGTAGGGCGACAGAT	2175	ATCTGTCGCCCTACCTCTTTTTTCT	3127
25	H45_167-191	GAAAAAAGAGGTAGGGCGACAGATC	2176	GATCTGTCGCCCTACCTCTTTTTTC	3128
25	H45_168-192	AAAAAAGAGGTAGGGCGACAGATCT	2177	AGATCTGTCGCCCTACCTCTTTTTT	3129
25	H45_169-193	AAAAAGAGGTAGGGCGACAGATCTA	2178	TAGATCTGTCGCCCTACCTCTTTTT	3130
25	H45_170-194	AAAAGAGGTAGGGCGACAGATCTAA	2179	TTAGATCTGTCGCCCTACCTCTTTT	3131
25	H45_171-195	AAAGAGGTAGGGCGACAGATCTAAT	2180	ATTAGATCTGTCGCCCTACCTCTTT	3132
25	H45_172-196	AAGAGGTAGGGCGACAGATCTAATA	2181	TATTAGATCTGTCGCCCTACCTCTT	3133
25	H45_173-197	AGAGGTAGGGCGACAGATCTAATAG	2182	CTATTAGATCTGTCGCCCTACCTCT	3134
25	H45_174-198	GAGGTAGGGCGACAGATCTAATAGG	2183	CCTATTAGATCTGTCGCCCTACCTC	3135
25	H45_175-199	AGGTAGGGCGACAGATCTAATAGGA	2184	TCCTATTAGATCTGTCGCCCTACCT	3136

[Table 7-34]

25	H45_176-200	GGTAGGGCGACAGATCTAATAGGAA	2185	TTCCTATTAGATCTGTCGCCCTACC	3137
25	H45_177-201	GTAGGGCGACAGATCTAATAGGAAT	2186	ATTCCTATTAGATCTGTCGCCCTAC	3138
25	H45_178-202	TAGGGCGACAGATCTAATAGGAATG	2187	CATTCCTATTAGATCTGTCGCCCTA	3139
25	H45_179-203	AGGGCGACAGATCTAATAGGAATGA	2188	TCATTCCTATTAGATCTGTCGCCCT	3140
25	H45_180-204	GGGCGACAGATCTAATAGGAATGAA	2189	TTCATTCCTATTAGATCTGTCGCCC	3141
25	H45_181-205	GGCGACAGATCTAATAGGAATGAAA	2190	TTTCATTCCTATTAGATCTGTCGCC	3142
25	H45_182-206	GCGACAGATCTAATAGGAATGAAAA	2191	TTTTCATTCCTATTAGATCTGTCGC	3143
25	H45_183-207	CGACAGATCTAATAGGAATGAAAAC	2192	GTTTTCATTCCTATTAGATCTGTCG	3144
25	H45_184-208	GACAGATCTAATAGGAATGAAAACA	2193	TGTTTTCATTCCTATTAGATCTGTC	3145
25	H45_185-209	ACAGATCTAATAGGAATGAAAACAT	2194	ATGTTTTCATTCCTATTAGATCTGT	3146
25	H45_186-210	CAGATCTAATAGGAATGAAAACATT	2195	AATGTTTTCATTCCTATTAGATCTG	3147
25	H45_187-211	AGATCTAATAGGAATGAAAACATTT	2196	AAATGTTTTCATTCCTATTAGATCT	3148
25	H45_188-212	GATCTAATAGGAATGAAAACATTTT	2197	AAAATGTTTTCATTCCTATTAGATC	3149
25	H45_189-213	ATCTAATAGGAATGAAAACATTTTA	2198	TAAAATGTTTTCATTCCTATTAGAT	3150
25	H45_190-214	TCTAATAGGAATGAAAACATTTTAG	2199	CTAAAATGTTTTCATTCCTATTAGA	3151
25	H45_191-215	CTAATAGGAATGAAAACATTTTAGC	2200	GCTAAAATGTTTTCATTCCTATTAG	3152
25	H45_192-216	TAATAGGAATGAAAACATTTTAGCA	2201	TGCTAAAATGTTTTCATTCCTATTA	3153
25	H45_193-217	AATAGGAATGAAAACATTTTAGCAG	2202	CTGCTAAAATGTTTTCATTCCTATT	3154

[Table 7-35]

25	H45_194-218	ATAGGAATGAAAACATTTTAGCAGA	2203	TCTGCTAAAATGTTTTCATTCCTAT	3155
25	H45_195-219	TAGGAATGAAAACATTTTAGCAGAC	2204	GTCTGCTAAAATGTTTTCATTCCTA	3156
25	H45_196-220	AGGAATGAAAACATTTTAGCAGACT	2205	AGTCTGCTAAAATGTTTTCATTCCT	3157
25	H45_197-221	GGAATGAAAACATTTTAGCAGACTT	2206	AAGTCTGCTAAAATGTTTTCATTCC	3158
25	H45_198-222	GAATGAAAACATTTTAGCAGACTTT	2207	AAAGTCTGCTAAAATGTTTTCATTC	3159
25	H45_199-223	AATGAAAACATTTTAGCAGACTTTT	2208	AAAAGTCTGCTAAAATGTTTTCATT	3160
25	H45_200-224	ATGAAAACATTTTAGCAGACTTTTT	2209	AAAAAGTCTGCTAAAATGTTTTCAT	3161
25	H45_201-225	TGAAAACATTTTAGCAGACTTTTTA	2210	TAAAAAGTCTGCTAAAATGTTTTCA	3162
25	H45_202-226	GAAAACATTTTAGCAGACTTTTTAA	2211	TTAAAAAGTCTGCTAAAATGTTTTC	3163
25	H45_203-227	AAAACATTTTAGCAGACTTTTTAAG	2212	CTTAAAAAGTCTGCTAAAATGTTTT	3164
25	H45_204-228	AAACATTTTAGCAGACTTTTTAAGC	2213	GCTTAAAAAGTCTGCTAAAATGTTT	3165
25	H45_205-229	AACATTTTAGCAGACTTTTTAAGCT	2214	AGCTTAAAAAGTCTGCTAAAATGTT	3166
25	H45_206-230	ACATTTTAGCAGACTTTTTAAGCTT	2215	AAGCTTAAAAAGTCTGCTAAAATGT	3167
25	H45_207-231	CATTTTAGCAGACTTTTTAAGCTTT	2216	AAAGCTTAAAAAGTCTGCTAAAATG	3168
25	H45_208-232	ATTTTAGCAGACTTTTTAAGCTTTC	2217	GAAAGCTTAAAAAGTCTGCTAAAAT	3169
25	H45_209-233	TTTTAGCAGACTTTTTAAGCTTTCT	2218	AGAAAGCTTAAAAAGTCTGCTAAAA	3170
25	H45_210-234	TTTAGCAGACTTTTTAAGCTTTCTT	2219	AAGAAAGCTTAAAAAGTCTGCTAAA	3171
25	H45_211-235	TTAGCAGACTTTTTAAGCTTTCTTT	2220	AAAGAAAGCTTAAAAAGTCTGCTAA	3172

[Table 7-36]

25	H45_212-236	TAGCAGACTTTTTAAGCTTTCTTTA	2221	TAAAGAAAGCTTAAAAAGTCTGCTA	3173
25	H45_213-237	AGCAGACTTTTTAAGCTTTCTTTAG	2222	CTAAAGAAAGCTTAAAAAGTCTGCT	3174
25	H45_214-238	GCAGACTTTTTAAGCTTTCTTTAGA	2223	TCTAAAGAAAGCTTAAAAAGTCTGC	3175
25	H45_215-239	CAGACTTTTTAAGCTTTCTTTAGAA	2224	TTCTAAAGAAAGCTTAAAAAGTCTG	3176
25	H45_216-240	AGACTTTTTAAGCTTTCTTTAGAAG	2225	CTTCTAAAGAAAGCTTAAAAAGTCT	3177
25	H45_217-241	GACTTTTTAAGCTTTCTTTAGAAGA	2226	TCTTCTAAAGAAAGCTTAAAAAGTC	3178
25	H45_218-242	ACTTTTTAAGCTTTCTTTAGAAGAA	2227	TTCTTCTAAAGAAAGCTTAAAAAGT	3179
25	H45_219-243	CTTTTTAAGCTTTCTTTAGAAGAAT	2228	ATTCTTCTAAAGAAAGCTTAAAAAG	3180
25	H45_220-244	TTTTTAAGCTTTCTTTAGAAGAATA	2229	TATTCTTCTAAAGAAAGCTTAAAAA	3181
26	H45_158-183	TGTCAGACAGAAAAAAGAGGTAGGGC	2230	GCCCTACCTCTTTTTTCTGTCTGACA	3182
26	H45_159-184	GTCAGACAGAAAAAAGAGGTAGGGCG	2231	CGCCCTACCTCTTTTTTCTGTCTGAC	3183
26	H45_160-185	TCAGACAGAAAAAAGAGGTAGGGCGA	2232	TCGCCCTACCTCTTTTTTCTGTCTGA	3184
26	H45_161-186	CAGACAGAAAAAAGAGGTAGGGCGAC	2233	GTCGCCCTACCTCTTTTTTCTGTCTG	3185
26	H45_162-187	AGACAGAAAAAAGAGGTAGGGCGACA	2234	TGTCGCCCTACCTCTTTTTTCTGTCT	3186
26	H45_163-188	GACAGAAAAAAGAGGTAGGGCGACAG	2235	CTGTCGCCCTACCTCTTTTTTCTGTC	3187
26	H45_164-189	ACAGAAAAAAGAGGTAGGGCGACAGA	2236	TCTGTCGCCCTACCTCTTTTTTCTGT	3188
26	H45_165-190	CAGAAAAAAGAGGTAGGGCGACAGAT	2237	ATCTGTCGCCCTACCTCTTTTTTCTG	3189
26	H45_166-191	AGAAAAAAGAGGTAGGGCGACAGATC	2238	GATCTGTCGCCCTACCTCTTTTTTCT	3190

[Table 7-37]

26	H45_167-192	GAAAAAAGAGGTAGGGCGACAGATCT	2239	AGATCTGTCGCCCTACCTCTTTTTTC	3191
26	H45_168-193	AAAAAAGAGGTAGGGCGACAGATCTA	2240	TAGATCTGTCGCCCTACCTCTTTTTT	3192
26	H45_169-194	AAAAAGAGGTAGGGCGACAGATCTAA	2241	TTAGATCTGTCGCCCTACCTCTTTTT	3193
26	H45_170-195	AAAAGAGGTAGGGCGACAGATCTAAT	2242	ATTAGATCTGTCGCCCTACCTCTTTT	3194
26	H45_171-196	AAAGAGGTAGGGCGACAGATCTAATA	2243	TATTAGATCTGTCGCCCTACCTCTTT	3195
26	H45_172-197	AAGAGGTAGGGCGACAGATCTAATAG	2244	CTATTAGATCTGTCGCCCTACCTCTT	3196
26	H45_173-198	AGAGGTAGGGCGACAGATCTAATAGG	2245	CCTATTAGATCTGTCGCCCTACCTCT	3197
26	H45_174-199	GAGGTAGGGCGACAGATCTAATAGGA	2246	TCCTATTAGATCTGTCGCCCTACCTC	3198
26	H45_175-200	AGGTAGGGCGACAGATCTAATAGGAA	2247	TTCCTATTAGATCTGTCGCCCTACCT	3199
26	H45_176-201	GGTAGGGCGACAGATCTAATAGGAAT	2248	ATTCCTATTAGATCTGTCGCCCTACC	3200
26	H45_177-202	GTAGGGCGACAGATCTAATAGGAATG	2249	CATTCCTATTAGATCTGTCGCCCTAC	3201
26	H45_178-203	TAGGGCGACAGATCTAATAGGAATGA	2250	TCATTCCTATTAGATCTGTCGCCCTA	3202
26	H45_179-204	AGGGCGACAGATCTAATAGGAATGAA	2251	TTCATTCCTATTAGATCTGTCGCCCT	3203
26	H45_180-205	GGGCGACAGATCTAATAGGAATGAAA	2252	TTTCATTCCTATTAGATCTGTCGCCC	3204
26	H45_181-206	GGCGACAGATCTAATAGGAATGAAAA	2253	TTTTCATTCCTATTAGATCTGTCGCC	3205
26	H45_182-207	GCGACAGATCTAATAGGAATGAAAAC	2254	GTTTTCATTCCTATTAGATCTGTCGC	3206
26	H45_183-208	CGACAGATCTAATAGGAATGAAAACA	2255	TGTTTTCATTCCTATTAGATCTGTCG	3207
26	H45_184-209	GACAGATCTAATAGGAATGAAAACAT	2256	ATGTTTTCATTCCTATTAGATCTGTC	3208

[Table 7-38]

26	H45_185-210	ACAGATCTAATAGGAATGAAAACATT	2257	AATGTTTTCATTCCTATTAGATCTGT	3209
26	H45_186-211	CAGATCTAATAGGAATGAAAACATTT	2258	AAATGTTTTCATTCCTATTAGATCTG	3210
26	H45_187-212	AGATCTAATAGGAATGAAAACATTTT	2259	AAAATGTTTTCATTCCTATTAGATCT	3211
26	H45_188-213	GATCTAATAGGAATGAAAACATTTTA	2260	TAAAATGTTTTCATTCCTATTAGATC	3212
26	H45_189-214	ATCTAATAGGAATGAAAACATTTTAG	2261	CTAAAATGTTTTCATTCCTATTAGAT	3213
26	H45_190-215	TCTAATAGGAATGAAAACATTTTAGC	2262	GCTAAAATGTTTTCATTCCTATTAGA	3214
26	H45_191-216	CTAATAGGAATGAAAACATTTTAGCA	2263	TGCTAAAATGTTTTCATTCCTATTAG	3215
26	H45_192-217	TAATAGGAATGAAAACATTTTAGCAG	2264	CTGCTAAAATGTTTTCATTCCTATTA	3216
26	H45_193-218	AATAGGAATGAAAACATTTTAGCAGA	2265	TCTGCTAAAATGTTTTCATTCCTATT	3217
26	H45_194-219	ATAGGAATGAAAACATTTTAGCAGAC	2266	GTCTGCTAAAATGTTTTCATTCCTAT	3218
26	H45_195-220	TAGGAATGAAAACATTTTAGCAGACT	2267	AGTCTGCTAAAATGTTTTCATTCCTA	3219
26	H45_196-221	AGGAATGAAAACATTTTAGCAGACTT	2268	AAGTCTGCTAAAATGTTTTCATTCCT	3220
26	H45_197-222	GGAATGAAAACATTTTAGCAGACTTT	2269	AAAGTCTGCTAAAATGTTTTCATTCC	3221
26	H45_198-223	GAATGAAAACATTTTAGCAGACTTTT	2270	AAAAGTCTGCTAAAATGTTTTCATTC	3222
26	H45_199-224	AATGAAAACATTTTAGCAGACTTTTT	2271	AAAAAGTCTGCTAAAATGTTTTCATT	3223
26	H45_200-225	ATGAAAACATTTTAGCAGACTTTTTA	2272	TAAAAAGTCTGCTAAAATGTTTTCAT	3224
26	H45_201-226	TGAAAACATTTTAGCAGACTTTTTAA	2273	TTAAAAAGTCTGCTAAAATGTTTTCA	3225
26	H45_202-227	GAAAACATTTTAGCAGACTTTTTAAG	2274	CTTAAAAAGTCTGCTAAAATGTTTTC	3226

[Table 7-39]

26	H45_203-228	AAAACATTTTAGCAGACTTTTTAAGC	2275	GCTTAAAAAGTCTGCTAAAATGTTTT	3227
26	H45_204-229	AAACATTTTAGCAGACTTTTTAAGCT	2276	AGCTTAAAAAGTCTGCTAAAATGTTT	3228
26	H45_205-230	AACATTTTAGCAGACTTTTTAAGCTT	2277	AAGCTTAAAAAGTCTGCTAAAATGTT	3229
26	H45_206-231	ACATTTTAGCAGACTTTTTAAGCTTT	2278	AAAGCTTAAAAAGTCTGCTAAAATGT	3230
26	H45_207-232	CATTTTAGCAGACTTTTTAAGCTTTC	2279	GAAAGCTTAAAAAGTCTGCTAAAATG	3231
26	H45_208-233	ATTTTAGCAGACTTTTTAAGCTTTCT	2280	AGAAAGCTTAAAAAGTCTGCTAAAAT	3232
26	H45_209-234	TTTTAGCAGACTTTTTAAGCTTTCTT	2281	AAGAAAGCTTAAAAAGTCTGCTAAAA	3233
26	H45_210-235	TTTAGCAGACTTTTTAAGCTTTCTTT	2282	AAAGAAAGCTTAAAAAGTCTGCTAAA	3234
26	H45_211-236	TTAGCAGACTTTTTAAGCTTTCTTTA	2283	TAAAGAAAGCTTAAAAAGTCTGCTAA	3235
26	H45_212-237	TAGCAGACTTTTTAAGCTTTCTTTAG	2284	CTAAAGAAAGCTTAAAAAGTCTGCTA	3236
26	H45_213-238	AGCAGACTTTTTAAGCTTTCTTTAGA	2285	TCTAAAGAAAGCTTAAAAAGTCTGCT	3237
26	H45_214-239	GCAGACTTTTTAAGCTTTCTTTAGAA	2286	TTCTAAAGAAAGCTTAAAAAGTCTGC	3238
26	H45_215-240	CAGACTTTTTAAGCTTTCTTTAGAAG	2287	CTTCTAAAGAAAGCTTAAAAAGTCTG	3239
26	H45_216-241	AGACTTTTTAAGCTTTCTTTAGAAGA	2288	TCTTCTAAAGAAAGCTTAAAAAGTCT	3240
26	H45_217-242	GACTTTTTAAGCTTTCTTTAGAAGAA	2289	TTCTTCTAAAGAAAGCTTAAAAAGTC	3241
26	H45_218-243	ACTTTTTAAGCTTTCTTTAGAAGAAT	2290	ATTCTTCTAAAGAAAGCTTAAAAAGT	3242
26	H45_219-244	CTTTTTAAGCTTTCTTTAGAAGAATA	2291	TATTCTTCTAAAGAAAGCTTAAAAAG	3243
26	H45_220-245	TTTTTAAGCTTTCTTTAGAAGAATAT	2292	ATATTCTTCTAAAGAAAGCTTAAAAA	3244

[Table 7-40]

27	H45_157-183	CTGTCAGACAGAAAAAAGAGGTAGGGC	2293	GCCCTACCTCTTTTTTCTGTCTGACAG	3245
27	H45_158-184	TGTCAGACAGAAAAAAGAGGTAGGGCG	2294	CGCCCTACCTCTTTTTTCTGTCTGACA	3246
27	H45_159-185	GTCAGACAGAAAAAAGAGGTAGGGCGA	2295	TCGCCCTACCTCTTTTTTCTGTCTGAC	3247
27	H45_160-186	TCAGACAGAAAAAAGAGGTAGGGCGAC	2296	GTCGCCCTACCTCTTTTTTCTGTCTGA	3248
27	H45_161-187	CAGACAGAAAAAAGAGGTAGGGCGACA	2297	TGTCGCCCTACCTCTTTTTTCTGTCTG	3249
27	H45_162-188	AGACAGAAAAAAGAGGTAGGGCGACAG	2298	CTGTCGCCCTACCTCTTTTTTCTGTCT	3250
27	H45_163-189	GACAGAAAAAAGAGGTAGGGCGACAGA	2299	TCTGTCGCCCTACCTCTTTTTTCTGTC	3251
27	H45_164-190	ACAGAAAAAAGAGGTAGGGCGACAGAT	2300	ATCTGTCGCCCTACCTCTTTTTTCTGT	3252
27	H45_165-191	CAGAAAAAAGAGGTAGGGCGACAGATC	2301	GATCTGTCGCCCTACCTCTTTTTTCTG	3253
27	H45_166-192	AGAAAAAAGAGGTAGGGCGACAGATCT	2302	AGATCTGTCGCCCTACCTCTTTTTTCT	3254
27	H45_167-193	GAAAAAAGAGGTAGGGCGACAGATCTA	2303	TAGATCTGTCGCCCTACCTCTTTTTTC	3255
27	H45_168-194	AAAAAAGAGGTAGGGCGACAGATCTAA	2304	TTAGATCTGTCGCCCTACCTCTTTTTT	3256
27	H45_169-195	AAAAAGAGGTAGGGCGACAGATCTAAT	2305	ATTAGATCTGTCGCCCTACCTCTTTTT	3257
27	H45_170-196	AAAAGAGGTAGGGCGACAGATCTAATA	2306	TATTAGATCTGTCGCCCTACCTCTTTT	3258
27	H45_171-197	AAAGAGGTAGGGCGACAGATCTAATAG	2307	CTATTAGATCTGTCGCCCTACCTCTTT	3259
27	H45_172-198	AAGAGGTAGGGCGACAGATCTAATAGG	2308	CCTATTAGATCTGTCGCCCTACCTCTT	3260
27	H45_173-199	AGAGGTAGGGCGACAGATCTAATAGGA	2309	TCCTATTAGATCTGTCGCCCTACCTCT	3261
27	H45_174-200	GAGGTAGGGCGACAGATCTAATAGGAA	2310	TTCCTATTAGATCTGTCGCCCTACCTC	3262

[Table 7-41]

27	H45_175-201	AGGTAGGGCGACAGATCTAATAGGAAT	2311	ATTCCTATTAGATCTGTCGCCCTACCT	3263
27	H45_176-202	GGTAGGGCGACAGATCTAATAGGAATG	2312	CATTCCTATTAGATCTGTCGCCCTACC	3264
27	H45_177-203	GTAGGGCGACAGATCTAATAGGAATGA	2313	TCATTCCTATTAGATCTGTCGCCCTAC	3265
27	H45_178-204	TAGGGCGACAGATCTAATAGGAATGAA	2314	TTCATTCCTATTAGATCTGTCGCCCTA	3266
27	H45_179-205	AGGGCGACAGATCTAATAGGAATGAAA	2315	TTTCATTCCTATTAGATCTGTCGCCCT	3267
27	H45_180-206	GGGCGACAGATCTAATAGGAATGAAAA	2316	TTTTCATTCCTATTAGATCTGTCGCCC	3268
27	H45_181-207	GGCGACAGATCTAATAGGAATGAAAAC	2317	GTTTTCATTCCTATTAGATCTGTCGCC	3269
27	H45_182-208	GCGACAGATCTAATAGGAATGAAAACA	2318	TGTTTTCATTCCTATTAGATCTGTCGC	3270
27	H45_183-209	CGACAGATCTAATAGGAATGAAAACAT	2319	ATGTTTTCATTCCTATTAGATCTGTCG	3271
27	H45_184-210	GACAGATCTAATAGGAATGAAAACATT	2320	AATGTTTTCATTCCTATTAGATCTGTC	3272
27	H45_185-211	ACAGATCTAATAGGAATGAAAACATTT	2321	AAATGTTTTCATTCCTATTAGATCTGT	3273
27	H45_186-212	CAGATCTAATAGGAATGAAAACATTTT	2322	AAAATGTTTTCATTCCTATTAGATCTG	3274
27	H45_187-213	AGATCTAATAGGAATGAAAACATTTTA	2323	TAAAATGTTTTCATTCCTATTAGATCT	3275
27	H45_188-214	GATCTAATAGGAATGAAAACATTTTAG	2324	CTAAAATGTTTTCATTCCTATTAGATC	3276
27	H45_189-215	ATCTAATAGGAATGAAAACATTTTAGC	2325	GCTAAAATGTTTTCATTCCTATTAGAT	3277
27	H45_190-216	TCTAATAGGAATGAAAACATTTTAGCA	2326	TGCTAAAATGTTTTCATTCCTATTAGA	3278
27	H45_191-217	CTAATAGGAATGAAAACATTTTAGCAG	2327	CTGCTAAAATGTTTTCATTCCTATTAG	3279
27	H45_192-218	TAATAGGAATGAAAACATTTTAGCAGA	2328	TCTGCTAAAATGTTTTCATTCCTATTA	3280

[Table 7-42]

27	H45_193-219	AATAGGAATGAAAACATTTTAGCAGAC	2329	GTCTGCTAAAATGTTTTCATTCCTATT	3281
27	H45_194-220	ATAGGAATGAAAACATTTTAGCAGACT	2330	AGTCTGCTAAAATGTTTTCATTCCTAT	3282
27	H45_195-221	TAGGAATGAAAACATTTTAGCAGACTT	2331	AAGTCTGCTAAAATGTTTTCATTCCTA	3283
27	H45_196-222	AGGAATGAAAACATTTTAGCAGACTTT	2332	AAAGTCTGCTAAAATGTTTTCATTCCT	3284
27	H45_197-223	GGAATGAAAACATTTTAGCAGACTTTT	2333	AAAAGTCTGCTAAAATGTTTTCATTCC	3285
27	H45_198-224	GAATGAAAACATTTTAGCAGACTTTTT	2334	AAAAAGTCTGCTAAAATGTTTTCATTC	3286
27	H45_199-225	AATGAAAACATTTTAGCAGACTTTTTA	2335	TAAAAAGTCTGCTAAAATGTTTTCATT	3287
27	H45_200-226	ATGAAAACATTTTAGCAGACTTTTTAA	2336	TTAAAAAGTCTGCTAAAATGTTTTCAT	3288
27	H45_201-227	TGAAAACATTTTAGCAGACTTTTTAAG	2337	CTTAAAAAGTCTGCTAAAATGTTTTCA	3289
27	H45_202-228	GAAAACATTTTAGCAGACTTTTTAAGC	2338	GCTTAAAAAGTCTGCTAAAATGTTTTC	3290
27	H45_203-229	AAAACATTTTAGCAGACTTTTTAAGCT	2339	AGCTTAAAAAGTCTGCTAAAATGTTTT	3291
27	H45_204-230	AAACATTTTAGCAGACTTTTTAAGCTT	2340	AAGCTTAAAAAGTCTGCTAAAATGTTT	3292
27	H45_205-231	AACATTTTAGCAGACTTTTTAAGCTTT	2341	AAAGCTTAAAAAGTCTGCTAAAATGTT	3293
27	H45_206-232	ACATTTTAGCAGACTTTTTAAGCTTTC	2342	GAAAGCTTAAAAAGTCTGCTAAAATGT	3294
27	H45_207-233	CATTTTAGCAGACTTTTTAAGCTTTCT	2343	AGAAAGCTTAAAAAGTCTGCTAAAATG	3295
27	H45_208-234	ATTTTAGCAGACTTTTTAAGCTTTCTT	2344	AAGAAAGCTTAAAAAGTCTGCTAAAAT	3296
27	H45_209-235	TTTTAGCAGACTTTTTAAGCTTTCTTT	2345	AAAGAAAGCTTAAAAAGTCTGCTAAAA	3297
27	H45_210-236	TTTAGCAGACTTTTTAAGCTTTCTTTA	2346	TAAAGAAAGCTTAAAAAGTCTGCTAAA	3298

[Table 7-43]

27	H45_211-237	TTAGCAGACTTTTTAAGCTTTCTTTAG	2347	CTAAAGAAAGCTTAAAAAGTCTGCTAA	3299
27	H45_212-238	TAGCAGACTTTTTAAGCTTTCTTTAGA	2348	TCTAAAGAAAGCTTAAAAAGTCTGCTA	3300
27	H45_213-239	AGCAGACTTTTTAAGCTTTCTTTAGAA	2349	TTCTAAAGAAAGCTTAAAAAGTCTGCT	3301
27	H45_214-240	GCAGACTTTTTAAGCTTTCTTTAGAAG	2350	CTTCTAAAGAAAGCTTAAAAAGTCTGC	3302
27	H45_215-241	CAGACTTTTTAAGCTTTCTTTAGAAGA	2351	TCTTCTAAAGAAAGCTTAAAAAGTCTG	3303
27	H45_216-242	AGACTTTTTAAGCTTTCTTTAGAAGAA	2352	TTCTTCTAAAGAAAGCTTAAAAAGTCT	3304
27	H45_217-243	GACTTTTTAAGCTTTCTTTAGAAGAAT	2353	ATTCTTCTAAAGAAAGCTTAAAAAGTC	3305
27	H45_218-244	ACTTTTTAAGCTTTCTTTAGAAGAATA	2354	TATTCTTCTAAAGAAAGCTTAAAAAGT	3306
27	H45_219-245	CTTTTTAAGCTTTCTTTAGAAGAATAT	2355	ATATTCTTCTAAAGAAAGCTTAAAAAG	3307
27	H45_220-246	TTTTTAAGCTTTCTTTAGAAGAATATT	2356	AATATTCTTCTAAAGAAAGCTTAAAAA	3308
28	H45_156-183	GCTGTCAGACAGAAAAAAGAGGTAGGGC	2357	GCCCTACCTCTTTTTTCTGTCTGACAGC	3309
28	H45_157-184	CTGTCAGACAGAAAAAAGAGGTAGGGCG	2358	CGCCCTACCTCTTTTTTCTGTCTGACAG	3310
28	H45_158-185	TGTCAGACAGAAAAAAGAGGTAGGGCGA	2359	TCGCCCTACCTCTTTTTTCTGTCTGACA	3311
28	H45_159-186	GTCAGACAGAAAAAAGAGGTAGGGCGAC	2360	GTCGCCCTACCTCTTTTTTCTGTCTGAC	3312
28	H45_160-187	TCAGACAGAAAAAAGAGGTAGGGCGACA	2361	TGTCGCCCTACCTCTTTTTTCTGTCTGA	3313
28	H45_161-188	CAGACAGAAAAAAGAGGTAGGGCGACAG	2362	CTGTCGCCCTACCTCTTTTTTCTGTCTG	3314
28	H45_162-189	AGACAGAAAAAAGAGGTAGGGCGACAGA	2363	TCTGTCGCCCTACCTCTTTTTTCTGTCT	3315
28	H45_163-190	GACAGAAAAAAGAGGTAGGGCGACAGAT	2364	ATCTGTCGCCCTACCTCTTTTTTCTGTC	3316

[Table 7-44]

28	H45_164-191	ACAGAAAAAAGAGGTAGGGCGACAGATC	2365	GATCTGTCGCCCTACCTCTTTTTTCTGT	3317
28	H45_165-192	CAGAAAAAAGAGGTAGGGCGACAGATCT	2366	AGATCTGTCGCCCTACCTCTTTTTTCTG	3318
28	H45_166-193	AGAAAAAAGAGGTAGGGCGACAGATCTA	2367	TAGATCTGTCGCCCTACCTCTTTTTTCT	3319
28	H45_167-194	GAAAAAAGAGGTAGGGCGACAGATCTAA	2368	TTAGATCTGTCGCCCTACCTCTTTTTTC	3320
28	H45_168-195	AAAAAAGAGGTAGGGCGACAGATCTAAT	2369	ATTAGATCTGTCGCCCTACCTCTTTTTT	3321
28	H45_169-196	AAAAAGAGGTAGGGCGACAGATCTAATA	2370	TATTAGATCTGTCGCCCTACCTCTTTTT	3322
28	H45_170-197	AAAAGAGGTAGGGCGACAGATCTAATAG	2371	CTATTAGATCTGTCGCCCTACCTCTTTT	3323
28	H45_171-198	AAAGAGGTAGGGCGACAGATCTAATAGG	2372	CCTATTAGATCTGTCGCCCTACCTCTTT	3324
28	H45_172-199	AAGAGGTAGGGCGACAGATCTAATAGGA	2373	TCCTATTAGATCTGTCGCCCTACCTCTT	3325
28	H45_173-200	AGAGGTAGGGCGACAGATCTAATAGGAA	2374	TTCCTATTAGATCTGTCGCCCTACCTCT	3326
28	H45_174-201	GAGGTAGGGCGACAGATCTAATAGGAAT	2375	ATTCCTATTAGATCTGTCGCCCTACCTC	3327
28	H45_175-202	AGGTAGGGCGACAGATCTAATAGGAATG	2376	CATTCCTATTAGATCTGTCGCCCTACCT	3328
28	H45_176-203	GGTAGGGCGACAGATCTAATAGGAATGA	2377	TCATTCCTATTAGATCTGTCGCCCTACC	3329
28	H45_177-204	GTAGGGCGACAGATCTAATAGGAATGAA	2378	TTCATTCCTATTAGATCTGTCGCCCTAC	3330
28	H45_178-205	TAGGGCGACAGATCTAATAGGAATGAAA	2379	TTTCATTCCTATTAGATCTGTCGCCCTA	3331
28	H45_179-206	AGGGCGACAGATCTAATAGGAATGAAAA	2380	TTTTCATTCCTATTAGATCTGTCGCCCT	3332
28	H45_180-207	GGGCGACAGATCTAATAGGAATGAAAAC	2381	GTTTTCATTCCTATTAGATCTGTCGCCC	3333
28	H45_181-208	GGCGACAGATCTAATAGGAATGAAAACA	2382	TGTTTTCATTCCTATTAGATCTGTCGCC	3334

[Table 7-45]

28	H45_182-209	GCGACAGATCTAATAGGAATGAAAACAT	2383	ATGTTTTCATTCCTATTAGATCTGTCGC	3335
28	H45_183-210	CGACAGATCTAATAGGAATGAAAACATT	2384	AATGTTTTCATTCCTATTAGATCTGTCG	3336
28	H45_184-211	GACAGATCTAATAGGAATGAAAACATTT	2385	AAATGTTTTCATTCCTATTAGATCTGTC	3337
28	H45_185-212	ACAGATCTAATAGGAATGAAAACATTTT	2386	AAAATGTTTTCATTCCTATTAGATCTGT	3338
28	H45_186-213	CAGATCTAATAGGAATGAAAACATTTTA	2387	TAAAATGTTTTCATTCCTATTAGATCTG	3339
28	H45_187-214	AGATCTAATAGGAATGAAAACATTTTAG	2388	CTAAAATGTTTTCATTCCTATTAGATCT	3340
28	H45_188-215	GATCTAATAGGAATGAAAACATTTTAGC	2389	GCTAAAATGTTTTCATTCCTATTAGATC	3341
28	H45_189-216	ATCTAATAGGAATGAAAACATTTTAGCA	2390	TGCTAAAATGTTTTCATTCCTATTAGAT	3342
28	H45_190-217	TCTAATAGGAATGAAAACATTTTAGCAG	2391	CTGCTAAAATGTTTTCATTCCTATTAGA	3343
28	H45_191-218	CTAATAGGAATGAAAACATTTTAGCAGA	2392	TCTGCTAAAATGTTTTCATTCCTATTAG	3344
28	H45_192-219	TAATAGGAATGAAAACATTTTAGCAGAC	2393	GTCTGCTAAAATGTTTTCATTCCTATTA	3345
28	H45_193-220	AATAGGAATGAAAACATTTTAGCAGACT	2394	AGTCTGCTAAAATGTTTTCATTCCTATT	3346
28	H45_194-221	ATAGGAATGAAAACATTTTAGCAGACTT	2395	AAGTCTGCTAAAATGTTTTCATTCCTAT	3347
28	H45_195-222	TAGGAATGAAAACATTTTAGCAGACTTT	2396	AAAGTCTGCTAAAATGTTTTCATTCCTA	3348
28	H45_196-223	AGGAATGAAAACATTTTAGCAGACTTTT	2397	AAAAGTCTGCTAAAATGTTTTCATTCCT	3349
28	H45_197-224	GGAATGAAAACATTTTAGCAGACTTTTT	2398	AAAAAGTCTGCTAAAATGTTTTCATTCC	3350
28	H45_198-225	GAATGAAAACATTTTAGCAGACTTTTTA	2399	TAAAAAGTCTGCTAAAATGTTTTCATTC	3351
28	H45_199-226	AATGAAAACATTTTAGCAGACTTTTTAA	2400	TTAAAAAGTCTGCTAAAATGTTTTCATT	3352

[Table 7-46]

28	H45_200-227	ATGAAAACATTTTAGCAGACTTTTTAAG	2401	CTTAAAAAGTCTGCTAAAATGTTTTCAT	3353
28	H45_201-228	TGAAAACATTTTAGCAGACTTTTTAAGC	2402	GCTTAAAAAGTCTGCTAAAATGTTTTCA	3354
28	H45_202-229	GAAAACATTTTAGCAGACTTTTTAAGCT	2403	AGCTTAAAAAGTCTGCTAAAATGTTTTC	3355
28	H45_203-230	AAAACATTTTAGCAGACTTTTTAAGCTT	2404	AAGCTTAAAAAGTCTGCTAAAATGTTTT	3356
28	H45_204-231	AAACATTTTAGCAGACTTTTTAAGCTTT	2405	AAAGCTTAAAAAGTCTGCTAAAATGTTT	3357
28	H45_205-232	AACATTTTAGCAGACTTTTTAAGCTTTC	2406	GAAAGCTTAAAAAGTCTGCTAAAATGTT	3358
28	H45_206-233	ACATTTTAGCAGACTTTTTAAGCTTTCT	2407	AGAAAGCTTAAAAAGTCTGCTAAAATGT	3359
28	H45_207-234	CATTTTAGCAGACTTTTTAAGCTTCTT	2408	AAGAAAGCTTAAAAAGTCTGCTAAAATG	3360
28	H45_208-235	ATTTTAGCAGACTTTTTAAGCTTTCTTT	2409	AAAGAAAGCTTAAAAAGTCTGCTAAAAT	3361
28	H45_209-236	TTTTAGCAGACTTTTTAAGCTTTCTTTA	2410	TAAAGAAAGCTTAAAAAGTCTGCTAAAA	3362
28	H45_210-237	TTTAGCAGACTTTTTAAGCTTTCTTTAG	2411	CTAAAGAAAGCTTAAAAAGTCTGCTAAA	3363
28	H45_211-238	TTAGCAGACTTTTTAAGCTTTCTTTAGA	2412	TCTAAAGAAAGCTTAAAAAGTCTGCTAA	3364
28	H45_212-239	TAGCAGACTTTTTAAGCTTTCTTTAGAA	2413	TTCTAAAGAAAGCTTAAAAAGTCTGCTA	3365
28	H45_213-240	AGCAGACTTTTTAAGCTTTCTTTAGAAG	2414	CTTCTAAAGAAAGCTTAAAAAGTCTGCT	3366
28	H45_214-241	GCAGACTTTTTAAGCTTTCTTTAGAAGA	2415	TCTTCTAAAGAAAGCTTAAAAAGTCTGC	3367
28	H45_215-242	CAGACTTTTTAAGCTTTCTTTAGAAGAA	2416	TTCTTCTAAAGAAAGCTTAAAAAGTCTG	3368
28	H45_216-243	AGACTTTTTAAGCTTTCTTTAGAAGAAT	2417	ATTCTTCTAAAGAAAGCTTAAAAAGTCT	3369
28	H45_217-244	GACTTTTTAAGCTTTCTTTAGAAGAATA	2418	TATTCTTCTAAAGAAAGCTTAAAAAGTC	3370

[Table 7-47]

28	H45_218-245	ACTTTTTAAGCTTTCTTTAGAAGAATAT	2419	ATATTCTTCTAAAGAAAGCTTAAAAAGT	3371
28	H45_219-246	CTTTTTAAGCTTTCTTTAGAAGAATATT	2420	AATATTCTTCTAAAGAAAGCTTAAAAAG	3372
28	H45_220-247	TTTTTAAGCTTTCTTTAGAAGAATATTT	2421	AAATATTCTTCTAAAGAAAGCTTAAAAA	3373
29	H45_155-183	AGCTGTCAGACAGAAAAAAGAGGTAGGGC	2422	GCCCTACCTCTTTTTTCTGTCTGACAGCT	3374
29	H45_156-184	GCTGTCAGACAGAAAAAAGAGGTAGGGCG	2423	CGCCCTACCTCTTTTTTCTGTCTGACAGC	3375
29	H45_157-185	CTGTCAGACAGAAAAAAGAGGTAGGGCGA	2424	TCGCCCTACCTCTTTTTTCTGTCTGACAG	3376
29	H45_158-186	TGTCAGACAGAAAAAAGAGGTAGGGCGAC	2425	GTCGCCCTACCTCTTTTTTCTGTCTGACA	3377
29	H45_159-187	GTCAGACAGAAAAAAGAGGTAGGGCGACA	2426	TGTCGCCCTACCTCTTTTTTCTGTCTGAC	3378
29	H45_160-188	TCAGACAGAAAAAAGAGGTAGGGCGACAG	2427	CTGTCGCCCTACCTCTTTTTTCTGTCTGA	3379
29	H45_161-189	CAGACAGAAAAAAGAGGTAGGGCGACAGA	2428	TCTGTCGCCCTACCTCTTTTTTCTGTCTG	3380
29	H45_162-190	AGACAGAAAAAAGAGGTAGGGCGACAGAT	2429	ATCTGTCGCCCTACCTCTTTTTTCTGTCT	3381
29	H45_163-191	GACAGAAAAAAGAGGTAGGGCGACAGATC	2430	GATCTGTCGCCCTACCTCTTTTTTCTGTC	3382
29	H45_164-192	ACAGAAAAAAGAGGTAGGGCGACAGATCT	2431	AGATCTGTCGCCCTACCTCTTTTTTCTGT	3383
29	H45_165-193	CAGAAAAAAGAGGTAGGGCGACAGATCTA	2432	TAGATCTGTCGCCCTACCTCTTTTTTCTG	3384
29	H45_166-194	AGAAAAAAGAGGTAGGGCGACAGATCTAA	2433	TTAGATCTGTCGCCCTACCTCTTTTTTCT	3385
29	H45_167-195	GAAAAAAGAGGTAGGGCGACAGATCTAAT	2434	ATTAGATCTGTCGCCCTACCTCTTTTTTC	3386
29	H45_168-196	AAAAAAGAGGTAGGGCGACAGATCTAATA	2435	TATTAGATCTGTCGCCCTACCTCTTTTTT	3387
29	H45_169-197	AAAAAGAGGTAGGGCGACAGATCTAATAG	2436	CTATTAGATCTGTCGCCCTACCTCTTTTT	3388

[Table 7-48]

29	H45_170-198	AAAAGAGGTAGGGCGACAGATCTAATAGG	2437	CCTATTAGATCTGTCGCCCTACCTCTTTT	3389
29	H45_171-199	AAAGAGGTAGGGCGACAGATCTAATAGGA	2438	TCCTATTAGATCTGTCGCCCTACCTCTTT	3390
29	H45_172-200	AAGAGGTAGGGCGACAGATCTAATAGGAA	2439	TTCCTATTAGATCTGTCGCCCTACCTCTT	3391
29	H45_173-201	AGAGGTAGGGCGACAGATCTAATAGGAAT	2440	ATTCCTATTAGATCTGTCGCCCTACCTCT	3392
29	H45_174-202	GAGGTAGGGCGACAGATCTAATAGGAATG	2441	CATTCCTATTAGATCTGTCGCCCTACCTC	3393
29	H45_175-203	AGGTAGGGCGACAGATCTAATAGGAATGA	2442	TCATTCCTATTAGATCTGTCGCCCTACCT	3394
29	H45_176-204	GGTAGGGCGACAGATCTAATAGGAATGAA	2443	TTCATTCCTATTAGATCTGTCGCCCTACC	3395
29	H45_177-205	GTAGGGCGACAGATCTAATAGGAATGAAA	2444	TTTCATTCCTATTAGATCTGTCGCCCTAC	3396
29	H45_178-206	TAGGGCGACAGATCTAATAGGAATGAAAA	2445	TTTTCATTCCTATTAGATCTGTCGCCCTA	3397
29	H45_179-207	AGGGCGACAGATCTAATAGGAATGAAAAC	2446	GTTTTCATTCCTATTAGATCTGTCGCCCT	3398
29	H45_180-208	GGGCGACAGATCTAATAGGAATGAAAACA	2447	TGTTTTCATTCCTATTAGATCTGTCGCCC	3399
29	H45_181-209	GGCGACAGATCTAATAGGAATGAAAACAT	2448	ATGTTTTCATTCCTATTAGATCTGTCGCC	3400
29	H45_182-210	GCGACAGATCTAATAGGAATGAAAACATT	2449	AATGTTTTCATTCCTATTAGATCTGTCGC	3401
29	H45_183-211	CGACAGATCTAATAGGAATGAAAACATTT	2450	AAATGTTTTCATTCCTATTAGATCTGTCG	3402
29	H45_184-212	GACAGATCTAATAGGAATGAAAACATTTT	2451	AAAATGTTTTCATTCCTATTAGATCTGTC	3403
29	H45_185-213	ACAGATCTAATAGGAATGAAAACATTTTA	2452	TAAAATGTTTTCATTCCTATTAGATCTGT	3404
29	H45_186-214	CAGATCTAATAGGAATGAAAACATTTTAG	2453	CTAAAATGTTTTCATTCCTATTAGATCTG	3405
29	H45_187-215	AGATCTAATAGGAATGAAAACATTTTAGC	2454	GCTAAAATGTTTTCATTCCTATTAGATCT	3406

[Table 7-49]

29	H45_188-216	GATCTAATAGGAATGAAAACATTTTAGCA	2455	TGCTAAAATGTTTTCATTCCTATTAGATC	3407
29	H45_189-217	ATCTAATAGGAATGAAAACATTTTAGCAG	2456	CTGCTAAAATGTTTTCATTCCTATTAGAT	3408
29	H45_190-218	TCTAATAGGAATGAAAACATTTTAGCAGA	2457	TCTGCTAAAATGTTTTCATTCCTATTAGA	3409
29	H45_191-219	CTAATAGGAATGAAAACATTTTAGCAGAC	2458	GTCTGCTAAAATGTTTTCATTCCTATTAG	3410
29	H45_192-220	TAATAGGAATGAAAACATTTTAGCAGACT	2459	AGTCTGCTAAAATGTTTTCATTCCTATTA	3411
29	H45_193-221	AATAGGAATGAAAACATTTTAGCAGACTT	2460	AAGTCTGCTAAAATGTTTTCATTCCTATT	3412
29	H45_194-222	ATAGGAATGAAAACATTTTAGCAGACTTT	2461	AAAGTCTGCTAAAATGTTTTCATTCCTAT	3413
29	H45_195-223	TAGGAATGAAAACATTTTAGCAGACTTTT	2462	AAAAGTCTGCTAAAATGTTTTCATTCCTA	3414
29	H45_196-224	AGGAATGAAAACATTTTAGCAGACTTTTT	2463	AAAAAGTCTGCTAAAATGTTTTCATTCCT	3415
29	H45_197-225	GGAATGAAAACATTTTAGCAGACTTTTTA	2464	TAAAAAGTCTGCTAAAATGTTTTCATTCC	3416
29	H45_198-226	GAATGAAAACATTTTAGCAGACTTTTTAA	2465	TTAAAAAGTCTGCTAAAATGTTTTCATTC	3417
29	H45_199-227	AATGAAAACATTTTAGCAGACTTTTTAAG	2466	CTTAAAAAGTCTGCTAAAATGTTTTCATT	3418
29	H45_200-228	ATGAAAACATTTTAGCAGACTTTTTAAGC	2467	GCTTAAAAAGTCTGCTAAAATGTTTTCAT	3419
29	H45_201-229	TGAAAACATTTTAGCAGACTTTTTAAGCT	2468	AGCTTAAAAAGTCTGCTAAAATGTTTTCA	3420
29	H45_202-230	GAAAACATTTTAGCAGACTTTTTAAGCTT	2469	AAGCTTAAAAAGTCTGCTAAAATGTTTTC	3421
29	H45_203-231	AAAACATTTTAGCAGACTTTTTAAGCTTT	2470	AAAGCTTAAAAAGTCTGCTAAAATGTTTT	3422
29	H45_204-232	AAACATTTTAGCAGACTTTTTAAGCTTTC	2471	GAAAGCTTAAAAAGTCTGCTAAAATGTTT	3423
29	H45_205-233	AACATTTTAGCAGACTTTTTAAGCTTTCT	2472	AGAAAGCTTAAAAAGTCTGCTAAAATGTT	3424

[Table 7-50]

29	H45_206-234	ACATTTTAGCAGACTTTTTAAGCTTTCTT	2473	AAGAAAGCTTAAAAAGTCTGCTAAAATGT	3425
29	H45_207-235	CATTTTAGCAGACTTTTTAAGCTTTCTTT	2474	AAAGAAAGCTTAAAAAGTCTGCTAAAATG	3426
29	H45_208-236	ATTTTAGCAGACTTTTTAAGCTTTCTTTA	2475	TAAAGAAAGCTTAAAAAGTCTGCTAAAAT	3427
29	H45_209-237	TTTTAGCAGACTTTTTAAGCTTTCTTTAG	2476	CTAAAGAAAGCTTAAAAAGTCTGCTAAAA	3428
29	H45_210-238	TTTAGCAGACTTTTTAAGCTTTCTTTAGA	2477	TCTAAAGAAAGCTTAAAAAGTCTGCTAAA	3429
29	H45_211-239	TTAGCAGACTTTTTAAGCTTTCTTTAGAA	2478	TTCTAAAGAAAGCTTAAAAAGTCTGCTAA	3430
29	H45_212-240	TAGCAGACTTTTTAAGCTTTCTTTAGAAG	2479	CTTCTAAAGAAAGCTTAAAAAGTCTGCTA	3431
29	H45_213-241	AGCAGACTTTTTAAGCTTTCTTTAGAAGA	2480	TCTTCTAAAGAAAGCTTAAAAAGTCTGCT	3432
29	H45_214-242	GCAGACTTTTTAAGCTTTCTTTAGAAGAA	2481	TTCTTCTAAAGAAAGCTTAAAAAGTCTGC	3433
29	H45_215-243	CAGACTTTTTAAGCTTTCTTTAGAAGAAT	2482	ATTCTTCTAAAGAAAGCTTAAAAAGTCTG	3434
29	H45_216-244	AGACTTTTTAAGCTTTCTTTAGAAGAATA	2483	TATTCTTCTAAAGAAAGCTTAAAAAGTCT	3435
29	H45_217-245	GACTTTTTAAGCTTTCTTTAGAAGAATAT	2484	ATATTCTTCTAAAGAAAGCTTAAAAGTC	3436
29	H45_218-246	ACTTTTTAAGCTTTCTTTAGAAGAATATT	2485	AATATTCTTCTAAAGAAAGCTTAAAAGT	3437
29	H45_219-247	CTTTTTAAGCTTTCTTTAGAAGAATATTT	2486	AAATATTCTTCTAAAGAAAGCTTAAAAAG	3438
29	H45_220-248	TTTTTAAGCTTTCTTTAGAAGAATATTTC	2487	GAAATATTCTTCTAAAGAAAGCTTAAAAA	3439
30	H45_154-183	CAGCTGTCAGACAGAAAAAAGAGGTAGGGC	2488	GCCCTACCTCTTTTTTCTGTCTGACAGCTG	3440
30	H45_155-184	AGCTGTCAGACAGAAAAAAGAGGTAGGGCG	2489	CGCCCTACCTCTTTTTTCTGTCTGACAGCT	3441
30	H45_156-185	GCTGTCAGACAGAAAAAAGAGGTAGGGCGA	2490	TCGCCCTACCTCTTTTTTCTGTCTGACAGC	3442

[Table 7-51]

30	H45_157-186	CTGTCAGACAGAAAAAAGAGGTAGGGCGAC	2491	GTCGCCCTACCTCTTTTTTCTGTCTGACAG	3443
30	H45_158-187	TGTCAGACAGAAAAAAGAGGTAGGGCGACA	2492	TGTCGCCCTACCTCTTTTTTCTGTCTGACA	3444
30	H45_159-188	GTCAGACAGAAAAAAGAGGTAGGGCGACAG	2493	CTGTCGCCCTACCTCTTTTTTCTGTCTGAC	3445
30	H45_160-189	TCAGACAGAAAAAAGAGGTAGGGCGACAGA	2494	TCTGTCGCCCTACCTCTTTTTTCTGTCTGA	3446
30	H45_161-190	CAGACAGAAAAAAGAGGTAGGGCGACAGAT	2495	ATCTGTCGCCCTACCTCTTTTTTCTGTCTG	3447
30	H45_162-191	AGACAGAAAAAAGAGGTAGGGCGACAGATC	2496	GATCTGTCGCCCTACCTCTTTTTTCTGTCT	3448
30	H45_163-192	GACAGAAAAAAGAGGTAGGGCGACAGATCT	2497	AGATCTGTCGCCCTACCTCTTTTTTCTGTC	3449
30	H45_164-193	ACAGAAAAAAGAGGTAGGGCGACAGATCTA	2498	TAGATCTGTCGCCCTACCTCTTTTTCTGT	3450
30	H45_165-194	CAGAAAAAAGAGGTAGGGCGACAGATCTAA	2499	TTAGATCTGTCGCCCTACCTCTTTTTCTG	3451
30	H45_166-195	AGAAAAAAGAGGTAGGGCGACAGATCTAAT	2500	ATTAGATCTGTCGCCCTACCTCTTTTTCT	3452
30	H45_167-196	GAAAAAAGAGGTAGGGCGACAGATCTAATA	2501	TATTAGATCTGTCGCCCTACCTCTTTTTC	3453
30	H45_168-197	AAAAAAGAGGTAGGGCGACAGATCTAATAG	2502	CTATTAGATCTGTCGCCCTACCTCTTTTTT	3454
30	H45_169-198	AAAAAGAGGTAGGGCGACAGATCTAATAGG	2503	CCTATTAGATCTGTCGCCCTACCTCTTTTT	3455
30	H45_170-199	AAAAGAGGTAGGGCGACAGATCTAATAGGA	2504	TCCTATTAGATCTGTCGCCCTACCTCTTTT	3456
30	H45_171-200	AAAGAGGTAGGGCGACAGATCTAATAGGAA	2505	TTCCTATTAGATCTGTCGCCCTACCTCTTT	3457
30	H45_172-201	AAGAGGTAGGGCGACAGATCTAATAGGAAT	2506	ATTCCTATTAGATCTGTCGCCCTACCTCTT	3458
30	H45_173-202	AGAGGTAGGGCGACAGATCTAATAGGAATG	2507	CATTCCTATTAGATCTGTCGCCCTACCTCT	3459
30	H45_174-203	GAGGTAGGGCGACAGATCTAATAGGAATGA	2508	TCATTCCTATTAGATCTGTCGCCCTACCTC	3460

[Table 7-52]

30	H45_175-204	AGGTAGGGCGACAGATCTAATAGGAATGAA	2509	TTCATTCCTATTAGATCTGTCGCCCTACCT	3461
30	H45_176-205	GGTAGGGCGACAGATCTAATAGGAATGAAA	2510	TTTCATTCCTATTAGATCTGTCGCCCTACC	3462
30	H45_177-206	GTAGGGCGACAGATCTAATAGGAATGAAAA	2511	TTTTCATTCCTATTAGATCTGTCGCCCTAC	3463
30	H45_178-207	TAGGGCGACAGATCTAATAGGAATGAAAAC	2512	GTTTTCATTCCTATTAGATCTGTCGCCCTA	3464
30	H45_179-208	AGGGCGACAGATCTAATAGGAATGAAAACA	2513	TGTTTTCATTCCTATTAGATCTGTCGCCCT	3465
30	H45_180-209	GGGCGACAGATCTAATAGGAATGAAAACAT	2514	ATGTTTTCATTCCTATTAGATCTGTCGCCC	3466
30	H45_181-210	GGCGACAGATCTAATAGGAATGAAAACATT	2515	AATGTTTTCATTCCTATTAGATCTGTCGCC	3467
30	H45_182-211	GCGACAGATCTAATAGGAATGAAAACATTT	2516	AAATGTTTTCATTCCTATTAGATCTGTCGC	3468
30	H45_183-212	CGACAGATCTAATAGGAATGAAAACATTTT	2517	AAAATGTTTTCATTCCTATTAGATCTGTCG	3469
30	H45_184-213	GACAGATCTAATAGGAATGAAAACATTTTA	2518	TAAAATGTTTTCATTCCTATTAGATCTGTC	3470
30	H45_185-214	ACAGATCTAATAGGAATGAAAACATTTTAG	2519	CTAAAATGTTTTCATTCCTATTAGATCTGT	3471
30	H45_186-215	CAGATCTAATAGGAATGAAAACATTTTAGC	2520	GCTAAAATGTTTTCATTCCTATTAGATCTG	3472
30	H45_187-216	AGATCTAATAGGAATGAAAACATTTTAGCA	2521	TGCTAAAATGTTTTCATTCCTATTAGATCT	3473
30	H45_188-217	GATCTAATAGGAATGAAAACATTTTAGCAG	2522	CTGCTAAAATGTTTTCATTCCTATTAGATC	3474
30	H45_189-218	ATCTAATAGGAATGAAAACATTTTAGCAGA	2523	TCTGCTAAAATGTTTTCATTCCTATTAGAT	3475
30	H45_190-219	TCTAATAGGAATGAAAACATTTTAGCAGAC	2524	GTCTGCTAAAATGTTTTCATTCCTATTAGA	3476
30	H45_191-220	CTAATAGGAATGAAAACATTTTAGCAGACT	2525	AGTCTGCTAAAATGTTTTCATTCCTATTAG	3477
30	H45_192-221	TAATAGGAATGAAAACATTTTAGCAGACTT	2526	AAGTCTGCTAAAATGTTTTCATTCCTATTA	3478

[Table 7-53]

30	H45_193-222	AATAGGAATGAAAACATTTTAGCAGACTTT	2527	AAAGTCTGCTAAAATGTTTTCATTCCTATT	3479
30	H45_194-223	ATAGGAATGAAAACATTTTAGCAGACTTTT	2528	AAAAGTCTGCTAAAATGTTTTCATTCCTAT	3480
30	H45_195-224	TAGGAATGAAAACATTTTAGCAGACTTTTT	2529	AAAAAGTCTGCTAAAATGTTTTCATTCCTA	3481
30	H45_196-225	AGGAATGAAAACATTTTAGCAGACTTTTTA	2530	TAAAAAGTCTGCTAAAATGTTTTCATTCCT	3482
30	H45_197-226	GGAATGAAAACATTTTAGCAGACTTTTTAA	2531	TTAAAAAGTCTGCTAAAATGTTTTCATTCC	3483
30	H45_198-227	GAATGAAAACATTTTAGCAGACTTTTTAAG	2532	CTTAAAAAGTCTGCTAAAATGTTTTCATTC	3484
30	H45_199-228	AATGAAAACATTTTAGCAGACTTTTTAAGC	2533	GCTTAAAAAGTCTGCTAAAATGTTTTCATT	3485
30	H45_200-229	ATGAAAACATTTTAGCAGACTTTTTAAGCT	2534	AGCTTAAAAAGTCTGCTAAAATGTTTTCAT	3486
30	H45_201-230	TGAAAACATTTTAGCAGACTTTTTAAGCTT	2535	AAGCTTAAAAAGTCTGCTAAAATGTTTTCA	3487
30	H45_202-231	GAAAACATTTTAGCAGACTTTTTAAGCTTT	2536	AAAGCTTAAAAAGTCTGCTAAAATGTTTTC	3488
30	H45_203-232	AAAACATTTTAGCAGACTTTTTAAGCTTTC	2537	GAAAGCTTAAAAAGTCTGCTAAAATGTTTT	3489
30	H45_204-233	AAACATTTTAGCAGACTTTTTAAGCTTTCT	2538	AGAAAGCTTAAAAAGTCTGCTAAAATGTTT	3490
30	H45_205-234	AACATTTTAGCAGACTTTTTAAGCTTTCTT	2539	AAGAAAGCTTAAAAAGTCTGCTAAAATGTT	3491
30	H45_206-235	ACATTTTAGCAGACTTTTTAAGCTTTCTTT	2540	AAAGAAAGCTTAAAAAGTCTGCTAAAATGT	3492
30	H45_207-236	CATTTTAGCAGACTTTTTAAGCTTTCTTTA	2541	TAAAGAAAGCTTAAAAAGTCTGCTAAAATG	3493
30	H45_208-237	ATTTTAGCAGACTTTTTAAGCTTTCTTTAG	2542	CTAAAGAAAGCTTAAAAAGTCTGCTAAAAT	3494
30	H45_209-238	TTTTAGCAGACTTTTTAAGCTTTCTTTAGA	2543	TCTAAAGAAAGCTTAAAAAGTCTGCTAAAA	3495
30	H45_210-239	TTTAGCAGACTTTTTAAGCTTTCTTTAGAA	2544	TTCTAAAGAAAGCTTAAAAAGTCTGCTAAA	3496

[Table 7-54]

30	H45_211-240	TTAGCAGACTTTTTAAGCTTTCTTTAGAAG	2545	CTTCTAAAGAAAGCTTAAAAAGTCTGCTAA	3497
30	H45_212-241	TAGCAGACTTTTTAAGCTTTCTTTAGAAGA	2546	TCTTCTAAAGAAAGCTTAAAAAGTCTGCTA	3498
30	H45_213-242	AGCAGACTTTTTAAGCTTTCTTTAGAAGAA	2547	TTCTTCTAAAGAAAGCTTAAAAAGTCTGCT	3499
30	H45_214-243	GCAGACTTTTTAAGCTTTCTTTAGAAGAAT	2548	ATTCTTCTAAAGAAAGCTTAAAAAGTCTGC	3500
30	H45_215-244	CAGACTTTTTAAGCTTTCTTTAGAAGAATA	2549	TATTCTTCTAAAGAAAGCTTAAAAAGTCTG	3501
30	H45_216-245	AGACTTTTTAAGCTTTCTTTAGAAGAATAT	2550	ATATTCTTCTAAAGAAAGCTTAAAAAGTCT	3502
30	H45_217-246	GACTTTTTAAGCTTTCTTTAGAAGAATATT	2551	AATATTCTTCTAAAGAAAGCTTAAAAAGTC	3503
30	H45_218-247	ACTTTTTAAGCTTTCTTTAGAAGAATATTT	2552	AAATATTCTTCTAAAGAAAGCTTAAAAAGT	3504
30	H45_219-248	CTTTTTAAGCTTTCTTTAGAAGAATATTTC	2553	GAAATATTCTTCTAAAGAAAGCTTAAAAAG	3505
30	H45_220-249	TTTTTAAGCTTTCTTTAGAAGAATATTTCA	2554	TGAAATATTCTTCTAAAGAAAGCTTAAAAA	3506

[0107]

In one embodiment, the third antisense oligomer of the present invention comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group

consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

[0108]

In one embodiment, the third antisense oligomer comprises or consists of a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 1611 to 1654, 1664 to 1707, 1718 to 1761, 1773 to 1816, 1829 to 1872, 1886 to 1929, 1944 to 1987, 2003 to 2046, 2063 to 2106, 2124 to 2167, 2186 to 2229, 2249 to 2292, 2313 to 2356, 2378 to 2421, 2444 to 2487, and 2511 to 2554;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 1611 to 1654, 1664 to 1707, 1718 to 1761, 1773 to 1816, 1829 to 1872, 1886 to 1929, 1944 to 1987, 2003 to 2046, 2063 to 2106, 2124 to 2167, 2186 to 2229, 2249 to 2292, 2313 to 2356, 2378 to 2421, 2444 to 2487, and 2511 to 2554;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1611 to 1654, 1664 to 1707,

1718 to 1761, 1773 to 1816, 1829 to 1872, 1886 to 1929, 1944 to 1987, 2003 to 2046, 2063 to 2106, 2124 to 2167, 2186 to 2229, 2249 to 2292, 2313 to 2356, 2378 to 2421, 2444 to 2487, and 2511 to 2554, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

In one embodiment, the third antisense oligomer comprises or consists of a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 1614 to 1654, 1667 to 1707, 1721 to 1761, 1776 to 1816, 1832 to 1872, 1889 to 1929, 1947 to 1987, 2006 to 2046, 2066 to 2106, 2127 to 2167, 2189 to 2229, 2252 to 2292, 2316 to 2356, 2381 to 2421, 2447 to 2487, and 2514 to 2554;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 1614 to 1654, 1667 to 1707, 1721 to 1761, 1776 to 1816, 1832 to 1872, 1889 to 1929, 1947 to 1987, 2006 to 2046, 2066 to 2106, 2127 to 2167, 2189 to 2229, 2252 to 2292, 2316 to 2356, 2381 to 2421, 2447 to 2487, and 2514 to 2554;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1614 to 1654, 1667 to 1707, 1721 to 1761, 1776 to 1816, 1832 to 1872, 1889 to 1929, 1947 to 1987, 2006 to 2046, 2066 to 2106, 2127 to 2167, 2189 to 2229, 2252 to 2292, 2316 to 2356, 2381 to 2421, 2447 to 2487, and 2514 to 2554, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

In one embodiment, the third antisense oligomer comprises or consists of a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 1617 to 1654, 1670 to 1707, 1724 to 1761, 1779 to 1816, 1835 to 1872, 1892 to 1929, 1950 to 1987, 2009 to 2046, 2069 to 2106, 2130 to 2167, 2192 to 2229, 2255 to 2292, 2319 to 2356, 2384 to 2421, 2450 to 2487, and 2517 to 2554;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 1617 to 1654, 1670 to 1707, 1724 to 1761, 1779 to 1816, 1835 to 1872, 1892 to 1929, 1950 to 1987, 2009 to 2046, 2069 to 2106, 2130 to 2167, 2192 to 2229, 2255 to

2292, 2319 to 2356, 2384 to 2421, 2450 to 2487, and 2517 to 2554;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1617 to 1654, 1670 to 1707, 1724 to 1761, 1779 to 1816, 1835 to 1872, 1892 to 1929, 1950 to 1987, 2009 to 2046, 2069 to 2106, 2130 to 2167, 2192 to 2229, 2255 to 2292, 2319 to 2356, 2384 to 2421, 2450 to 2487, and 2517 to 2554, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

[0109]

Herein, the base sequence (c) is a mutant type of the base sequence (a), and examples of such a mutant type also include:

(c-1) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±15% of the length of the any one base sequence selected,

(c-2) a base sequence that has at least 86% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length

within ±14% of the length of the any one base sequence selected,

(c-3) a base sequence that has at least 87% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±13% of the length of the any one base sequence selected,

(c-4) a base sequence that has at least 88% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±12% of the length of the any one base sequence selected,

(c-5) a base sequence that has at least 89% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±11% of the length of the any one base sequence selected,

(c-6) a base sequence that has at least 90% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±10% of the length of the any one base sequence selected,

(c-7) a base sequence that has at least 91% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±9% of the length of the any one base sequence selected,

(c-8) a base sequence that has at least 92% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±8% of the length of the any one base sequence selected,

(c-9) a base sequence that has at least 93% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±7% of the length of the any one base sequence selected,

(c-10) a base sequence that has at least 94% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±6% of the length of the any one base sequence selected,

(c-11) a base sequence that has at least 95% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±5% of the length of the any one base sequence selected,

(c-12) a base sequence that has at least 96% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±4% of the length of the any one base sequence selected,

(c-13) a base sequence that has at least 97% identity with any one base sequence selected from the

group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±3% of the length of the any one base sequence selected,

(c-14) a base sequence that has at least 98% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±2% of the length of the any one base sequence selected,

(c-15) a base sequence that has at least 99% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±1% of the length of the any one base sequence selected, and

(c-16) a base sequence that has at least 99.5% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±0.5% of the length of the any one base sequence selected.

[0110]

In one embodiment, the third antisense oligomer comprises or consists of:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506; or

(b) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a length

within ±15% of the length of the any one base sequence selected.

[0111]

Herein, the base sequence (b) is a mutant type of the base sequence (a), and examples of such a mutant type also include:

(b-1) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a length within ±15% of the length of the any one base sequence selected,

(b-2) a base sequence that has at least 86% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a length within ±14% of the length of the any one base sequence selected,

(b-3) a base sequence that has at least 87% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a length within ±13% of the length of the any one base sequence selected,

(b-4) a base sequence that has at least 88% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a length within ±12% of the length of the any one base sequence selected,

(b-5) a base sequence that has at least 89% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a length within ±11% of the length of the any one base sequence selected,

(b-6) a base sequence that has at least 90% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a length within ±10% of the length of the any one base sequence selected,

(b-7) a base sequence that has at least 91% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a length within ±9% of the length of the any one base sequence selected,

(b-8) a base sequence that has at least 92% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a length within ±8% of the length of the any one base sequence selected,

(b-9) a base sequence that has at least 93% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a length within ±7% of the length of the any one base sequence selected,

(b-10) a base sequence that has at least 94% identity with any one base sequence selected from the

group consisting of SEQ ID NOs: 2555 to 3506, and has a length within ±6% of the length of the any one base sequence selected,

(b-11) a base sequence that has at least 95% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a length within ±5% of the length of the any one base sequence selected,

(b-12) a base sequence that has at least 96% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a length within ±4% of the length of the any one base sequence selected,

(b-13) a base sequence that has at least 97% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a length within ±3% of the length of the any one base sequence selected,

(b-14) a base sequence that has at least 98% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a length within ±2% of the length of the any one base sequence selected,

(b-15) a base sequence that has at least 99% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a

length within ±1% of the length of the any one base sequence selected, and

(b-16) a base sequence that has at least 99.5% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506, and has a length within ±0.5% of the length of the any one base sequence selected.

[0112]

In one embodiment, the third antisense oligomer of the present invention comprises or consists of any one base sequence selected from the group consisting of SEQ ID NOs: 2555 to 3506.

[0113]

In one embodiment, the third antisense oligomer comprises or consists of a base sequence selected from the group consisting of SEQ ID NOs: 3060, 3065, 3077, 3082, 3087, 3090, 3096, 3108, 3119, and 3320. In one embodiment, the third antisense oligomer comprises or consists of a base sequence selected from the group consisting of SEQ ID NOs: 3077, 3082, 3087, 3090, 3096, 3108, and 3119. In one embodiment, the third antisense oligomer comprises or consists of a base sequence selected from the group consisting of SEQ ID NOs: 3082, 3087, 3090, 3096, 3108, and 3119.

[0114]

A combination of the first unit oligomer and the second unit oligomer comprised in the first antisense

oligomer of the present invention, and the second antisense oligomer of the present invention (optionally the third antisense oligomer of the present invention) is not limited, and any combination can be used.

[0115]

In one embodiment, the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, and

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 201, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 203, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 205, and the second antisense

oligomer comprises or consists of a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1239, the second unit oligomer comprises a base sequence of SEQ ID NO: 114, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1224, the second unit oligomer comprises a base sequence of SEQ ID NO: 124, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1180, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1190, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1212, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1222, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4698,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4702,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4752,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4923,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a

base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4926,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4936,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4977, or

the first unit oligomer comprises a base sequence of SEQ ID NO: 1180, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4977.

[0116]

In one embodiment, the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, the first unit oligomer comprises any one base sequence selected from SEQ ID NOs: 907 to 1602, the second unit oligomer comprises any one base sequence selected from SEQ ID NOs: 106 to 210, and the second antisense oligomer comprises any one base sequence selected from SEQ ID NOs: 4299 to

5090. In one embodiment, the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, the first unit oligomer comprises a base sequence of SEQ ID No: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950 or 4880 (preferably 4950).

[0117]

In one embodiment, the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, and

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 201, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 203, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 205, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1239, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 114, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1224, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 124, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the

third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1180, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1190, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1212, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1222, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or

consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3060,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3065,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3077,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ

ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3087,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3090,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3096,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3108,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit

oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3119,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3320,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4698, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4702, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4752, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4923, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4926, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4936, and the

third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4977, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4977, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3096, or

the first unit oligomer comprises or consists of a base sequence of SEQ ID NO: 1180, the second unit oligomer comprises or consists of a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 4977, and the third antisense oligomer comprises or consists of a base sequence of SEQ ID NO: 3096.

[0118]

In one embodiment, the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, the first unit

oligomer comprises any one base sequence selected from SEQ ID NOs: 907 to 1602, the second unit oligomer comprises any one base sequence selected from the SEQ ID NOs: 106 to 210, the second antisense oligomer comprises any one base sequence selected from SEQ ID NOs: 4299 to 5090, and the third antisense oligomer comprises any one base sequence selected from SEQ ID NOs: 2555 to 3506. In one embodiment, the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950 or 4880 (preferably 4950), and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082, 3090, or 3096.

[0119]

The antisense oligomer of the present invention (including the linked-type antisense oligomer of the present invention) may be an oligonucleotide, morpholino oligomer or peptide nucleic acid (PNA) oligomer (hereinafter, also referred to as the "antisense oligonucleotide of the present invention", the "antisense morpholino oligomer of the present invention", or the "antisense peptide nucleic acid oligomer of the present invention").

[0120]

The antisense oligonucleotide of the present invention is an antisense oligomer composed of nucleotides as constituent units. Such nucleotides may be any of ribonucleotides, deoxyribonucleotides and modified nucleotides.

[0121]

The modified nucleotide refers to one having fully or partly modified nucleobases, sugar moieties and/or phosphate-binding regions, which constitute the ribonucleotide or deoxyribonucleotide.

[0122]

The nucleobase includes, for example, adenine, guanine, hypoxanthine, cytosine, thymine, uracil, and modified bases thereof. Examples of such modified bases include, but not limited to, pseudouracil, 3-methyluracil, dihydrouracil, 5-alkylcytosines (*e.g.*, 5-methylcytosine), 5-alkyluracils (*e.g.*, 5-ethyluracil), 5-halouracils (*e.g.*, 5-bromouracil), 6-azapyrimidine, 6-alkylpyrimidines (*e.g.*, 6-methyluracil), 2-thiouracil, 4-thiouracil, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5'-carboxymethylaminomethyl-2-thiouracil, 5-carboxymethylaminomethyluracil, 1-methyladenine, 1-methylhypoxanthine, 2,2-dimethylguanine, 3-methylcytosine, 2-methyladenine, 2-methylguanine, N6-methyladenine, 7-methylguanine, 5-methoxyaminomethyl-2-thiouracil, 5-methylaminomethyluracil, 5-methylcarbonylmethyluracil, 5-methyloxyuracil, 5-methyl-

2-thiouracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid, 2-thiocytosine, purine, 2,6-diaminopurine, 2-aminopurine, isoguanine, indole, imidazole, xanthine, etc.

[0123]

Modification of the sugar moiety may include, for example, modifications at the 2'-position of ribose and modifications of the other positions of the sugar. The modification at the 2'-position of ribose includes a modification of replacing the 2'-OH of ribose with -OR, -R, -R'OR, -SH, -SR, $-NH_2$, -NHR, $-NR_2$, $-N_3$, -CN, -F, -Cl, -Br or -I, wherein R represents an alkyl or an aryl and R' represents an alkylene.

The modification for the other positions of the sugar includes, for example, replacement of O at the 4' position of ribose or deoxyribose with S, bridging between 2' and 4' positions of the sugar, *e.g.*, LNA (locked nucleic acid) or ENA (2'-O,4'-C-ethylene-bridged nucleic acids), but is not limited thereto.

[0124]

A modification of the phosphate-binding region includes, for example, a modification of replacing phosphodiester bond with phosphorothioate bond, phosphorodithioate bond, alkyl phosphonate bond, phosphoramidate bond or boranophosphate bond (cf., *e.g.*, Enya et al: Bioorganic & Medicinal Chemistry, 2008, 18,

9154-9160) (cf., *e.g.*, Japan Domestic Re-Publications of PCT Application Nos. 2006/129594 and 2006/038608).

[0125]

As used herein, the alkyl is preferably a straight or branched alkyl having 1 to 6 carbon atoms. Specific examples include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *tert*-pentyl, *n*-hexyl and isohexyl. The alkyl may optionally be substituted. Examples of such substituents are a halogen, an alkoxy, cyano and nitro. The alkyl may be substituted with 1 to 3 substituents.

[0126]

As used herein, the cycloalkyl is preferably a cycloalkyl having 3 to 12 carbon atoms. Specific examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl.

[0127]

As used herein, the halogen includes fluorine, chlorine, bromine and iodine.

[0128]

As used herein, the alkoxy is a straight or branched alkoxy having 1 to 6 carbon atoms such as methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy, *n*-pentyloxy, isopentyloxy, *n*-

hexyloxy, isohexyloxy, etc. Among others, an alkoxy having 1 to 3 carbon atoms is preferred.

[0129]

As used herein, the aryl is preferably an aryl having 6 to 10 carbon atoms. Specific examples include phenyl, α-naphthyl and β-naphthyl. Among others, phenyl is preferred. The aryl may optionally be substituted. Examples of such substituents are an alkyl, a halogen, an alkoxy, cyano and nitro. The aryl may be substituted with one to three of such substituents.

[0130]

As used herein, the alkylene is preferably a straight or branched alkylene having 1 to 6 carbon atoms. Specific examples include methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, 2-(ethyl) trimethylene and 1-(methyl) tetramethylene.

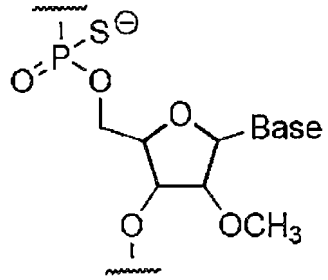
[0131]

As used herein, the acyl includes a straight or branched alkanoyl or aroyl. Examples of the alkanoyl include formyl, acetyl, 2-methylacetyl, 2,2-dimethylacetyl, propionyl, butyryl, isobutyryl, pentanoyl, 2,2-dimethylpropionyl, hexanoyl, etc. Examples of the aroyl include benzoyl, toluoyl and naphthoyl. The aroyl may optionally be substituted at substitutable positions and may be substituted with an alkyl(s).

[0132]

Preferably, the antisense oligonucleotide of the present invention is the antisense oligomer of the present invention having a group represented by general formula below as a constituent unit wherein the -OH group at position 2' of ribose is substituted with methoxy and the phosphate-binding region is a phosphorothioate bond:

[Chem. 3]



wherein Base represents a nucleobase.

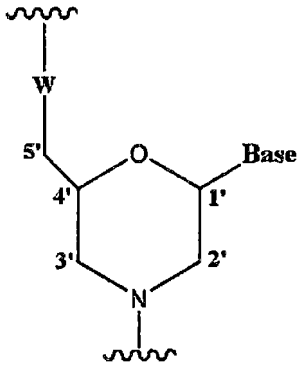
[0133]

The antisense oligonucleotide of the present invention may be easily synthesized using various automated synthesizer (*e.g.*, AKTA oligopilot plus 10/100 (GE Healthcare)). Alternatively, the synthesis may also be entrusted to a third-party organization (*e.g.*, Promega Corp. or Takara Co.), etc.

[0134]

The antisense morpholino oligomer of the present invention is an antisense oligomer comprising the constituent unit represented by general formula below:

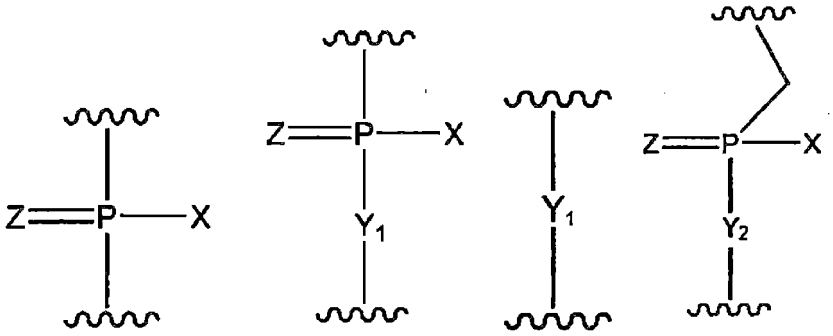
[Chem. 4]



wherein Base has the same significance as defined above, and,

W represents a group shown by any one of the following groups:

[Chem. 5]



wherein X represents $-CH_2R^1$, $-O-CH_2R^1$, $-S-CH_2R^1$, $-NR^2R^3$, or F;

R^1 represents H or an alkyl;

R^2 and R^3, which may be the same or different, each represents H, an alkyl, a cycloalkyl, or an aryl;

Y_1 represents O, S, CH_2, or NR^1;

Y_2 represents O, S, or NR^1;

Z represents O or S.

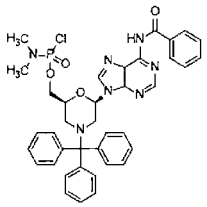
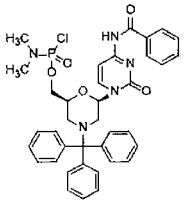
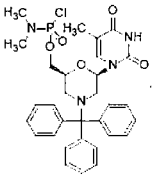
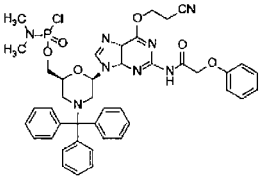
[0135]

Examples of morpholino monomer compounds that are used in synthesis of the antisense morpholino oligomer of the present invention include, but not limited to, the following morpholino monomer compound (A), morpholino monomer compound (C), morpholino monomer compound (T), and morpholino monomer compound (G) shown in Table 8.

[0136]

[Table 8]

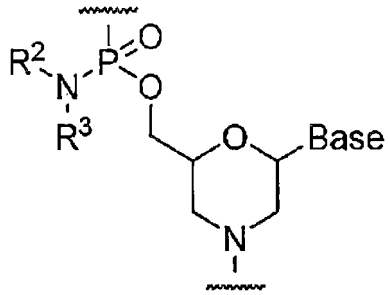
Table 8

Morpholino monomer compound (A)	Morpholino monomer compound (C)	Morpholino monomer compound (T)	Morpholino monomer compound (G)
			

[0137]

In the present invention, preferably, the morpholino oligomer is an oligomer having a group represented by general formula below as a constituent unit (phosphorodiamidate morpholino oligomer (hereinafter referred to as "PMO")).

[Chem. 6]



wherein Base, R^2 and R^3 have the same significance as defined above.

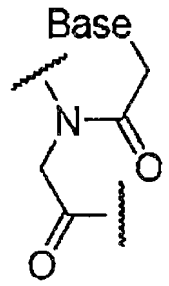
[0138]

The morpholino oligomer may be produced by the procedure described in, *e.g.*, WO 1991/009033 or WO 2009/064471. In particular, PMO can be produced by the procedure described in WO 2009/064471 or WO2013/100190.

[0139]

The antisense peptide nucleic acid oligomer of the present invention is an antisense oligomer having a group represented by general formula below as a constituent unit:

[Chem. 7]



wherein Base has the same significance as defined above.

The peptide nucleic acid oligomer can be produced in accordance with, *e.g.*, the following literatures:

1)P. E. Nielsen, M. Egholm, R. H. Berg, O. Buchardt, Science, 254, 1497 (1991)2)M. Egholm, O. Buchardt, P. E. Nielsen, R. H. Berg, JACS, 114, 1895 (1992)3)K. L. Dueholm, M. Egholm, C. Behrens, L. Christensen, H. F. Hansen, T. Vulpius, K. H. Petersen, R. H. Berg, P. E. Nielsen, O. Buchardt, J. Org. Chem., 59, 5767 (1994) 4)L. Christensen, R. Fitzpatrick, B. Gildea, K. H. Petersen, H. F. Hansen, T. Koch, M. Egholm, O. Buchardt, P. E. Nielsen, J. Coull, R. H. Berg, J. Pept. Sci., 1, 175 (1995)5)T. Koch, H. F. Hansen, P. Andersen, T. Larsen, H. G. Batz, K. Otteson, H. Orum, J. Pept. Res., 49, 80 (1997)

[0140]

The antisense oligomer of the present invention (including the linked-type antisense oligomer of the present invention) may be in the form of a pharmaceutically acceptable salt thereof, in the form of a hydrate thereof, or in the form of a hydrate of the pharmaceutically acceptable salt.

[0141]

Examples of the pharmaceutically acceptable salt of the antisense oligomer of the present invention are alkali metal salts such as salts of sodium, potassium and lithium; alkaline earth metal salts such as salts of calcium and magnesium; metal salts such as salts of aluminum, iron, zinc, copper, nickel, cobalt, etc.; ammonium salts; organic amine salts such as salts of t-

octylamine, dibenzylamine, morpholine, glucosamine, phenylglycine alkyl ester, ethylenediamine, *N*-methylglucamine, guanidine, diethylamine, triethylamine, dicyclohexylamine, *N,N'* -dibenzylethylenediamine, chloroprocaine, procaine, diethanolamine, *N*-benzylphenethylamine, piperazine, tetramethylammonium, tris(hydroxymethyl)aminomethane; hydrohalide salts such as salts of hydrofluorates, hydrochlorides, hydrobromides and hydroiodides; inorganic acid salts such as nitrates, perchlorates, sulfates, phosphates, etc.; lower alkane sulfonates such as methanesulfonates, trifluoromethanesulfonates and ethanesulfonates; arylsulfonates such as benzenesulfonates and p-toluenesulfonates; organic acid salts such as acetates, malates, fumarates, succinates, citrates, tartarates, oxalates, maleates, etc.; and, amino acid salts such as salts of glycine, lysine, arginine, ornithine, glutamic acid and aspartic acid. These salts may be produced by known methods. Alternatively, the antisense oligomer of the present invention may be in the form of a hydrate thereof.

[0142]

The third antisense oligomer of the present invention may have a function as a suppressor antisense oligomer. In the present invention, a suppressor antisense oligomer means an antisense oligomer which suppresses single exon skipping (hereinafter, referred to

as "single skipping"). The suppressor antisense oligomer can suppress single skipping and thereby enhance an effect of multi-exon skipping by an antisense oligomer. Accordingly, a combination of the present invention comprising the third antisense oligomer may have a higher effect of multi-exon skipping as compared with one not comprising the third antisense oligomer.

[0143]

Specifically, the third antisense oligomer of the present invention can suppress single skipping of any one exon selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA. More specifically, the third antisense oligomer of the present invention can suppress single skipping of the 45th exon in human dystrophin pre-mRNA.

[0144]

The third antisense oligomer of the present invention can suppress single skipping by, for example, targeting the site of a splicing silencer sequence, a branch site sequence, or a splice site sequence in human dystrophin pre-mRNA and inhibiting splicing. The third antisense oligomer of the present invention reduces the efficiency of single skipping of an intended exon as compared with a control.

[0145]

In one embodiment, the third antisense oligomer of the present invention targets a recognition sequence of

heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1) that is a splicing silencer sequence. A splicing silencer sequence refers to a base sequence element that functions to suppress recognition of an exon in pre-mRNA. A target sequence of the third antisense oligomer has been herein described.

[0146]

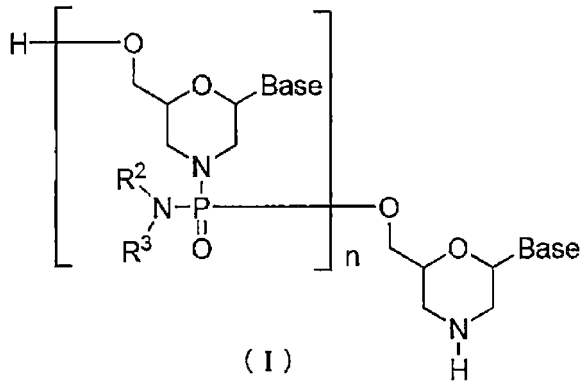
Whether the suppressor antisense oligomer enhances a multi-exon skipping effect or not can be confirmed by providing (i) an experimental system for multi-exon skipping using only the antisense oligomer of the present invention alone and (ii) an experimental system for multi-exon skipping using the antisense oligomer and the suppressor antisense oligomer of the present invention such that the other conditions are the same therebetween, and observing the difference between a multi-exon skipping effect obtained in the experimental system (ii) and a multi-exon skipping effect obtained in the experimental system (i).

[0147]

[Method for producing PMO]

The antisense oligomer of the present invention may be PMO. An aspect of PMO is, for example, the compound represented by general formula (I) below (hereinafter, referred to as PMO (I)).

[Chem. 8]



(I)

wherein Base, R^2 and R^3 have the same significance as defined above; and,

n is a given integer of 1 to 99, preferably a given integer of 18 to 28.

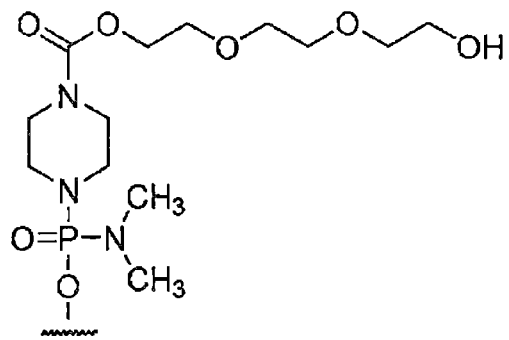
[0148]

PMO (I) can be produced in accordance with a known method (cf., *e.g.*, WO2009/064471 or WO2013/100190).

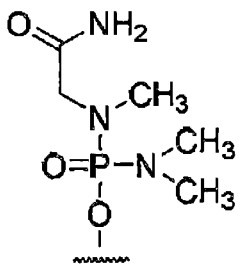
[0149]

In the antisense oligomer of the present invention, the 5' end may be a group represented by any of chemical structures (1) to (3) below, and preferably is (3)-OH.

[Chem. 9]



(1)



(2)



(3)

Hereinafter, the groups shown by (1), (2) and (3) above are referred to as "Group (1)," "Group (2)" and "Group (3)," respectively.

[0150]

The antisense oligomer of the present invention may be in the form of a complex formed together with a functional peptide for purpose of improving effectiveness (for example, a cell-penetrating peptide for purpose of improving transport efficiency to a target cell) or an antibody fragment (for example, a Fab of an antibody to a muscle cell specific receptor such as a transferrin receptor) (International Publications WO2008/036127, WO2009/005793, WO2012/150960, WO2016/187425, WO2018/118662, WO2011/013700, WO2018/118599, and WO2018/118627, Japanese Patent Laid-Open No. 2022-47613, J. D. Ramsey, N. H. Flynn, Pharmacology & Therapeutics 154, 78-86 (2015), M. K. Tsoumpra et al., EBioMedicine, 45, 630-645 (2019), International Publications WO2020/028832, WO2021/142307, WO2021/142313, WO2022/020107, and WO2022/020108). A binding site is not especially limited, and it is preferable that the 5' end or the 3' end of the antisense oligomer is bonded to the amino terminal or carboxyl terminal of a functional peptide or an antibody fragment.

In another aspect, the antisense oligomer of the present invention and a functional peptide or an antibody fragment may form a complex via a linker. The linker is

not especially limited, and it is preferable that the 5' end or the 3' end of the antisense oligomer is bonded to one end of the linker, and that the amino terminal or the carboxyl terminal of the functional peptide or the antibody fragment is bounded to the other end of the linker. An additional amino acid may be present between the functional peptide or the antibody fragment and the linker.

[0151]

Medical use

In one embodiment, the present invention provides a pharmaceutical composition comprising the first antisense oligomer and the second antisense oligomer of the present invention (also including a pharmaceutically acceptable salt thereof, or a hydrate thereof) (hereinafter, also referred to as the "pharmaceutical composition of the present invention"). The pharmaceutical composition of the present invention may further comprise the third antisense oligomer of the present invention (also including a pharmaceutically acceptable salt thereof, or a hydrate thereof) and/or a pharmaceutically acceptable carrier.

[0152]

In one embodiment, the present invention provides a pharmaceutical combination of a pharmaceutical composition comprising the first antisense oligomer of the present invention and a pharmaceutical composition

comprising the second antisense oligomer of the present invention (hereinafter, also referred to as the "pharmaceutical combination of the present invention"). The pharmaceutical combination of the present invention may further comprise the third antisense oligomer and/or a pharmaceutically acceptable carrier.

[0153]

The pharmaceutical composition of the present invention comprises any combination of the antisense oligomers of the present invention. The pharmaceutical combination of the present invention also comprises any combination of the antisense oligomers of the present invention. Details of the combinations of the antisense oligomers are as described herein.

[0154]

In one embodiment, the antisense oligomers in the combination of the present invention are comprised in one pharmaceutical composition to be simultaneously administered. In another embodiment, the antisense oligomers in the combination of the present invention are comprised in a plurality of pharmaceutical compositions (pharmaceutical combination of the present invention) to be separately (simultaneously or sequentially) administered. As used herein, the term "simultaneously" administering a plurality of pharmaceutical compositions means that a plurality of pharmaceutical compositions are administered at the same time. As used herein, the term

"sequentially" administering a plurality of pharmaceutical compositions means that these are administered at different times. Specifically, one pharmaceutical composition may be administered before or after another pharmaceutical composition, and an administration interval in this case is not limited, but may be, for example, a few minutes, a few hours, or a few days.

[0155]

The pharmaceutical composition of the present invention and the pharmaceutical combination of the present invention can each be used for the treatment of, for example, Duchenne muscular dystrophy, Becker muscular dystrophy, limb-girdle muscular dystrophy (LGMD), congenital muscular dystrophy, Emery-Dreifuss muscular dystrophy, facioscapulohumeral muscular dystrophy, oculopharyngeal muscular dystrophy, cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL), and Alport's syndrome. The pharmaceutical combination of the present invention and the pharmaceutical composition of the present invention can each be administered to a human patient and in particular, a human patient with muscular dystrophy. The patient to receive the pharmaceutical combination of the present invention or the pharmaceutical composition of the present invention may be a human patient having a mutation that is the target of skipping of two or more

exons selected from the group consisting of exons 45 to 55 in the dystrophin gene. Herein, the mutation that is the target of exon skipping is not limited, and an example includes a patient having deletion of exon (for example, having deletion of exon 46, exon 46 to 47, exon 46 to 48, exon 46 to 50, exon 46 to 51, exon 46 to 52, exon 46 to 53, exon 46 to 55, exon 47 to 50, exon 47 to 52, exon 48 to 50, exon 48 to 52, exon 48 to 54, exon 49 to 50, exon 49 to 52, exon 49 to 54, exon 50, exon 50 to 52, exon 51, exon 51 to 53, exon 52, exon 53, or exon 53 to 54) in the dystrophin gene.

[0156]

One aspect of the present invention provides a method for treatment of muscular dystrophy, which comprises administering to a patient with muscular dystrophy a combination of the antisense oligomer of the present invention. Another aspect of the present invention provides a method for treatment of muscular dystrophy, which comprises administering to a patient with muscular dystrophy the pharmaceutical composition of the present invention or the pharmaceutical combination of the present invention.

The method for treatment may involve performing skipping of any two or more numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA. In the method for treatment, the patient with muscular dystrophy

may be a patient having a mutation that is the target of exon 45 to 55 skipping in the dystrophin gene. The patient may be a human and may be a human patient having a mutation that is the target of exon 45 to 55 skipping in the dystrophin gene.

[0157]

The present invention further provides use of a combination of the antisense oligomer of the present invention, or the pharmaceutical composition of the present invention or the pharmaceutical combination of the present invention in manufacturing of a medicament for the treatment of muscular dystrophy.

[0158]

The present invention further provides a combination of the antisense oligomer of the present invention, or the pharmaceutical composition of the present invention or the pharmaceutical combination of the present invention for use in the treatment of muscular dystrophy. The treatment may involve performing skipping of any two or more numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA. In the treatment, the patient with muscular dystrophy may be a patient having a mutation that is the target of exon 45 to 55 skipping in the dystrophin gene. The patient may be a human and may be a human patient having a mutation that is the target of exon 45 to 55 skipping in the dystrophin gene.

[0159]

Administration route for the combination of the antisense oligomer of the present invention, or the pharmaceutical composition of the present invention or the pharmaceutical combination of the present invention is not particularly limited so long as it is pharmaceutically acceptable route for administration, and can be chosen depending upon method of treatment. In view of easiness in delivery to muscle tissues, preferred are intravenous administration, intraarterial administration, intramuscular administration, subcutaneous administration, oral administration, tissue administration, transdermal administration, etc. Also, dosage forms which are available for the composition of the present invention are not particularly limited, and include, for example, various injections, oral agents, drips, inhalations, ointments, lotions, etc.

[0160]

In administration of the antisense oligomer of the present invention to patients with muscular dystrophy, preferably, the composition of the present invention contains a carrier to promote delivery of the oligomer to muscle tissues. Such a carrier is not particularly limited as far as it is pharmaceutically acceptable, and examples include cationic carriers such as cationic liposomes, cationic polymers, etc., or carriers using viral envelope. The cationic liposomes are, for example,

liposomes composed of 2-O-(2-diethylaminoethyl)carabamoyl-1,3-O-dioleoylglycerol and phospholipids as the essential constituents (hereinafter referred to as "liposome A"), Oligofectamine (registered trademark) (manufactured by Invitrogen Corp.), Lipofectin (registered trademark) (manufactured by Invitrogen Corp.), Lipofectamine (registered trademark) (manufactured by Invitrogen Corp.), Lipofectamine 2000 (registered trademark) (manufactured by Invitrogen Corp.), DMRIE-C (registered trademark) (manufactured by Invitrogen Corp.), GeneSilencer (registered trademark) (manufactured by Gene Therapy Systems), TransMessenger (registered trademark) (manufactured by QIAGEN, Inc.), TransIT TKO (registered trademark) (manufactured by Mirus) and Nucleofector II (Lonza). Among others, liposome A is preferred. Examples of cationic polymers are JetSI (registered trademark) (manufactured by Qbiogene, Inc.) and Jet-PEI (registered trademark) (polyethylenimine, manufactured by Qbiogene, Inc.). An example of carriers using viral envelop is GenomeOne (registered trademark) (HVJ-E liposome, manufactured by Ishihara Sangyo). Alternatively, the medical devices described in Japanese Patent Nos. 2924179 and the cationic carriers described in Japanese Domestic Re-Publication PCT Nos. 2006/129594 and 2008/096690 may be used as well.

[0161]

A concentration of the antisense oligomer of the present invention contained in the pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention may vary depending on kind of the carrier, etc., and is appropriately in a range of 0.1 nM to 100 μM, preferably in a range of 1 nM to 10 μM, and more preferably in a range of 10 nM to 1 μM. A weight ratio of the antisense oligomer of the present invention contained in the composition of the present invention and the carrier (carrier/antisense oligomer of the present invention) may vary depending on property of the oligomer, type of the carrier, etc., and is appropriately in a range of 0.1 to 100, preferably in a range of 1 to 50, and more preferably in a range of 10 to 20.

[0162]

In one embodiment, the antisense oligomers in the combination of the present invention are comprised in one pharmaceutical composition to be simultaneously administered. In another embodiment, the antisense oligomers in the combination of the present invention are comprised in a plurality of pharmaceutical compositions (pharmaceutical combination of the present invention) to be separately (simultaneously or sequentially) administered. When the antisense oligomers in the combination of the present invention are comprised in one

or a plurality of pharmaceutical compositions, concentrations of the antisense oligomers are as follows.

[0163]

The pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention may be in the form of an aqueous solution. In this case, the pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention may comprise the antisense oligomer of the present invention in a concentration of 2.5 to 500 mg/mL, 5 to 450 mg/mL, 10 to 400 mg/mL, 15 to 350 mg/mL, 20 to 300 mg/mL, 20 to 250 mg/mL, 20 to 200 mg/mL, 20 to 150 mg/mL, 20 to 100 mg/mL, 20 to 50 mg/mL, 20 to 40 mg/mL, 20 to 30 mg/mL, 23 to 27 mg/mL, 24 to 26 mg/mL, or 25 mg/mL. The pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention may comprise the antisense oligomer of the present invention in a concentration of 10 to 100 mg/mL, 15 to 95 mg/mL, 20 to 80 mg/mL, 25 to 75 mg/mL, 30 to 70 mg/mL, 35 to 65 mg/mL, 40 to 60 mg/mL, 45 to 55 mg/mL, 47 to 53 mg/mL, 48 to 52 mg/mL, 49 to 51 mg/mL, or 50 mg/mL.

[0164]

The pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention may be in a dry form. In this case, in order to prepare the pharmaceutical composition of the

present invention and/or the pharmaceutical combination of the present invention in an aqueous solution form, for example, 125 mg or 250 mg of the antisense oligomer of the present invention in a dry form may be mixed with 0.5 mL to 100 mL of water (which corresponds to a concentration of 1.25 mg/mL to 250 mg/mL or 2.5 mg/mL to 500 mg/mL of the antisense oligomer of the present invention), preferably with 1 mL to 50 mL of water (which corresponds to a concentration of 2.5 mg/mL to 125 mg/mL or 5 mg/mL to 250 mg/mL of the antisense oligomer of the present invention), more preferably with 5 mL to 10 mL of water (which corresponds to a concentration of 12.5 mg/mL to 25 mg/mL or 25 mg/mL to 50 mg/mL of the antisense oligomer of the present invention) for use.

[0165]

When the antisense oligomers in the combination of the present invention are comprised in one or a plurality of pharmaceutical compositions, a total concentration of the antisense oligomers is as follows.

When the pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention is in an aqueous solution form, the pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention may comprise the antisense oligomers of the present invention in a total concentration of 2.5 to 500 mg/mL, 5 to 450 mg/mL, 10 to 400 mg/mL, 15 to 350 mg/mL,

20 to 300 mg/mL, 20 to 250 mg/mL, 20 to 200 mg/mL, 20 to 150 mg/mL, 20 to 100 mg/mL, 20 to 50 mg/mL, 20 to 40 mg/mL, 20 to 30 mg/mL, 23 to 27 mg/mL, 24 to 26 mg/mL, or 25 mg/mL, or 5 to 1000 mg/mL, 10 to 900 mg/mL, 20 to 800 mg/mL, 30 to 700 mg/mL, 40 to 600 mg/mL, 40 to 500 mg/mL, 40 to 400 mg/mL, 40 to 300 mg/mL, 40 to 200 mg/mL, 40 to 100 mg/mL, 40 to 80 mg/mL, 40 to 60 mg/mL, 46 to 54 mg/mL, 48 to 52 mg/mL, or 50 mg/mL, or 7.5 to 1500 mg/mL, 15 to 1350 mg/mL, 30 to 1200 mg/mL, 45 to 1150 mg/mL, 60 to 900 mg/mL, 60 to 750 mg/mL, 60 to 600 mg/mL, 60 to 450 mg/mL, 60 to 300 mg/mL, 60 to 150 mg/mL, 60 to 120 mg/mL, 60 to 90 mg/mL, 69 to 81 mg/mL, 72 to 78 mg/mL, or 75 mg/mL. Alternatively, the pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention may comprise the antisense oligomers of the present invention in a total concentration of 10 to 100 mg/mL, 15 to 95 mg/mL, 20 to 80 mg/mL, 25 to 75 mg/mL, 30 to 70 mg/mL, 35 to 65 mg/mL, 40 to 60 mg/mL, 45 to 55 mg/mL, 47 to 53 mg/mL, 48 to 52 mg/mL, 49 to 51 mg/mL, or 50 mg/mL, or 20 to 200 mg/mL, 30 to 190 mg/mL, 40 to 160 mg/mL, 50 to 150 mg/mL, 60 to 140 mg/mL, 70 to 130 mg/mL, 80 to 120 mg/mL, 90 to 110 mg/mL, 94 to 106 mg/mL, 96 to 104 mg/mL, 98 to 102 mg/mL, or 100 mg/mL, or 30 to 300 mg/mL, 45 to 285 mg/mL, 60 to 240 mg/mL, 75 to 225 mg/mL, 90 to 210 mg/mL, 105 to 195 mg/mL, 120 to 180 mg/mL, 130 to 165 mg/mL, 141 to 159 mg/mL, 144 to 156 mg/mL, 147 to 153 mg/mL, or 150 mg/mL.

[0166]

When the pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention is in a dry form, in order to prepare the pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention in an aqueous solution form, for example, 125 mg or 250 mg of the antisense oligomer of the present invention in a dry form may be mixed with 0.5 mL to 100 mL of water (which corresponds to a total concentration of 1.25 mg/mL to 250 mg/mL or 2.5 mg/mL to 500 mg/mL of the antisense oligomers of the present invention), preferably with 1 mL to 50 mL of water (which corresponds to a total concentration of 2.5 mg/mL to 125 mg/mL or 5 mg/mL to 250 mg/mL of the antisense oligomers of the present invention), more preferably with 5 mL to 10 mL of water (which correspond to a total concentration of 12.5 mg/mL to 25 mg/mL or 25 mg/mL to 50 mg/mL of the antisense oligomers of the present invention), or for example, 250 mg or 500 mg in total of the antisense oligomers of the present invention in a dry form may be mixed with 0.5 mL to 100 mL of water (which corresponds to a total concentration of 2.5 mg/mL to 500 mg/mL or 5 mg/mL to 1000 mg/mL of the antisense oligomers of the present invention), preferably with 1 mL to 50 mL of water (which corresponds to a total concentration of 5 mg/mL to 250 mg/mL or 10 mg/mL to 500 mg/mL of the

antisense oligomers of the present invention), more preferably with 5 mL to 10 mL of water (which correspond to a total concentration of 25 mg/mL to 50 mg/mL or 50 mg/mL to 100 mg/mL of the antisense oligomers of the present invention), or for example, 375 mg or 750 mg in total of the antisense oligomers of the present invention in a dry form may be mixed with 0.5 mL to 100 mL of water (which corresponds to a total concentration of 3.75 mg/mL to 750 mg/mL or 7.5 mg/mL to 150 mg/mL of the antisense oligomers of the present invention), preferably with 1 mL to 50 mL of water (which corresponds to a total concentration of 7.5 mg/mL to 375 mg/mL or 15 mg/mL to 750 mg/mL of the antisense oligomers of the present invention), more preferably with 5 mL to 10 mL of water (which corresponds to a total concentration of 37.5 mg/mL to 75 mg/mL or 75 mg/mL to 150 mg/mL of the antisense oligomers of the present invention) for use.

[0167]

In addition to the antisense oligomer of the present invention and the carrier described above, pharmaceutically acceptable additives may also be optionally formulated in the pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention. Examples of such additives are emulsification aids (*e.g.*, fatty acids having 6 to 22 carbon atoms and their pharmaceutically acceptable salts, albumin and dextran), stabilizers

(*e.g.*, cholesterol, phosphatidic acid, mannitol, and sorbitol), isotonizing agents (*e.g.*, sodium chloride, glucose, maltose, lactose, sucrose, and trehalose), and pH controlling agents (*e.g.*, hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid, sodium hydroxide, potassium hydroxide and triethanolamine). One or more of these additives can be used. The content of the additive in the composition of the present invention is appropriately 90 wt% or less, preferably 70 wt% or less and more preferably, 50 wt% or less.

[0168]

The pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention can be prepared by adding the antisense oligomer of the present invention to a carrier dispersion and adequately stirring the mixture. Additives may be added at an appropriate step either before or after addition of the antisense oligomer of the present invention. An aqueous solvent that can be used in adding the antisense oligomer of the present invention is not particularly limited as far as it is pharmaceutically acceptable, and examples are injectable water or injectable distilled water, electrolyte fluid such as physiological saline, etc., and sugar fluid such as glucose fluid, maltose fluid, etc. A person skilled in the art can appropriately choose conditions for pH and temperature for such matter.

[0169]

The pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention may be prepared into, *e.g.*, a liquid form and its lyophilized preparation. The lyophilized preparation can be prepared by lyophilizing the composition of the present invention in a liquid form in a conventional manner. The lyophilization can be performed, for example, by appropriately sterilizing the composition of the present invention in a liquid form, dispensing an aliquot into a vial container, performing preliminary freezing for 2 hours at conditions in a range of about -40°C to -20°C, performing a primary drying in a range of about 0°C to 10°C under reduced pressure, and then performing a secondary drying in a range of about 15°C to 25°C under reduced pressure. In general, the lyophilized preparation of the composition of the present invention can be obtained by replacing the content of the vial with nitrogen gas and capping.

[0170]

The lyophilized preparation of the pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention can be used in general upon reconstitution by adding an optional suitable solution (reconstitution liquid) and redissolving the preparation. Such a reconstitution liquid includes injectable water, physiological saline

and other infusion fluids. A volume of the reconstitution liquid may vary depending on the intended use, etc., is not particularly limited, and is suitably 0.5-fold to 2-fold greater than the volume prior to lyophilization or no more than 500 mL.

[0171]

It is desired to control a dose of the pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention to be administered, by taking the following factors into account: the type and dosage form of the antisense oligomer of the present invention contained; patients' conditions including age, body weight, etc.; administration route; and the characteristics and extent of the disease. A single dose calculated as the amount of the antisense oligomer of the present invention can be 0.1 mg to 1 g per kg body weight, preferably 1 mg to 100 mg per kg body weight, more preferably 1 mg to 90 mg per kg body weight, and further preferably 1 mg to 80 mg per kg body weight. The frequency of administration may be once per 1 to 3 days, once per week, or once per 2 to 3 weeks. This numerical range may vary occasionally depending on type of the target disease, administration route and target molecule. Therefore, a dose or frequency of administration lower than the range may be sufficient in some occasion and conversely, a dose or

frequency of administration higher than the range may be required occasionally.

[0172]

In still another aspect of the pharmaceutical composition of the present invention and/or the pharmaceutical combination of the present invention, there is provided a pharmaceutical composition comprising a vector capable of expressing the antisense oligomer of the present invention and the carrier described above. Such an expression vector may be a vector capable of expressing a plurality of the antisense oligomers of the present invention of the present invention. The composition may be formulated with pharmaceutically acceptable additives as in the case with the composition of the present invention containing the antisense oligomer of the present invention. A concentration of the expression vector contained in the composition may vary depending upon type of the career, etc., and is appropriately in a range of 0.1 nM to 100 μM, preferably in a range of 1 nM to 10 μM, and more preferably in a range of 10 nM to 1 μM. A weight ratio of the expression vector contained in the composition and the carrier (carrier/expression vector) may vary depending on property of the expression vector, type of the carrier, etc., and is appropriately in a range of 0.1 to 100, preferably in a range of 1 to 50, and more preferably in a range of 10 to 20. The content of the carrier

contained in the composition is the same as in the case with the composition of the present invention containing the antisense oligomer of the present invention, and a method for producing the same is also the same as in the case with the composition of the present invention.

Examples

[0173]

Hereinafter, the present invention will be described in more detail with reference to Examples and Test Examples below, but is not limited thereto.

[0174]

[Example 1: Production of antisense oligomers]

In accordance with the method described in Example 1 of International Publication WO2013/100190, antisense oligomers shown in Table 9 (PMO Nos. 1 to 5 (SEQ ID NOs: 5098 to 5102)) were synthesized. Theoretical values and actual values measured by ESI-TOF-MS of the molecular weights of the antisense oligomers are also shown. The 5' end of each PMO is Group (1) below. The synthesized PMO was dissolved in water for injection (manufactured by Otsuka Pharmaceutical Factory, Inc.).

[0175]

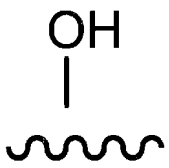
[Table 9]

Table 9

PMO No.	SEQ ID NO:	Target base sequence	Base sequence of PMO	Molecular weight	
				Theoretical value	Actual value
1	5098	M45_(-66)-(-61)_19-40	TGACAACAGCTTGACGCTGCCCGTTTAA	9247.21	9247.66
2	5099	M55_(-4)-24	AAAGCAGCCTCTTGCTCACTTACTCTGC	9158.18	9158.3
3	5100	M45_183-206	AGCTCTGCTAAAAAGTCTCTGTCA	7906.75	7906.12
4	5101	M45_197-220	TTAAAGGATAGTGTAGCTCTGCTA	8001.77	8001.77
5	5102	M45_191-214	GATAGTGTAGCTCTGCTAAAAAGT	8010.78	8010.48

[0176]

[Chem. 10]



(1)

[0177]

The target base sequence of the antisense oligomer of the present invention was described as "$Ma_1\_b_1\text{-}c_1$", "$Ma_2\_b_2\text{-}c_2\_Ma_3\_b_3\text{-}c_3$".

[0178]

"Ma_1" represents the ath exon of the mouse dystrophin gene, "b_1" represents the 5'-terminal base of the target base sequence, and "c_1" represents the 3'-terminal base of the target base sequence.

When "b_1" and "c_1" are positive integers, "b_1" and "c_1" each represent a base number in the downstream

direction when the 5'-terminal base of the ath exon is counted as the 1st base. On the other hand, when "b_1" and "c_1" are negative numbers, "b_1" and "c_1" each represent a base number in the upstream direction when the 3'-terminal base of the (a - 1)th intron is counted as the 1st base.

[0179]

For example, "M55_(-4)-24" means a base sequence in which the 5' end of the target base sequence is the 4th base in the upstream direction from the 3' end of the 54th intron and the 3' end of the target base sequence is the 24th base in the downstream direction from the 5' end of the 55th exon.

[0180]

"$Ma_2\_b_2$-c_2" which is the first part of "$Ma_2\_b_2$-$c_2\_Ma_3\_b_3$-c_3" means the target base sequence of a 3' unit oligomer constituting the antisense oligomer, and the second part "$Ma_3\_b_3$-c_3" means the target base sequence of a 5' unit oligomer constituting the antisense oligomer.

[0181]

When "Ma_2" and "Ma_3" are the same, the "$\_Ma_3$" part may be omitted.

[0182]

For example, "M45_(-66)-(-61)_19-40" or "M45_(-66)-(-61)_M45_19-40" means a base sequence in which the target base sequence of the 3' unit oligomer constituting the antisense oligomer is "M45_(-66)-(-61)" and the

target base sequence of the 5' unit oligomer constituting the antisense oligomer is "M45_19-40".

[0183]

[Example 2: Test on multi-exon skipping activity of antisense oligomer]

<Test Example 1>

Assay of exon 45 to 55 multi-exon skipping in model mouse-derived cultured cells - (1): induction of multi-exon skipping (total addition concentration: 30 μM)

Procedures

[0184]

H2K-mdx52 cells (immortalized myoblasts established from a crossbred individual of a mdx52 mouse, that is, Duchenne muscular dystrophy model, and a H-2kb-tsA58 transgenic mouse) were seeded in a 0.4% Gelatine-coated 48-well plate (manufactured by AGC Techno Glass Co., Ltd.) at 1 x 10^4/well, and were cultured for 3 days under conditions of 37°C and 5% CO_2 in 0.5 mL of a growth medium (High glucose Dulbecco's Modified Eagle Medium (DMEM) (containing GlutaMax) (manufactured by Thermo Fisher Scientific) supplemented with 20% FBS (manufactured by Sigma Aldrich), 2% chick embryo extract (manufactured by US Biological, hereinafter the same), 2% L-glutamine (manufactured by Sigma Aldrich, hereinafter the same), 1% penicillin/streptomycin (manufactured by Sigma Aldrich, hereinafter the same), and 20 U/mL Recombinant Murine IFN-γ (manufactured by PeproTech)).

After 48 hours, the growth medium was changed to a differentiation medium (DMEM supplemented with 5% horse serum (manufactured by Thermo Fisher Scientific), 2% L-glutamine, and 1% penicillin/streptomycin). After culturing for 3 days, transfection was performed with 30 μM PMO using 6 μM Endo-Porter (manufactured by Gene Tools, hereinafter the same). PMOs used here are shown in Table 10.

[0185]

[Table 10]

Table 10

PMO No.	Base sequence of PMO (5' to 3')	SEQ ID NO:
1	TGACAACAGCTTGACGCTGCCCGTTTAA	5098
2	AAAGCAGCCTCTTGCTCACTTACTCTGC	5099
3	AGCTCTGCTAAAAAGTCTCTGTCA	5100

[0186]

After culturing for another 3 days, the resultant cells were washed once with PBS (manufactured by Takara Bio Inc.), and then, the total RNA was extracted with RNeasy Mini Kit (manufactured by Qiagen K. K.). 350 μL of Buffer RLT (manufactured by Qiagen K. K.) containing 1% 2-mercaptoethanol (manufactured by Nacalai Tesque, Inc.) was added to the cells, and after the cells were allowed to stand at room temperature for a few minutes to lyse the cells, the lysate was collected into a QIAshredder homogenizer (manufactured by Qiagen K. K.). A homogenate was produced by centrifugation at 15,000 rpm

for 2 minutes. The total RNA was extracted according to the protocol attached to RNeasy Mini Kit (manufactured by Qiagen K. K.). The concentration of the total RNA extracted was determined using a NanoDrop One C (manufactured by Thermo Fisher Scientific). One-Step RT-PCR was performed with 400 ng of the extracted total RNA using a QIAGEN One Step RT-PCR Kit (manufactured by Qiagen K. K.). A reaction solution was prepared in accordance with the protocol attached to the kit. Veriti 96 Well Thermal Cycler (manufactured by Thermo Fisher Scientific) was used as the thermal cycler. The RT-PCR program used was as follows.

[0187]

50°C, 30 mins: reverse transcription reaction

95°C, 15 mins: polymerization activation, reverse transcriptase inactivation, cDNA thermal denaturation

[94°C, 10 seconds; 57°C, 30 seconds; 72°C, 1 minute] x 33 cycles: PCR amplification

72°C, 10 mins: final extension

[0188]

The base sequences of the forward primer and reverse primer used for RT-PCR are given below.

Forward primer: 5'-cagttgaaaaatggcgacac-3' (SEQ ID NO: 5103)

Reverse primer 1: 5'-ttagctgctgctcatctcca-3' (SEQ ID NO: 5104)

Reverse primer 2: 5'-ttccagggatctcaggattt-3' (SEQ ID NO: 5105)

[0189]

Transcripts (429 bp) having no skipping and transcripts (253 bp) having single exon skipping of exon 45 can be detected by a combination of the forward primer and the reverse primer 1, and transcripts (218 bp) having multi-exon skipping of exons 45 to 55 can be detected by a combination of the forward primer and the reverse primer 2.

[0190]

The reaction product of the PCR above was analyzed using MultiNA (manufactured by Shimadzu Corp.).

The polynucleotide level "A" of the band with skipping of exons 45 to 55, the polynucleotide level "B" of the band with skipping of exon 45, and the polynucleotide level "C" of the band having no skipping were measured. Based on these measurement values of "A", "B", and "C", the skipping efficiencies of exon 45 to 55 skipping and exon 45 skipping were determined by the following equations:

Skipping efficiency of exon 45 to 55 skipping (%) = A / (A + B + C) x 100

Skipping efficiency of exon 45 skipping (%) = B / (A + B + C) x 100

[0191]

Results

The results are shown in Figures 1 to 2.

As compared with the mixture of PMO No. 1 and PMO No. 2 (15 μM each, Mixture 2) used singly, the mixture additionally containing PMO No. 3 targeting hnRNP A1 (10 μM each, Mixture 2 + PMO No. 3) increased the skipping efficiency of exon 45 to 55 skipping (Figure 1), and reduced the skipping efficiency of exon 45 skipping (Figure 2).

[0192]

<Test Example 2>

Assay of exon 45 to 55 multi-exon skipping in model mouse-derived cultured cells - (2): induction of multi-exon skipping (total addition concentration: 15 μM, mixing ratio changed)

[0193]

Procedures

H2K-mdx52 cells were seeded in a 0.4% Gelatine-coated 24-well plate at 5 x 10^4/well and cultured for 48 hours under conditions of 37°C and 5% CO_2 in 1 mL of a growth medium, and then the growth medium was changed to a differentiation medium. After culturing for 3 days, transfection was performed with 15 μM PMO using 6 μM Endo-Porter.

A PMO shown in Table 11 was used in addition to those used in Test Example 1.

[0194]

[Table 11]

Table 11

PMO No.	Base sequence of PMO (5' to 3')	SEQ ID NO:
4	TTAAAGGATAGTGTAGCTCTGCTA	5101

After culturing for another 3 days, the resultant cells were collected in the same manner as in Test Example 1, the total RNA was extracted, and subjected to One-Step RT-PCR, and the reaction product of the PCR thus obtained was analyzed to obtain the skipping efficiencies of exon 45 to 55 skipping and exon 45 skipping.

[0195]

(Results)

The results are shown in Figures 3 to 8.

As compared with the mixture of PMO No. 1 and PMO No. 2 (Mixture 2) used singly, the mixture additionally containing PMO No. 3 targeting hnRNP A1 (Mixture 2 + hnRNP A1) increased the skipping efficiency of exon 45 to 55 skipping (Figure 3), and reduced the skipping efficiency of exon 45 skipping (Figure 4).

The mixture of Mixture 2 and PMO No. 4 targeting hnRNP A1 (Mixture 2 + PMO No. 4) caused exon 45 to 55 skipping (Figure 5), and reduced the skipping efficiency of exon 45 skipping (Figure 6).

[0196]

As a result of studying the case where the ratio between Mixture 2 and PMO No. 3 targeting hnRNP A1 was changed, when these were formulated at 3:1, the skipping efficiency of exon 45 to 55 skipping was the highest

(Figure 7), and the skipping efficiency of exon 45 skipping was most largely suppressed (Figure 8).

[0197]

<Test Example 3>

Assay of exon 45 to 55 multi-exon skipping in model mouse-derived cultured cells - (3): induction of multi-exon skipping (total addition concentration: 50 μM)

[0198]

Procedures

H2K-mdx52 cells were seeded in a 0.4% Gelatine-coated 24-well plate at 6.7 x 10^4/well and cultured for 1 day under conditions of 37°C and 5% CO_2 in 2 mL of a growth medium. After culturing for 2 days, the growth medium was changed to a differentiation medium. After culturing for 3 days, transfection was performed with 50 μM PMO using 6 μM Endo-Porter. After culturing for another 3 days, the resultant cells were collected in the same manner as in Test Example 1, the total RNA was extracted, and subjected to One-Step RT-PCR, and the reaction product of the PCR thus obtained was analyzed to obtain skipping efficiencies of exon 45 to 55 skipping and exon 45 skipping.

[0199]

(Results)

The results are shown in Figures 9 and 10.

As compared with the mixture of PMO No. 1 and PMO No. 2 (Mix 2) used singly, the mixture additionally

containing PMO No. 3 targeting hnRNP A1 (Mix 2 + hnRNP A1) increased the skipping efficiency of exon 45 to 55 skipping (Figure 9), and reduced the skipping efficiency of exon 45 skipping (Figure 10). Mix 2 had the same definition as Mixture 2 used in Test Example 1 and Test Example 2.

[0200]

<Test Example 4>

Assay of exon 45 to 55 multi-exon skipping in model mouse-derived cultured cells - (4): restoration of dystrophin protein by multi-exon skipping

[0201]

Procedures

H2K-mdx52 cells were seeded in a 0.4% Gelatine-coated 24-well plate at 6.7 x 10^4/well and cultured for 1 day under conditions of 37°C and 5% CO_2 in 2 mL of a growth medium. After culturing for 2 days, the growth medium was changed to a differentiation medium. After culturing for 3 days, transfection was performed with 50 μM PMO using 6 μM Endo-Porter. After culturing for another 3 days, the medium was changed to a differentiation medium, and after culturing for another 1 day, the resultant cells were collected with a cell lysis buffer, Pierce RIPA Buffer (Thermo Fisher Scientific) containing protease inhibitor cocktail, cOmplete, Mini (manufactured by Roche Diagnostics) added thereto. The cells were crushed with a sonicator, Bioruptor UCD-250

(manufactured by Sonicbio Co., Ltd.) (output: H, three times each for 30 seconds), and centrifuged (15,000 rpm, 4°C, 15 minutes) with a cooling centrifuge (TOMY MX-305, rotor: AR015-24, manufactured by Tomy Seiko Co., Ltd.) to obtain a supernatant as a cell lysate. Pierce BCA Protein Assay Kit (manufactured by Thermo Fisher Scientific) was used to measure an absorbance at 562 nm with a plate reader, Synergy HTX Multi-Mode Microplate Reader (manufactured by BioTek Instruments), and a protein concentration in the cell lysate was obtained with data analysis software, Gen5 version 2.09.2 (manufactured by BioTek Instruments). The cell lysate (in an amount corresponding to 30 μg of protein) was subjected to electrophoresis (150 V, 75 minutes) with polyacrylamide gel NuPAGE 3 to 8%, Tris-Acetate, 1.5 mm, Mini Protein Gel, 15-well (manufactured by Thermo Fisher Scientific). As a molecular weight marker, HiMark Pre-Stained Protein Standard (manufactured by Thermo Fisher Scientific) was used.

[0202]

After the electrophoresis, transcription (4 mA/cm^2, 30 minutes) was conducted into Immobilon-P Transfer membrane (manufactured by Merck Millipore) by semi-dry blotting. Western blotting was conducted by using, as a primary antibody, a 100-fold diluted anti-dystrophin antibody (NCL-Dys1, manufactured by Leica Biosystems Newcastle Ltd.), and as a secondary antibody, a 2,500-

fold diluted goat anti-mouse IgG (H + L) - Horseradish Peroxidase complex (manufactured by Bio-Rad Laboratories). After completing the antibody reaction, light emission was caused with ECL Prime Western Blotting Detection System (manufactured by Cytiva), and the light emission was detected with a chemiluminescence gel imaging apparatus, ChemiDoc Touch MP Imaging System (manufactured by Bio-Rad Laboratories) to take an image.

[0203]

(Results)

The results are shown in Figure 11.

In a negative control, or the mixture of PMO No. 1 and PMO No. 2 (Mix 2), the dystrophin protein was not expressed, but in the mixture additionally containing PMO No. 3 targeting hnRNP A1 (Mix 2 + hnRNP A1), the expression of the dystrophin protein corresponding to exon 45 to 55 skipping was confirmed (Figure 11). Mix 2 had the same definition as Mixture 2 used in Test Example 1 and Test Example 2.

[0204]

[Example 3: Production of Antisense Oligomer - (2)]

In the same manner as in Example 1, antisense oligomers shown in Table 12 (PMO Nos. 6 to 33) were synthesized. Theoretical values and actual values measured by ESI-TOR-MS of the molecular weights of the antisense oligomers are also shown. The 5' end of each PMO is Group (1) as in Example 1. The synthesized PMO

was dissolved in water for injection (manufactured by Otsuka Pharmaceutical Factory, Inc.).

[0205]

[Table 12-1]

Table 12

PMO No.	SEQ ID NO:	Target base sequence	Base sequence of PMO	Molecular weight	
				Theoretical value	Actual value
6	1201, 151	H45_(-66)-(-61)_19-40	TGACAACAGTTTGCCGCTGCCCGATTAA	9247.20	9247.20
7	3082	H45_183-206	TTTTCATTCCTATTAGATCTGTCG	7869.71	7869.72
8	4950	H55_(-4)-24	AAAGCAGCCTCTCGCTCACTCACCCTGC	9113.17	9113.17
9	1201, 201	H45_(-66)-(-57)_19-40	TGACAACAGTTTGCCGCTGCCCAAAAGATTAA	10603.68	10603.69
10	1201, 203	H45_(-68)-(-59)_19-40	TGACAACAGTTTGCCGCTGCCCAAGATTAAAC	10579.67	10579.67
11	1201, 205	H45_(-70)-(-61)_19-40	TGACAACAGTTTGCCGCTGCCCGATTAAACAG	10595.67	10595.68
12	1239, 114	H45_(-63)-(-62)_13-35	ACAGTTTGCCGCTGCCCAATGCCAT	8198.85	8198.49
13	1224, 124	H45_(-66)-(-64)_(-3)-20	CCAATGCCATCCTGGAGTTCCTGTAA	8552.97	8553.61
14	1180, 151	H45_(-66)-(-61)_(-3)-19	CAATGCCATCCTGGAGTTCCTGGATTAA	9262.21	9262.21
15	1190, 151	H45_(-66)-(-61)_8-29	TGCCGCTGCCCAATGCCATCCTGATTAA	9183.19	9183.22
16	1212, 151	H45_(-66)-(-61)_30-51	ATTCAATGTTCTGACAACAGTTGATTAA	9284.22	9284.25

[Table 12-2]

17	1222, 151	H45_(-66)-(-61)_40-61	CCCCAGTTGCATTCAATGTTCTGATTAA	9212.19	9212.19
18	3060	H45_161-184	CGCCCTACCTCTTTTTTCTGTCTG	7782.68	7782.67
19	3077	H45_178-201	ATTCCTATTAGATCTGTCGCCCTA	7848.72	7848.99
20	3090	H45_191-214	CTAAAATGTTTTCATTCCTATTAG	7886.73	7886.37
21	3096	H45_197-220	AGTCTGCTAAAATGTTTTCATTCC	7887.73	7887.49
22	3108	H45_209-232	GAAAGCTTAAAAAGTCTGCTAAAA	7996.80	7996.82
23	3119	H45_220-243	ATTCTTCTAAAGAAAGCTTAAAAA	7946.78	7946.79
24	3065	H45_166-189	TCTGTCGCCCTACCTCTTTTTTCT	7757.67	7757.89
25	3087	H45_188-211	AAATGTTTTCATTCCTATTAGATC	7886.73	7886.24
26	3320	H45_167-194	TTAGATCTGTCGCCCTACCTCTTTTTTC	9121.14	9121.27
27	4698	H55_10-32	TTTCTTCCAAAGCAGCCTCTCGC	7479.60	7479.54
28	4702	H55_14-36	TGAGTTTCTTCCAAAGCAGCCTC	7543.62	7543.28
29	4752	H55_13-36	TGAGTTTCTTCCAAAGCAGCCTCT	7873.73	7873.59
30	4923	H55_(-31)-(-4)	CAAAGGACCAAATGTTCAGATGCAATTA	9312.25	9312.25
31	4926	H55_(-28)-(-1)	CTGCAAAGGACCAAATGTTCAGATGCAA	9313.25	9313.24
32	4936	H55_(-18)-10	CTCACTCACCCTGCAAAGGACCAAATGT	9185.21	9185.24
33	4977	H55_24-51	TGTTGCAGTAATCTATGAGTTTCTTCCA	9258.19	9258.19

[0206]

A target base sequence of the antisense oligomer of the present invention was described as "Ha_1_b_1-c_1" or "Ha_2_b_2-c_2_Ha_3_b_3-c_3".

[0207]

"Ha_1" represents the ath exon of the human dystrophin gene, "b_1" represents the 5'-terminal base of the target base sequence, and "c_1" represents the 3'-terminal base of the target base sequence.

When "b_1" and "c_1" are positive integers, "b_1" and "c_1" each represent a base number in the downstream

direction when the 5'-terminal base of the ath exon is counted as the 1st base. On the other hand, when "b_1" and "c_1" are negative numbers, "b_1" and "c_1" each represent a base number in the upstream direction when the 3'-terminal base of the (a - 1)th intron is counted as the 1st base.

[0208]

For example, "H55_(-18)-10" means a base sequence in which the 5' end of the target base sequence is the 18th base in the upstream direction from the 3' end of the 54th intron and the 3' end of the target base sequence is the 10th base in the downstream direction from the 5' end of the 55th intron.

[0209]

"Ha_2_b_2-c_2" which is the first part of "Ha_2_b_2-c_2_Ha_3_b_3-c_3" means the target base sequence of a 3' unit oligomer constituting the antisense oligomer, and the second part "Ha_3_b_3-c_3" means the target base sequence of a 5' unit oligomer constituting the antisense oligomer.

[0210]

When "Ha_2" and "Ha_3" are the same, the "_Ha_3" part may be omitted.

[0211]

For example, "H45_(-66)-(-61)_19-40" or "H45_(-66)-(-61)_H45_19-40" means a base sequence in which the target base sequence of the 3' unit oligomer constituting the antisense oligomer is "H45_(-66)-(-61)" and the

target base sequence of the 5' unit oligomer is "H45_19-40".

[0212]

[Example 4: Test on multi-exon skipping activity of antisense oligomer - (2)]

<Test Example 1>

Assay of exon 45 to 55 multi-exon skipping in normal human-derived myoblasts - (1): induction of multi-exon skipping

[0213]

Procedures

Normal human-derived myoblasts (manufactured by LONZA) were subjected to direct immunofluorescence staining with PE anti-human CD82 antibody (manufactured by BioLegend, hereinafter the same), and the resultant was sorted with Cell Sorter SH800S (manufactured by Sony, hereinafter the same) to obtain CD82-positive normal human-derived myoblasts. The CD82-positive normal human-derived myoblasts were seeded in a collagen I coat microplate 96-well (manufactured by AGC Techno Glass Co., Ltd.) coated with Corning(R) Matrigel Basement Membrane Matrix (manufactured by Corning, hereinafter the same) at 5×10^4/well, and cultured for 1 day under conditions of 37°C and 5% CO_2 in 0.1 mL of a growth medium for normal human myoblasts (DMEM, high glucose, GlutaMAX(TM) Supplement, Pyruvate (manufactured by Thermo Fisher Scientific, hereinafter the same) supplemented with 20%

fetal bovine serum (FBS) (manufactured by Corning, hereinafter the same), 0.1% hBFGF (manufactured by Sigma Aldrich), and 1% penicillin/streptomycin (P/S) (manufactured by Sigma Aldrich, hereinafter the same)). On the next day of the seeding, the medium was changed from the growth medium to 0.2 mL of a differentiation medium for normal human myoblasts (DMEM, High Glucose, GlutaMAX(TM) Supplement, Pyruvate supplemented with 2% horse serum (manufactured by Thermo Fisher Scientific), 1% ITS liquid medium supplement (100x) (manufactured by Sigma Aldrich), and P/S). After culturing for 7 days, transfection was performed with PMO using 6 μM Endo-Porter (manufactured by Gene Tools). PMOs used here are shown in Table 13 below. PMOs targeting the same position in the human dystrophin gene as PMO Nos. 1 to 3 targeting the mouse dystrophin gene were used.

[0214]

[Table 13]

Table 13

PMO No.	Base sequence of PMO (5' to 3')	SEQ ID NO:
6	TGACAACAGTTTGCCGCTGCCCGATTAA	1201, 151
7	TTTTCATTCCTATTAGATCTGTCG	3082
8	AAAGCAGCCTCTCGCTCACTCACCCTGC	4950

[0215]

The used PMOs and concentrations thereof in the medium are shown in Table 14 below.

[Table 14]

Table 14

Condition	PMO No. 6(μM)	PMO No. 7(μM)	PMO No. 8(μM)
1	-	-	-
2	10	10	10
3	20	20	20
4	30	30	30
5	30	-	30
6	30	30	-
7	-	30	30
8	60	-	-
9	-	60	-
10	-	-	60

[0216]

After culturing for another 3 days, the medium was changed to 0.25 mL of a differentiation medium for normal human myoblasts. Seven days after the addition of PMO, the cells were washed once with PBS (manufactured by Takara Bio Inc.), and the total RNA was extracted with RNeasy Micro Kit (manufactured by Qiagen K. K.). 75 μL of Buffer RLT (manufactured by Qiagen K. K.) containing 1% 2-mercaptoethanol (manufactured by Nacalai Tesque, Inc.) was added to the cells, and after the cells were allowed to stand at room temperature for a few minutes to lyse the cells, the total RNA was extracted according to the protocol attached to RNeasy Mini Kit (manufactured by Qiagen K. K.). The concentration of the total RNA extracted was determined using a NanoDrop One C (manufactured by Thermo Fisher Scientific). One-Step RT-PCR was performed with 100 ng of the extracted total RNA using QIAGEN One Step RT-PCR Kit (manufactured by Qiagen

K. K.). A reaction solution was prepared in accordance with the protocol attached to the kit. Veriti 96 Well Thermal Cycler (manufactured by Thermo Fisher Scientific) was used as the thermal cycler. The RT-PCR program used here was as follows.

50°C, 30 mins: reverse transcription reaction

95°C, 15 mins: polymerization activation, reverse transcriptase inactivation, cDNA thermal denaturation

[94°C, 30 seconds; 57°C, 30 seconds; 72°C, 1 minute] x 33 cycles: PCR amplification

72°C, 10 mins: final extension

[0217]

The base sequences of forward primers and reverse primers used in the RT-PCR are shown in Table 15 below.

[Table 15]

Table 15

Primer	Base sequence (5' to 3')	SEQ ID NO:
Forward primer 1	GTTGAGAAATGGCGGCGTTT	5106
Forward primer 2	ATGACATACGCCCAAAGGTG	5107
Reverse primer 1	TGTTGAGAGACTTTTTCCGAAGT	5108
Reverse primer 2	ATTCACCCCCTGCTGAATTT	5109

[0218]

Transcripts (301 bp) having multi-exon skipping of exons 45 to 55 can be detected by a combination of the forward primer 1 and the reverse primer 1. Transcripts (245 bp) of a region of exons 37 to 38 not affected by skipping can be detected by a combination of the forward primer 2 and the reverse primer 2.

[0219]

The reaction product of the PCR was analyzed with MultiNA (manufactured by Shimadzu Corporation). The polynucleotide level "A" of the band with skipping of exons 45 to 55, and the polynucleotide level "B" of the band having no skipping were measured. Based on these measurement values of "A" and "B", the skipping efficiency of exon 45 to 55 skipping was determined by the following equation:

Skipping efficiency of exon 45 to 55 skipping (%) = A /B x 100

[0220]

One-Step RT-PCR was performed for exon 45 skipping in the same manner as in the detection of exon 45 to 55 skipping by using primers shown in Table 16 below.

[Table 16]

Table 16

Primer	Base sequence (5' to 3')	SEQ ID NO:
Forward primer	ATTTGACAGATCTGTTGAGAAATGG	5110
Reverse primer	AGTTGCTGCTCTTTTCCAGGT	5111

[0221]

Transcripts (268 bp) having skipping of exon 45 and transcripts (444 bp) having no skipping can be detected by a combination of the forward primer and the reverse primer.

[0222]

The reaction product of the PCR was analyzed with MultiNA (manufactured by Shimadzu Corporation). The polynucleotide level "A" of the band with skipping of exon 45, and the polynucleotide level "B" of the band having no skipping were measured. Based on these measurement values of "A" and "B", the skipping efficiency of exon 45 skipping was determined by the following equation:

Skipping efficiency of exon 45 skipping (%) = A /(A + B) x 100

[0223]

Results

The results are shown in Figures 12 and 13. It was confirmed that in the normal human cultured cells, exon 45 to 55 skipping is inducted by PMO No. 6 used singly (condition 8) and the mixture containing PMO No. 6 (conditions 2 to 6) (Figure 12). On the other hand, the skipping efficiency of exon 45 skipping was reduced by the mixtures containing, in addition to PMO No. 6, PMO No. 7 targeting hnRNP A1 (conditions 2 to 4, and 6), and single skipping was thus suppressed (Figure 13).

[0224]

<Test Example 2>

Assay of exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 48 to 50 deletion - (1): induction of multi-exon skipping

Procedures

DMD patient-derived myoblasts with exon 48 to 50 deletion obtained from NCNP BioBank were subjected to direct immunofluorescence staining with PE anti-human CD82 antibody and APC anti-human CD56 antibody (manufactured by Milternyi Biotec, hereinafter the same), and the resultant was sorted with Cell Sorter SH800S to obtain CD56- and CD82-positive DMD patient-derived myoblasts with exon 48 to 50 deletion. The DMD patient-derived myoblasts with exon 48 to 50 deletion (CD56-positive and CD82-positive) were seeded in a Corning BioCoat collagen I 48-well transparent microplate coated with Corning(R) Matrigel Basement Membrane Matrix at 5 x 10^4/well, and cultured for 1 day under conditions of 37°C and 5% CO_2 in 0.25 mL of a growth medium for DMD patient-derived myoblasts (Dulbecco's Modified Eagle Medium: Nutrient Mixture F-12 (DMD/F12) (manufactured by Thermo Fisher Scientific, hereinafter the same) supplemented with 20% fetal bovine serum (FBS) and 1% P/S). On the next day of the seeding, the medium was changed from the growth medium to 0.5 mL of a differentiation medium for DMD patient-derived myoblasts (DMEM/F12 supplemented with 2% horse serum, 1% ITS liquid medium supplement (100x), and 1% P/S). After culturing for 6 days in the differentiation medium, transfection was performed with PMO using 6 μM Endo-Porter. The same PMOs as those used in Text Example 1 were used, and concentrations thereof in the medium are shown in Table 17 below.

[0225]

[Table 17]

Table 17

Condition	PMO No. 6 (μM)	PMO No. 7 (μM)	PMO No. 8 (μM)
1	-	-	-
2	10	10	10
3	30	30	30
4	30	-	30

[0226]

After culturing for another 3 days, the medium was changed to 0.5 mL of a differentiation medium. Seven days after the addition of PMO, the total RNA was extracted from the cells in the same manner as in Test Example 1 of Example 2, and One-Step RT-PCR was performed with 200 ng of the extracted total RNA in the same manner as in Test Example 1, and the reaction product of the PCR thus obtained was analyzed to obtain skipping efficiencies of exon 45 to 55 skipping and exon 45 skipping.

[0227]

Results

The results are shown in Figures 14 and 15.

In the DMD patient-derived myoblasts with exon 48 to 50 deletion, exon 45 to 55 skipping was confirmed to be caused by the mixture of PMO No. 6 and PMO No. 8 (condition 4). Exon 45 to 55 skipping was confirmed to be induced also by the mixtures further containing PMO NO. 7 targeting hnRNP A1 (conditions 2 and 3) (Figure

14), but the skipping efficiency of exon 45 skipping was reduced, and single skipping was thus suppressed (Figure 15).

[0228]

<Test Example 3>

Assay of exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 48 to 50 deletion - (2): induction of multi-exon skipping

[0229]

Procedures

DMD patient-derived myoblasts with exon 48 to 50 deletion (CD56-positive and CD82-positive) prepared in the same manner as in Test Example 2 were seeded in a Corning BioCoat collagen I 48-well transparent microplate coated with Corning(R) Matrigel Basement Membrane Matrix at 2 x 10^4/well, and cultured for 3 days under conditions of 37°C and 5% CO_2 in 0.25 mL of a growth medium for DMD patient-derived myoblasts. 3 days after the seeding, the medium was changed from the growth medium to 0.5 mL of a differentiation medium for DMD patient-derived myoblasts. After culturing for 8 days in the differentiation medium, transfection was performed with PMO using 6 μM Endo-Porter. The same PMOs as those used in Text Examples 1 and 2 were used, and concentrations thereof in the medium are shown in Table 18 below.

[0230]

[Table 18]

Table 18

Condition	PMO No. 6 (μM)	PMO No. 7 (μM)	PMO No. 8 (μM)
1	-	-	-
2	20	20	20
3	30	-	30
4	60	-	-

[0231]

After culturing for another 3 days, the medium was changed to 0.5 mL of a differentiation medium. Six days after the addition of PMO, the total RNA was extracted in the same manner as in Test Example 2, and One-Step RT-PCR was performed with 200 ng of the extracted total RNA in the same manner as in Test Examples 1 and 2, and the reaction product of the PCR thus obtained was analyzed to obtain skipping efficiencies of exon 45 to 55 skipping and exon 45 skipping.

[0232]

Results

The results are shown in Figures 16 and 17.

As compared with PMO No. 6 used singly (condition 4), the mixtures additionally containing PMO No. 8 or PMO No. 7 and PMO No. 8 in addition to PMO No. 6 (conditions 2 and 3) increased the skipping efficiency of exon 45 to 55 skipping (Figure 16). On the other hand, the mixture containing PMO No. 7 targeting hnRNP A1 (condition 2) reduced the skipping efficiency of exon 45 skipping, and single skipping was thus suppressed (Figure 17).

[0233]

<Test Example 4>

Assay of exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 48 to 50 deletion - (3): restoration of dystrophin protein by multi-exon skipping

[0234]

Procedures

DMD patient-derived myoblasts with exon 48 to 50 deletion (CD56-positive and CD82-positive) were seeded in a collagen I coat microplate 24-well (manufactured by AGC Techno Glass Co., Ltd., hereinafter the same) coated with Corning(R) Matrigel Basement Membrane Matrix at 1.0 x 10^5/well, and cultured for 1 day under conditions of 37°C and 5% CO_2 in 1 mL of a growth medium for DMD patient-derived myoblasts. On the next day of the seeding, the medium was changed from the growth medium for DMD patient derived myoblasts to a differentiation medium for DMD patient-derived myoblasts. After culturing for 6 days, transfection was performed with PMO using 6 μM Endo-Porter. After culturing for another 3 days, the medium was changed to a differentiation medium, and after culturing for 7 days after the addition of PMO, a cell lysate was prepared in the same manner as in Test Example 4 of Example 2, and a protein concentration in the cell lysate was obtained. Western blotting was performed in the same manner as in Test Example 4 of Example 2 except that the cell lysate was used in an amount corresponding

to 30 μg of protein, that the electrophoresis time was 120 minutes, and that a 250-fold diluted anti-dystrophin antibody (NCL-DYS1) was used, and thus the dystrophin protein was detected. Samples subjected to the electrophoresis are shown in Table 19. As a positive control of dystrophin expression, a lysate of mouse C2C12 cells having been muscle differentiation cultured for 12 days (normal dystrophin control), and a lysate of skeletal muscle of exon 45 to 55 deletion transgenic mouse (exon 45 to 55 deletion dystrophin expression control) were used.

[0235]

[Table 19]

Table 19

Condition	Sample
1	Normal dystrophin control
2	Exon 45 to 55 deletion dystrophin expression control
3	No PMO added
4	30 μM PMO No. 6 + 30 μM PMO No. 7 +30 μM PMO No. 8
5	30 μM PMO No. 6 + 30 μM PMO No. 8
6	10 μM PMO No. 6 + 10 μM PMO No. 7 +10 μM PMO No. 8

[0236]

(Results)

The results are shown in Figure 18.

In the negative control (condition 3), the dystrophin protein was not expressed, but expression of the dystrophin protein corresponding to exon 45 to 55 skipping caused by the mixture of PMO No. 6 and PMO No. 8

(condition 5) and the mixtures of PMO Nos. 6 to 8 (conditions 4 and 6) was confirmed (Figure 18: arrowhead).

[0237]

<Test Example 5>

Assay of exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 46 to 51 deletion - (1): induction of multi-exon skipping

[0238]

Procedures

DMD patient-derived myoblasts with exon 46 to 51 deletion (CD56-positive and CD82-positive) obtained by sorting DMD patient-derived myoblasts with exon 46 to 51 deletion obtained from NCNP BioBank in the same manner as in Test Example 2 were seeded in a Corning BioCoat collagen I 48-well transparent microplate coated with Corning(R) Matrigel Basement Membrane Matrix at 5 x 10^4/well, and cultured for 1 day under conditions of 37°C and 5% CO_2 in 0.25 mL of a growth medium for DMD patient-derived myoblasts. On the next day of the seeding, the medium was changed from the growth medium to 0.3 mL of a differentiation medium for DMD patient-derived myoblasts. After culturing for 6 days in the differentiation medium, transfection was performed with PMO using 6 μM Endo-Porter. The same PMOs as those used in Text Examples 1 to 4 were used, and concentrations thereof in the medium are shown in Table 20 below.

[0239]

[Table 20]

Table 20

Condition	PMO No. 6 (μM)	PMO No. 7 (μM)	PMO No. 8 (μM)
1	-	-	-
2	30	30	30
3	30	-	-

[0240]

After culturing for another 3 days, the medium was changed to 0.3 mL of a differentiation medium. Five days after the addition of PMO, the total RNA was extracted in the same manner as in Test Examples 2 to 3, One-Step RT-PCR was performed with 100 ng of the extracted total RNA in the same manner as in Test Examples 1 to 3, and the reaction product of the PCR thus obtained was analyzed to obtain skipping efficiency of exon 45 to 55 skipping. Besides, One-Step RT-PCR was performed in the same manner as in Test Examples 1 to 3 except that primers shown in Table 21 below were used, and the reaction product of the PCR thus obtained was analyzed to obtain skipping efficiency of exon 45 skipping. Transcripts (162 bp) having exon 45 skipping and transcripts (338 bp) having no skipping can be detected by a combination of the forward primer and the reverse primer.

[0241]

[Table 21]

Table 21

Primer	Base sequence (5' to 3')	SEQ ID NO:
Forward primer	GAGAAATGGCGGCGTTTTCA	5112
Reverse primer	GGGACGCCTCTGTTCCAAAT	5113

[0242]

Results

The results are shown in Figures 19 and 20.

In the DMD patient-derived myoblasts with exon 46 to 51 deletion, exon 45 to 55 skipping was confirmed to be induced by PMO No. 6 used singly (condition 3) and the mixture of PMO Nos. 6 to 8 (condition 2) (Figure 19). The efficiency of exon 45 skipping was reduced by the mixture containing PMO Nos. 6 to 8 (condition 2) as compared with that by PMO No. 6 used singly (condition 3), and single skipping was thus suppressed (Figure 20).

[0243]

<Test Example 6>

Assay of exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 46 to 51 deletion - (2): induction of multi-exon skipping

[0244]

Procedures

DMD patient-derived myoblasts with exon 46 to 51 deletion (CD56-positive and CD82-positive) prepared in the same manner as in Test Example 5 were seeded in a Corning BioCoat collagen I 48-well transparent microplate

coated with Corning(R) Matrigel Basement Membrane Matrix at 6.3 x 10^3/well, and cultured for 4 days under conditions of 37°C and 5% CO_2 in 0.25 mL of a growth medium for DMD patient-derived myoblasts. Four days after the seeding, the medium was changed from the growth medium to 0.3 mL of a differentiation medium for DMD patient-derived myoblasts. After culturing for 7 days in the differentiation medium, transfection was performed with PMO using 6 μM Endo-Porter. The same PMOs as those used in Text Examples 1 to 5 were used, and concentrations thereof in the medium are shown in Table 22 below.

[0245]

[Table 22]

Table 22

Condition	PMO No. 6 (μM)	PMO No. 7 (μM)	PMO No. 8 (μM)
1	-	-	-
2	20	20	20
3	30	-	30
4	-	30	30
5	30	30	-
6	60	-	-

[0246]

After culturing for another 3 days, the medium was changed to 0.3 mL of a differentiation medium. Seven days after the addition of PMO, the total RNA was extracted in the same manner as in Test Examples 2 to 3 and 5, and One-Step RT-PCR was performed in the same

manner as in Test Example 5 except that 100 ng of the extracted total RNA was used, and the reaction product of the PCR thus obtained was analyzed to obtain skipping efficiencies of exon 45 to 55 skipping and exon 45 skipping.

[0247]

Results

The results are shown in Figures 21 and 22. In the DMD patient-derived myoblasts with exon 46 to 51 deletion, exon 45 to 55 skipping was confirmed to be induced by PMO No. 6 used singly (condition 6) and the mixtures containing PMO No. 6 (conditions 2, 3 and 5) (Figure 21). The efficiency of exon 45 skipping was reduced by the mixture containing PMO No. 7 in addition to PMO No. 6 (condition 5) as compared with that by the mixture containing PMO No. 8 in addition to PMO No. 6 (condition 3), and single skipping was thus suppressed (Figure 22).

[0248]

<Test Example 7>

Assay of exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 46 to 51 deletion - (4): restoration of dystrophin protein by multi-exon skipping

[0249]

Procedures

DMD patient-derived myoblasts with exon 46 to 51 deletion (CD56-positive and CD82-positive) were seeded in a collagen I coat microplate 24-well coated with Corning(R) Matrigel Basement Membrane Matrix at 8.0 x 10^4/well, and cultured for 1 day under conditions of 37°C and 5% CO_2 in 1 mL of a growth medium for DMD patient-derived myoblasts. On the next day of the seeding, the medium was changed from the growth medium for DMD patient derived myoblasts to 1 mL of a differentiation medium for DMD patient-derived myoblasts. After culturing 4 days, the medium was changed, and after culturing for 7 days, transfection was performed with PMO using 6 μM Endo-Porter. After culturing for another 3 days, the medium was changed to a differentiation medium, and after culturing for 7 days after the addition of PMO, a cell lysate was prepared in the same manner as in Test Example 4 of Example 2 and Test Example 4 of the present example, and Western blotting was performed in the same manner as in Test Example 4 of Example 2 and Test Example 4 of the present example except that the cell lysate was used in an amount corresponding to 24 μg of protein to detect the dystrophin protein. Samples subjected to the electrophoresis are shown in Table 23 below.

[0250]

[Table 23]

Table 23

Condition	Sample
1	Normal dystrophin control
2	Exon 45 to 55 deletion dystrophin expression control
3	No PMO added
4	30 μM PMO No. 6 + 30 μM PMO No. 7 +30 μM PMO No. 8
5	30 μM PMO No. 6 + 30 μM PMO No. 8

[0251]

(Results)

The results are shown in Figure 23.

In the negative control (condition 3), the dystrophin protein was not expressed, but expression of the dystrophin protein corresponding to exon 45 to 55 skipping caused by the mixture of PMO No. 6 and PMO No. 8 (condition 5) and the mixture of PMO Nos. 6 to 8 (condition 4) was confirmed (Figure 23: arrowhead).

[0252]

<Test Example 8>

Assay of exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion - (1): study of first antisense oligomer - (1)

[0253]

Procedures

DMD patient-derived myoblasts with exon 51 deletion (CD-56 positive, CD-82 positive) obtained by sorting DMD patient-derived myoblasts with exon 51 deletion obtained from NCNP BioBank in the same manner as in Example 3 and 6 were seeded in a collagen I coat microplate 24-well

(manufactured by AGC Techno Glass Co., Ltd.) coated with Corning(R) Matrigel Basement Membrane Matrix at 5 x 10^4/well, and cultured for 3 days under conditions of 37°C and 5% CO_2 in 0.5 mL of a growth medium for DMD patient-derived myoblasts. Three days after the seeding, the medium was changed from the growth medium to 0.5 mL of a differentiation medium for DMD patient-derived myoblasts. After culturing for 4 days in the differentiation medium for DMD patient-derived myoblasts, transfection was performed with PMO using 6 μM Endo-Porter. In addition to the PMOs used in Text Examples 1 to 7, PMOs shown in Table 24 below were also used.

[0254]

[Table 24]

Table 24

PMO No.	Base sequence of PMO (5' to 3')	SEQ ID NO:
9	TGACAACAGTTTGCCGCTGCCCAAAAGATTAA	1201, 201
10	TGACAACAGTTTGCCGCTGCCCAAGATTAAAC	1201, 203
11	TGACAACAGTTTGCCGCTGCCCGATTAAACAG	1201, 205

[0255]

The PMOs were added in concentrations in the medium shown in Table 25 below.

[0256]

[Table 25]

Table 25

Condition	PMO
1	No PMO added
2	30 μM PMO No. 6 + 30 μM PMO No. 8
3	20 μM PMO No. 6 + 20 μM PMO No. 7 + 20 μM PMO No. 8
4	30 μM PMO No. 9 + 30 μM PMO No. 8
5	20 μM PMO No. 9 + 20 μM PMO No. 7 + 20 μM PMO No. 8
6	30 μM PMO No. 10 + 30 μM PMO No. 8
7	20 μM PMO No. 10 + 20 μM PMO No. 7 + 20 μM PMO No. 8
8	30 μM PMO No. 11 + 30 μM PMO No. 8
9	20 μM PMO No. 11 + 20 μM PMO No. 7 + 20 μM PMO No. 8

[0257]

After culturing for another 3 days, the medium was changed to 0.5 mL of a differentiation medium for DMD patient-derived myoblasts. Seven days after the addition of PMO, the total RNA was extracted in the same manner as in Test Examples 2, 3, 5, and 6, One-Step RT-PCR was performed with 200 ng of the extracted total RNA in the same manner as in Test Examples 1 to 3, and the reaction product of the PCR thus obtained was analyzed to obtain skipping efficiencies of exon 45 to 55 skipping and exon 45 skipping.

[0258]

Results

The results are shown in Figures 24 and 25. In the DMD patient-derived myoblasts with exon 51 deletion, exon 45 to 55 skipping was confirmed to be induced by the mixture of PMO No. 6 and PMO No. 8 (condition 2) (Figure 24). Exon 45 to 55 skipping was also confirmed to be

induced by the mixture containing, in addition to PMO No. 6 and PMO No. 8, PMO No. 7 targeting hnRNPA1 (condition 3) (Figure 24). Besides, exon 45 to 55 skipping was confirmed to be induced in the conditions 4, 6 and 8 in which PMO Nos. 9 to 11 were added as the first antisense oligomer together with PMO No. 8. Exon 45 to 55 skipping was also confirmed to be induced in the conditions 5, 7, and 9 in which PMO No. 7 targeting hnRNP A1 was further added (Figure 24), but the skipping efficiency of exon 45 skipping was reduced, and single skipping was thus suppressed (Figure 25).

[0259]

<Test Example 9>

Assay of exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion - (2): study of first antisense oligomer - (2)

[0260]

Procedures

DMD patient-derived myoblasts with exon 51 deletion (CD-56 positive, CD-82 positive) prepared in the same manner as in Test Example 8 were seeded in a Corning BioCoat collagen I 48-well transparent microplate coated with Corning(R) Matrigel Basement Membrane Matrix at 5 x 10^4/well, and cultured for 1 day under conditions of 37°C and 5% CO_2 in 0.25 mL of a growth medium for DMD patient-derived myoblasts. On the next day of the seeding, the medium was changed from the growth medium to 0.25 mL of a

differentiation medium for DMD patient-derived myoblasts. After culturing for 7 days in the differentiation medium for DMD patient-derived myoblasts, transfection was performed with PMO using 6 μM Endo-Porter. In addition to the PMOs used in Text Examples 1 to 7, PMOs shown in Table 26 below were used.

[0261]

[Table 26]

Table 26

PMO No.	Base sequence of PMO (5' to 3')	SEQ ID NO:
12	ACAGTTTGCCGCTGCCCAATGCCAT	1239, 114
13	CCAATGCCATCCTGGAGTTCCTGTAA	1224, 124
14	CAATGCCATCCTGGAGTTCCTGGATTAA	1180, 151
15	TGCCGCTGCCCAATGCCATCCTGATTAA	1190, 151
16	ATTCAATGTTCTGACAACAGTTGATTAA	1212, 151
17	CCCCAGTTGCATTCAATGTTCTGATTAA	1222, 151

[0262]

The PMOs were added in concentrations in the medium shown in Table 27 below.

[Table 27]

Table 27

Condition	PMO
1	No PMO added
2	30 μM PMO No. 6 + 30 μM PMO No. 8
3	20 μM PMO No. 6 + 20 μM PMO No. 7 + 20 μM PMO No. 8
4	30 μM PMO No. 12 + 30 μM PMO No. 8
5	20 μM PMO No. 12 + 20 μM PMO No. 7 + 20 μM PMO No. 8
6	30 μM PMO No. 13 + 30 μM PMO No. 8
7	20 μM PMO No. 13 + 20 μM PMO No. 7 + 20 μM PMO No. 8
8	30 μM PMO No. 14 + 30 μM PMO No. 8
9	20 μM PMO No. 14 + 20 μM PMO No. 7 + 20 μM PMO No. 8
10	30 μM PMO No. 15 + 30 μM PMO No. 8
11	20 μM PMO No. 15 + 20 μM PMO No. 7 + 20 μM PMO No. 8
12	30 μM PMO No. 16 + 30 μM PMO No. 8
13	20 μM PMO No. 16 + 20 μM PMO No. 7 + 20 μM PMO No. 8
14	30 μM PMO No. 17 + 30 μM PMO No. 8
15	20 μM PMO No. 17 + 20 μM PMO No. 7 + 20 μM PMO No. 8

[0263]

After culturing for another 3 days, the medium was changed to 0.3 mL of a differentiation medium for DMD patient-derived myoblasts. Seven days after the addition of PMO, the total RNA was extracted in the same manner as in Test Examples 2, 3, 5, 6, and 8, One-Step RT-PCR was performed with 200 ng of the extracted total RNA in the same manner as in Test Examples 1 to 3 and 8, and the reaction product of the PCR thus obtained was analyzed to obtain skipping efficiencies of exon 45 to 55 skipping and exon 45 skipping.

[0264]

Results

The results are shown in Figures 26 and 27. Exon 45 to 55 skipping was confirmed to be induced also in the conditions 4, 6, 8, and 10 in which PMO Nos. 12 to 17 were added as the first antisense oligomer together with PMO No. 8. Exon 45 to 55 skipping was confirmed to be induced also in the conditions 5, 7, 9, and 11 in which PMO No. 7 targeting hnRNP A1 was further added (Figure 26), but the skipping efficiency of exon 45 skipping was reduced, and single skipping was thus suppressed (Figure 27).

[0265]

<Test Example 10>

Assay of exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion - (3): study of third antisense oligomer - (1)

[0266]

Procedures

DMD patient-derived myoblasts with exon 51 deletion (CD-56 positive, CD-82 positive) prepared in the same manner as in Test Examples 8 and 9 were seeded in a Corning BioCoat collagen I 48-well transparent microplate coated with Corning(R) Matrigel Basement Membrane Matrix at 5 x 10^4/well, and cultured for 1 day under conditions of 37°C and 5% CO_2 in 0.25 mL of a growth medium for DMD patient-derived myoblasts. On the next day of the seeding, the medium was changed from the growth medium to 0.25 mL of a differentiation medium for DMD patient-

derived myoblasts. After culturing for 7 days in the differentiation medium for DMD patient-derived myoblasts, transfection was performed with PMO using 6 μM Endo-Porter. In addition to the PMOs used in Text Examples 1 to 7, PMOs shown in Table 28 below were used.

[0267]

[Table 28]

Table 28

PMO No.	Base sequence of PMO (5' to 3')	SEQ ID NO:
18	CGCCCTACCTCTTTTTTCTGTCTG	3060
19	ATTCCTATTAGATCTGTCGCCCTA	3077
20	CTAAAATGTTTTCATTCCTATTAG	3090
21	AGTCTGCTAAAATGTTTTCATTCC	3096
22	GAAAGCTTAAAAAGTCTGCTAAAA	3108
23	ATTCTTCTAAAGAAAGCTTAAAAA	3119

[0268]

The PMOs were added in concentrations in the medium shown in Table 29 below.

[0269]

[Table 29]

Table 29

Condition	PMO
1	No PMO added
2	30 μM PMO No. 6 + 30 μM PMO No. 8
3	20 μM PMO No. 6 + 20 μM PMO No. 18 + 20 μM PMO No. 8
4	20 μM PMO No. 6 + 20 μM PMO No. 19 + 20 μM PMO No. 8
5	20 μM PMO No. 6 + 20 μM PMO No. 7 + 20 μM PMO No. 8
6	20 μM PMO No. 6 + 20 μM PMO No. 20 + 20 μM PMO No. 8
7	20 μM PMO No. 6 + 20 μM PMO No. 21 + 20 μM PMO No. 8
8	20 μM PMO No. 6 + 20 μM PMO No. 22 + 20 μM PMO No. 8
9	20 μM PMO No. 6 + 20 μM PMO No. 23 + 20 μM PMO No. 8

[0270]

After culturing for another 3 days, the medium was changed to 0.3 mL of a differentiation medium for DMD patient-derived myoblasts. Seven days after the addition of PMO, the total RNA was extracted in the same manner as in Test Examples 2, 3, 5, 6, 8, and 9, One-Step RT-PCR was performed with 200 ng of the extracted total RNA in the same manner as in Test Examples 1 to 3, 8, and 9, and the reaction product of the PCR thus obtained was analyzed to obtain skipping efficiencies of exon 45 to 55 skipping and exon 45 skipping.

[0271]

Results

The results are shown in Figures 28 and 29. As a result of adding PMO Nos. 20 to 23 as the third antisense oligomer to PMO No. 6 and PMO No. 8, exon 45 to 55 skipping was confirmed to be induced to the same extent as in a case where PMO No. 7 was added (conditions 5)

(Figure 28). Exon 45 skipping was reduced, and single skipping tended to be suppressed (Figure 29). On the other hand, although exon 45 skipping efficiency was not reduced by the mixture containing PMO Nos. 18 and 19 (conditions 3 and 4) as compared with the mixture containing PMO No. 7 (condition 5), exon 45 to 55 skipping was confirmed to be more highly induced as compared with that in a negative control (condition 1).

[0272]

<Test Example 11>

Assay of exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion - (4): study of third antisense oligomer - (2)

[0273]

Procedures

DMD patient-derived myoblasts with exon 51 deletion (CD-56 positive, CD-82 positive) prepared in the same manner as in Test Examples 8 to 10 were seeded in a Corning BioCoat collagen I 48-well transparent microplate coated with Corning(R) Matrigel Basement Membrane Matrix at 5 x 10^4/well, and cultured for 1 day under conditions of 37°C and 5% CO_2 in 0.25 mL of a growth medium for DMD patient-derived myoblasts. On the next day of the seeding, the medium was changed from the growth medium to 0.25 mL of a differentiation medium for DMD patient-derived myoblasts. After culturing for 3 days in the differentiation medium for DMD patient-derived myoblasts,

transfection was performed with PMO using 6 μM Endo-Porter. In addition to the PMOs used in Text Examples 1 to 7, PMOs shown in Table 30 below were used.

[0274]

[Table 30]

Table 30

PMO No.	Base sequence of PMO (5' to 3')	SEQ ID NO:
19	ATTCCTATTAGATCTGTCGCCCTA	3077
20	CTAAAATGTTTTCATTCCTATTAG	3090
21	AGTCTGCTAAAATGTTTTCATTCC	3096
24	TCTGTCGCCCTACCTCTTTTTTCT	3065
25	AAATGTTTTCATTCCTATTAGATC	3087
26	TTAGATCTGTCGCCCTACCTCTTTTTTC	3320

[0275]

The PMOs were added in concentrations in the medium shown in Table 31 below.

[Table 31]

Table 31

Condition	PMO
1	No PMO added
2	20 μM PMO No. 6 + 20 μM PMO No. 24 + 20 μM PMO No. 8
3	20 μM PMO No. 6 + 20 μM PMO No. 19 + 20 μM PMO No. 8
4	20 μM PMO No. 6 + 20 μM PMO No. 7 + 20 μM PMO No. 8
5	20 μM PMO No. 6 + 20 μM PMO No. 25 + 20 μM PMO No. 8
6	20 μM PMO No. 6 + 20 μM PMO No. 20 + 20 μM PMO No. 8
7	20 μM PMO No. 6 + 20 μM PMO No. 21 + 20 μM PMO No. 8
8	20 μM PMO No. 6 + 20 μM PMO No. 26 + 20 μM PMO No. 8

[0276]

After culturing for another 3 days, the medium was changed to 0.3 mL of a differentiation medium for DMD

patient-derived myoblasts. Seven days after the addition of PMO, the total RNA was extracted in the same manner as in Test Examples 2, 3, 5, 6, and 8 to 10, One-Step RT-PCR was performed with 200 ng of the extracted total RNA in the same manner as in Test Examples 1 to 3 and 8 to 10, and the reaction product of the PCR thus obtained was analyzed to obtain skipping efficiencies of exon 45 to 55 skipping and exon 45 skipping.

[0277]

Results

The results are shown in Figures 30 and 31. As a result of adding PMO Nos. 24 to 26 as the third antisense oligomer to PMO No. 6 and PMO No. 8 (conditions 2, 5, and 8), exon 45 to 55 skipping efficiency was reduced when PMO Nos. 24 and 26 were added (conditions 2 and 8) as compared with a case where PMO No. 7 was added (condition 4), but exon 45 to 55 skipping was confirmed to be induced to the same extent when PMO No. 25 was added (condition 5) (Figure 30). Exon 45 skipping efficiency was reduced when PMO No. 25 was added (condition 5), and single skipping was thus suppressed (Figure 31).

[0278]

<Test Example 12>

Assay of exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion - (5): study of second antisense oligomer - (1)

[0279]

Procedures

DMD patient-derived myoblasts with exon 51 deletion (CD-56 positive, CD-82 positive) prepared in the same manner as in Test Examples 8 to 11 were seeded in a Corning BioCoat collagen I 48-well transparent microplate coated with Corning(R) Matrigel Basement Membrane Matrix at 5 x 10^4/well, and cultured for 1 day under conditions of 37°C and 5% CO_2 in 0.25 mL of a growth medium for DMD patient-derived myoblasts. On the next day of the seeding, the medium was changed from the growth medium to 0.25 mL of a differentiation medium for DMD patient-derived myoblasts. After culturing for 7 days in the differentiation medium for DMD patient-derived myoblasts, transfection was performed with PMO using 6 μM Endo-Porter.

[0280]

In addition to the PMOs used in Text Examples 1 to 7, PMOs shown in Table 32 below were used.

[Table 32]

Table 32

PMO No.	Base sequence of PMO (5' to 3')	SEQ ID NO:
27	TTTCTTCCAAAGCAGCCTCTCGC	4698
28	TGAGTTTCTTCCAAAGCAGCCTC	4702
29	TGAGTTTCTTCCAAAGCAGCCTCT	4752
30	CAAAGGACCAAATGTTCAGATGCAATTA	4923
31	CTGCAAAGGACCAAATGTTCAGATGCAA	4926
32	CTCACTCACCCTGCAAAGGACCAAATGT	4936
33	TGTTGCAGTAATCTATGAGTTTCTTCCA	4977

[0281]

The PMOs were added in concentrations in the medium shown in Table 33 below.

[Table 33]

Table 33

Condition	PMO
1	No PMO added
2	30 μM PMO No. 6 + 30 μM PMO No. 27
3	30 μM PMO No. 6 + 30 μM PMO No. 28
4	30 μM PMO No. 6 + 30 μM PMO No. 29
5	30 μM PMO No. 6 + 30 μM PMO No. 30
6	30 μM PMO No. 6 + 30 μM PMO No. 31
7	30 μM PMO No. 6 + 30 μM PMO No. 32
8	30 μM PMO No. 6 + 30 μM PMO No. 8
9	30 μM PMO No. 6 + 30 μM PMO No. 33
10	20 μM PMO No. 6 + 20 μM PMO No. 7 + 20 μM PMO No. 8

[0282]

After culturing for another 3 days, the medium was changed to 0.3 mL of a differentiation medium for DMD patient-derived myoblasts. Seven days after the addition of PMO, the total RNA was extracted in the same manner as in Test Examples 2, 3, 5, 6, and 8 to 11, One-Step RT-PCR was performed with 200 ng of the extracted total RNA in the same manner as in Test Examples 1 to 3 and 8 to 11, and the reaction product of the PCR thus obtained was analyzed to obtain skipping efficiencies of exon 45 to 55 skipping and exon 45 skipping.

[0283]

Results

The results are shown in Figures 32 and 33.

As a result of adding PMO Nos. 27 to 33 as the second antisense oligomer together with PMO No. 6 (conditions 2 to 7, and 9), exon 45 to 55 skipping was confirmed to be induced to the same extent as in a case where PMO No. 8 was added (condition 8) (Figure 32). Even when the second antisense oligomer was changed, exon 45 skipping efficiency was not reduced, and single skipping was not suppressed (Figure 33).

[0284]

<Test Example 13>

Assay of exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion - (6): study of second antisense oligomer - (2)

[0285]

Procedures

DMD patient-derived myoblasts with exon 51 deletion (CD-56 positive, CD-82 positive) prepared in the same manner as in Test Examples 8 to 12 were seeded in a Corning BioCoat collagen I 48-well transparent microplate coated with Corning(R) Matrigel Basement Membrane Matrix at 5 x 10^4/well, and cultured for 1 day under conditions of 37°C and 5% CO_2 in 0.25 mL of a growth medium for DMD patient-derived myoblasts. On the next day of the seeding, the medium was changed from the growth medium to 0.25 mL of a differentiation medium for DMD patient-derived myoblasts. After culturing for 3 days in the

differentiation medium for DMD patient-derived myoblasts, transfection was performed with PMO using 6 μM Endo-Porter. The PMOs used in Text Example 12 were used in concentrations in the medium shown in Table 34 below.

[0286]

[Table 34]

Table 34

Condition	PMO
1	No PMO added
2	20 μM PMO No. 6 + 20 μM PMO No. 7 + 20 μM PMO No. 27
3	20 μM PMO No. 6 + 20 μM PMO No. 7 + 20 μM PMO No. 28
4	20 μM PMO No. 6 + 20 μM PMO No. 7 + 20 μM PMO No. 29
5	20 μM PMO No. 6 + 20 μM PMO No. 7 + 20 μM PMO No. 32
6	20 μM PMO No. 6 + 20 μM PMO No. 7 + 20 μM PMO No. 8

[0287]

After culturing for another 3 days, the medium was changed to 0.3 mL of a differentiation medium for DMD patient-derived myoblasts. Seven days after the addition of PMO, the total RNA was extracted in the same manner as in Test Examples 2, 3, 5, 6, and 8 to 12, One-Step RT-PCR was performed with 200 ng of the extracted total RNA in the same manner as in Test Examples 1 to 3 and 8 to 12, and the reaction product of the PCR thus obtained was analyzed to obtain skipping efficiencies of exon 45 to 55 skipping and exon 45 skipping.

[0288]

Results

The results are shown in Figures 34 and 35. As a result of respectively adding PMO Nos. 27 to 29 and 32 together with PMO No. 6 and PMO No. 7 (conditions 2 to 5), exon 45 to 55 skipping was confirmed to be induced to the same extent as in a case where PMO No. 8 was added (condition 6) (Figure 34). The induction of exon 45 skipping was little confirmed excluding a case where PMO No. 32 was added (condition 5), and single skipping was thus suppressed (Figure 35).

[0289]

<Test Example 14>

Assay of exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion - (7): study of second antisense oligomer - (3)

[0290]

Procedures

DMD patient-derived myoblasts with exon 51 deletion (CD-56 positive, CD-82 positive) prepared in the same manner as in Test Examples 8 to 13 were seeded in a Corning BioCoat collagen I 48-well transparent microplate coated with Corning(R) Matrigel Basement Membrane Matrix at 5 x 10^4/well, and cultured for 1 day under conditions of 37°C and 5% CO_2 in 0.25 mL of a growth medium for DMD patient-derived myoblasts. On the next day of the seeding, the medium was changed from the growth medium to 0.25 mL of a differentiation medium for DMD patient-derived myoblasts. After culturing for 7 days in the

differentiation medium for DMD patient-derived myoblasts, transfection was performed with PMO using 6 μM Endo-Porter. The PMOs used in Text Example were added in concentrations in the medium shown in Table 35 below.

[0291]

[Table 35]

Table 35

Condition	PMO
1	No PMO added
2	30 μM PMO No. 6 + 30 μM PMO No. 8
3	20 μM PMO No. 6 + 20 μM PMO No. 7 + 20 μM PMO No. 30
4	20 μM PMO No. 6 + 20 μM PMO No. 7 + 20 μM PMO No. 31
5	20 μM PMO No. 6 + 20 μM PMO No. 7 + 20 μM PMO No. 8
6	20 μM PMO No. 6 + 20 μM PMO No. 7 + 20 μM PMO No. 33

[0292]

After culturing for another 3 days, the medium was changed to 0.3 mL of a differentiation medium for DMD patient-derived myoblasts. Seven days after the addition of PMO, the total RNA was extracted in the same manner as in Test Examples 2, 3, 5, 6, and 8 to 13, One-Step RT-PCR was performed with 200 ng of the extracted total RNA in the same manner as in Test Examples 1 to 3 and 8 to 13, and the reaction product of the PCR thus obtained was analyzed to obtain skipping efficiencies of exon 45 to 55 skipping and exon 45 skipping.

[0293]

Results

The results are shown in Figures 36 and 37.

As a result of respectively adding PMO No. 30, 31, or 33 as the second antisense oligomer together with PMO No. 6 and PMO No. 7 (conditions 3, 4, and 6), exon 45 to 55 skipping was confirmed to the same extent as in a case where PMO No. 8 was added (condition 5) (Figure 36). As compared with a case where only PMO No. 6 and PMO No. 8 were added (condition 2), the skipping efficiency of exon 45 skipping was all reduced, and single skipping was thus suppressed (Figure 37).

[0294]

<Test Example 15>

Assay of exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion - (8): restoration of dystrophin protein by multi-exon skipping

[0295]

Procedures

DMD patient-derived myoblasts with exon 51 deletion (CD56-positive and CD82-positive) were seeded in a collagen I coat microplate 24-well (manufactured by AGC Techno Glass Co., Ltd.) coated with Corning(R) Matrigel Basement Membrane Matrix at 2.0 x 10^5/well, and cultured for 1 day under conditions of 37°C and 5% CO_2 in 1 mL of a growth medium for DMD patient-derived myoblasts. On the next day of the seeding, the medium was changed from the growth medium for DMD patient derived myoblasts to a differentiation medium for DMD patient-derived myoblasts. After culturing for 3 days in the differentiation medium,

transfection was performed with PMO using 6 μM Endo-Porter. After culturing for 3 days, the medium was changed to a differentiation medium. After culturing for 7 days or 11 days after the addition of PMO, Western blotting was performed in the same manner as in Test Examples 4 and 7 of the present example to detect the dystrophin protein. Samples subjected to electrophoresis are shown in Table 36. As a positive control of dystrophin expression, a lysate of mouse C2C12 cells having been muscle differentiation cultured for 12 days (normal dystrophin control), and a lysate of skeletal muscle of exon 45 to 55 deletion transgenic mouse (exon 45 to 55 deletion dystrophin expression control) were used.

[0296]

[Table 36]

Table 36

Condition	Sample	Collection date
1	Normal dystrophin control	
2	Exon 45 to 55 deletion dystrophin expression control	
3	No PMO added	7 days after PMO addition
4	30 μM PMO No. 6 + 30 μM PMO No. 7 +30 μM PMO No. 8	
5	30 μM PMO No. 6 + 30 μM PMO No. 8	
6	No PMO added	11 days after PMO addition
7	30 μM PMO No. 6 + 30 μM PMO No. 7 +30 μM PMO No. 8	
8	30 μM PMO No. 6 + 30 μM PMO No. 8	
9	30 μM PMO No. 6	

[0297]

(Results)

The results are shown in Figure 38. In the negative control (conditions 3 and 6), the band was not confirmed in the same position (Figure 38: arrowhead) as the band of exon 45 to 55 deletion dystrophin-positive control (condition 2), but in the samples transfected with a cocktail of PMOs (conditions 4, 5, 7, and 8), expression of the dystrophin protein corresponding to exon 45 to 55 skipping was confirmed (Figure 38: arrowhead).

[0298]

<Test Example 16>

Assay of exon 45 to 55 multi-exon skipping in DMD patient-derived myoblasts with exon 51 deletion - (9): restoration of dystrophin protein by multi-exon skipping - (2)

[0299]

Procedures

DMD patient-derived myoblasts with exon 51 deletion (CD56-positive and CD82-positive) prepared in the same manner as in Test Examples 8 to 15 were seeded in a collagen I coat microplate 24-well (manufactured by AGC Techno Glass Co., Ltd.) coated with Corning(R) Matrigel Basement Membrane Matrix at 2.0 x 10^5/well, and cultured for 1 day under conditions of 37°C and 5% CO_2 in 1 mL of a growth medium for DMD patient-derived myoblasts. On the next day of the seeding, the medium was changed from the growth medium for DMD patient-derived myoblasts to a differentiation medium for DMD patient-derived myoblasts.

After culturing for 7 days in the differentiation medium, transfection was performed with PMO using 6 μM Endo-Porter. The PMOs used here are shown in Table 37 below.

[0300]

[Table 37]

Table 37

PMO No.	Base sequence of PMO (5' to 3')	SEQ ID NO:
6	TGACAACAGTTTGCCGCTGCCCGATTAA	1201, 151
7	TTTTCATTCCTATTAGATCTGTCG	3082
8	AAAGCAGCCTCTCGCTCACTCACCCTGC	4950
14	CAATGCCATCCTGGAGTTCCTGGATTAA	1180, 151
21	AGTCTGCTAAAATGTTTTCATTCC	3096
33	TGTTGCAGTAATCTATGAGTTTCTTCCA	4977

[0301]

After culturing for another 3 days, the medium was changed to a differentiation medium. After culturing for 7 days after the addition of PMO, Western blotting was performed in the same manner as in Test Examples 4, 7, and 15 of the present example to detect the dystrophin protein. Samples subjected to the electrophoresis are shown in Table 38 below.

[0302]

[Table 38]

Table 38

Condition	Sample
1	Normal dystrophin control
2	Exon 45 to 55 deletion dystrophin expression control
3	No PMO added
4	30 μM PMO No. 14 + 30 μM PMO No. 8
5	20 μM PMO No. 14 + 20 μM PMO No. 7 + 20 μM PMO No. 8
6	30 μM PMO No. 6 + 30 μM PMO No. 33
7	20 μM PMO No. 6 + 20 μM PMO No. 21 + 20 μM PMO No. 33
8	20 μM PMO No. 14 + 20 μM PMO No. 21 + 20 μM PMO No. 33

[0303]

(Results)

The results are shown in Figure 39.

In the negative control (condition 3), the band was not confirmed in the same position as the band of exon 45 to 55 deletion dystrophin-positive control (condition 2), but in the samples transfected with a cocktail of PMOs (conditions 4, 5, and 6), expression of the dystrophin protein corresponding to exon 45 to 55 skipping was confirmed (Figure 39: arrowhead).

Claims

[Claim 1]

A combination of antisense oligomers or pharmaceutically acceptable salts thereof, or hydrates thereof which cause simultaneous skipping of any two or more numerically consecutive exons selected from the group consisting of the 45th exon to the 55th exon in human dystrophin pre-mRNA,

the combination comprising:

(i) a first antisense oligomer or a pharmaceutically acceptable salt thereof, or a hydrate thereof, comprising:

a first unit oligomer comprising a base sequence complementary to a base sequence consisting of a base sequence of 11 bases in the upstream direction from the 3' end of the 44th intron and a base sequence of 69 bases in the downstream direction from the 5' end of the 45th exon in the human dystrophin pre-mRNA, or a partial base sequence thereof; and

a second unit oligomer comprising a base sequence complementary to a base sequence of from the 52nd to 75th bases in the upstream direction from the 3' end of the 44th intron in the human dystrophin pre-mRNA, or a partial base sequence thereof; and

(ii) a second antisense oligomer or a pharmaceutically acceptable salt thereof, or a hydrate

thereof, comprising a base sequence complementary to a base sequence consisting of a base sequence of 33 bases in the upstream direction from the 3' end of the 54th intron and a base sequence of 53 bases in the downstream direction from the 5' end of the 55th exon in the human dystrophin pre-mRNA, or a partial base sequence thereof.

[Claim 2]

The combination according to claim 1, wherein

the first unit oligomer comprises a base sequence complementary to consecutive 15 to 30 bases of a base sequence consisting of a base sequence of 11 bases in the upstream direction from the 3' end of the 44th intron and a base sequence of 69 bases in the downstream direction from the 5' end of the 45th exon in the human dystrophin pre-mRNA,

the second unit oligomer comprises a base sequence complementary to consecutive 1 to 10 bases of a base sequence of from the 52nd to 75th bases in the upstream direction from the 3' end of the 44th intron in the human dystrophin pre-mRNA, and

the second antisense oligomer comprises a base sequence complementary to consecutive 15 to 30 bases of a base sequence consisting of a base sequence of 33 bases in the upstream direction from the 3' end of the 54th intron and a base sequence of 53 bases in the downstream direction from the 5' end of the 55th exon in the human dystrophin pre-mRNA.

[Claim 3]

The combination according to claim 1 or 2, wherein

the first unit oligomer comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 211 to 906, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c), and/or

the second unit oligomer comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1 to 105, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

[Claim 4]

The combination according to any one of claims 1 to 3, wherein

the second antisense oligomer comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 3507 to 4298, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

[Claim 5]

The combination according to any one of claims 1 to 4, wherein the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, the first unit oligomer comprises any one base sequence selected from SEQ ID NOs: 907 to 1602, the second unit oligomer comprises any one base sequence selected from SEQ ID NOs: 106 to 210, and the second antisense oligomer comprises any one base sequence selected from SEQ ID NOs: 4299 to 5090.

[Claim 6]

The combination according to any one of claims 1 to 5, wherein the first unit oligomer comprises any one base sequence selected from the group consisting of SEQ ID NOs: 1180, 1190, 1201, 1212, 1222, 1224, and 1239.

[Claim 7]

The combination according to any one of claims 1 to 6, wherein the second unit oligomer comprises any one base sequence selected from the group consisting of SEQ ID NOs: 114, 124, 151, 201, 203, and 205.

[Claim 8]

The combination according to claim 6 or 7, wherein

the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, and

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, and the second unit oligomer comprises a base sequence of SEQ ID NO: 151,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, and the second unit oligomer comprises a base sequence of SEQ ID NO: 201,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, and the second unit oligomer comprises a base sequence of SEQ ID NO: 203,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, and the second unit oligomer comprises a base sequence of SEQ ID NO: 205,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1239, and the second unit oligomer comprises a base sequence of SEQ ID NO: 114,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1224, and the second unit oligomer comprises a base sequence of SEQ ID NO: 124,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1180, and the second unit oligomer comprises a base sequence of SEQ ID NO: 151,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1190, and the second unit oligomer comprises a base sequence of SEQ ID NO: 151,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1212, and the second unit oligomer comprises a base sequence of SEQ ID NO: 151, or

the first unit oligomer comprises a base sequence of SEQ ID NO: 1222, and the second unit oligomer comprises a base sequence of SEQ ID NO: 151.

[Claim 9]

The combination according to any one of claims 1 to 8, wherein the second antisense oligomer comprises a base sequence selected from the group consisting of SEQ ID NOs: 4698, 4702, 4752, 4923, 4926, 4936, 4950, and 4977.

[Claim 10]

The combination according to any one of claims 1 to 9, wherein

the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, and

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 201, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 203, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 205, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1239, the second unit oligomer comprises a base sequence of SEQ ID NO: 114, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1224, the second unit oligomer comprises a base sequence of SEQ ID NO: 124, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1180, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1190, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1212, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1222, the second unit oligomer comprises a

base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4698,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4702,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4752,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4923,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4926,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4936,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4977, or

the first unit oligomer comprises a base sequence of SEQ ID NO: 1180, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4977.

[Claim 11]

The combination according to any one of claims 5 to 10, wherein the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, and the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950.

[Claim 12]

The combination according to any one of claims 1 to 11, further comprising:

(iii) a third antisense oligomer or a pharmaceutically acceptable salt thereof, or a hydrate thereof, comprising a base sequence complementary to a base sequence consisting of a base sequence of 23 bases in the upstream direction from the 3' end of the 45th exon and a base sequence of 73 bases in the downstream direction from the 5' end of the 45th intron in the human dystrophin pre-mRNA, or a partial base sequence thereof.

[Claim 13]

The combination according to claim 12, wherein the third antisense oligomer comprises a base sequence complementary to consecutive 15 to 30 bases of a base sequence consisting of a base sequence of 23 bases in the upstream direction from the 3' end of the 45th exon and a base sequence of 73 bases in the downstream direction from the 5' end of the 45th intron in the human dystrophin pre-mRNA.

[Claim 14]

The combination according to claim 12 or 13, wherein

the third antisense oligomer comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1603 to 2554, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

[Claim 15]

The combination according to (14), wherein the third antisense oligomer comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 1611 to 1654, 1664 to 1707, 1718 to 1761, 1773 to 1816, 1829 to 1872, 1886 to 1929, 1944 to 1987, 2003 to 2046, 2063 to 2106, 2124 to 2167, 2186 to 2229, 2249 to 2292, 2313 to 2356, 2378 to 2421, 2444 to 2487, and 2511 to 2554;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 1611 to 1654, 1664 to 1707, 1718 to 1761, 1773 to 1816, 1829 to 1872, 1886 to 1929, 1944 to 1987, 2003 to 2046, 2063 to 2106, 2124 to 2167, 2186 to 2229, 2249 to 2292, 2313 to 2356, 2378 to 2421, 2444 to 2487, and 2511 to 2554;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1611 to 1654, 1664 to 1707, 1718 to 1761, 1773 to 1816, 1829 to 1872, 1886 to 1929, 1944 to 1987, 2003 to 2046, 2063 to 2106, 2124 to 2167, 2186 to 2229, 2249 to 2292, 2313 to 2356, 2378 to 2421, 2444 to 2487, and 2511 to 2554, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

[Claim 16]

The combination according to claim 15, wherein the third antisense oligomer comprises a base sequence complementary to:

(a) any one base sequence selected from the group consisting of SEQ ID NOs: 1617 to 1654, 1670 to 1707, 1724 to 1761, 1779 to 1816, 1835 to 1872, 1892 to 1929, 1950 to 1987, 2009 to 2046, 2069 to 2106, 2130 to 2167, 2192 to 2229, 2255 to 2292, 2319 to 2356, 2384 to 2421, 2450 to 2487, and 2517 to 2554;

(b) a base sequence that hybridizes under stringent conditions to a base sequence complementary to any one base sequence selected from the group consisting of SEQ ID NOs: 1617 to 1654, 1670 to 1707, 1724 to 1761, 1779 to 1816, 1835 to 1872, 1892 to 1929, 1950 to 1987, 2009 to 2046, 2069 to 2106, 2130 to 2167, 2192 to 2229, 2255 to 2292, 2319 to 2356, 2384 to 2421, 2450 to 2487, and 2517 to 2554;

(c) a base sequence that has at least 85% identity with any one base sequence selected from the group consisting of SEQ ID NOs: 1617 to 1654, 1670 to 1707, 1724 to 1761, 1779 to 1816, 1835 to 1872, 1892 to 1929, 1950 to 1987, 2009 to 2046, 2069 to 2106, 2130 to 2167, 2192 to 2229, 2255 to 2292, 2319 to 2356, 2384 to 2421,

2450 to 2487, and 2517 to 2554, and has a length within ±15% of the length of the any one base sequence selected; or

(d) a partial base sequence of any one base sequence selected from the group consisting of the base sequences (a), (b), and (c).

[Claim 17]

The combination according to any one of claims 1 to 14, wherein the third antisense oligomer comprises a base sequence selected from the group consisting of SEQ ID NOs: 3060, 3065, 3077, 3082, 3087, 3090, 3096, 3108, 3119, and 3320.

[Claim 18]

The combination according to any one of claims 12 to 17, wherein the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, the first unit oligomer comprises any one base sequence selected from SEQ ID NOs: 907 to 1602, the second unit oligomer comprises any one base sequence selected from SEQ ID NOs: 106 to 210, the second antisense oligomer comprises any one base sequence selected from SEQ ID NOs: 4299 to 5090, and the third antisense oligomer comprises any one base sequence selected from SEQ ID NOs: 2555 to 3506.

[Claim 19]

The combination according to any one of claims 1 to 18, wherein

the first antisense oligomer comprises the first unit oligomer and the second unit oligomer from the 5' ends in this order, and

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 201, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 203, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 205, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1239, the second unit oligomer comprises a base sequence of SEQ ID NO: 114, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1224, the second unit oligomer comprises a base sequence of SEQ ID NO: 124, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1180, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1190, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1212, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense

oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1222, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3060,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3065,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3077,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3087,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3090,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3096,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3108,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense

oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3119,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3320,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4698, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4702, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4752, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4923, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4926, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4936, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4977, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082,

the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense

oligomer comprises a base sequence of SEQ ID NO: 4977, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3096, or

the first unit oligomer comprises a base sequence of SEQ ID NO: 1180, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4977, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3096.

[Claim 20]

The combination according to claim 18 or 19, wherein the first unit oligomer comprises a base sequence of SEQ ID NO: 1201, the second unit oligomer comprises a base sequence of SEQ ID NO: 151, the second antisense oligomer comprises a base sequence of SEQ ID NO: 4950, and the third antisense oligomer comprises a base sequence of SEQ ID NO: 3082, 3090, or 3096.

[Claim 21]

The combination according to any one of claims 1 to 20, the combination causing skipping of all exons from the 45th exon to the 55th exon in the human dystrophin pre-mRNA.

[Claim 22]

The combination according to any one of claims 1 to 11, wherein the first and second antisense oligomers are oligonucleotides, or the combination according to any one

of claims 12 to 21, wherein the first to third antisense oligomers are oligonucleotides.

[Claim 23]

The combination according to claim 22, wherein a sugar moiety and/or a phosphate-binding region of at least one base constituting the oligonucleotide is modified.

[Claim 24]

The combination according to claim 22 or 23, wherein the sugar moiety of at least one base constituting the oligonucleotide is a ribose in which a 2'-OH group is replaced by any one group selected from the group consisting of -OR, -R, -R'OR, -SH, -SR, $-NH_2$, -NHR, $-NR_2$, $-N_3$, -CN, -F, -Cl, -Br, and -I (wherein R is an alkyl or an aryl and R' is an alkylene).

[Claim 25]

The combination according to any one of claims 22 to 24, wherein the phosphate-binding region of at least one base constituting the oligonucleotide is any one selected from the group consisting of a phosphorothioate bond, a phosphorodithioate bond, an alkylphosphonate bond, a phosphoramidate bond, and a boranophosphate bond.

[Claim 26]

The combination according to any one of claims 1 to 11, wherein the first and second antisense oligomers are morpholino oligomers, or the combination according to any

one of claims 12 to 21, wherein the first to third antisense oligomers are oligonucleotides.

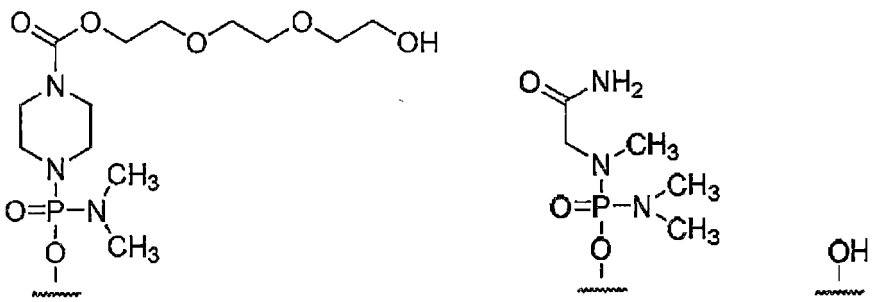
[Claim 27]

The combination according to claim 26, wherein the first to third antisense oligomers are phosphorodiamidate morpholino oligomers.

[Claim 28]

The combination according to claim 26 or 27, wherein the 5' end of each of the first to third antisense oligomers is a group represented by any one of the following chemical formulae (1) to (3):

[Chem. 1]



(1) (2) (3)

[Claim 29]

(a) A pharmaceutical composition comprising the first and second antisense oligomers according to any one of claims 1 to 28, or pharmaceutically acceptable salts thereof, or hydrates thereof, or

(b) a pharmaceutical combination comprising (i) a pharmaceutical composition comprising the first antisense oligomer according to any one of claims 1 to 28, or a

pharmaceutically acceptable salt thereof, or a hydrate thereof, and (ii) a pharmaceutical composition comprising the second antisense oligomer according to any one of claims 1 to 28, or a pharmaceutically acceptable salt thereof, or a hydrate thereof.

[Claim 30]

(a) A pharmaceutical composition comprising the first to third antisense oligomers according to any one of claims 12 to 28, or pharmaceutically acceptable salts thereof, or hydrates thereof, or

(b) a pharmaceutical combination comprising (i) a pharmaceutical composition comprising the first antisense oligomer according to any one of claims 12 to 28, or a pharmaceutically acceptable salt thereof, or a hydrate thereof, (ii) a pharmaceutical composition comprising the second antisense oligomer according to any one of claims 12 to 28, or a pharmaceutically acceptable salt thereof, or a hydrate thereof, and (iii) a pharmaceutical composition comprising the third antisense oligomer according to any one of claims 12 to 28, or a pharmaceutically acceptable salt thereof, or a hydrate thereof.

[Claim 31]

The pharmaceutical composition or the pharmaceutical combination according to claim 29 or 30, wherein the pharmaceutical composition further comprises a pharmaceutically acceptable carrier.

[Claim 32]

The pharmaceutical composition or the pharmaceutical combination according to any one of claims 29 to 31 for treatment of muscular dystrophy.

[Claim 33]

The pharmaceutical composition or the pharmaceutical combination according to any one of claims 29 to 32 for being administered to a human patient.

[Claim 34]

A method for treatment of muscular dystrophy, comprising administering to a patient with muscular dystrophy (i) the first and second antisense oligomers according to any one of claims 1 to 28, or pharmaceutically acceptable salts thereof, or hydrates thereof, (ii) the first to third antisense oligomers according to any one of claims 12 to 28, or pharmaceutically acceptable salts thereof, or hydrates thereof, or (iii) the pharmaceutical composition or the pharmaceutical combination according to any one of claims 29 to 33.

[Claim 35]

The method for treatment according to claim 34, wherein the muscular dystrophy patient is a patient with a mutation that is a target of exon 45 to 55 skipping in dystrophin gene.

[Claim 36]

The method for treatment according to claim 34 or 35, wherein the patient is a human.