CLAIMS

1. A nucleic acid comprising:

(a) a 5’ end and a 3’ end;

(b) a seed region that is complementary to a region of a gene comprising an allelic polymorphism;

(c) a single nucleotide polymorphism (SNP) position nucleotide at a position within the seed region, wherein the SNP position nucleotide is complementary to the allelic polymorphism;

(d) a mismatch (MM) position nucleotide that is a mismatch with a nucleotide in the gene; and

(e) at least one modified nucleotide (X) on either side of the SNP position nucleotide, wherein each X is located within four, three, or two nucleotides from the SNP position nucleotide~~.~~; and/or

~~2. A nucleic acid comprising:~~

~~(a) a 5’ end and a 3’ end;~~

~~(b) a seed region that is complementary to a region of a gene comprising an allelic polymorphism;~~

~~(c) a single nucleotide polymorphism (SNP) position nucleotide at a position within the seed region, wherein the SNP position nucleotide is complementary to the allelic polymorphism;~~

~~(d) a mismatch (MM) position nucleotide that is a mismatch with a nucleotide in the gene; and~~

~~(e)~~(f) at least one modified nucleotide (Y) on either side of the MM position nucleotide, wherein each Y is located within four, three or two nucleotides from the MM position nucleotide.

~~3~~2. The nucleic acid of claim 1, wherein X comprises a sugar modification selected from the group consisting of 2’-O-methyl (2’-OMe), 2’-fluoro (2’-F), 2’-ribo, 2’-deoxyribo, 2′-F-4′-thioarabino (2’-F-ANA), 2’-O-(2-methoxyethyl) (2’-MOE), 4’-S-RNA, locked nucleic acid (LNA), 4’-S-F-ANA, 2’-O-allyl, 2’-O-ethylamine, 2’-O-cyanoethyl-RNA (CNet-RNA), tricyclo-DNA, cyclohexenyl nucleic acid (CeNA), arabino nucleic acid (ANA), and hexitol nucleic acid (HNA).

43. The nucleic acid of claim 21, wherein Y comprises a sugar modification selected from the group consisting of 2’-OMe, 2’-F, 2’-ribo, 2’-deoxyribo, 2’-F-ANA, 2’-MOE, 4’-S-RNA, LNA, 4’-S-F-ANA, 2’-O-allyl, 2’-O-ethylamine, CNet-RNA, tricyclo-DNA, CeNA, ANA, and HNA.

54. The nucleic acid of claim 1, wherein an X is positioned immediately 5’ to the SNP position nucleotide or immediately 3’ to the SNP position nucleotide.

65. The nucleic acid of claim 1, wherein an X is positioned immediately 5’ to the SNP position nucleotide and immediately 3’ to the SNP position nucleotide.

76. The nucleic acid of claim 21, wherein a Y is positioned immediately 5’ to the MM position nucleotide or immediately 3’ to the MM position nucleotide.

87. The nucleic acid of claim 21, wherein a Y is positioned immediately 5’ to the MM position nucleotide and immediately 3’ to the MM position nucleotide.

98. The nucleic acid of claim 1 or 2, wherein the SNP position nucleotide is present from position 2 to position 6 from the 5’ end.

109. The nucleic acid of claim 1 or 2, wherein the MM position nucleotide is located 2-11 nucleotides from the SNP position nucleotide.

11. The nucleic acid of claim 1 or 2, wherein the MM position nucleotide is located 2-6 nucleotides from the SNP position nucleotide.

12. A nucleic acid comprising:

(a) a 5’ end and a 3’ end;

(b) a seed region that is complementary to a region of a gene comprising an allelic polymorphism;

(c) a single nucleotide polymorphism (SNP) position nucleotide at a position within the seed region, wherein the SNP position nucleotide is complementary to the allelic polymorphism;

(d) a mismatch (MM) position nucleotide that is a mismatch with a nucleotide in the gene;

(e) at least one modified nucleotide (X) on either side of the SNP position nucleotide, wherein each X is located within four, three or two nucleotides from the SNP position nucleotide; and

(f) at least one modified nucleotide (Y) on either side of the MM position nucleotide, wherein each Y is located within four, three or two nucleotides from the MM position nucleotide.

13. The nucleic acid of claim 12, wherein X comprises a sugar modification selected from the group consisting of 2'-OMe, 2'-F, 2'-ribo, 2'-deoxyribo, 2'-F-ANA, 2'-MOE, 4'-S-RNA, LNA, 4'-S-F-ANA, 2'-O-allyl, 2'-O-ethylamine, CNet-RNA, tricyclo-DNA, CeNA, ANA, and HNA.

14. The nucleic acid of claim 12, wherein Y comprises a sugar modification selected from the group consisting of 2'-OMe, 2'-F, 2'-ribo, 2'-deoxyribo, 2'-F-ANA, 2'-MOE, 4'-S-RNA, LNA, 4'-S-F-ANA, 2'-O-allyl, 2'-O-ethylamine, CNet-RNA, tricyclo-DNA, CeNA, ANA, and HNA.

15. The nucleic acid of claim 12, wherein an X is positioned immediately 5' to the SNP position nucleotide or immediately 3' to the SNP position nucleotide.

16. The nucleic acid of claim 12, wherein an X is positioned immediately 5' to the SNP position nucleotide and immediately 3' to the SNP position nucleotide.

17. The nucleic acid of claim 12, wherein a Y is positioned immediately 5' to the MM position nucleotide or immediately 3' to the MM position nucleotide.

18. The nucleic acid of claim 12, wherein a Y is positioned immediately 5' to the MM position nucleotide or immediately 3' to the MM position nucleotide.

19. The nucleic acid of claim 12, wherein the SNP position nucleotide is present from position 2 to position 6 from the 5' end.

~~20. The nucleic acid of claim 12, wherein the MM position nucleotide is located 2-11 nucleotides from the SNP position nucleotide.~~

~~21. The nucleic acid of claim 12, wherein the MM position nucleotide is located 2-6 nucleotides from the SNP position nucleotide.~~

~~22. The nucleic acid of claim 12, wherein X and Y comprise identical nucleotide modifications.~~

~~23. The nucleic acid of claim 12, wherein X and Y comprise different nucleotide modifications.~~

~~24~~10. A nucleic acid comprising:

(a) a 5’ end and a 3’ end;

(b) a seed region that is complementary to a region of a gene comprising an allelic polymorphism;

(c) a single nucleotide polymorphism (SNP) position nucleotide that is complementary to the allelic polymorphism;

(d) a mismatch (MM) position nucleotide that is a mismatch with a nucleotide in the gene;

(e) at least one 2’-fluoro-ribonucleotide on either side of the SNP position nucleotide, wherein each 2’-fluoro-ribonucleotide is located within four, three or two nucleotides from the SNP position nucleotide; and

(f) at least one 2’-methoxy-ribonucleotide on either side of the MM position nucleotide, wherein each 2’-methoxy-ribonucleotide is located within four, three or two nucleotides from the MM position nucleotide.

~~25~~11. The nucleic acid of claim ~~24~~10, wherein a 2’-fluoro-ribonucleotide is positioned immediately 5’ to the SNP position nucleotide and/or a 2’-fluoro-ribonucleotide is positioned immediately 3’ to the SNP position nucleotide.

~~26. The nucleic acid of claim 24, wherein a 2’-fluoro-ribonucleotide is positioned immediately 5’ to the SNP position nucleotide and a 2’-fluoro-ribonucleotide is positioned immediately 3’ to the SNP position nucleotide.~~

~~27~~12. The nucleic acid of claim ~~24~~10, wherein a 2'-methoxy-ribonucleotide is positioned immediately 5' to the MM position nucleotide and/or a 2'-methoxy-ribonucleotide is positioned immediately 3' to the MM position nucleotide.

~~28. The nucleic acid of claim 24, wherein a 2'-methoxy-ribonucleotide is positioned immediately 5' to the MM position nucleotide and a 2'-methoxy-ribonucleotide is positioned immediately 3' to the MM position nucleotide.~~

~~29~~13. The nucleic acid of claim ~~24~~10, wherein the SNP position nucleotide is present in a seed region, and wherein the MM position nucleotide is located 2-11 nucleotides from the SNP position nucleotide.

~~30~~14. The nucleic acid of claim ~~29~~13, wherein the SNP position nucleotide is present from position 2 to position 6 from the 5' end, and wherein the MM position nucleotide is located 2-6 nucleotides from the SNP position nucleotide.

~~31~~15. The nucleic acid of claim ~~24~~10, comprising three, four, five or six 2'-fluoro-ribonucleotides or~~.~~

~~32. The nucleic acid of claim 24, comprising three, four, five or six~~ 2'-methoxy-ribonucleotides.

~~33~~16. A nucleic acid comprising:

(a) a 5' end and a 3' end;

(b) a seed region that is complementary to a region of a gene comprising an allelic polymorphism;

(c) a single nucleotide polymorphism (SNP) position nucleotide that is complementary to the allelic polymorphism;

(d) a mismatch (MM) position nucleotide that is a mismatch with a nucleotide in the gene;

(e) at least three 2'-fluoro-ribonucleotides located within four, three or two nucleotides from the SNP position nucleotide; and

(f) at least three 2'-methoxy-ribonucleotides located within four, three or two nucleotides from the MM position nucleotide.

~~34~~17. The nucleic acid of claim ~~33~~16, wherein a 2'-fluoro-ribonucleotide is positioned immediately 5' to the SNP position nucleotide and/or a 2'-fluoro-ribonucleotide is positioned immediately 3' to the SNP position nucleotide.

~~35. The nucleic acid of claim 33, wherein a 2'-fluoro-ribonucleotide is positioned immediately 5' to the SNP position nucleotide and a 2'-fluoro-ribonucleotide is positioned immediately 3' to the SNP position nucleotide.~~

~~36~~18. The nucleic acid of claim ~~33~~16, wherein a 2'-methoxy-ribonucleotide is positioned immediately 5' to the MM position nucleotide and/or a 2'-methoxy-ribonucleotide is positioned immediately 3' to the MM position nucleotide.

~~37. The nucleic acid of claim 33, wherein a 2'-methoxy-ribonucleotide is positioned immediately 5' to the MM position nucleotide and a 2'-methoxy-ribonucleotide is positioned immediately 3' to the MM position nucleotide.~~

~~38~~19. The nucleic acid of claim ~~33~~16, wherein the SNP position nucleotide is present in a seed region, and wherein the MM position nucleotide is located 2-11 nucleotides from the SNP position nucleotide.

~~39~~20. The nucleic acid of claim ~~38~~19, wherein the SNP position nucleotide is present from position 2 to position 6 from the 5' end, and wherein the MM position nucleotide is located 2-6 nucleotides from the SNP position nucleotide.

~~40. An siRNA molecule comprising a sense strand having complementarity to a target gene and an antisense strand having complementarity to the sense strand, wherein the antisense strand comprises the nucleic acid of any one of claims 1-39.~~

~~41. The siRNA molecule of claim 40, wherein the sense strand has a length of from 13 nucleotides or nucleotide analogs to 17 nucleotides or nucleotide analogs.~~

~~42. The siRNA molecule of claim 40 or 41, wherein the antisense strand has a length of from 18 nucleotides or nucleotide analogs to 22 nucleotides or nucleotide analogs.~~

43. The siRNA molecule of any one of claims 40-42, wherein the sense strand has a length of 15 nucleotides or nucleotide analogs and the antisense strand has a length of 20 nucleotides or nucleotide analogs.

44. The siRNA molecule of any one of claims 40-42, wherein the sense strand has a length of 16 nucleotides or nucleotide analogs and the antisense strand has a length of 20 nucleotides or nucleotide analogs.

45. A branched oligonucleotide comprising two or more siRNA molecules covalently bound to one another, wherein each siRNA molecule is, independently, an siRNA molecule of any one of claims 40-44.

46. The branched oligonucleotide of claim 45, wherein the branched oligonucleotide comprises two siRNA molecules covalently bound to one another.

47. The branched oligonucleotide of claim 45 or 46, wherein the siRNA molecules are covalently bound to one another by way of a linker.

48. A double-stranded nucleic acid comprising:

(a) a first strand of nucleotides comprising:

(i) a 5' end and a 3' end;

(ii) a seed region that is complementary to a region of a gene comprising an allelic polymorphism;

(iii) a single nucleotide polymorphism (SNP) position nucleotide at a position within the seed region, wherein the SNP position nucleotide is complementary to the allelic polymorphism;

(iv) a mismatch (MM) position nucleotide that is not complementary to a nucleotide in the gene; and

(v) at least one modified nucleotide located on either side of the SNP position nucleotide, on either side of the MM position nucleotide, or a combination thereof; wherein each modified nucleotide is located within four, three, or two nucleotides from the SNP position nucleotide or from the MM position nucleotide, respectively;

(b) a second strand of nucleotides that is complementary to the first strand of nucleotides.

~~49. The double-stranded nucleic acid of claim 48, wherein the modified nucleotide comprises a modification selected from the group consisting of 2'-O-methyl (2'-OMe), 2'-fluoro (2'-F), 2'-ribo, 2'-deoxyribo, 2′-F-4′-thioarabino (2'-F-ANA), 2'-O-(2-methoxyethyl) (2'-MOE), 4'-S-RNA, locked nucleic acid (LNA), 4'-S-F-ANA, 2'-O-allyl, 2'-O-ethylamine, 2'-O-cyanoethyl-RNA (CNet-RNA), tricyclo-DNA, cyclohexenyl nucleic acid (CeNA), arabino nucleic acid (ANA), hexitol nucleic acid (HNA), and a combination thereof.~~

~~50. The nucleic acid of claim 48, wherein the modified nucleotide is positioned immediately 5' to the SNP position nucleotide, immediately 3' to the SNP position nucleotide, or a mixture thereof.~~

~~51. The nucleic acid of claim 48, wherein the modified nucleotide is positioned immediately 5' to the MM position nucleotide, immediately 3' to the MM position nucleotide., or a mixture thereof.~~

~~52. The nucleic acid of claim 48, wherein the SNP position nucleotide is present from position 2 to position 6 from the 5' end of the first strand of nucleotides.~~

~~53. The nucleic acid of claim 48, wherein the MM position nucleotide is located 2-11 nucleotides from the SNP position nucleotide of the first strand of nucleotides.~~

~~54. The nucleic acid of claim 48, wherein the MM position nucleotide is located 2-6 nucleotides from the SNP position nucleotide of the first strand of nucleotides.~~

~~55. The nucleic acid of claim 48, wherein the modified nucleotides comprise identical nucleotide modifications, different nucleotide modifications, or a mixture thereof.~~

~~56. The nucleic acid of claim 48, wherein the first strand has a length of from 13-17 nucleotides.~~

~~57. The nucleic acid of claim 48, wherein the second strand has a length of from 18-22 nucleotides.~~

58. The nucleic acid of claim 48, wherein the first strand has a length of 15 nucleotides and the second strand has a length of 20 nucleotides.

59. The nucleic acid of claim 48, wherein the first strand has a length of 16 nucleotides and the second strand has a length of 20 nucleotides.

60. The nucleic acid of claim 48, wherein the first strand has 3-7 more nucleotides than the second strand.

61. A branched oligonucleotide comprising two or more siRNA molecules covalently bound to one another, wherein each siRNA molecule comprises a double-stranded nucleic acid comprising:

(a) a first strand of nucleotides comprising:

(i) a 5' end, a 3' end;

(ii) a seed region that is complementary to a region of a gene comprising an allelic polymorphism;

(iii) a single nucleotide polymorphism (SNP) position nucleotide at a position within the seed region, wherein the SNP position nucleotide is complementary to the allelic polymorphism;

(iv) a mismatch (MM) position nucleotide that not complementary to a nucleotide in the gene; and

(v) at least one modified nucleotide located on either side of the SNP position nucleotide, on either side of the MM position nucleotide, or a combination thereof; wherein each modified nucleotide is located within four, three, or two nucleotides from the SNP position nucleotide or from the MM position nucleotide, respectively;

(b) a second strand of nucleotides that is complementary to the first strand of nucleotides.

62. The branched oligonucleotide of claim 61, wherein the branched oligonucleotide comprises two siRNA molecules covalently bound to one another.

63. The branched oligonucleotide of claim 61, wherein the siRNA molecules are covalently bound to one another by way of a linker.