

CLAIMS

1. A method of determining a susceptibility to cardiac arrhythmia or stroke in a human individual, the method comprising determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample from the individual, wherein the at least one polymorphic marker is selected from the polymorphic markers set forth in Table 5, and markers in linkage disequilibrium therewith,
and wherein determination of the presence or absence of the at least one allele is indicative of a susceptibility to cardiac arrhythmia or stroke in the individual.
2. A method of determining a susceptibility to cardiac arrhythmia or stroke in a human individual, comprising determining whether at least one at-risk allele in at least one polymorphic marker is present in a genotype dataset derived from the individual, wherein the at least one polymorphic marker is selected from the markers set forth in Table 5, and markers in linkage disequilibrium therewith, and wherein determination of the presence of the at least one at-risk allele is indicative of increased susceptibility to cardiac arrhythmia or stroke in the individual.
3. The method of Claim 1 or 2, wherein the at least one polymorphic marker is selected from the markers set forth in Table 9, and markers in linkage disequilibrium therewith.
4. The method of any of the preceding Claims, wherein the at least one polymorphic marker is selected from D4S406 (SEQ ID NO:45), rs2634073 (SEQ ID NO:33), rs2200733 (SEQ ID NO:28), rs2220427 (SEQ ID NO:1), rs10033464 (SEQ ID NO:41), and rs13143308 (SEQ ID NO:51), and markers in linkage disequilibrium therewith.
5. The method of any of the preceding Claims, wherein the presence of alleles -2, -4 and/or -8 in marker D4S406, allele A of marker rs2634073, allele T of marker rs2200733, allele T of marker rs2220427, allele T of marker rs10033464, and/or allele G of marker rs13143308 is indicative of increased susceptibility of cardiac arrhythmia or stroke in the individual.
6. The method of any of the preceding Claims, wherein the susceptibility is increased susceptibility characterized by an odds ratio (OR) of at least 1.3.

7. The method of any of the preceding Claims, wherein the susceptibility is increased susceptibility characterized by an odds ratio (OR) of at least 1.4.
8. The method of any of the preceding Claims, wherein the susceptibility is increased susceptibility characterized by an odds ratio (OR) of at least 1.5.
- 5 9. The method of any of the preceding Claims, wherein the susceptibility is increased susceptibility characterized by an odds ratio (OR) of at least 1.6.
10. The method of any of the preceding Claims, wherein the susceptibility is increased susceptibility characterized by an odds ratio (OR) of at least 1.8.
- 10 11. A method of assessing a susceptibility to cardiac arrhythmia or stroke in a human individual, comprising screening a nucleic acid from the individual for at least one polymorphic marker allele or haplotype in SEQ ID NO:50 that correlates with increased occurrence of cardiac arrhythmia or stroke in a human population;
 wherein determination of the presence of an at-risk marker allele in the at least one polymorphism or an at-risk haplotype in the nucleic acid identifies the
 15 individual as having elevated susceptibility to cardiac arrhythmia and/or stroke, and
 wherein the absence of the at least one at-risk marker allele or at-risk haplotype in the nucleic acid identifies the individual as not having the elevated susceptibility.
12. The method of Claim 11, wherein the at least one polymorphic marker is selected
 20 from the markers set forth in Table 9, and markers in linkage disequilibrium therewith.
13. The method of Claim 11, wherein the at least one polymorphic marker is selected from the markers set forth in Table 5, and markers in linkage disequilibrium therewith.
- 25 14. The method of any of the Claims 11-13, wherein the at least one polymorphic marker is selected from D4S406 (SEQ ID NO:45), rs2634073 (SEQ ID NO:33), rs2200733 (SEQ ID NO:28), rs2220427 (SEQ ID NO:1), rs10033464 (SEQ ID NO:41), and rs13143308 (SEQ ID NO:51),
- 30 15. The method of any of the Claims 11-14, wherein the presence of alleles -2, -4 and/or -8 in marker D4S406, allele A of marker rs2634073, allele T of marker rs2200733, allele T of marker rs2220427, allele T of marker rs10033464, and/or allele G of marker rs13143308 is indicative of increased susceptibility of cardiac arrhythmia or stroke in the individual.

16. A method of identification of a marker for use in assessing susceptibility to cardiac arrhythmia and/or stroke in human individuals, the method comprising

- 5
- a. identifying at least one polymorphic marker within SEQ ID NO:50, or at least one polymorphic marker in linkage disequilibrium with at least one marker within SEQ ID NO:50;
 - b. determining the genotype status of a sample of individuals diagnosed with cardiac arrhythmia and/or stroke; and
 - c. determining the genotype status of a sample of control individuals;

10 wherein a significant difference in frequency of at least one allele in at least one polymorphism in individuals diagnosed with cardiac arrhythmia and/or stroke as compared with the frequency of the at least one allele in the control sample is indicative of the at least one polymorphism being useful for assessing susceptibility to cardiac arrhythmia and/or stroke.

15 17. The method of Claim 16, wherein an increase in frequency of the at least one allele in the at least one polymorphism in individuals diagnosed with cardiac arrhythmia and/or stroke, as compared with the frequency of the at least one allele in the control sample, is indicative of the at least one polymorphism being useful for assessing increased susceptibility to cardiac arrhythmia.

20 18. The method of Claim 16, wherein a decrease in frequency of the at least one allele in the at least one polymorphism in individuals diagnosed with cardiac arrhythmia and/or stroke, as compared with the frequency of the at least one allele in the control sample, is indicative of the at least one polymorphism being useful for assessing decreased susceptibility to, or protection against, cardiac arrhythmia and/or stroke.

25 19. The method of any of the Claims 16-18, wherein the significant difference in frequency is characterized by a statistical measure.

30 20. A method of genotyping a nucleic acid sample obtained from a human individual, comprising determining the presence or absence of at least one allele of at least one polymorphic marker predictive of increased risk of cardiac arrhythmia and/or stroke in the sample, wherein the at least one marker is selected from the markers set forth in Table 5, and markers in linkage disequilibrium therewith, and wherein determination of the presence or absence of the at least one allele of the at least one polymorphic marker is predictive of increased risk of cardiac arrhythmia and/or stroke in the individual.

21. The method of Claim 20, wherein genotyping comprises amplifying a segment of a nucleic acid that comprises the at least one polymorphic marker, by Polymerase Chain Reaction (PCR), using a nucleotide primer pair flanking the at least one polymorphic marker.

22. The method of Claim 20 or 21, wherein genotyping is performed using a process selected from allele-specific probe hybridization, allele-specific primer extension, allele-specific amplification, nucleic acid sequencing, 5'-exonuclease digestion, molecular beacon assay, oligonucleotide ligation assay, size analysis, and single-stranded conformation analysis.

23. The method of Claim 22, wherein the process comprises allele-specific probe hybridization.

24. The method of any of the Claims 20-23, comprising:

1. contacting copies of the nucleic acid with a detection oligonucleotide probe and an enhancer oligonucleotide probe under conditions for specific hybridization of the oligonucleotide probe with the nucleic acid;

wherein

- e) the detection oligonucleotide probe is from 5-100 nucleotides in length and specifically hybridizes to a first segment of the nucleic acid whose nucleotide sequence is given by SEQ ID NO:50 that comprises at least one polymorphic site;

- f) the detection oligonucleotide probe comprises a detectable label at its 3' terminus and a quenching moiety at its 5' terminus;

- g) the enhancer oligonucleotide is from 5-100 nucleotides in length and is complementary to a second segment of the nucleotide sequence that is 5' relative to the oligonucleotide probe, such that the enhancer oligonucleotide is located 3' relative to the detection oligonucleotide probe when both oligonucleotides are hybridized to the nucleic acid; and

- h) a single base gap exists between the first segment and the second segment, such that when the oligonucleotide probe and the enhancer oligonucleotide probe are both hybridized to the nucleic acid, a single base gap exists between the oligonucleotides;

2. treating the nucleic acid with an endonuclease that will cleave the detectable label from the 3' terminus of the detection probe to release free detectable label when the detection probe is hybridized to the nucleic acid; and

3. measuring free detectable label, wherein the presence of the free detectable label indicates that the detection probe specifically hybridizes to the first segment of the nucleic acid, and indicates the sequence of the polymorphic site as the complement of the detection probe.

25. The method of Claim 24, wherein the copies of the nucleic acid are provided by amplification by Polymerase Chain Reaction (PCR)

26. A method of determining a susceptibility to cardiac arrhythmia or stroke in a human individual, the method comprising determining the identity of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one marker is selected from the group of markers associated with the PITX2 gene, wherein the presence of the at least one allele is indicative of a susceptibility to cardiac arrhythmia or stroke in the individual.

27. The method according to Claim 16, wherein the at least one marker is selected from rs7668322 (SEQ ID NO:46), rs2197815 (SEQ ID NO:47), rs6831623 (SEQ ID NO:48) and rs259110 (SEQ ID NO:49), and markers in linkage disequilibrium therewith.

28. The method of Claim 26 or 27, wherein the susceptibility is increased susceptibility.

29. The method of Claim 26 or 27, wherein the susceptibility is decreased susceptibility.

30. The method of any of the preceding Claims, wherein the cardiac arrhythmia is atrial fibrillation or atrial flutter.

31. The method of Claim 30, wherein atrial fibrillation or atrial flutter is further characterized by an age of onset in the individual of less than 80 years.

32. The method of Claim 30, wherein atrial fibrillation or atrial flutter is further characterized by an age of onset in the individual of less than 70 years.

33. The method of Claim 30, wherein atrial fibrillation or atrial flutter is further characterized by an age of onset in the individual of less than 60 years.

34. The method of any of the preceding Claims, wherein the stroke is ischemic stroke.

35. The method of any of the preceding Claims, wherein linkage disequilibrium is characterized by numerical values for r^2 of greater than 0.2.
36. A method of assessing an individual for probability of response to a therapeutic agent for preventing and/or ameliorating symptoms associated with cardiac arrhythmia and/or stroke, comprising: determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is selected from the markers set forth in Table 9, and markers in linkage disequilibrium therewith, wherein determination of the presence of the at least one allele of the at least one marker is indicative of a probability of a positive response to the therapeutic agent for cardiac arrhythmia and/or stroke.
37. The method according to Claim 36, wherein the therapeutic agent is an anticoagulant, an anti-arrhythmic agent, a heart rate control agent, a cardioversion agent, or a heart rhythm control agent.
38. The method according to Claim 36 or 37, wherein the therapeutic agent is selected from warfarin, heparin, low molecular weight heparins, factor Xa inhibitors, thrombin inhibitors, sodium channel blockers, beta blockers, potassium channel blockers, and calcium channel blockers.
39. The method according to any of the Claims 36 – 38, wherein the therapeutic agent is selected from warfarin, ximelagatran, heparin, enoxaparin, dalteparin, tinzaparin, ardeparin, nadroparin, reviparin, fondaparinux, idraparin, lepirudin, bivalirudin, argatroban, danaparoid, disopyramide, moricizine, procainamide, quinidine, lidocaine, mexiletine, tocainide, phenytoin, encainide, flecainide, propafenone, ajmaline, dibenzoline, diltiazem, esmolol, propranolol, metoprolol, alprenolol, atenolol, carvedilol, bisoprolol, acebutolol, nadolol, pindolol, labetalol, oxprenolol, penbutolol, timolol, betaxolol, carteolol, sotalol, levobunolol, amlodarone, azimilide, bretylium, dofetilide, tedisamil, ibutilide, sotalol, N-acetyl procainamide, nifedipine hydrochloride, verapamil, diltiazem, digoxin, adenosine, ibutilide, amlodarone, procainamide, propafenone and flecainide.
40. A method of predicting prognosis of an individual diagnosed with, cardiac arrhythmia and/or stroke, the method comprising determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is selected from the the markers set forth in Table 9, and markers in linkage disequilibrium therewith, wherein determination of the presence of the at least one

allele is indicative of a worse prognosis of the cardiac arrhythmia and/or stroke in the individual.

41. A method of monitoring progress of a treatment of an individual undergoing treatment for cardiac arrhythmia and/or stroke, the method comprising determining the presence or absence of at least one allele of at least one polymorphic marker in a nucleic acid sample obtained from the individual, wherein the at least one polymorphic marker is selected from the markers set forth in Table 9, and markers in linkage disequilibrium therewith, wherein determination of the presence of the at least one allele is indicative of the treatment outcome of the individual.

42. The method of any of the Claims 36 - 41, wherein the at least one polymorphic marker is selected from D4S406 (SEQ ID NO:45), rs2634073 (SEQ ID NO:33), rs2200733 (SEQ ID NO:28), rs2220427 (SEQ ID NO:1), rs10033464 (SEQ ID NO:41), and rs13143306 (SEQ ID NO:51).

43. The method of any of the Claims 36 - 41, wherein linkage disequilibrium is characterized by numerical values of r^2 of at least 0.2.

44. The method of any of the Claims 36 - 43, wherein the cardiac arrhythmia is atrial fibrillation or atrial flutter.

45. The method of any of the Claims 36 - 44, wherein atrial fibrillation or atrial flutter is further characterized by an age of onset in the individual of less than 80 years.

46. The method of any of the Claims 36 - 44, wherein atrial fibrillation or atrial flutter is further characterized by an age of onset in the individual of less than 70 years.

47. The method of any of the Claims 36 - 44, wherein atrial fibrillation or atrial flutter is further characterized by an age of onset in the individual of less than 60 years.

48. The method of any of the Claims 36 - 44, wherein the stroke is ischemic stroke.

49. The method of any of the preceding Claims, further comprising assessing at least one biomarker for atrial fibrillation, atrial flutter and/or stroke in a sample from the individual.

50. The method of any of the preceding Claims, further comprising analyzing non-genetic information to make risk assessment, diagnosis, or prognosis of the individual.

51. The method of Claim 50, wherein the non-genetic information is selected from age, age at onset of disease, gender, ethnicity, socioeconomic status, previous disease diagnosis, medical history of subject, family history of atrial fibrillation, atrial flutter and/or stroke, biochemical measurements, and clinical measurements.
- 5 52. The method of any of the Claims 49 - 51, further comprising calculating overall risk by logistic regression.
53. A kit for assessing susceptibility to cardiac arrhythmia and/or stroke in a human individual, the kit comprising reagents for selectively detecting at least one allele of at least one polymorphic marker in the genome of the individual, wherein the
10 polymorphic marker is selected from the group consisting of the polymorphic markers within the segment whose sequence is set forth in SEQ ID NO:50, and markers in linkage disequilibrium therewith, and wherein the presence of the at least one allele is indicative of a susceptibility to cardiac arrhythmia and/or stroke.
54. The kit of Claim 53, wherein the at least one polymorphic marker is selected from
15 the markers set forth in Table 5.
55. The kit of Claim 53 or 54, wherein the at least one polymorphic marker is selected from the group of markers set forth in Table 9, and markers in linkage disequilibrium therewith.
56. The kit of any of the Claims 53 - 55, wherein the at least one polymorphic marker is
20 selected from D4S406 (SEQ ID NO:45), rs2624073 (SEQ ID NO:33), rs2200733 (SEQ ID NO:28), rs2220427 (SEQ ID NO:1), rs10033464 (SEQ ID NO:41), and rs13143308 (SEQ ID NO:51).
57. The kit of any of the Claims 53 - 56, wherein the cardiac arrhythmia is atrial fibrillation or atrial flutter.
- 25 58. The kit of any of the Claims 53 - 57, wherein the stroke is ischemic stroke.
59. The kit of any of the Claims 53 - 58, wherein linkage disequilibrium is characterized by numerical values of r^2 of greater than 0.2.
60. The kit of any of the Claims 53 - 59, wherein the reagents comprise at least one
30 contiguous oligonucleotide that hybridizes to a fragment of the genome of the individual comprising the at least one polymorphic marker, a buffer and a detectable label.
61. The kit of any of the Claims 53 - 60, wherein the reagents comprise at least one pair of oligonucleotides that hybridize to opposite strands of a genomic nucleic acid

segment obtained from the subject, wherein each oligonucleotide primer pair is designed to selectively amplify a fragment of the genome of the individual that includes one polymorphic marker, and wherein the fragment is at least 30 base pairs in size.

- 5 62. The kit of Claim 60 or 61, wherein the at least one oligonucleotide is completely complementary to the genome of the individual.
63. The kit of any of the Claims 60 - 62, wherein the oligonucleotide is about 18 to about 50 nucleotides in length.
64. The kit of any of the Claims 60 - 63, wherein the oligonucleotide is 20-30
10 nucleotides in length.
65. The kit of any of the Claims 53 - 64, wherein the kit comprises:
 - a. a detection oligonucleotide probe that is from 5-100 nucleotides in length;
 - b. an enhancer oligonucleotide probe that is from 5-100 nucleotides in length;
and
 - .15 c. an endonuclease enzyme;

wherein the detection oligonucleotide probe specifically hybridizes to a first segment of the nucleic acid whose nucleotide sequence is given by SEQ ID NO: 50 that comprises at least one polymorphic site; and

wherein the detection oligonucleotide probe comprises a detectable label at its 3' terminus and a quenching moiety at its 5' terminus;

wherein the enhancer oligonucleotide is from 5-100 nucleotides in length and is complementary to a second segment of the nucleotide sequence that is 5' relative to the oligonucleotide probe, such that the enhancer oligonucleotide is located 3' relative to the detection oligonucleotide probe when both oligonucleotides are
25 hybridized to the nucleic acid;

wherein a single base gap exists between the first segment and the second segment, such that when the oligonucleotide probe and the enhancer oligonucleotide probe are both hybridized to the nucleic acid, a single base gap exists between the oligonucleotides; and

wherein treating the nucleic acid with the endonuclease will cleave the detectable label from the 3' terminus of the detection probe to release free detectable label when the detection probe is hybridized to the nucleic acid.

66. Use of an oligonucleotide probe in the manufacture of a diagnostic reagent for diagnosing and/or assessing susceptibility to cardiac arrhythmia and/or stroke in a human individual, wherein the probe hybridizes to a segment of a nucleic acid whose nucleotide sequence is given by SEQ ID NO:50 that comprises at least one polymorphic site, wherein the fragment is 15-500 nucleotides in length.

67. The use according to Claim 66, wherein the polymorphic site is selected from the polymorphic markers set forth in Table 5, and polymorphisms in linkage disequilibrium therewith.

68. The use according to Claim 66 or 67, wherein the at least one polymorphic site is selected from D45406 (SEQ ID NO:45), rs2634073 (SEQ ID NO:33), rs2200733 (SEQ ID NO:28), rs2220427 (SEQ ID NO:1), rs10033464 (SEQ ID NO:41), and rs13143308 (SEQ ID NO:51).

69. The use of any of the Claims 66 - 68, wherein the cardiac arrhythmia is atrial fibrillation or atrial flutter.

70. The use of any of the Claims 66 - 69, wherein the stroke is ischemic stroke.

71. The use of any of the Claims 66 - 70, wherein linkage disequilibrium is defined by numerical values of r^2 of at least 0.2 and/or values of $|D'|$ of at least 0.8.

72. A computer-readable medium on which is stored:

- a. an identifier for at least one polymorphic marker;
- b. an indicator of the frequency of at least one allele of said at least one polymorphic marker in a plurality of individuals diagnosed with atrial fibrillation, atrial flutter and/or stroke; and
- c. an indicator of the frequency of the least one allele of said at least one polymorphic markers in a plurality of reference individuals;

wherein the at least one polymorphic marker is selected from the polymorphic markers set forth in Table 5, and polymorphisms in linkage disequilibrium therewith.

73. The medium according to Claim 72, wherein the at least one polymorphic marker is selected from D45406 (SEQ ID NO:45), rs2634073 (SEQ ID NO:33), rs2200733

(SEQ ID NO:28), rs2220427 (SEQ ID NO:1), rs10033464 (SEQ ID NO:41), and rs13143308 (SEQ ID NO:51),

74. The medium of Claim 72 or 73, wherein the stroke is ischemic stroke.

75. An apparatus for determining a genetic indicator for cardiac arrhythmia and/or stroke in a human individual, comprising:

a computer readable memory; and

a routine stored on the computer readable memory;

wherein the routine is adapted to be executed on a processor to analyze genotype and/or haplotype data for at least one human individual with respect to at least one polymorphic marker selected from the markers set forth in Table 5, and markers in linkage disequilibrium therewith, and generate an output based on the marker or haplotype data, wherein the output comprises a risk measure of the at least one marker or haplotype as a genetic indicator of cardiac arrhythmia and/or stroke for the human individual.

76. The apparatus of Claim 75, wherein the routine further comprises determining an indicator of the frequency of at least one allele of at least one polymorphic marker and/or at least one haplotype in a plurality of individuals diagnosed with cardiac arrhythmia and/or stroke, and an indicator of the frequency of at the least one allele of at least one polymorphic marker or at least one haplotype in a plurality of reference individuals, and calculating a risk measure for the at least one allele and/or haplotype based thereupon;

and wherein a risk measure for the individual is calculated based on a comparison of the at least one marker and/or haplotype status for the individual to the calculated risk for the at least one marker and/or haplotype information for the plurality of individuals diagnosed with atrial fibrillation, atrial flutter and/or stroke.

77. The apparatus of Claim 75 or 76, wherein the at least one polymorphic marker is selected from D4S406 (SEQ ID NO:45), rs2634073 (SEQ ID NO:33), rs2200733 (SEQ ID NO:28), rs2220427 (SEQ ID NO:1), rs10033464 (SEQ ID NO:41), and rs13143308 (SEQ ID NO:51).

78. The apparatus of any of the Claims 75 - 77, wherein the risk measure is characterized by an Odds Ratio (OR) or a Relative Risk (RR).

79. The apparatus or medium of any of the Claims 75 - 78, wherein linkage disequilibrium is characterized by values of r^2 of greater than 0.2.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of determining a susceptibility to cardiac arrhythmia or stroke in a human individual, the method comprising determining the presence or absence of
5 at least one allele of at least one polymorphic marker in a nucleic acid sample from the individual, wherein the at least one polymorphic marker is selected from the polymorphic markers rs2200733 and rs10033464, and markers in linkage disequilibrium therewith,

and wherein determination of the presence or absence of the at least one allele is
10 indicative of a susceptibility to cardiac arrhythmia or stroke in the individual.
2. The method of Claim 1, wherein the at least one polymorphic marker is selected from the markers set forth in Table 19.
3. The method of any of the preceding Claims, wherein the at least one polymorphic
15 marker is selected from D4S406 (SEQ ID NO:45), rs2634073 (SEQ ID NO:33), rs2200733 (SEQ ID NO:28), rs2220427 (SEQ ID NO:1), rs10033464 (SEQ ID NO:41), and rs13143308 (SEQ ID NO:51).
4. The method of any of the preceding Claims, wherein the presence of alleles -2, -4 and/or -8 in marker D4S406, allele A of marker rs2634073, allele T of marker
20 rs2200733, allele T of marker rs2220427, allele T of marker rs10033464, and/or allele G of marker rs13143308 is indicative of increased susceptibility of cardiac arrhythmia or stroke in the individual.
5. The method of any of the preceding Claims, wherein the susceptibility is increased susceptibility characterized by an odds ratio (OR) of at least 1.3.
6. The method of any of the preceding Claims, wherein the susceptibility is increased
25 susceptibility characterized by an odds ratio (OR) of at least 1.5.
7. The method of any of the preceding Claims, wherein the susceptibility is increased susceptibility characterized by an odds ratio (OR) of at least 1.8.
8. A method of assessing a susceptibility to cardiac arrhythmia or stroke in a human
30 individual, comprising screening a nucleic acid from the individual for at least one polymorphic marker allele that correlates with increased occurrence of cardiac arrhythmia or stroke in a human population, wherein the at least one polymorphic marker allele is an allele in a marker selected from rs2200733 and rs10033464, and markers in linkage disequilibrium therewith;

wherein determination of the presence of the marker allele identifies the individual as having elevated susceptibility to cardiac arrhythmia and/or stroke, and

wherein the absence of the at least one allele or at-risk haplotype in the nucleic acid identifies the individual as not having the elevated susceptibility.

- 5 9. The method of Claim 8, wherein the at least one polymorphic marker is selected from the markers set forth in Table 19.
10. The method of claim 8 or claim 9, wherein the at least one polymorphic marker is selected from D4S406 (SEQ ID NO:45), rs2634073 (SEQ ID NO:33), rs2200733 (SEQ ID NO:28), rs2220427 (SEQ ID NO:1), rs10033464 (SEQ ID NO:41), and
10 rs13143308 (SEQ ID NO:51),
11. The method of any of the Claims 8-10, wherein the at least one allele is selected from -2, -4 and/or -8 in marker D4S406, allele A of marker rs2634073, allele T of marker rs2200733, allele T of marker rs2220427, allele T of marker rs10033464, and/or allele G of marker rs13143308.
- 15 12. A method of genotyping a nucleic acid sample obtained from a human individual, comprising determining the presence or absence of at least one allele of at least one polymorphic marker predictive of increased risk of cardiac arrhythmia and/or stroke in the sample, wherein the at least one marker is selected from the markers rs2200733 and rs10033464, and markers in linkage disequilibrium therewith, and
20 wherein determination of the presence or absence of the at least one allele of the at least one polymorphic marker is predictive of increased risk of cardiac arrhythmia and/or stroke in the individual.
13. The method of Claim 12, wherein genotyping comprises amplifying a segment of a nucleic acid that comprises the at least one polymorphic marker, by Polymerase
25 Chain Reaction (PCR), using a nucleotide primer pair flanking the at least one polymorphic marker.
14. The method of Claim 12 or 13, wherein genotyping is performed using a process selected from allele-specific probe hybridization, allele-specific primer extension, allele-specific amplification, nucleic acid sequencing, 5'-exonuclease digestion,
30 molecular beacon assay, oligonucleotide ligation assay, size analysis, and single-stranded conformation analysis.
15. The method of any of the preceding Claims, wherein the cardiac arrhythmia is atrial fibrillation or atrial flutter.

16. The method of any of the preceding Claims, wherein the stroke is ischemic stroke.
17. The method of any of the preceding Claims, further comprising analyzing non-genetic information to make risk assessment, diagnosis, or prognosis of the individual.
- 5 18. The method of Claim 17, wherein the non-genetic information is selected from age, age at onset of disease, gender, ethnicity, socioeconomic status, previous disease diagnosis, medical history of subject, family history of atrial fibrillation, atrial flutter and/or stroke, biochemical measurements, and clinical measurements.
- 10 19. An apparatus when used in a method according to any one of claims 1 to 18, comprising:

a computer readable memory; and

a routine stored on the computer readable memory;

wherein the routine is adapted to be executed on a processor to analyze genotype data for at least one human individual with respect to at least one polymorphic

- 15 marker selected from the markers rs2200733 and rs10033464, and markers in linkage disequilibrium therewith, and generate an output based on the marker data, wherein the output comprises a risk measure of the at least one marker as a genetic indicator of cardiac arrhythmia and/or stroke for the human individual.
- 20 20. The apparatus of Claim 19, wherein the routine further comprises determining an indicator of the frequency of at least one allele of at least one polymorphic marker and/or at least one haplotype in a plurality of individuals diagnosed with cardiac arrhythmia and/or stroke, and an indicator of the frequency of at the least one
- 25 allele of at least one polymorphic marker or at least one haplotype in a plurality of reference individuals, and calculating a risk measure for the at least one allele and/or haplotype based thereupon;

and wherein a risk measure for the individual is calculated based on a comparison of the at least one marker and/or haplotype status for the individual to the calculated risk for the at least one marker and/or haplotype information for the plurality of individuals diagnosed with atrial fibrillation, atrial flutter and/or stroke.

- 30 21. The apparatus of Claim 20, wherein the at least one polymorphic marker is selected from the markers set forth in Table 19.
- 22. The apparatus of Claim 20 or 21, wherein the at least one polymorphic marker is selected from D4S406 (SEQ ID NO:45), rs2634073 (SEQ ID NO:33), rs2200733

(SEQ ID NO:28), rs2220427 (SEQ ID NO:1), rs10033464 (SEQ ID NO:41), and rs13143308 (SEQ ID NO:51).