

THAT WHICH IS CLAIMED IS:

1. A method for identifying a genetic variant that is associated with development of a condition of interest, comprising:

(a) determining from biological samples containing DNA the nucleotide sequences carried by a plurality of individual human subjects at a genetic locus of interest, wherein said subjects include both (i) subjects affected with the condition of interest and (ii) subjects unaffected with the condition of interest;

(b) performing multiple sequence alignment analysis to identify genetic variants at said genetic locus from nucleotide sequences observed in said plurality of subjects;

(c) mapping said genetic variants to construct a phylogenetic tree of said subjects, said tree comprising branches that identify variant changes between said subjects on the same cistron;

(d) examining the genetic variants represented as branches in said tree and determining the ratio of affected and unaffected subjects to identify those changes that lead to a changed ratio of affected to unaffected subjects; and then

(e) identifying a genetic variant where the ratio of affected to unaffected subjects is at least 5% different from one or more adjacent variants on said tree

to thereby identify a genetic variant associated with the development of said condition of interest.

2. The method of claim 1, wherein all subjects carry a same known polymorphism for said condition of interest.

3. The method of claim 1 or claim 2, wherein the known polymorphism is an Apolipoprotein E allele.

4. The method of any of claims 1-3, wherein the genetic locus of interest is in linkage disequilibrium with the known polymorphism.

5. The method of any of claims 1-4, wherein the genetic locus of interest is on the same chromosome and less than 10, 20, 30, 40, or 50 kilobases away from the known polymorphism.

6. The method of any of claims 1-5, wherein said genetic locus is TOMM40.

7. The method of any of claims 1-6, wherein said condition of interest is associated with increased or decreased mitochondrial dysfunction.

8. The method any of claims 1-7, wherein said condition of interest is a neurodegenerative disease, a metabolic disease, a cardiovascular disease, a psychiatric disorder, or cancer.

9. The method of any of claims 1-7, wherein the condition of interest is coronary artery disease.

10. The method of any of claims 1-7, wherein the condition of interest is diabetes mellitus, type II.

11. The method of any of claims 1-7, wherein the condition of interest is Parkinson's disease.

12. The method of any of claims 1-7, wherein the condition of interest is Alzheimer's disease.

13. A method of determining increased risk for development of the condition of interest, comprising:

(a) determining from a biological sample containing DNA a genetic variant identified by the method of any of claims 1-12 carried by an individual subject; and then

(b) determining that said subject is at increased risk for development of the condition of interest when said genetic variant is present.

14. A method of determining increased risk for development of Alzheimer's disease in a subject, comprising:

(a) detecting from a biological sample containing DNA taken from said subject the presence or absence of a genetic variant of the TOMM40 gene associated with increased or decreased risk of Alzheimer's disease, wherein said variant is a deletion/insertion polymorphism in intron 6 or intron 9 of the TOMM40 gene; and

(b) determining said subject is at increased or decreased risk of Alzheimer's disease when said genetic variant is present or absent.

15. The method of claim 14, further comprising detecting whether said subject is an Apo E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, or E4/E4 subject.

16. The method of claim 14, further comprising detecting whether said subject is an Apo E3/E3 or E3/E4 subject.

17. The method of any of claims 14-16, further comprising the step of:

(c) administering an anti-Alzheimer's disease active agent to said subject in a treatment effective amount when said subject is determined to be at increased risk of Alzheimer's disease.

18. The method of claim 17, wherein said administering step is carried out in said subject at an earlier age when said subject is determined to be at increased risk by the presence or absence of said genetic variant as compared to a subject in which said genetic variant is not present or absent.

19. The method of claim 17 or claim 18, wherein said active agent is selected from the group consisting of acetylcholinesterase inhibitors, NMDA receptor antagonists, peroxisome proliferator-activated receptor agonists or modulators, antibodies, fusion proteins, therapeutic RNA molecules, and combinations thereof.

20. The method of claim 17 or claim 18, wherein said active agent is rosiglitazone or a pharmaceutically acceptable salt thereof.

21. The method of any of claims 14-20, wherein said genetic variant of the TOMM40 is a poly-T insertion variant at genomic location 50,094,889 of NCBI Build 36.3.

22. In a method of treating a subject for Alzheimer's disease by administering an anti-Alzheimer's disease active agent to said subject in a treatment-effective amount; the improvement comprising:

administering said active agent to said subject at an earlier age when said subject carries a genetic variant of the TOMM40 gene associated with increased risk of Alzheimer's disease as compared to a corresponding subject who does not carry said genetic variant,

wherein said genetic variant of the TOMM40 is a deletion/insertion polymorphism (DIP) in intron 6 or intron 9 of the TOMM40 gene.

23. The method of claim 22, further comprising detecting whether said subject is an Apo E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, or E4/E4 subject.

24. The method of claim 23, further comprising detecting whether said subject is an Apo E3/E3 or E3/E4 subject.

25. The method of any of claims 22-24, wherein said active agent is selected from the group consisting of acetylcholinesterase inhibitors, NMDA receptor antagonists, peroxisome proliferator-activated receptor agonists or modulators, antibodies, fusion proteins, therapeutic RNA molecules, and combinations thereof.

26. The method of any of claims 22-24, wherein said active agent is rosiglitazone or a pharmaceutically acceptable salt thereof.

27. The method of any of claims 22-26, wherein said genetic variant of the TOMM40 gene is a variant selected from the group consisting of: rs10524523, rs10602329, and DIP3.

28. The method of any of claims 22-26, wherein said DIP is an insertion polymorphism.

29. The method of any of claims 22-26, wherein said DIP is a poly-T deletion/insertion polymorphism.

30. The method of any of claims 22-26, wherein said genetic variant of the TOMM40 gene is rs10524523.

31. The method of claim any of claims 22-26, wherein said DIP is a poly-T deletion/insertion polymorphism having a poly-T of at least a 27 contiguous base pairs.

32. The method of any of claims 22-26, wherein said DIP is a poly-T deletion/insertion polymorphism having a poly-T of at least a 27 contiguous base pairs at rs10524523.

33. A method of treatment for a condition of interest, wherein said condition of interest is associated with ApoE and/or TOMM40, for a patient in need thereof, said method comprising:

(a) determining the presence or absence of a genetic variant identified by the method of any of claims 1-12 carried by an individual subject to generate a genetic profile of said patient; and then, if said profile is indicative of said patient being responsive to an active agent,

(b) administering said active agent to said subject in a treatment effective amount to treat said condition of interest.

34. The method of claim 33, wherein said active agent is selected from the group consisting of acetylcholinesterase inhibitors, NMDA receptor antagonists, peroxisome proliferator-activated receptor agonists or modulators, antibodies, fusion proteins, therapeutic RNA molecules, and combinations thereof.

35. The method of claim 33, wherein said active agent is rosiglitazone or a pharmaceutically acceptable salt thereof.

36. The method of any of claims 33-35, wherein said genetic variant of the TOMM40 is a variant of TOMM40 is at a genetic location of NCBI Build 36.3 selected from the group consisting of: 50,092,565, 50,092,587, 50,093,506, 50,093,609, 50,094,317, 50,094,558, 50,094,716, 50,094,733, 50,094,889, 50,095,252, 50,095,506, 50,095,698, 50,095,764, 50,096,271, 50,096,531, 50,096,647, 50,096,697, 50,096,812, 50,096,902, 50,097,361, 50,098,378, 50,098,513, and 50,099,628.

37. The method of any of claims 33-36, wherein said genetic variant of the TOMM40 gene is a deletion/insertion polymorphism (DIP).

38. The method of claim 37, wherein said DIP is an insertion polymorphism.

39. The method of claim 37, wherein said DIP is a poly-T deletion/insertion polymorphism.

40. The method of any of claims 37-39, wherein said DIP is rs10524523, rs10602329 or DIP3.

41. The method of any of claims 37-39, wherein said DIP is rs10524523.
42. A method of treatment for Alzheimer's disease in a subject comprising:
(a) detecting from a biological sample containing DNA taken from said subject the presence or absence of a genetic variant of the TOMM40 gene associated with responsiveness to an active agent; and, if said genetic variant is present,
(b) administering said active agent to said subject in a treatment effective amount to treat said Alzheimer's disease.
43. The method of claim 42, further comprising detecting whether said subject is an Apo E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, or E4/E4 subject.
44. The method of claim 42, further comprising detecting whether said subject is an Apo E3/E3 or E3/E4 subject.
45. The method of any of claims 42-44, wherein said active agent is selected from the group consisting of acetylcholinesterase inhibitors, NMDA receptor antagonists, peroxisome proliferator-activated receptor agonists or modulators, antibodies, fusion proteins, therapeutic RNA molecules, and combinations thereof.
46. The method of any of claims 42-44, wherein said active agent is rosiglitazone or a pharmaceutically acceptable salt thereof.
47. The method of any of claims 42-46, wherein said genetic variant of the TOMM40 gene is at the genetic location of NCBI Build 36.3 selected from the group consisting of: 50,092,565, 50,092,587, 50,093,506, 50,093,609, 50,094,317, 50,094,558, 50,094,716, 50,094,733, 50,094,889, 50,095,252, 50,095,506, 50,095,698, 50,095,764, 50,096,271, 50,096,531, 50,096,647, 50,096,697, 50,096,812, 50,096,902, 50,097,361, 50,098,378, 50,098,513, and 50,099,628.
48. The method of any of claims 42-47, wherein said genetic variant of the TOMM40 gene is a deletion/insertion polymorphism (DIP)
49. The method of any of claims 48, wherein said DIP is rs10524523, rs10602329 or DIP3.

50. The method of claim 48 or claim 49, wherein said DIP is an insertion polymorphism.

51. The method of claim 48 or claim 49, wherein said DIP is poly-T deletion/insertion polymorphism.

52. The method of any of claim 48 or claim 49, wherein said DIP is rs10524523.

53. The use of an anti-Alzheimer's disease active agent for the preparation of a medicament for carrying out a method of any of claims 17-52.

54. The use of an anti-Alzheimer's disease active agent for carrying out a method of any of claims 17-52.

55. A method of determining a prognosis or the risk for developing Alzheimer's disease in a patient comprising obtaining a patient profile, wherein said obtaining a patient profile comprises:

detecting the presence or absence of at least one ApoE 2, ApoE 3, or ApoE 4 allele in a biological sample of said patient, and

detecting the presence or absence of at least one TOMM40 deletion/insertion polymorphism (DIP) located in intron 6 or intron 9 of the TOMM40 gene, and then

converting said patient profile into said prognosis, wherein the presence of said ApoE 2, ApoE 3 or ApoE 4 allele and the presence of said at least one TOMM40 DIP polymorphism identifies said patient as a patient at risk for developing Alzheimer's disease.

56. The method of claim 55, wherein said DIP is rs10524523, rs10602329 or DIP3.

57. The method of claim 55, wherein said DIP is an insertion polymorphism.

58. The method of claim 55, wherein said DIP is a poly-T deletion/insertion polymorphism.

59. The method of claim 55, wherein said DIP is rs10524523.

60. The method of any of claims 55-59, further comprising detecting whether said subject is an Apo E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, or E4/E4 subject.

61. A method for stratifying a subject into a subgroup of a clinical trial of a therapy for the treatment of Alzheimer's disease, said method comprising:

detecting the presence or absence of at least one ApoE 2, ApoE 3, or ApoE 4 allele in a biological sample of said patient,

detecting the presence or absence of at least one TOMM40 deletion/insertion polymorphism (DIP) located in intron 6 or intron 9 of the TOMM40 gene, and

stratifying said subject into said subgroup for said clinical trial of said therapy based upon the presence or absence of said at least one ApoE 2, ApoE 3, or ApoE 4 allele and/or TOMM40 DIP allele.

62. The method of claim 61, wherein said DIP is an insertion polymorphism.

63. The method of claim 61, wherein said DIP is poly-T deletion/insertion polymorphism.

64. The method of claims 61, wherein said DIP is rs10524523, rs10602329 or DIP3.

65. The method of claim 61, wherein said DIP is rs10524523.

66. The method of any of claims 61-65, further comprising detecting whether said subject is an Apo E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, or E4/E4 subject.

67. A method for identifying a patient in a clinical trial of a treatment for Alzheimer's disease comprising:

a) identifying a patient diagnosed with Alzheimer's disease; and

b) determining a prognosis for said patient diagnosed with Alzheimer's disease comprising obtaining a patient profile, wherein said patient profile comprises

i) detecting the presence or absence of at least one ApoE 3, ApoE 4, and/or ApoE 2 allele in a biological sample of said patient,

ii) detecting the presence or absence of at least one TOMM40 deletion/insertion polymorphism (DIP) located in intron 6 or intron 9 of the TOMM40 gene, and

iii) converting the patient profile into said prognosis,

said prognosis including a prediction of whether the patient is a candidate for said clinical trial for said treatment of Alzheimer's disease.

68. The method of claim 67, wherein said DIP is an insertion polymorphism.

69. The method of claim 67, wherein said DIP is poly-T deletion/insertion polymorphism.

70. The method of claim 67, wherein said DIP is rs10524523, rs10602329 or DIP3.

71. The method of claim 67, wherein said DIP is rs10524523.

72. The method of any of claims 67-71, further comprising detecting whether said subject is an Apo E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, or E4/E4 subject.

73. A kit for determining if a subject is at increased risk of developing late onset Alzheimer's disease comprising:

(A) at least one reagent that specifically detects ApoE 3, ApoE 4, and/or ApoE 2, wherein said reagent is selected from the group consisting of antibodies that selectively bind ApoE isoforms, and oligonucleotide probes that selectively bind to DNA encoding ApoE alleles;

(B) at least one reagent that specifically detects the presence or absence of at least one TOMM40 deletion/insertion polymorphism (DIP) located in intron 6 or intron 9 of the TOMM40 gene; and

(C) instructions for determining that the subject is at increased risk of developing late onset Alzheimer's disease by

(i) detecting the presence or absence of an ApoE 3, ApoE4, and/or ApoE 2 isoform in said subject with said at least one reagent;

(ii) detecting the presence or absence of at least one TOMM40 deletion/insertion polymorphism (DIP) located in intron 6 or intron 9 of the TOMM40 gene; and

(iii) observing whether or not the subject is at increased risk of developing late onset Alzheimer's disease by observing if the presence of ApoE 3, ApoE 4, and/or ApoE 2 and said TOMM40 DIP is or is not detected with said at least one reagent, wherein the presence of ApoE 3, ApoE 4 and/or ApoE 2 isoform and said TOMM40 DIP indicates said subject is at increased risk of developing late onset Alzheimer's disease.

74. The kit of claim 73, wherein said at least one reagent and said instructions are packaged in a single container.

75. The kit of claim 73 or claim 74, wherein said DIP is an insertion polymorphism.

76. The kit of claim 73 or claim 74, wherein said DIP is a poly-T deletion/insertion polymorphism.

77. The kit of claim 73 or claim 74, wherein said DIP is rs10524523, rs10602329 or DIP3.

78. The kit of claim 73 or claim 74, wherein said DIP is rs10524523.

79. The kit of any of claims 73-78, wherein said determining step further comprises detecting whether said subject is an Apo E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, or E4/E4 subject.

80. A kit for determining if a subject is responsive to treatment for a condition of interest, wherein said condition of interest is associated with ApoE and/or TOMM40, with an active agent, said kit comprising:

(A) at least one reagent that specifically detects ApoE 3, ApoE 4, and/or ApoE 2, wherein said reagent is selected from the group consisting of antibodies that selectively bind ApoE isoforms, and oligonucleotide probes that selectively bind to DNA encoding ApoE alleles;

(B) at least one reagent that specifically detects the presence or absence of at least one TOMM40 deletion/insertion polymorphism (DIP) located in intron 6 or intron 9 of the TOMM40 gene; and

(C) instructions for determining that the subject is responsive to treatment for said condition of interest with said active agent of interest by

(i) detecting the presence or absence of an ApoE 3, ApoE4, and/or ApoE 2 isoform in said subject with said at least one reagent;

(ii) detecting the presence or absence of at least one TOMM40 deletion/insertion polymorphism (DIP) located in intron 6 or intron 9 of the TOMM40 gene; and

(iii) determining whether or not the subject is responsive to treatment by observing if the presence of ApoE 3, ApoE 4, and/or ApoE 2 isoform and said TOMM40 DIP is or is not detected with said at least one reagent, wherein the presence of ApoE 3, ApoE 4 and/or ApoE 2

and said TOMM40 DIP indicates that said subject is responsive to said treatment with said active agent.

81. The kit of claim 80, wherein said at least one reagent and said instructions are packaged in a single container.

82. The kit of claim 80 or claim 81, wherein said DIP is an insertion polymorphism.

83. The kit of claim 80 or claim 81, wherein said DIP is a poly-T deletion/insertion polymorphism.

84. The kit of claim 80 or claim 81, wherein said DIP is rs10524523, rs10602329 or DIP3.

85. The kit of claim 80 or claim 81, wherein said DIP is rs10524523.

86. The kit of any of claims 80-85, wherein said determining step further comprises detecting whether said subject is an Apo E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, or E4/E4 subject.

CLAIMS

1. A method of determining increased risk for development of Alzheimer's disease in a subject, comprising:

(a) detecting from a biological sample containing DNA taken from said subject the presence or absence of a genetic variant of the TOMM40 gene associated with increased or decreased risk of Alzheimer's disease, wherein said variant is a deletion/insertion polymorphism in intron 6 or intron 9 of the TOMM40 gene; and

(b) determining said subject is at increased or decreased risk of Alzheimer's disease when said genetic variant is present or absent; and

(c) providing an anti-Alzheimer's disease active agent which is to be administered to said subject in a treatment effective amount when said subject is determined to be at increased risk of Alzheimer's disease.

2. The method of claim 1, wherein the anti-Alzheimer's disease active agent is to be administered in said subject at an earlier age when said subject is determined to be at increased risk by the presence or absence of said genetic variant as compared to a subject in which said genetic variant is not present or absent.

3. The method of claim 1 or claim 2, wherein said active agent is selected from the group consisting of acetylcholinesterase inhibitors, NMDA receptor antagonists, peroxisome proliferator-activated receptor agonists or modulators, antibodies, fusion proteins, therapeutic RNA molecules, and combinations thereof.

4. The method of any of claims 1-3, 26-27, 30 wherein said genetic variant of the TOMM40 is a poly-T insertion variant at genomic location 50,094,889 of NCBI Build 36.3 (rs10524523).

5. Use of an anti-Alzheimer's disease active agent in the manufacture of a medicament for treating Alzheimer's disease in a subject, wherein said medicament is to be administered to said subject at an earlier age when said subject carries a genetic variant of the TOMM40 gene associated with increased risk of Alzheimer's disease as compared to a corresponding subject who does not carry said genetic variant,

wherein said genetic variant of the TOMM40 is a deletion/insertion polymorphism (DIP) in intron 6 or intron 9 of the TOMM40 gene.

6. The use of claim 5, further comprising detecting whether said subject is an Apo E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, or E4/E4 subject.

7. The use of claim 6, further comprising detecting whether said subject is an Apo E3/E3 or E3/E4 subject.

8. The use of any of claims 5-7, wherein said active agent is selected from the group consisting of acetylcholinesterase inhibitors, NMDA receptor antagonists, peroxisome proliferator-activated receptor agonists or modulators, antibodies, fusion proteins, therapeutic RNA molecules, and combinations thereof.

9. The use of any of claims 5-8, 29-30 wherein said genetic variant of the TOMM40 gene is a variant selected from the group consisting of: rs10524523, rs10602329, and DIP3.

10. The use of any of claims 5-8, 29-30 wherein said DIP is an insertion polymorphism.

11. The use of any of claims 5-8, 29-30 wherein said DIP is a poly-T deletion/insertion polymorphism.

12. The use of any of claims 5-8, 29-30 wherein said genetic variant of the TOMM40 gene is rs10524523.

13. The use of any of claims 5-8, 29-30 wherein said DIP is a poly-T deletion/insertion polymorphism having a poly-T of between 20 and 50 contiguous base pairs.

14. The use of any of claims 5-8, 29-30 wherein said DIP is a poly-T deletion/insertion polymorphism having a poly-T of between 20 and 50 contiguous base pairs at rs10524523.

15. A method of determining increased risk for development of Alzheimer's disease in a subject, comprising:

(a) detecting from a biological sample containing DNA taken from said subject the presence or absence of a genetic variant of the TOMM40 gene associated with increased or decreased risk of Alzheimer's disease, wherein said variant is at a genetic location of NCBI Build 36.3 selected from the group consisting of: 50,092,565, 50,092,587, 50,093,506, 50,093,609, 50,094,317, 50,094,558, 50,094,716, 50,094,733, 50,094,889, 50,095,252, 50,095,506, 50,095,764, 50,096,531, 50,096,647, 50,096,697, 50,096,812, 50,096,902, 50,097,361, 50,098,378, and 50,098,513; and

(b) determining said subject is at increased or decreased risk of Alzheimer's disease when said genetic variant is present or absent.

16. The method of claim 15, further comprising detecting whether said subject is an Apo E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, or E4/E4 subject.

17. The method of claim 15, further comprising detecting whether said subject is an Apo E3/E3 or E3/E4 subject.

18. The method of any of claims 15-17, further comprising the step of:

(c) providing an anti-Alzheimer's disease active agent which is to be administered to said subject in a treatment effective amount when said subject is determined to be at increased risk of Alzheimer's disease.

19. The method of claim 18, wherein the anti-Alzheimer's disease active agent is to be administered in said subject at an earlier age when said subject is determined to be at increased risk by the presence or absence of said genetic variant as compared to a subject in which said genetic variant is not present or absent.

20. The method of claim 18 or claim 19, wherein said active agent is selected from the group consisting of acetylcholinesterase inhibitors, NMDA receptor antagonists, peroxisome proliferator-activated receptor agonists or modulators, antibodies, fusion proteins, therapeutic RNA molecules, and combinations thereof.

21. Use of an anti-Alzheimer's disease active agent in the manufacture of a medicament for treating Alzheimer's disease in a subject wherein said medicament is to be administered to said subject at an earlier age when said subject carries a genetic variant of the TOMM40 gene associated with increased risk of Alzheimer's disease as compared to a corresponding subject who does not carry said genetic variant,

wherein said genetic variant of the TOMM40 is at a genetic location of NCBI Build 36.3 selected from the group consisting of: 50,092,565, 50,092,587, 50,093,506, 50,093,609, 50,094,317, 50,094,558, 50,094,716, 50,094,733, 50,094,889, 50,095,252, 50,095,506, 50,095,764, 50,096,531, 50,096,647, 50,096,697, 50,096,812, 50,096,902, 50,097,361, 50,098,378, and 50,098,513.

22. The use of claim 21, further comprising detecting whether said subject is an Apo E2/E2, E2/E3, E2/E4, E3/E3, E3/E4, or E4/E4 subject.

23. The use of claim 21, further comprising detecting whether said subject is an Apo E3/E3 or E3/E4 subject.

24. The use of any or claims 21-23, wherein said active agent is selected from the group consisting of acetylcholinesterase inhibitors, NMDA receptor antagonists, peroxisome proliferator-activated receptor agonists or modulators, antibodies, fusion proteins, therapeutic RNA molecules, and combinations thereof.

25. The method or kit of any of claims 4, wherein the genetic variant of the TOMM40 gene is the deletion/insertion polymorphism rs10524523 having a poly-T of between 20 and 50 contiguous base pairs.

26. The method of claim 1 or claim 2, wherein said active agent is a thiazolidinedione.

27. The method of claim 1 or claim 2, wherein said active agent is a thiazolidinedione drug.

28. The use of any of claims 5-7, wherein said active agent is a thiazolidinedione.

29. The use of any of claims 5-7, wherein said active agent is a thiazolidinedione drug.

30. The method or use of any one of claims 1-3, 5-14, 18-29, wherein said treating comprises delaying the onset of Alzheimer's disease.