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(54) **Title**: GENETIC IDENTIFICATION OF RESPONSE TO ANTIDEPRESSANT MEDICATIONS

(57) **Abstract**: The present invention addresses the significant fraction of patients exposed to elevations in serotonergic neurotransmission, with or without concomitant changes in adrenergic neurotransmission, who do now and/or will in the future suffer degradation of treatment response with antidepressants. Along with decreased dopaminergic neurotransmission efficiency, the identification of certain psychiatric symptoms correlated with mood, reward and attentional dysfunctions may occur. Genetic profile in patients who are either not responsive to first line antidepressant medications or can remit to therapies targeting changes in serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission for major depressive disorder.

Genetic Identification of Response to Antidepressant Medications

FIELD OF THE INVENTION

[0001] The present invention identifies genes, single nucleotide polymorphisms and haplotypes which predict a high probability of failure of first line antidepressant therapy targeting increases in serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission for major depressive disorder. The present invention also discloses genes, single nucleotide polymorphisms and haplotypes which predict a high probability of response to first line antidepressant therapy targeting increases in serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission in major depressive disorder.

BACKGROUND OF THE INVENTION

[0002] The discovery that chlorpromazine (originally developed as an antihistamine) was useful in major psychiatric disorders, and the subsequent investigation of its pharmacological activity, led to an understanding of the importance of neurotransmitter imbalance in mental diseases. Contemporary clinical wisdom now takes for granted that alterations of neurotransmitters are responsible for the circuitry distortions associated with affective and/or mood disorders. Among the hosts of agents found useful in the treatment of mental disorders are the antidepressant drugs, a class of medications that ameliorate the symptoms of depression. Among the first widely available agents were such tricyclic antidepressants as imipramine, nortryptyline, doxepin, amitriptyline, and desipramine. Investigation of the tricyclic antidepressants defined reuptake inhibition of catecholamines and serotonin as primary mechanisms of action. The observation that tricyclic antidepressants modulate both adrenergic and serotonergic neurotransmission stimulated the search for compounds that would selectively inhibit the reuptake of either neurotransmitter alone.

SEQUENCE LISTING

[0003] The nucleic acid sequences listed in the accompanying sequence listing are shown using standard letter abbreviations for nucleotide bases, as defined in 37 C.F.R. 1.822. Only one strand of each nucleic acid sequence is shown, but the complementary strand is understood as included by any reference to the displayed strand. In the accompanying sequence listing:

[0004] SEQ ID NO: 1 is a nucleic acid sequence context of a Single Nucleotide Polymorphism (SNP) assigned RefSNP accession ID (rs number), rs666693, in the Single Nucleotide Polymorphism (SNP) database (dbSNP) at the National Center for Biotechnology Information (NCBI) and comprising human SNP alleles A/G (single nucleotide variation), or rs666693-A and rs666693-G, within the 5-hydroxytryptamine (serotonin) receptor 2A (HTR2A) gene:

TCTGAGAAGCACTGCCTACACTATCA[A/G]TTTAGGATTGGAGCAGACTTTTAAC

[0005] SEQ ID NO: 2 is a nucleic acid sequence context of a SNP assigned rs number rs582385 in the dbSNP at NCBI and comprising human SNP alleles –C/T (deletion/insertion variation), or rs582385-[-/C/T], within the HTR2A gene:

TTCTTTCCAGCTCTATAATTCCATTT[C/T]CTACTGTTGGGTTTCAACACCTAAA

[0006] SEQ ID NO: 3 is a nucleic acid sequence context of a SNP assigned rs number rs9316232 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs9316232-A and rs9316232-G, within the HTR2A gene:

AACTTCTAAGCTTTCCTATGATTAAG[A/G]TAATTGTTCTATGATATGAGGAGCG

[0007] SEQ ID NO: 4, is a nucleic acid sequence context of a SNP assigned rs number rs17275521 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs17275521-A and rs17275521-G, within the mu-opiod receptor (OPRM1) gene:

TATTGAAAATGATACGGTGAGCAATA[A/G]GAATGAGACAAAGTAAAAAGAACTG

[0008] SEQ ID NO: 5 is a nucleic acid sequence context of a SNP assigned rs number rs17209711 in the dbSNP at NCBI and comprising human SNP alleles A/T (single nucleotide variation), or rs17209711-A and rs17209711-T, within the OPRM1 gene:

AAATAATCAGTTACAAGTATTGAAAA[A/T]GATACGGTGAGCAATAGGAATGAGA

[0009] SEQ ID NO: 6 is a nucleic acid sequence context of a SNP assigned rs number rs3778149 in the dbSNP at NCBI and comprising human SNP alleles C/G (single nucleotide variation), or rs3778149-C and rs3778149-G, within the OPRM1 gene:

AAATATTGGCAAATATCTCACTCTCA[C/G]TAAAATGGGTAGTAAAATTTGTGAA

[00010] SEQ ID NO: 7 is a nucleic acid sequence context of a SNP assigned rs number rs3778146 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs3778146-C and rs3778146-T, within the OPRM1 gene:

TTAATTGAAAAACGTTGCCAGCAGTA[A/C/G/T]AACCTGAACATCAGAGCCTCATTGT

[00011] SEQ ID NO: 8 is a nucleic acid sequence context of a SNP assigned rs number rs7773995 in the dbSNP at NCBI and comprising human SNP alleles C/T (single nucleotide variation), or rs7773995-C and rs7773995-T, within the OPRM1 gene:

CCCAGTAAGTGAATTAAATACTTTCA[C/T]AGACACTCTCCATCTAGTAGAACAA

[00012] SEQ ID NO: 9, is a nucleic acid sequence context of a SNP assigned rs number rs3778145 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs3778145-A and rs3778145-C, within the OPRM1 gene:

CCCGCCCACATTGTGACCGTCTCAAA[A/C]ACATGCCTCGTTTTCCTCTTCCCTG

[00013] SEQ ID NO: 10, is a nucleic acid sequence context of a SNP assigned rs number rs885345 in the dbSNP at NCBI and comprising human SNP alleles C/T (single nucleotide variation), or rs885345-C and rs885345-T, within the neuronal calcium sensor 1 (FREQ) gene, which is also known as NCS1:

CTCCAGTGCCGGTCAGGTCCCAAGTC[C/T]CCAGGAGAGCACAGGCCAGGGCACG

[00014] SEQ ID NO: 11 is a nucleic acid sequence context of a SNP assigned rs number rs10052016 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs10052016-A and rs10052016-G, within the solute carrier family 6 (neurotransmitter transporter, dopamine), member 3 (SLC6A3) gene:

ACCTGAAAAACACAGTGACCTAACAT[A/G]ACCTCTCTGACATTTATGCAACTTT

[00015] SEQ ID NO: 12 is a nucleic acid sequence context of a SNP assigned rs number rs1861646 in the dbSNP at NCBI and comprising human SNP alleles G/T (single nucleotide variation), or rs1861646-G and rs1861646-T, within the norepinephrine transporter (SLC6A2) gene:

TCTCTCTGATACTCTTAGAGTTCTTG[G/T]TCATGCCATTGAGAGCAAAGAAAGT

[00016] SEQ ID NO: 13, is a nucleic acid sequence context of a SNP assigned rs number rs6495308 in the dbSNP at NCBI and comprising human SNP alleles C/T (single nucleotide variation), or rs6495308-C and rs6495308-T, within the cholinergic receptor, nicotinic alpha-3 (CHRNA3) gene:

GTAACTGTCTGATGGCAGGTTTGCTG[C/T]TGGGAGAGTAGAGAAGAGGTTTGGG

[00017] SEQ ID NO: 14 is a nucleic acid sequence context of a SNP assigned rs number rs10053602 in the dbSNP at NCBI and comprising human SNP alleles C/T (single nucleotide variation), or rs10053602-C and rs10053602-T, within the solute carrier family 6 (neurotransmitter transporter, dopamine) SLC6A3, gene:

ATAACCTCTCTGACATTTATGCAACT[C/T]TCCAACCAAAGACAGCAGAATACAT

[00018] SEQ ID NO: 15 is a nucleic acid sequence context of a SNP assigned rs number rs2350786 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs2350786-A and rs2350786-G, within the cholinergic receptor, muscarinic 2 (CHRM2) gene:

TACTCTTTGTCATGGAGGCAAACTAC[A/G]GTAGCTGATTACCATTTTTTAATGA

[00019] SEQ ID NO: 16 is a nucleic acid sequence context of a SNP assigned rs number rs6960707 in the dbSNP at NCBI and comprising human SNP alleles C/T (single

nucleotide variation), or rs6960707-C and rs6960707-T, within the cholinergic receptor; muscarinic 2 (CHRM2) gene:

CTTGCTCTGTATCTCAGGTTACAATA[C/T]TGTGGCAAAAACATGGCTCACTGCA

[00020] SEQ ID NO: 17 is a nucleic acid sequence context of a SNP assigned rs number rs929492 in the dbSNP at NCBI and comprising human SNP alleles C/T (single nucleotide variation), or rs929492-C and rs929492-T, within the calcium channel voltage-dependent, L type, alpha 1C subunit (CACNA1C) gene:

TTTTACGCAGAGGAGGCCTGTGAGCG[C/T]TGTGCTAGCTACTGAGTATCTGGTG

[00021] SEQ ID NO: 18 is a nucleic acid sequence context of a SNP assigned rs number rs6678672 in the dbSNP at NCBI and comprising human SNP alleles C/T (single nucleotide variation), or rs6678672-C and rs6678672-T, within the S100 calcium binding protein A10 (S100A10) gene:

CAAGCTACACCCTCTCCTGATTGGTT[C/T]TCCTAGTTCTGCCTTAGGTTTGCTG

[00022] SEQ ID NO: 19 is a nucleic acid sequence context of a SNP assigned rs number rs6587640 in the dbSNP at NCBI and comprising human SNP alleles C/T (single nucleotide variation), or rs6587640-C and rs6587640-T, within the S100A10 gene:

TACAAGGGCAGAACAATTAGAGAAGT[C/T]AGACTCCAAGCCTGAATGAAGAGTG

[00023] SEQ ID NO: 20 is a nucleic acid sequence context of a SNP assigned rs number rs17047279 in the dbSNP at NCBI and comprising human SNP alleles G/T (single nucleotide variation), or rs17047279-G and rs17047279-T, within the glutamate receptor metabotropic 7 receptor (GRM7) gene:

TGTAAATACATGGCTACAACAAGATC[G/T]CTCTTAAAAACTTAAGTCTCTCGTG

[00024] SEQ ID NO: 21 is a nucleic acid sequence context of a SNP assigned rs number rs17047286 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs17047286-A and rs17047286-G, within the GRM7 gene:

ACTTATCCATTCCAATACCTGAACAC[A/G]TGATTGTTTTGCTCTTCTACCTGTC

[00025] SEQ ID NO: 22, is a nucleic acid sequence context of a SNP assigned rs number rs9368881 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs9368881-A and rs9368881-G, within the FK506 binding protein (FKBP5) gene:

AAAAATAAAGACACAGTTACAAACGA[A/C/G/T]TTGATATGGAAAGTTTAAGAATGCC

[00026] SEQ ID NO: 23 is a nucleic acid sequence context of a SNP assigned rs number rs4765933 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs4765933-A and rs4765933-G, within the CACNA1C gene:

AAAGAGAGACTCAGCAAAGTGAGAGA[A/G]TGCGCTTCCTGCCCATGGGCTTCCC

[00027] SEQ ID NO: 24 is a nucleic acid sequence context of a SNP assigned rs number rs7782904 in the dbSNP at NCBI and comprising human SNP alleles A/T (single nucleotide variation), or rs7782904-A and rs7782904-T, within the CHRM2 gene:

CCAAAGCACTGAAAGAAGCCAAAAAT[A/T]TACACCATTGCTTTCTGACTCCTCT

[00028] SEQ ID NO: 25 is a nucleic acid sequence context of a SNP assigned rs number rs1455857 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs1455857-A and rs1455857-G, within the CHRM2 gene:

AAAGGAAGCAGTCAGGATGCATTTCA[A/G]AATCATGAGAAAGAAGGAGGAGAGG

[00029] SEQ ID NO: 26 is a nucleic acid sequence context of a SNP assigned rs number rs11862589 in the dbSNP at NCBI and comprising human SNP alleles C/T (single nucleotide variation), or rs11862589-C and rs11862589-T, within the SLC6A2 gene:

TTTGACTTAGTCGTCCACTAACTTTC[C/T]GATTTATCACTTACCCACTCATTCA

[00030] SEQ ID NO: 27 is a nucleic acid sequence context of a SNP assigned rs number rs879522 in the dbSNP at NCBI and comprising human SNP alleles C/T (single nucleotide variation), or rs879522-C and rs879522-T, within the SLC6A2 gene:

CTGAAACATGAGAAGGCCTATAAC[C/T]TAAATGCCAGATGGTTCCACCCCTC

[00031] SEQ ID NO: 28 is a nucleic acid sequence context of a SNP assigned rs number rs4564560 in the dbSNP at NCBI and comprising human SNP alleles C/T (single nucleotide variation), or rs4564560-C and rs4564560-T, within the SLC6A2 gene:

GGATGGGGGTGTTATATAGGTTTCCT[C/T]GCTATTCCTTCTCACCCTTGGCTAC

[00032] SEQ ID NO: 29 is a nucleic acid sequence context of a SNP assigned rs number rs1002513 in the dbSNP at NCBI and comprising human SNP alleles C/T (single nucleotide variation), or rs1002513-C and rs1002513-T, within the HTR2A gene:

CTCTCTCCAGATCAGTCTTTTCTGGG[C/T]TAAGAGATAGGAATCGTCACCATGC

[00033] SEQ ID NO: 30 is a nucleic acid sequence context of a SNP assigned rs number rs1378646 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs1378646-A and rs1378646-G, within the CHRM2 gene:

GTCCTGATGAGGAACGAGGGCACTTC[A/G]TCTTCTTGATGCAAACTCTACATTT

[00034] SEQ ID NO: 31 is a nucleic acid sequence context of a SNP assigned rs number rs11198986 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs11198986-A and rs11198986-G within the gene RGS10:

GAGACCTGAAGTGTCCAGCATCTGAG[A/G]CTGTCCTGGCAGGTGCTGGAGAGGG

[00035] SEQ ID NO: 32 is a nucleic acid sequence context of a SNP assigned rs number rs16965623 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs16965623-A and rs16965623-G within the gene SLC6A4;

TATAGCCAGGAGCAACCCGTACCTGA[A/G]CAAGCATGTAATTATCCCGATTGGT

[00036] SEQ ID NO: 33 is a nucleic acid sequence context of a SNP assigned rs number rs6916787 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs6916787-A and rs6916787-G within the gene OPRM1:

AAATATGTCTTCACGAAAAGCCAAAG[A/G]AAAGCATTCAAAGCTATTCACAAAC

[00037] SEQ ID NO: 34 is a nucleic acid sequence context of a SNP assigned rs number rs17047321 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs17047321-A and rs17047321-G within the gene GRM7:

CTTTCAGGGAGCTTTTATTCCAGTAC[A/G]GGAGGCAGAAAGAAAACCAAAAGCA

[00038] SEQ ID NO: 35 is a nucleic acid sequence context of a SNP assigned rs number rs2113545 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs2113545-A and rs2113545-G within the gene CHRM2:

TGGTATTCCCGTACCATTTACTGCAT[A/G]GAGAGCCCTTTACCCATTACTTATT

[00039] SEQ ID NO: 36 is a nucleic acid sequence context of a SNP assigned rs number rs985934 in the dbSNP at NCBI and comprising human SNP alleles C/T (single nucleotide variation), or rs985934-C and rs985934-T within the gene OPRM1:

TAAGTTAGCATCTACCAGAATACAAA[C/T]GGAAACTTGAATTAGTCCAAGTCTC

[00040] SEQ ID NO: 37 is a nucleic acid sequence context of a SNP assigned rs number rs1814270 in the dbSNP at NCBI and comprising human SNP alleles C/T (single nucleotide variation), or rs1814270-C and rs1814270-T within the SLC6A2 gene:

CTGTACTGTTTCAGCAGTCAGTCTTA[C/T]TTGACCTTTCCTTAGCTCCTAACCA

SEQ ID NO: 38 is a nucleic acid sequence context of a SNP assigned rs number rs9462104 in the dbSNP at NCBI and comprising human SNP alleles C/T (single nucleotide variation), or rs9462104-C and rs9462104-T within the FKBP5 gene:

TGGAAAGATATGCAAGAAACTCTTAA[C/T]GGTGGTTATGCCTAAGGGGATGGGA

[00041] SEQ ID NO: 39 is a nucleic acid sequence context of a SNP assigned rs number rs6900677 in the dbSNP at NCBI and comprising human SNP alleles C/G (single nucleotide variation), or rs6900677-C and rs6900677-G within the OPRM1 gene;

TAATCAAATGACTTTGGTAGACAACT[C/G]TTCAAGATATGTCTTGTTAAGATTA

[00042] SEQ ID NO: 40 is a nucleic acid sequence complement of the nucleic acid sequence (rs666693) of SEQ ID NO: 1:

AGACTCTTCGTGACGGATGTGATAGT[T/C]AAATCCTAACCTCGTCTGAAAATTG

[00043] SEQ ID NO: 41 is a nucleic acid sequence complement of the nucleic acid sequence (rs582385) of SEQ ID NO: 2:

AAGAAAGGTCGAGATATTAAGGTAAA[G/A]GATGACAACCCAAAGTTGTGGATTT

[00044] SEQ ID NO: 42 is a nucleic acid sequence complement of the nucleic acid sequence (rs9316232) of SEQ ID NO: 3:

TTGAAGATTCGAAAGGATACTAATTC[T/C]ATTAACAAGATACTATACTCCTCGC

[00045] SEQ ID NO: 43 is a nucleic acid sequence complement of the nucleic acid sequence (rs17275521) of SEQ ID NO: 4:

ATAACTTTTACTATGCCACTCGTTAT[T/C]CTTACTCTGTTTCATTTTTCTTGAC

[00046] SEQ ID NO: 44 is a nucleic acid sequence complement of the nucleic acid sequence (rs17209711) of SEQ ID NO: 5:

TTTATTAGTCAATGTTCATAACTTTT[T/A]CTATGCCACTCGTTATCCTTACTCT

[00047] SEQ ID NO: 45 is a nucleic acid sequence complement of the nucleic acid sequence (rs3778149) of SEQ ID NO: 6:

TTTATAACCGTTTATAGAGTGAGAGT[G/C]ATTTTACCCATCATTTTAAACACTT

[00048] SEQ ID NO: 46 is a nucleic acid sequence complement of the nucleic acid sequence (rs3778146) of SEQ ID NO: 7:

AATTAACTTTTTGCAACGGTCGTCAT[T/G/C/A]TTGGACTTGTAGTCTCGGAGTAACA

[00049] SEQ ID NO: 47 is a nucleic acid sequence complement of the nucleic acid sequence (rs7773995) of SEQ ID NO: 8:

GGGTCATTCACTTAATTTATGAAAGT[G/A]TCTGTGAGAGGTAGATCATCTTGTT

[00050] SEQ ID NO: 48 is a nucleic acid sequence complement of the nucleic acid sequence (rs3778145) of SEQ ID NO: 9:

GGGCGGGTGTAACACTGGCAGAGTTT[T/G]TGTACGGAGCAAAAGGAGAAGGGAC

[00051] SEQ ID NO: 49 is a nucleic acid sequence complement of the nucleic acid sequence (rs885345) of SEQ ID NO: 10:

GAGGTCACGGCCAGTCCAGGGTTCAG[G/A]GGTCCTCTCGTGTCCGGTCCCGTGC

[00052] SEQ ID NO: 50 is a nucleic acid sequence complement of the nucleic acid sequence (rs10052016) of SEQ ID NO: 11:

TGGACTTTTTGTGTCACTGGATTGTA[T/C]TGGAGAGACTGTAAATACGTTGAAA

[00053] SEQ ID NO: 51 is a nucleic acid sequence complement of the nucleic acid sequence (rs1861646) of SEQ ID NO: 12:

AGAGAGACTATGAGAATCTCAAGAAC[C/A]AGTACGGTAACTCTCGTTTCTTTCA

[00054] SEQ ID NO: 52 is a nucleic acid sequence complement of the nucleic acid sequence (rs6495308) of SEQ ID NO: 13:

CATTGACAGACTACCGTCCAAACGAC[G/A]ACCCTCTCATCTCTTCTCCAAACCC

[00055] SEQ ID NO: 53 is a nucleic acid sequence complement of the nucleic acid sequence (rs10053602) of SEQ ID NO: 14:

TATTGGAGAGACTGTAAATACGTTGA[G/A]AGGTTGGTTTCTGTCGTCTTATGTA

[00056] SEQ ID NO: 54 is a nucleic acid sequence complement of the nucleic acid sequence (rs2350786) of SEQ ID NO: 15:

ATGAGAAACAGTACCTCCGTTTGATG[T/C]CATCGACTAATGGTAAAAAATTACT

[00057] SEQ ID NO: 55 is a nucleic acid sequence complement of the nucleic acid sequence (rs6960707) of SEQ ID NO: 16:

GAACGAGACATAGAGTCCAATGTTAT[G/A]ACACCGTTTTTGTACCGAGTGACGT

[00058] SEQ ID NO: 56 is a nucleic acid sequence complement of the nucleic acid sequence (rs929492) of SEQ ID NO: 17:

AAAATGCGTCTCCTCCGGACACTCGC[G/A]ACACGATCGATGACTCATAGACCAC

[00059] SEQ ID NO: 57 is a nucleic acid sequence complement of the nucleic acid sequence (rs6678672) of SEQ ID NO: 18:

GTTCGATGTGGGAGAGGACTAACCAA[G/A]AGGATCAAGACGGAATCCAAACGAC

[00060] SEQ ID NO: 58 is a nucleic acid sequence complement of the nucleic acid sequence (rs6587640) of SEQ ID NO: 19:

ATGTTCCCGTCTTGTTAATCTCTTCA[G/A]TCTGAGGTTCGGACTTACTTCTCAC

[00061] SEQ ID NO: 59 is a nucleic acid sequence complement of the nucleic acid sequence (rs17047279) of SEQ ID NO: 20:

ACATTTATGTACCGATGTTGTTCTAG[C/A]GAGAATTTTTGAATTCAGAGAGCAC

[00062] SEQ ID NO: 60 is a nucleic acid sequence complement of the nucleic acid sequence (rs17047286) of SEQ ID NO: 21:

TGAATAGGTAAGGTTATGGACTTGTG[T/C]ACTAACAAAACGAGAAGATGGACAG

[00063] SEQ ID NO: 61 is a nucleic acid sequence complement of the nucleic acid sequence (rs9368881) of SEQ ID NO: 22:

TTTTTATTTCTGTGTCAATGTTTGCT[T/G/C/A]AACTATACCTTTCAAATTCTTACGG

[00064] SEQ ID NO: 62 is a nucleic acid sequence complement of the nucleic acid sequence (rs4765933) of SEQ ID NO: 23:

TTTCTCTCTGAGTCGTTTCACTCTCT[T/C]ACGCGAAGGACGGGTACCCGAAGGG

[00065] SEQ ID NO: 63 is a nucleic acid sequence complement of the nucleic acid sequence (rs7782904) of SEQ ID NO: 24:

GGTTTCGTGACTTTCTTCGGTTTTTA[T/A]ATGTGGTAACGAAAGACTGAGGAGA

[00066] SEQ ID NO: 64 is a nucleic acid sequence complement of the nucleic acid sequence (rs1455857) of SEQ ID NO: 25:

TTTCCTTCGTCAGTCCTACGTAAAGT[T/C]TTAGTACTCTTTCTTCCTCCTCTCC

[00067] SEQ ID NO: 65 is a nucleic acid sequence complement of the nucleic acid sequence (rs11862589) of SEQ ID NO: 26:

AAACTGAATCAGCAGGTGATTGAAAG[G/A]CTAAATAGTGAATGGGTGAGTAAGT

[00068] SEQ ID NO: 66 is a nucleic acid sequence complement of the nucleic acid sequence (rs879522) of SEQ ID NO: 27:

GACTTTGTACTCTTCCGGATATTG[G/A]ATTTACGGTCTACCAAGGTGGGGAG

[00069] SEQ ID NO: 67 is a nucleic acid sequence complement of the nucleic acid sequence (rs4564560) of SEQ ID NO: 28:

CCTACCCCCACAATATATCCAAAGGA[G/A]CGATAAGGAAGAGTGGGAACCGATG

[00070] SEQ ID NO: 68 is a nucleic acid sequence complement of the nucleic acid sequence (rs1002513) of SEQ ID NO: 29:

GAGAGAGGTCTAGTCAGAAAAGACCC[G/A]ATTCTCTATCCTTAGCAGTGGTACG

[00071] SEQ ID NO: 69 is a nucleic acid sequence complement of the nucleic acid sequence (rs1378646) of SEQ ID NO: 30:

CAGGACTACTCCTTGCTCCCGTGAAG[T/C]AGAAGAACTACGTTTGAGATGTAAA

[00072] SEQ ID NO: 70 is a nucleic acid sequence complement of the nucleic acid sequence (rs11198986) of SEQ ID NO: 31:

CTCTGGACTTCACAGGTCGTAGACTC[T/C]GACAGGACCGTCCACGACCTCTCCC

[00073] SEQ ID NO: 71 is a nucleic acid sequence complement of the nucleic acid sequence (rs16965623) of SEQ ID NO: 32:

ATATCGGTCCTCGTTGGGCATGGACT[T/C]GTTCGTACATTAATAGGGCTAACCA

[00074] SEQ ID NO: 72 is a nucleic acid sequence complement of the nucleic acid sequence (rs6916787) of SEQ ID NO: 33:

TTTATACAGAAGTGCTTTTCGGTTTC[T/C]TTTCGTAAGTTTCGATAAGTGTTTG

[00075] SEQ ID NO: 73 is a nucleic acid sequence complement of the nucleic acid sequence (rs17047321) of SEQ ID NO: 34:

GAAAGTCCCTCGAAAATAAGGTCATG[T/C]CCTCCGTCTTTCTTTTGGTTTTCGT

[00076] SEQ ID NO: 74 is a nucleic acid sequence complement of the nucleic acid sequence (rs2113545) of SEQ ID NO: 35:

ACCATAAGGGCATGGTAAATGACGTA[T/C]CTCTCGGGAAATGGGTAATGAATAA

[00077] SEQ ID NO: 75 is a nucleic acid sequence complement of the nucleic acid sequence (rs985934) of SEQ ID NO: 36:

ATTCAATCGTAGATGGTCTTATGTTT[G/A]CCTTTGAACTTAATCAGGTTCAGAG

[00078] SEQ ID NO: 76 is a nucleic acid sequence complement of the nucleic acid sequence (rs1814270) of SEQ ID NO: 37:

TCCTACGGTCGTTTTAATCTTTGAGG[A/G]AGTACATTTAAATCCGTGACAGAGA

[00079] SEQ ID NO: 77 is a nucleic acid sequence complement of the nucleic acid sequence (rs9462104) of SEQ ID NO: 38:

ACCTTTCTATACGTTCTTTGAGAATT[G/A]CCACCAATACGGATTCCCCTACCCT

[00080] SEQ ID NO: 78 is a nucleic acid sequence complement of the nucleic acid sequence (rs6900677) of SEQ ID NO: 39:

ATTAGTTTACTGAAACCATCTGTTGA[G/C]AAGTTCTATACAGAACAATTCTAAT

[00081] SEQ ID NO: 79 is a nucleic acid sequence context of a SNP assigned rs number rs1814270 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs1814270-C and rs1814270-T, withing the SLC6A2 gene:

CTGTACTGTTTCAGCAGTCAGTCTTA[C/T]TTGACCTTTCCTTAGCTCCTAACCA

[00082] SEQ ID NO: 80 is a nucleic acid sequence context of a SNP assigned rs number rs9567739 in the dbSNP at NCBI and comprising human SNP alleles A/G (single nucleotide variation), or rs9567739-C and rs9567739-G, withing the HTR2A gene:

ATCTTTTAAGAACTTAATGCTAAGGA[C/G]CAGTTATGTTTTACTGCAAGTCTTT

[00083] SEQ ID NO: 81 is a nucleic acid sequence complement of the nucleic acid sequence (rs1814270) of SEQ ID NO: 79:

GACATGACAAAGTCGTCAGTCAGAAT[G/A]AACTGGAAAGGAATCGAGGATTGGT

and

[00084] SEQ ID NO: 82 is a nucleic acid sequence complement of the nucleic acid sequence (rs9567739) of SEQ ID NO: 80:

TAGAAAATTCTTGAATTACGATTCCT[G/C]GTCAATACAAAATGACGTTCAGAAA

SUMMARY OF THE INVENTION

[00085] The present invention addresses the significant fraction of patients exposed to elevations in serotonergic neurotransmission, with or without concomitant changes in adrenergic neurotransmission, who do now and/or will in the future suffer degradation of treatment response with antidepressants. Along with decreased dopaminergic neurotransmission efficiency, the identification of certain psychiatric symptoms correlated with mood, reward and attentional dysfunctions may occur.

[00086] In one embodiment, a genetic profile can be identified in patients who are not responsive to first line antidepressant medications targeting changes in serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission for major depressive disorder.

[00087] One aspect of the invention provides a method of predicting the outcome of treatment with antidepressant medication in a patient receiving antidepressant therapy targeting increases in serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission, the method comprising (a) obtaining a sample of genetic material from the patient; (b) assaying the sample for the presence of a genotype in the

patient which is associated with the outcome of treatment with antidepressant medication; and (c) predicting the outcome of treatment with antidepressant medication in the patient based on the presence of the genotype in the sample, wherein the genotype is characterized by a polymorphism in a gene having at least one marker, wherein the gene is selected from the group consisting of 5-hydroxytryptamine (serotonin) receptor 2A (HTR2A); the mu-opiod receptor gene (OPRM1); the neuronal calcium sensor 1 (FREQ) gene; the solute carrier family 6 (neurotransmitter transporter, dopamine) member 3 gene (SLC6A3); the norepinephrine transporter gene (SLC6A2); the cholinergic receptor, nicotinic alpha-3 gene (CHRNA3); the cholinergic receptor, muscarinic 2 gene (CHRM2); the calcium channel voltage-dependent, L type, alpha 1C subunit (CACNA1C) gene; the A100 calcium binding protein A10 (S100A10) gene; regulator of G-protein signaling 10 (RGS10); the serotonin transporter (SLC6A4); FK506 binding protein (FKBP5); glutamate receptor, metabotropic 7 (GRM7); and combinations thereof.

[00088] Another aspect of the present invention is to provide a method of screening patients to identify those patients with an increased risk of non-response to treatment with an antidepressant medication. The method comprises (a) obtaining a sample of genetic material from the patient; (b) assaying the sample for the presence of a genotype in the patient which is associated with the outcome of treatment with antidepressant medication; and (c) predicting the outcome of treatment with antidepressant medication in the patient based on the presence of the genotype in the sample, wherein the genotype is characterized by a polymorphism in a gene having at least one marker, wherein the gene is selected from the group consisting of 5-hydroxytryptamine (serotonin) receptor 2A (HTR2A); the mu-opiod receptor gene (OPRM1); the neuronal calcium sensor 1 (FREQ) gene; the solute carrier family 6 (neurotransmitter transporter, dopamine) member 3 gene (SLC6A3);the cholinergic receptor, nicotinic alpha-3 gene (CHRNA3); the cholinergic receptor; muscarinic 2 gene (CHRM2); the calcium channel voltage-dependent, L type, alpha 1C subunit (CACNA1C) gene; the A100 calcium binding protein A10 (S100A10) gene; the solute carrier family 6 (neurotransmitter transporter, noradrenalin) member 2 (SLC6A2); glutamate receptor, metabotropic 7 (GRM7); FK506 binding protein (FKBP5), regulator of G-protein signaling 10 (RGS10), the serotonin transporter (SLC6A4),and combinations thereof.

[00089] In yet another aspect, the present invention provides a method comprising assaying for the presence of a genotype in patients receiving antidepressant therapy targeting increases in serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission which is associated with a increased probability of response to treatment with antidepressant medication, wherein the genotype is characterized by a polymorphism in a gene selected from the group consisting of SLC6A3 and present as rs10053602-G and rs10052016-G/G genotype; CHRM2 and present as a genotype selected from the group consisting of rs2113545-T_T, rs2350786–C_C, rs7782904-T_T, rs1455857-A_A, rs1378646-C_C and rs6960707-G_G; HTR2A and present as a genotype selected from the group consisting of rs666693-T_T , rs1002513-A_A and rs582385-G_G; CACNA1C and present as rs929492-A_A and rs4765933-T_T genotype; S100A10 and present as rs6587640-A_A, and rs6678672-A_A genotype; GRM7 and present as rs17047279-G_T genotype and combinations thereof.

DETAILED DESCRIPTION OF THE INVENTION

[00090] "Elevations in serotonergic neurotransmission" as used herein refers to any compound that increases, directly or indirectly, the availability of serotonin in the central nervous system for binding to serotonin receptors at the post-synaptic membrane, including but not limited to serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants, serotonin agonists, amphetamines, serotonin precursors, serotonin prodrugs, intermediates in the biosynthesis of serotonin, co-factors and pharmaceutically acceptable salts thereof. Such compounds may be given alone or in combination with other serotonin enhancers and/or agents which modulate dopaminergic neurotransmission.

[00091] "Alterations in dopaminergic neurotransmission", as used herein, refers to the induction, directly or indirectly, of changes in the ability of dopamine to interact with dopamine receptors leading to alterations in dopaminergic neurotransmission. The alterations in dopaminergic neurotransmission can occur by the administration of drugs which, directly or indirectly, act upon the ability of dopamine to interact with postsynaptic receptors involved in neurotransmission and/or modulate receptor signal transduction.

[00092] "Alterations in dopaminergic neurotransmission" are accomplished by compounds that increase, directly or indirectly, the availability of dopamine in the central nervous system for binding to dopamine receptors. Such compounds include, but are not limited to, bupropion, monoamine oxidase inhibitors, tricyclic antidepressants, amphetamines, methylphenidate, atypical antipsychotics, centrally acting stimulants, dopamine precursors, dopamine prodrugs, and intermediates in the biosynthesis of dopamine, co-factors and pharmaceutically acceptable salts thereof. Such compounds may be given alone or in combination with other dopamine enhancers and or agents which modulate dopaminergic neurotransmission.

[00093] The identification of those subjects who will likely fail first line antidepressant therapies can be associated with specific genes, single nucleotide polymorphisms and haplotypes. The genetic biomarkers for high probability of failing first line antidepressant therapies include genes associated with dopaminergic, serotonergic, cholinergic and adrenergic neurotransmission.

[00094] Additional biomarkers for prediction of high probability of first line antidepressant failure include genes, single nucleotide polymorphisms and haplotypes associated with voltage gated calcium channels and proteins associated with dopaminergic neurotransmission which may or may not be associated with voltage gated calcium channels but do result in alterations in dopaminergic neurotransmission.

[00095] Further definition of those patients who are likely to fail first line antidepressant therapy can be identified by specific genes, single nucleotide polymorphisms and haplotypes. Genetic markers associated with a high probability of failing first line antidepressant therapies which target serotonergic neurotransmission, with or without concomitant changes in adrenergic neurotransmission, can be found in the norepinephrine transporter gene.

[00096] More broadly, it has been found that persons suffering from or prone to treatment resistant depression can be identified by specific genetic markers associated with chronic up regulation of serotonin neurotransmission, whether produced by SSRI drugs, SNRI drugs, plant derivatives, or by medications that cause quantitatively similar

increases in serotonin neurotransmission with or without concomitant changes in adrenergic neurotransmission.

[00097] Genetic markers associated with high probability of respondin or failing first line antidepressant therapies are aligned with Dopamine transporter (DAT) single nucleotide polymorphisms and specific haplotypes within the DAT gene (SLC6A3).

[00098] Genetic markers associated with a high probability of responding to first line antidepressant therapies are aligned with genes, single nucleotide polymorphisms and haplotypes involved in cholinergic and/or dopaminergic neurotransmission.

[00099] Genetic markers associated with FK506 binding protein (FKBP5) associated with a high probability of failing antidepressant therapy targeting serotonin transmission efficiency with or without concomitant changes in adrenergic neurotransmission.

[000100] Genetic markers associated with glutamate receptor, metabotropic 7 (GRM7) associated with a high probability of failing or responding to antidepressant therapy targeting serotonin transmission efficiency with or without concomitant changes in adrenergic neurotransmission.

[000101] Genetic markers in the serotonin transporter (SLC6A4), regulator of G-protein signaling (RGS10)are associated with a high probability of failing antidepressant therapy targeting serotonin transmission efficiency with or without concomitant changes in adrenergic neurotransmission.

[000102] Genetic markers associated with the norepinephrine transporter (SLC6A2) are associated with failing antidepressant therapy targeting serotonin transmission efficiency with or without concomitant changes in adrenergic neurotransmission.

[000103] Genetic markers associated with p11 protein (S100A10) are associated with either failng or responding to antidepressant therapy targeting serotonin transmission efficiency with or without concomitant changes in adrenergic neurotransmission

[000104] Genetic markers associated with the mu opiod receptor (OPRM1) are associated with failing to respond to antidepressant therapy targeting serotonin

transmission efficiency with or without concomitant changes in adrenergic neurotransmission.

[000105] Genetic markers asscoaited with L-type voltage gated calcium channel (CACNA1C) are associated with either failing or responding to antidepressant therapy targeting serotonin transmission efficiency with or without concomitant changes in adrenergic neurotransmission.

[000106] Genetic markers associated with the Serotonin 2A receptor (HTRA2) are associated with either failing or responding to to antidepressant therapy targeting serotonin transmission efficiency with or without concomitant changes in adrenergic neurotransmission.

[000107] Genetic markers associated with dopamine signaling proteins (FREQ/NCS1) are associated with failing to respond to antidepressant therapy targeting serotonin transmission efficiency with or without concomitant changes in adrenergic neurotransmission.

[000108] The identification of treatment resistant depression, its cause, and an adequate treatment for the condition has eluded the field.

[000109] Specific genetic markers can elucidate the outcome of antidepressant treatment and help to identify the response of individuals to treatment with antidepressant medication. For example, individuals who are likely to fail first line antidepressant therapy can be associated with genes, single nucleotide polymorphisms and haplotypes within the norepinephrine transporter. Thus, specific polymorphisms in particular genes can be used to identify individuals that are at an increased risk of non-response to antidepressant treatment, where such treatment targets elevations in serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission. Individuals with the identified polymorphisms can benefit from closer monitoring, earlier institution of alternative and/or adjunctive treatments, and/or more rapid exposure to specialty care.

[000110] Specific genetic markers can elucidate the outcome of antidepressant treatment and help to identify the response of individuals to treatment with antidepressant medication. These markers are found in genes in one or any combination of the following:

FREQ/NCS1, CHRM2, SLC6A3, SLC6A4, OPRM1, SLC6A2, CHRNA3, HTR2A, FKBP5, CACNA1C, S100A10, RGS10, and GRM7. Within each specific gene are SNPs and haplotypes which can predict a high probability of responding to first line antidepressant medications.

[000111] Genes, SNPs and haplotypes associated with a high probability of responding to first line antidepressant medications include one or any combination of the following, CHRM2, SLC6A3,HTR2A, CACNA1C, S100A10, and GRM7.

[000112] Other genetic polymorphic markers can indicate a high probability for an inidivdual not to respond to antidepressant medications. Haplotypes within specified genes can predict a high probability of not responding to first line antidepressant medications. These genes, SNPs and haplotypes include one or any combination of FREQ/NCS1, CHRM2, SLC6A3, OPRM1, SLC6A2, CHRNA3, HTR2A, FKBP5, CACNA1C, S100A10, RGS10, SLC6A4 and GRM7.

[000113] Genes, SNPs and haplotypes associated with a high probability of failing first line antidepressant medications include one or any combination of the following: FREQ, CHRM2, SLC6A3, OPRM1, SLC6A2, CHRNA3, HTR2A, FKBP5, CACNA1C, S100A10, RGS10, SLC6A4 and GRM7.

[000114] Treatment resistant depressed patients may also be identified from among those persons having undergone treatment for Major Depressive Illness with medications that modulate serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission.

I. Inducement Of Treatment Resistant Depression

[000115] Treatment resistant depression may be induced by such medications when chosen for therapeutic reasons by one practiced in the art of psychopharmacology to produce chronic increases in serotonergic transmission efficiency. The increase may result in alterations of dopaminergic transmission efficiency in conditions other than Major Depressive Illness such as but not limited to: depressive disorder, anxiety disorder, social anxiety disorder, generalized anxiety disorder, bipolar disorder, schizophrenia, autism, epilepsy, mood disorders, cigarette smoking, alcohol or substance abuse and associated

disorders, panic disorder, migraine, obesity, bulimia, anorexia, premenstrual syndrome, menopause, sleep disorders, attention-deficit/hyperactivity disorder (ADHD), Tourette syndrome, aggression, obsessive compulsive disorder, pathological gambling, novelty seeking, borderline personality disorders, antisocial personality disorder, suicidility, eating disorders, sexual dysfunction, dementia, social phobia, fibromyalgia, overactive bladder, chronic fatigue syndrome, chronic pain, sudden infant death syndrome, post-traumatic stress syndrome, and Alzheimer's disease. These terms have their usual meaning in the art (see, e.g., DSM-IV).

[000116] Treatment resistant depression may be produced by conditions that are now or may in the future be treated by chronic blockade of SERT, by SSRI or SNRI therapy, or by any future therapies that produce chronic up regulation of serotonergic transmission efficiency or increased synthesis and/or release of serotonin with or without concomitant changes in adrenergic neurotransmission.

II. Genes that Relate to Treatment Resistant Depression

[000117] The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, which is a large prospective treatment trial for major depression, can be used as test for whether specific genetic markers could predict the outcome of antidepressant treatment in patients treated with selective serotonin reuptake inhibitor (SSRI), e.g., citalopram.

[000118] The STAR*D trial indicates genetic markers in several genes, including HTR2A, OPRM1, FREQ/NCS1, SLC6A3, SLC6A2, CHRNA3, CHRM2, CACNA1C, GRM7, FKBP5, RGS10, SLC6A4 and S100A10 correlate with an increase in absolute risk of having no response to antidepressant treatment. Accordingly, assaying the genotype at these markers can be used to predict the outcome of treatment with antidepressant medication (e.g., a SSRI, such as citalopram).

[000119] HTR2A encodes the serotonin 2A receptor. HTR2A also is known as HTR2 and 5-HT2A receptor. HTR2A is located on chromosome 13q14-q21. HTR2A is identified by GenBank Accession Number NM000621.

[000120] Distinct 5-HT receptors have been identified (5-HT1-7). The 5HT2A, B, and C subtypes are positively coupled with the enzyme phospholipase C (PLC). The 5-HT2A

receptors are postsynaptic receptors that are highly enriched in neocortex and regulate the function of prefrontal-subcortical circuits. The 5-HT2A receptors interact with Gq/G11 guanine nucleotide binding proteins (G proteins) and thereby stimulate PLC to produce the intracellular second messengers sn-1,2-DAG (an endogenous activator of protein kinase C) and inositol-1,4,5-triphosphate (IP3), which stimulates the release of Ca2+ ions from intracellular stores.

[000121] The mu-opiod receptor (OPRM1) gene encodes the opioid receptor, mu1, which is a member of the G protein coupled receptor superfamily and the primary site of action for the most commonly used opioids, including morphine, heroin, fentanyl, and methadone as well as the primary receptor for endogenous opioid peptides.

[000122] The neuronal calcium sensor 1 (NCS-1) gene, also called FREQ, is a member of the neuronal calcium sensor gene family, which encodes calcium-binding proteins expressed predominantly in neurons. The protein encoded by FREQ regulates G protein-coupled receptor phosphorylation in a calcium-dependent manner and can substitute for calmodulin. The protein is associated with secretory granules and modulates synaptic transmission and synaptic plasticity.

[000123] The solute carrier family 6 (neurotransmitter transporter, dopamine) member 3 gene (SLC6A3), also called DAT gene and DAT1 gene, encodes a dopamine transporter, which is a member of the sodium- and chloride-dependent neurotransmitter transporter family. The 3' UTR of this gene contains a 40 bp tandem repeat, referred to as a variable number tandem repeat or VNTR, which can be present in 3 to 11 copies.

[000124] The solute carrier family 6 (neurotransmitter transporter, noradrenalin), member 2 gene (SLC6A2) is also known as the norepinephrine transporter (NET) gene. SLC6A2 encodes a member of the sodium- and chloride neurotransmitter symporter family. This member is a multi-pass membrane protein, which is responsible for reuptake of norepinephrine into presynaptic nerve terminals and is a regulator of norepinephrine homeostasis.

[000125] The cholinergic receptor, nicotinic alpha-3 (CHRNA3) gene encodes a member of the nicotinic acetylcholine receptor family of proteins. Members of this family of proteins form pentameric complexes comprised of both alpha and beta subunits. The CHRNA3

gene encodes an alpha-type subunit, as it contains characteristic adjacent cysteine residues. The encoded protein is a ligand-gated ion channel that likely plays a role in neurotransmission.

[000126] The cholinergic receptor, muscarinic 2 (CHRM2) gene encodes muscarinic acetylcholine receptor M2, also known as the cholinergic receptor, muscarinic 2. Muscarinic cholinergic receptors, including cholinergic receptor, muscarinic 2, belong to a large family of G protein-coupled receptors whose functional diversities are defined by the binding of acetylcholine and include cellular responses such as adenylate cyclase inhibition, phosphoinositide degeneration, and potassium channel mediation. In particular, the muscarinic cholinergic receptor 2 is involved in mediation of bradycardia and a decrease in cardiac contractility.

[000127] The calcium channel voltage-dependent, L type, alpha 1C subunit (CACNA1C) gene, also known as voltage-gated calcium channel subunit alpha Cav1 gene, encodes an alpha-1 subunit of a voltage-dependent calcium channel. Voltage-dependent calcium channels mediate the entry of calcium ions into excitable cells and are also involved in a variety of calcium-dependent processes, including muscle contraction, hormone or neurotransmitter release, gene expression, cell motility, cell division and cell death. The isoform alpha-1C gives rise to L-type calcium currents. Long-lasting (L-type) calcium channels belong to the "high-voltage activated" (HVA) group.

[000128] The S100 calcium binding protein A10 (S100A10) gene encodes a protein that is a member of the S100 family of proteins containing 2 EF-hand calcium-binding motifs. S100 proteins are localized in the cytoplasm and/or nucleus of a wide range of cells, and are involved in the regulation of a number of cellular processes including cell cycle progression and differentiation. S100 genes include at least 13 members which are located as a cluster on chromosome 1q21.

[000129] The glutamate receptor metabotropic 7 receptor (GRM7) is an L-glutamate group III receptor protein which is linked to the inhibition of the cAMP cascade and appears to modulate other neurotransmitters involved in mood disorders, attentional dysfunctions and reward.

[000130] The solute carrier family 6 (neurotransmitter transporter, serotonin) member 3 gene (SLC6A4), also called SERT gene, encodes a serotonin transporter. This member is a multi-pass membrane protein, which is responsible for reuptake of serotonin into presynaptic nerve terminals and is a regulator of serotonin homeostasis.

[000131] Regulator of G protein signaling (RGS10) family members are regulatory proteins that act as GTPase activating proteins (GAPs) for G-alpha subunits of heterotrimeric G-proteins. RGS proteins are able to deactivate G-protein subunits of the Gi alpha, Go alpha and Gq alpha subtypes. They drive G-proteins into their inactive GDP-bound forms. Regulator of G-protein signaling 10 belongs to this family. All RGS proteins share a conserved 120-amino acid sequence termed the RGS domain. This protein associates specifically with the activated forms of the two related G-protein subunits, G-alphai3 and G-alphaz but fails to interact with the structurally and functionally distinct G-alpha subunits. Regulator of G protein signaling 10 proteins are localized in the nucleus. Two transcript variants encoding different isoforms have been found for this gene.

[000132] The FK506 binding protein (FKBP5) is encoded by a member of the immunophilin protein family, which play a role in immunoregulation and basic cellular processes involving protein folding and trafficking. This encoded protein is a cis-trans prolyl isomerase that binds to the immunosuppressants FK506 and rapamycin. It is thought to mediate calcineurin inhibition. It also interacts functionally with mature hetero-oligomeric progesterone receptor complexes along with the 90 kDa heat shock protein and P23 protein. This gene has been found to have multiple polyadenylation sites. Alternative splicing results in multiple transcript variants. Recent analysis of subjects in STAR*D suggest that FKBP5 is associated with depression.

[000133] In an embodiment, suitable genetic markers and/or polymorphisms are associated with a nucleic acid sequence having at least about 98% sequence identity to the sequence of sequence identity number (SEQ ID NO) selected from the group consisting of SEQ ID NO: 1 (rs666693-A and/or rs666693-G); SEQ ID NO: 2 (rs5852385-[-/AT]); SEQ ID NO: 3 or namely (rs9316232-A and/or rs9316232-G); SEQ ID NO: 4 (rs17275521-A and/or rs17275521-G); SEQ ID NO: 5 (rs17209711-A and/or rs17209711-T); SEQ ID NO: 6 (rs3778149-C and/or rs3778149-G); SEQ ID NO: 7 (rs3778146-C and/or rs3778146-T); SEQ ID NO: 8 (rs7773995-C and/or rs7773995-T); SEQ ID NO: 9

(rs3778145-A and/or rs3778145-C); SEQ ID NO: 10 (rs885345-C and/or rs885345-T); SEQ ID NO: 11 (rs10052016-A and/or rs10052016-G); SEQ ID NO: 12 (rs1861646-G and/or rs1861646-T); SEQ ID NO: 13 (rs6495308-C and/or rs6495308-T); SEQ ID NO: 13 (rs6495308-C and/or rs6495308-T); SEQ ID NO: 144 (rs10053602-C and/or rs10053602-T); SEQ ID NO: 15 (rs2350786-A and/or rs2350786-G); SEQ ID NO: 16 (rs6960707-C and/or rs6960707-T); SEQ ID NO: 17 (rs929492-C and/or rs929492-T); SEQ ID NO: 18 (rs6678672-C and/or rs6678672-T); SEQ ID NO: 19 (rs6587640-C and/or rs6587640-T); SEQ ID NO: 20 (rs17047279-G and/or rs17047279-T); SEQ ID NO: 21 (rs17047286-A and/or rs17047286-G); SEQ ID NO: 22 (rs9368881-A and/or rs9368881-G); SEQ ID NO: 23 (rs4765933-A and/or rs4765933-G); SEQ ID NO: 24 (rs7782904-A and/or rs7782904-T); SEQ ID NO: 25 (rs1455857-A and/or rs1455857-G); SEQ ID NO: 26 (rs11862589-C and/or rs11862589-T); SEQ ID NO: 27 (rs879522-C and/or rs879522-T); SEQ ID NO: 28 (rs4564560-C and/or rs4564560-T); SEQ ID NO: 29 (rs1002513-C and/or rs1002513-T); SEQ ID NO: 30 (rs1378646-A and/or rs1378646-G); SEQ ID NO: 31 (rs11198986-A and/or rs11198986-G); SEQ ID NO: 32 (rs169655623-A and/or rs169655623-G) ; SEQ ID NO: 33 (rs6916787-A and/or rs6916787-G) ; SEQ ID NO: 34 (rs17047321-A and/or rs17047321-G); SEQ ID NO: 35 (rs2113545-A and/or rs2113545-G); SEQ ID NO: 36 (rs690067-C and/or rs690067-T); SEQ ID NO: 37 (rs17841329-A and/or rs17841329-G); SEQ ID NO: 38 (rs9462104-C and/or rs9462104-T); SEQ ID NO: 39 (rs6900677-C and/or rs6900677-G); SEQ ID NO: 79 (rs1814270-C and/or rs1814270-T); SEQ ID NO: 80 (rs9567739-C and/or rs9567739-G) and combinations thereof.

[000134] In an alternative embodiment, suitable genetic markers and/or polymorphisms are associated with a nucleic acid sequence having from about 98% to about 99% sequence identity to the sequence of SEQ ID NO selected from the group consisting of SEQ ID NO: 1 (rs666693-A and/or rs666693-G); SEQ ID NO: 2 (rs5852385-[-/AT]); SEQ ID NO: 3 or namely (rs9316232-A and/or rs9316232-G); SEQ ID NO: 4 (rs17275521-A and/or rs17275521-G); SEQ ID NO: 5 (rs17209711-A and/or rs17209711-T); SEQ ID NO: 6 (rs3778149-C and/or rs3778149-G); SEQ ID NO: 7 (rs3778146-C and/or rs3778146-T); SEQ ID NO: 8 (rs7773995-C and/or rs7773995-T); SEQ ID NO: 9 (rs3778145-A and/or rs3778145-C); SEQ ID NO: 10 (rs885345-C and/or rs885345-T); SEQ ID NO: 11 (rs10052016-A and/or rs10052016-G); SEQ ID NO: 12 (rs1861646-G and/or rs1861646-T); SEQ ID NO: 13 (rs6495308-C and/or rs6495308-T); SEQ ID NO: 13 (rs6495308-C and/or

rs6495308-T); SEQ ID NO: 14 (rs10053602-C and/or rs10053602-T); SEQ ID NO: 15 (rs2350786-A and/or rs2350786-G); SEQ ID NO: 16 (rs6960707-C and/or rs6960707-T); SEQ ID NO: 17 (rs929492-C and/or rs929492-T); SEQ ID NO: 18 (rs6678672-C and/or rs6678672-T); SEQ ID NO: 1920 (rs6587640-C and/or rs6587640-T); SEQ ID NO: 201 (rs17047279-G and/or rs17047279-T); SEQ ID NO: 21 (rs17047286-A and/or rs17047286-G); SEQ ID NO: 22 (rs9368881-A and/or rs9368881-G); SEQ ID NO: 23 (rs4765933-A and/or rs4765933-G); SEQ ID NO: 24 (rs7782904-A and/or rs7782904-T); SEQ ID NO: 25 (rs1455857-A and/or rs1455857-G); SEQ ID NO: 26 (rs11862589-C and/or rs11862589-T); SEQ ID NO: 27 (rs879522-C and/or rs879522-T); SEQ ID NO: 28 (rs4564560-C and/or rs4564560-T); SEQ ID NO: 29 (rs1002513-C and/or rs1002513-T); SEQ ID NO: 30 (rs1378646-A and/or rs1378646-G); SEQ ID NO: 31 (rs11198986-A and/or rs11198986-G); SEQ ID NO: 32 (rs169655623-A and/or rs169655623-G) ; SEQ ID NO: 33 (rs6916787-A and/or rs6916787-G) ; SEQ ID NO: 34 (rs17047321-A and/or rs17047321-G); SEQ ID NO: 35 (rs2113545-A and/or rs2113545-G); SEQ ID NO: 36 (rs690067-C and/or rs690067-T); SEQ ID NO: 37 (rs1814270-C and/or rs1814270-T); SEQ ID NO: 38 (rs9462104-C and/or rs9462104-T); SEQ ID NO: 39 (rs6900677-C and/or rs6900677-G); SEQ ID NO: 79 (rs1814270-C and/or rs1814270-T); SEQ ID NO: 80 (rs9567739-C and/or rs9567739-G) and combinations thereof.

[000135] In yet another embodiment, suitable genetic markers and/or polymorphisms are associated with a nucleic sequence having from about 98% to about 99.9% sequence identity to the sequence of SEQ ID NO selected from the group consisting of SEQ ID NO: 1 (rs666693-A and/or rs666693-G); SEQ ID NO: 2 (rs582385-[-/AT]); SEQ ID NO: 3 (rs9316232-A and/or rs9316232-G); SEQ ID NO: 4 (rs17275521-A and/or rs17275521-G); SEQ ID NO: 5 (rs17209711-A and/or rs17209711-T); SEQ ID NO: 6 (rs3778149-C and/or rs3778149-G); SEQ ID NO: 7 (rs3778146-C and/or rs3778146-T and/or r3778146-G and/or rs3778146-T); SEQ ID NO: 8 (rs7773995-C and/or rs7773995-T); SEQ ID NO: 9 (rs3778145-A and/or rs3778145-C); SEQ ID NO: 10 (rs885345-C and/or rs885345-T); SEQ ID NO: 11 (rs10052016-A and/or rs10052016-G); SEQ ID NO: 12 (rs1861646-G and/or rs1861646-T SEQ ID NO: 13 (rs6495308-C and/or rs6495308-T); SEQ ID NO: 14 (rs10053602-C and/or rs10053602—T); SEQ ID NO: 15 (rs2350786-A and/or rs2350786-G); SEQ ID NO: 16 (rs6960707-C and/or rs6960707-T); SEQ ID NO: 17 (rs929492-C and/or rs929492-T); SEQ ID NO: 18 (rs6678672-C and/or rs6678672-T); SEQ ID NO: 19

(rs6587640-C and/or rs6587640-T); SEQ ID NO: 20 (rs17047279-G and/or rs17047279-T); SEQ ID NO: 21 (rs17047286-A and/or rs17047286-G); SEQ ID NO: 22 (rs9368881-A a\nd/or rs936881-C and/or rs9368881-G and/or rs9368881-T); SEQ ID NO: 23 (rs4765933-A and/or rs4765933-G); SEQ ID NO: 24 (rs7782904-A and/or rs7782904-T); SEQ ID NO: 25 (rs1455857-A and/or rs1455857-G); SEQ ID NO: 26 (rs118625589-C and/or rs11862589-T); SEQ ID NO: 27 (rs879522-C and/or rs879522-T); SEQ ID NO: 28 (rs4564560-C and/or rs4564560-T); SEQ ID NO: 29 (rs1002513-C and/or rs1002513-T); SEQ ID NO: 30 (rs1378646-A and/ors1378646-G); SEQ ID NO: 31 (rs11198986-A and/or rs11198986-G); SEQ ID NO: 32 (rs16965623-A and/or rs16965623-G); and SEQ ID NO: 33 (rs6916787-A and/or rs6916787-G); SEQ ID NO 34 (rs17047321-A and/or rs17047321-G; SEQ ID NO 35 (rs2113545-A and/or rs2113545-G); SEQ ID NO 36 (rs985934-C and/or rs985934-T); SEQ ID NO 37 (rs1814270-T and/orrs1814270-C); SEQ ID NO 38 (rs9462104-C and/or rs9462104-T); SEQ ID NO 39 (rs6900677-C and/or rs6900677-G) and combinations thereof.

[000136] In another embodiment, suitable genetic markers and/or polymorphisms are associated with a nucleic sequence having at least about 98% sequence identity to the sequence of SEQ ID NO selected from the group consisting of SEQ ID NO: 40 (rs666693-T and/or rs666693-C); SEQ ID NO: 41 (rs5852385-[-/TA]); SEQ ID NO: 42 (rs9316232-T and/or rs9316232 -C); SEQ ID NO: 43 (rs17275521-T and/or rs17275521 -C); SEQ ID NO: 44 (rs17209711-T and/or rs17209711-A); SEQ ID NO: 45 (rs3778149-G and/or rs3778149 -C); SEQ ID NO: 46 (rs3778146-T and/or rs3778146-G and/or rs3778146 -C and/or rs3778146-A); SEQ ID NO: 47 (rs7773995-G and/or rs7773995-A); SEQ ID NO: 48 (rs3778145-T and/or rs3778145-G); SEQ ID NO: 49 (rs885345-G and/or rs885345-A); SEQ ID NO: 50 (rs10052016-T and/or rs10052016-C); SEQ ID NO: 51 (rs1861646-C and/or rs1861646-A); SEQ ID NO: 52 (rs6495308-G and/or rs6495308-A); SEQ ID NO: 53 (rs10053602-G and/or rs10053602-A); SEQ ID NO: 54 (rs2350786-T and/or rs2350786-C); SEQ ID NO: 55 (rs6960707-G and/or rs6960707-A); SEQ ID NO: 56 (rs929492-G and/or rs929492-A; SEQ ID NO: 57 (rs6678672-G and/or rs6678672-A); SEQ ID NO: 58 (rs6587640-G and/or rs6587640-A); SEQ ID NO: 59 (rs17047279-C and/or rs17047279-A); SEQ ID NO: 60 (rs17047286-T and/or rs17047286-C); SEQ ID NO: 61 (rs9368881-T and/or rs9368881-G and/or rs9368881-C and/or rs9368881-A); SEQ ID NO: 62 (rs4765933-T and/or rs4765933-C); SEQ ID NO: 63 (rs7782904-T and/or rs7782904-A);

SEQ ID NO: 64 (rs1455857-T and/or rs1455857-C); SEQ ID NO: 65 (rs11862589-G and/or rs11862589-A); SEQ ID NO: 66 (rs879522-G and/or rs879522-A); SEQ ID NO: 67 (rs4564560-G and/or rs4564560-A); SEQ ID NO: 68 (rs1002513-G and/or rs1002513-A); SEQ ID NO: 69 (rs1378646-T and/or rs1378646-C); SEQ ID NO: 70 (rs11198986-T and/or rs11198986-C); SEQ ID NO: 71 (rs169655623-T and/or rs169655623-C); SEQ ID NO: 72 (rs6916787-T and/or rs6916787-C); SEQ ID NO: 73 (rs17047321-T and/or rs17047321-C); SEQ ID NO: 74 (rs2113545-T and/or rs2113545-C); SEQ ID NO: 75 (rs690067-G and/or rs690067-A); SEQ ID NO: 76 (rs1814270-A and/or rs1814270-G); SEQ ID NO: 77 (rs9462104-G and/or rs9462104-A); SEQ ID NO: 78 (rs6900677-G and/or rs6900677-C); SEQ ID NO: 81 (rs1814270-G and/or rs1814270-A; SEQ ID NO: 82 (rs9567739-G and/or rs9567739-C); and combinations thereof.

[000137] In yet another embodiment, suitable genetic markers and/or polymorphisms are associated with a nucleic sequence having from about 98% to about 99.9% sequence identity to the sequence of SEQ ID NO selected from the group consisting of SEQ ID NO: 40 (rs666693-T and/or rs666693-C); SEQ ID NO: 41 (rs5852385-[-/TA]); SEQ ID NO: 42 (rs9316232-T and/or rs9316232 -C); SEQ ID NO: 43 (rs17275521-T and/or rs17275521 -C); SEQ ID NO: 44 (rs17209711-T and/or rs17209711-A); SEQ ID NO: 45 (rs3778149-G and/or rs3778149 -C); SEQ ID NO: 46 (rs3778146-T and/or rs3778146-G and/or rs3778146 -C and/or rs3778146-A); SEQ ID NO: 47 (rs7773995-G and/or rs7773995-A); SEQ ID NO: 48 (rs3778145-T and/or rs3778145-G); SEQ ID NO: 49 (rs885345-G and/or rs885345-A); SEQ ID NO: 50 (rs10052016-T and/or rs10052016-C); SEQ ID NO: 51 (rs1861646-C and/or rs1861646-A); SEQ ID NO: 52 (rs6495308-G and/or rs6495308-A); SEQ ID NO: 53 (rs10053602-G and/or rs10053602-A); SEQ ID NO: 54 (rs2350786-T and/or rs2350786-C); SEQ ID NO: 55 (rs6960707-G and/or rs6960707-A); SEQ ID NO: 56 (rs929492-G and/or rs929492-A; SEQ ID NO: 57 (rs6678672-G and/or rs6678672-A); SEQ ID NO: 58 (rs6587640-G and/or rs6587640-A); SEQ ID NO: 59 (rs17047279-C and/or rs17047279-A); SEQ ID NO: 60 (rs17047286-T and/or rs17047286-C); SEQ ID NO: 61 (rs9368881-T and/or rs9368881-G and/or rs9368881-C and/or rs9368881-A); SEQ ID NO: 62 (rs4765933-T and/or rs4765933-C); SEQ ID NO: 63 (rs7782904-T and/or rs7782904-A); SEQ ID NO: 64 (rs1455857-T and/or rs1455857-C); SEQ ID NO: 65 (rs11862589-G and/or rs11862589-A); SEQ ID NO: 66 (rs879522-G and/or rs879522-A); SEQ ID NO: 67 (rs4564560-G and/or rs4564560-A); SEQ ID NO: 68 (rs1002513-G and/or rs1002513-A);

SEQ ID NO: 69 (rs1378646-T and/or rs1378646-C); SEQ ID NO: 70 (rs11198986-T and/or rs11198986-C); SEQ ID NO: 71 (rs169655623-T and/or rs169655623-C); SEQ ID NO: 72 (rs6916787-T and/or rs6916787-C); SEQ ID NO: 73 (rs17047321-T and/or rs17047321-C); SEQ ID NO: 74 (rs2113545-T and/or rs2113545-C); SEQ ID NO: 75 (rs690067-G and/or rs690067-A); SEQ ID NO: 76 (rs17841329-T and/or rs17841329-C); SEQ ID NO: 77 (rs9462104-G and/or rs9462104-A); SEQ ID NO: 78 (rs6900677-G and/or rs6900677-C); SEQ ID NO: 81 (rs1814270-G and/or rs1814270-A; SEQ ID NO: 82 (rs9567739-G and/or rs9567739-C); and combinations thereof.

III. Methods of Using the Markers

[000138] In one embodiment a method is identified which can predict a high probability of first line antidepressant treatment failure using specific genes, single nucleotide polymorphims and haplotypes.

In one such embodiment, a method is identified which can predict the outcome (e.g., failure or success) of treatment with antidepressant medication in a patient receiving antidepressant therapy targeting increases in serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission. The method comprises: (a) obtaining a sample of genetic material from the patient; (b) assaying the sample for the presence of a genotype in the patient which is associated with a high probability of first line antidepressant treatment failure with the antidepressant therapy targeting increases in serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission; and (c) predicting the outcome of treatment with antidepressant medication in the patient based on the presence of the genotype in the sample, wherein the genotype is characterized by specific polymorphisms in a gene, wherein the gene and the polymorphisms are selected from the group consisting of: HTR2A and single nucleotide polymorphisms (SNPs) having reference sequence numbers SEQ ID NO: 1 (rs666693-A and/or rs666693-G), SEQ ID NO: 2 (rs582385-[-/AT]), SEQ ID NO: 3 (rs9316232-A and/or rs9316232-G), SEQ ID NO: 29 (rs1002513-C and/or rs1002513-T), and SEQ ID NO: 80 (rs9567739-C and/or rs9567739-G); OPRM1 and single nucleotide polymorphisms (SNPs) having SEQ ID NOs and reference sequence numbers SEQ ID NO: 4 (rs17275521-A and/or rs17275521-G); SEQ ID NO: 5 (rs17209711-A and/or rs17209711-T); SEQ ID NO: 6 (rs3778149-C and/or rs3778149-G); SEQ ID NO: 7 (rs3778146-C and/or rs3778146-T);

SEQ ID NO: 8 (rs7773995-C and/or rs7773995-T); SEQ ID NO: 9 (rs3778145-A and/or rs3778145-C); SEQ ID NO: 36 (rs690067-C and/or rs690067-T); FREQ (or NCS1) and a SNP having reference sequence number rs885345 (SEQ ID NO: 10); SLC6A3 and SNPs having reference sequence numbers SEQ ID NO: 11 (rs10052016-A and/or rs10052016-G), and SEQ ID NO: 14 (rs10053602-C and/or rs10053602-T); SLC6A2 and SNPs having reference sequence numbers SEQ ID NO: 12 (rs1861646-G and/or rs1861646-T), SEQ ID NO: 26 (rs11862589-C and/or rs11862589-T), SEQ ID NO: 27 (rs879522-C and/or rs879522-T), SEQ ID NO: 28 (rs4564560-C and/or rs4564560-T), SEQ ID NO: 37 (rs17841329-A and/or rs17841329-G) and SEQ ID NO: 79 (rs1814270-C and/or rs1814270-T); CHRNA3 and SNPs having reference sequence number SEQ ID NO: 13 (rs6495308-C and/or rs6495308-T); CHRM2 and SNPs having reference sequence numbers SEQ ID NO: 15 (rs2350786-A and/or rs2350786-G), SEQ ID NO: 16 (rs6960707-C and/or rs6960707-T), SEQ ID NO: 24 (rs7782904-A and/or rs7782904-T), SEQ ID NO: 25 (rs1455857-A and/or rs1455857-G), SEQ ID NO: 30 (rs1378646-A and/or rs1378646-G), and SEQ ID NO: 35 (rs2113545-A and/or rs2113545-G); CACNA1C and SNPs having reference sequence numbers SEQ ID NO: 17 (rs929492-C and/or rs929492-T), and SEQ ID NO: 23 (rs4765933-A and/or rs4765933-G); S100A10 and a SNP having reference sequence numbers SEQ ID NO: 18 (rs6678672-C and/or rs6678672-T) and SEQ ID NO: 19 (rs6587640-C and/or rs6587640-T); GRM7 and SNPs having reference sequence numbers SEQ ID NO: 20 (rs17047279-G and/or rs17047279-T), SEQ ID NO: 21 (rs17047286-A and/or rs17047286-G), and SEQ ID NO: 34 (rs17047321-A and/or rs17047321-G); FK506 (or FKBP5) and SNP having a reference sequence numbers SEQ ID NO: 22 (rs9368881-A and/or rs9368881-G), and SEQ ID NO: 38 (rs9462104-C and/or rs9462104-T); RGS10 and SNP having a reference sequence number SEQ ID NO: 31 (rs11198986-A and/or rs11198986-G); SLC6A4 and SNP having a reference sequence number SEQ ID NO: 32 (rs169655623-A and/or rs169655623-G); OPRM1and SNP having a reference sequence numbers SEQ ID NO: 33 (rs6916787-A and/or rs6916787-G) and SEQ ID NO: 39 (rs6900677-C and/or rs6900677-G); and combinations thereof.

[000139] It will be appreciated by one of skill in the art that where an antisense nucleic acid sequence is used in the present invention, the target polymorphisms provided in the sample would be complementary to that specified by the corresponding sense nucleic acid sequence. Therefore, the complements of all of the nucleic acid sequences disclosed

herein are suitable for use in all aspects of the present invention. In particular, single nucleotide polymorphisms (SNPs) having reference sequences of SEQ ID NO 40 through SEQ ID NO 78, and SEQ ID NOs 81 and 82 and combinations thereof are suitable for use in all aspects of the present invention.

[000140] The polymorphism can occur anywhere in a gene. Typically, the polymorphism is a single nucleotide polymorphism. In certain embodiments, the polymorphism is the same as that discussed herein. In other embodiments, it is a different polymorphism.

[000141] In an embodiment, a method is identified which can predict a high probability of responding to first line antidepressant treatment using specific genes, single nucleotide polymorphims and haplotypes.

[000142] In a preferred embodiment, a method is identified which can predict the outcome of treatment with antidepressant medication in a patient receiving antidepressant therapy targeting increases in serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission, the method comprising (a) obtaining a sample of genetic material from the patient; (b) assaying the sample for the presence of a genotype in the patient which is associated with a high probability of not responding to first line antidepressant treatment with the antidepressant therapy targeting increases in serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission; and (c) predicting the outcome of treatment with antidepressant medication in the patient based on the presence of the genotype in the sample, wherein the genotype is characterized by a polymorphism in a gene having at least one marker, wherein the gene is selected from the group consisting of HTR2A, OPRM1, FREQ, SLC6A3, SLC6A4, SLC6A2, CHRNA3, CHRM2, CACNA1C, S100A10, FKBP5; GRM7, RGS10, , and combinations thereof.

[000143] Another aspect of the present invention is to provide a method of screening patients to identify those patients with a increased risk of non-response to treatment with antidepressant medication, the method comprising (a) obtaining a sample of genetic material from the patient; (b) assaying the sample for the presence of a genotype in the patient which is associated with a decreased risk of non-response to treatment with antidepressant medication, wherein the genotype is characterized by a polymorphism in a

gene selected from the group consisting of HTR2A, , SLC6A3,, CHRM2, CACNA1C, S100A10, GRM7;and combinations thereof.

[000144] A patient refers to an individual awaiting or under medical care and treatment, such as treatment for depression. While the inventive methods are designed for human patients, such methods are applicable to any suitable individual, which includes, but is not limited to, a mammal, such as a mouse, rat, rabbit, hamster, guinea pig, cat, dog, goat, cow, horse, pig, and simian. Human patients include male and female patients of any ethnicity (e.g., Caucasian, Asian, Hispanic, Native American, and Black).

[000145] The sample of genetic material can be obtained from the patient by any suitable manner. The sample can be isolated from a source including saliva, buccal cells, hair roots, blood, cord blood, amniotic fluid, interstitial fluid, peritoneal fluid, chorionic villus, semen, or other suitable cell or tissue sample. Methods for isolating genomic DNA from various sources are well-known in the art.

IV. Detection and Identification of Markers

[000146] A. Detection:

[000147] A polymorphism refers to one of multiple alleles of a gene. Preferably, the polymorphism is a single nucleotide polymorphism (SNP). The polymorphism that is associated with treatment outcome to an antidepressant medication can be any suitable polymorphism. For example, the polymorphism can correlate with an increased or decreased risk of non-response to treatment with antidepressant medication.

[000148] The polymorphism included in a marker of a gene can be detected by any suitable manner known in the art. For example, the polymorphism can be detected by techniques, such as allele specific hybridization, allele specific oligonucleotide ligation, primer extension, minisequencing, mass spectroscopy, heteroduplex analysis, single strand conformational polymorphism (SSCP), denaturing gradient gel electrophoresis (DGGE), oligonucleotide microarray analysis, temperature gradient gel electrophoresis (TGGE), and combinations thereof.

[000149] B. Identification of Markers:

[000150] The markers in HTR2A that are associated with treatment outcome to antidepressant medication (e.g., that correlates an increased risk of non-response to treatment with antidepressant medication or a high probability of not achieving remission) in the HTR2A gene include markers rs666693 (SEQ ID NO: 1), rs9316232 (SEQ ID NO: 3), and rs582385 (SEQ ID NO: 2).

[000151] The markers in the OPRM1 gene that are associated with the outcome of treatment with antidepressant medication include rs17209711 (which identifies a SNP in OPRM1, e.g., SEQ ID NO: 5), rs3778149 (which identifies a SNP in the OPRM1, e.g., SEQ ID NO: 6), rs3778146 (which identifies a SNP in the OPRM1, e.g., SEQ ID NO: 7), rs7773995 (which identifies a SNP in the OPRM1, e.g., SEQ ID NO: 8); rs6900677 (which identifies SEQ ID NO: 39) and rs3778145 (which identifies a SNP in the OPRM1, e.g., SEQ ID NO: 9).

[000152] The marker in FREQ associated with the outcome of treatment with antidepressant medication is rs885345 (which identifies a SNP in FREQ, e.g., SEQ ID NO: 10).

[000153] The marker in SLC6A3 associated with the outcome of treatment with antidepressant medication is rs10052016 (which identifies a SNP in SLC6A3, e.g., SEQ ID NO: 11), rs10053602 (e.g. SEQ ID NO: 14)

[000154] The marker in SLC6A2 associated with the outcome of treatment with antidepressant medication is rs1814270 (which identifies a SNP in SLC6A2, e.g., SEQ ID NO: 79), rs11862589 (SEQ ID NO: 26); rs879522 (SEQ ID NO: 27), rs4564560 (SEQ ID NO: 28);); and rs1861646 (SEQ ID NO: 12). The SLC6A2 transporter is associated with modulating adrenergic neurotransmission.

[000155] The marker in SLC6A4 associated with the outcome of treatment with with antidepressant medication is rs16965623 (which identifies a SNP in SLC6A4, e.g. SEQ ID NO 32). The SLC6A4 transporter is associated with modulating serotonin neurotransmission.

[000156] The marker in RGS10 associated with the outcome of treatment with antidepressant medication is rs11198986 (which identifies a SNP in RGS10, e.g. SEQ ID NO 31). The RGS10 gene is associated with regulating G-protein signaling.

[000157] The marker in OPRM1 assocaited with the outcome of treatment with antidepressant medication is rs6916787 (which identifies a SNP in OPRM1, e.g. SEQ ID NO 33). The OPRM1 gene is associated withthe mu opiod receptor .

[000158] The marker in CHRNA3 associated with the outcome of treatment with antidepressant medication is rs6495308. CHRNA3 typically comprises SEQ ID NO: 13. The CHRNA3 gene is involved in modulating cholinergic neurotransmission through nicotinic receptors. Since some adjunctive antidepressant therapies include agents which can act upon cholinergic neurotransmission (e.g. bupropion), this gene can be involved in treatment outcomes for drug therapies directed towards modulating serotonergic neurotransmission with or without changes in adrenergic transmission.

[000159] The marker in the CHRM2 gene associated with the outcome of treatment with antidepressant medication is rs2113545 (which identifies a SNP in CHRM2, e.g., SEQ ID NO: 35). Other markers in the CHRM2 gene that correlate with treatment outcomes include: rs2350786 (which identifies a SNP in CHRM2, e.g., SEQ ID NO: 15) and rs1455857 (which identifies a SNP in CHRM2, e.g., SEQ ID NO: 25), rs7782904 SEQ ID NO: 24), rs2350786 (SEQ ID NO: 15), and rs1378646 (SEQ ID NO: 30); rs 2113545 (SEQ ID NO: 35). The CHRM2 gene is involved in modulating cholinergic neurotransmission through muscarinic receptors. Since some adjunctive antidepressant therapies include agents which can act upon cholinergic neurotransmission (e.g. bupropion), this gene can be involved in treatment outcomes for drug therapies directed towards modulating serotonergic neurotransmission with or without changes in adrenergic transmission.

[000160] The marker in CACNA1C associated with the outcome of treatment with antidepressant medication is rs929492 (which identifies a SNP in CACNA1C, e.g., SEQ ID NO: 17), and rs4765933 (SEQ ID NO: 24). The CACNA1C gene is involved in voltage-dependent L-type, alpha-1-C calcium channel subunits which are involved in neurotransmission. Therapies directed towards modulating serotonergic neurotransmission

with or without modulating adrenergic neurotransmission will involve changes in calcium gating across neuronal membranes. Calcium gating is intimately involved in excitation correlated with neurotransmission.

[000161] The marker in S100A10 associated with the outcome of treatment with antidepressant medication is rs6678672 (which identifies SNPs in S100A10, e.g., SEQ ID NO: 18) or rs6587640 (SEQ ID NO: 19) and rs929492 (SEQ ID NO: 17). The S100A10 gene is involved in calcium binding. Calcium is intimately involved in neurotransmission. Any therapies directed towards modulating serotonergic neurotransmission with or without modulating adrenergic neurotransmission will involve calcium binding.

[000162] In one embodiment, the invention also comprises assaying for the presence of a genotype that is associated with an increased risk of non-response to treatment with antidepressant medication, wherein the genotype is characterized by a polymorphism in a gene selected from the group consisting of HTR2A, OPRM1, FREQ, SLC6A3, SLC6A2, SLC6A4, RGS10,and CHRNA3, CHRM2, CACNA1C, S100A10, FKBP5, GRM7 and combinations thereof.

V. Treatment Outcomes:

[000163] The outcome of treatment with an antidepressant medication refers to whether or not a patient will remit and/or respond to treatment with the antidepressant medication (e.g., an SSRI, such as citalopram). The ability to remit and/or not respond to treatment is dependent upon the tolerability of an individual to the medication.

[000164] In individuals that can tolerate the antidepressant medication (i.e., are not allergic to or report serious side effects with the antidepressant medication, which would require halting treatment with the antidepressant medication), a non-response refers to a treatment response that does not improve the symptoms associated with depression to a clinically meaningful extent. For example, in the STAR*D trial, non-response to treatment with antidepressant medication refers to patients that achieved less than 50% reduction in baseline 16-item Quick Inventory of Depressive Symptomatology-Clinician-rated (QIDS-C_{16}) score at the last treatment visit (Trivedi et al., *Am. J. Psychiatry*, 163: 28-40 (2006); Rush et al., *Control Clin. Trials*, 25: 119-142 (2004); Rush et al., *Biol. Psychiatry*, 54: 573-583 (2003); and Trivedi et al., *Psychol. Med.*, 34: 73-82 (2004)).

[000165] In addition, non-response is defined as those subjects who's Quick Inventory of Depressive Symptomatology-Clinican-rate (QIDS-C_{16}) score was greater on study exit than on study entry. Accordingly, patients with a non-response to treatment ("non-responders") refers to patients that achieve less than 50% (e.g., less than 45%, less than 35%, less than 30%, less than 25%, less than 20%, less than 15%, than 10%or less than 5%) reduction in symptoms of depression following treatment with the antidepressant medication as measured by QIDS-C_{16} score. In some embodiments, non-responders refers to patients whose reduction in symptoms of depression following treatment is from about 0% to about 5%, from about 0% to about 10%, from about 0% to about 15%, from about 0% to about 20%, from about 0% to about 25%, from about 0% to about 30%, from about 0% to about 35%, from about 0% to about 45%, from about 0% to about 50%, from about 10% to about 15%, from 10% to about 20%, from 10% to about 25%, from about 10% to about 30%, from about 10% to about 35%, from about 10% to about 45%, from about 10% to about 50%, from about 15% to about 20%, from about 15% to about 25%, from about 15% to about 30%, from about 15% to about 35%, from about 15% to about 45%, from about 15% to about 50%, from about 20% to about 25%, from about 20% to about 30%, from about 20% to about 35%, from about 20% to about 45%, from about 20% to about 50%, from about 25% to about 30%, from about 25% to about 35%, from about 25% to about 45%, from about 25% to about 50%, from about 30% to about 35%, from about 30% to about 45%, from about 30% to about 50%, from about 40% to about 45%, from about 40% to about 50%, or from about 45% to about 50%.

[000166] Positive response to treatment also can be measured by an improvement in one or more symptoms of depression. Such symptoms include emotional and physical symptoms. Examples of emotional symptoms of depression include feelings of guilt, worthlessness, sadness, emptiness, hopelessness, numbness, helplessness, irritability, anxiety, indecisiveness, pessimism, and thoughts of death and suicide. Examples of physical symptoms of depression include headaches, back pain, muscle aches and joint pain, chest pain, digestive problems, exhaustion, fatigue, insomnia, a change in appetite or weight, and dizziness or lightheadedness.

[000167] In the STAR*D trial, and those analyzed in this disclosure, are patients in remission following antidepressant medication identified by a QIDS-C_{16} score of less than

or equal to 5 following administration of the antidepressant medication on exit of the study protocol. Therefore, patients that remit following treatment refers to patients that have a QIDS-C_{16} score of less than or equal to 5 (e.g., 5, 4, 3, 2, 1, or 0) following treatment with the antidepressant medication. Furthermore, remission was defined as having a CIRS score ≤ 6 on study entry and a QIDS-C_{16} score ≥ 18 on study entry to be genotyped and classified as in remission upon study exit.

[000168] Accordingly, the present invention also provides a method of identifying patients with an increased likelihood of experiencing remission following treatment with an antidepressant medication targeting increases in serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission, the method comprising (a) obtaining a sample of genetic material from the patients, and (b) assaying the sample for the presence of a genotype in the patients that is associated with an increased likelihood of experiencing remission following treatment with antidepressant medication, wherein the genotype is characterized by a polymorphism in a gene selected from the group consisting of HTR2A, SLC6A3, , CHRM2, CACNA1C, S100A10, GRM7, and combinations thereof

VI. Medications:

[000169] The antidepressant medication can be any suitable antidepressant medication known in the art. For example, the antidepressant medication can be a SSRI, a tricyclic antidepressant (TCA), a tetracyclic antidepressant, a MAOI, a reversible inhibitor of monoamine oxidase A (RIMA), a dopamine reuptake inhibitor (DARI), a norepinephrine-dopamine reuptake inhibitor, a norepinephrine reuptake inhibitor (NRI) or (NARI), a serotonin-norepinephrine reuptake inhibitor (SNRI), a selective serotonin reuptake enhancer (SSRE), a noradrenergic and specific serotonergic antidepressant (NaSSA), or another suitable antidepressant medication. Preferably, the antidepressant medication is a SSRI, such as citalopram, alaproclate, escitalopram, etoperidone, fluoxetine, fluvoxamine, paroxetine, sertraline, zimelidine, or combinations thereof.

VII. Kits:

[000170] In another aspect, the present invention provides a kit comprising reagents suitable for applying the methods of the invention. The kit provides the necessary materials for identifying a polymorphism packaged into a suitable container. At a minimum, the kit contains a reagent that identifies a polymorphism in the selected gene that is associated with a selected trait, such as treatment outcome. Preferably, the reagent is a set of primers or a PCR set (a set of primers, DNA polymerase, and 4 nucleoside triphosphates) that hybridizes with the gene or a fragment thereof. The kit also can include other reagents for detecting or measuring the detectable entity and/or a control. Other reagents used for hybridization, prehybridization, DNA extraction, visualization, and the like also can be included.

[000171] The kit may also utlilze methodologies for analysis of single stranded and/or double stranded DNA segments by whatever technology permits the anlaysis of a biological sample from patients (blood, stool, saliva, etc) to identify the disclosed genetic markers associated with treatment outcome which include genes, SNPs and haplotypes disclosed herein.

[000172] Sensitivity is the probability that a symptom is present (or the screening test is positive) when a patient has a disorder. The sensitivity of the polymorphism associated with the outcome of treatment with antidepressant medication in the inventive method can be any suitable sensitivity. Preferably, the sensitivity is about 0.5 or higher (e.g., about 0.55, about 0.6, about 0.65, about 0.7, about 0.75, about 0.8, about 0.85, about 0.9, or about 0.95). In some embodiments, the sensivity is from about 0.5 to about 0.95, from about 0.5 to about 0.9, from about 0.5 to about 0.85, from about 0.5 to 0.8, from about 0.5 to about 0.75, from about 0.5 to about 0.7, from about 0.5 to about 0.65, from about 0.5 to about 0.6, from about 0.5 to about 0.55, from about 0.55 to about 0.95, from about 0.55 to about 0.9, from about 0.55 to about 0.85, from about 0.55 to 0.8, from about 0.55 to about 0.75, from about 0.55 to about 0.7, from about 0.55 to about 0.65, from about 0.55 to about 0.6, from about 0.6 to about 0.95, from about 0.6 to about 0.9, from about 0.6 to about 0.85, from about 0.6 to 0.8, from about 0.6 to about 0.75, from about 0.6 to about 0.7, from about 0.6 to about 0.65, from about 0.65 to about 0.95, from about 0.65 to about 0.9, from about 0.65 to about 0.85, from about 0.65 to 0.8, from about 0.65 to about 0.75, from about

0.65 to about 0.7, from about 0.7 to about 0.95, from about 0.7 to about 0.9, from about 0.7 to about 0.85, from about 0.7 to 0.8, from about 0.7 to about 0.75, from about 0.75 to about 0.95, from about 0.75 to about 0.9, from about 0.75 to about 0.85, from about 0.75 to 0.8, from about 0.8 to about 0.95, from about 0.8 to about 0.9, from about 0.8 to about 0.85, from about 0.85 to about 0.95, from about 0.85 to about 0.9, or from about 0.9 to about 0.95.

[000173] Specificity is the probability that a symptom is not present (or the screening test is negative) when a patient does not have a disorder. The specificity of the polymorphism associated with the outcome of treatment with antidepressant medication in the inventive method can be any suitable specificity. Preferably, the specificity is about 0.5 or higher (e.g., about 0.55, about 0.6, about 0.65, about 0.7, about 0.75, about 0.8, about 0.85, about 0.9, or about 0.95). In some embodiments, the specificity is from about 0.5 to about 0.95, from about 0.5 to about 0.9, from about 0.5 to about 0.85, from about 0.5 to 0.8, from about 0.5 to about 0.75, from about 0.5 to about 0.7, from about 0.5 to about 0.65, from about 0.5 to about 0.6, from about 0.5 to about 0.55, from about 0.55 to about 0.95, from about 0.55 to about 0.9, from about 0.55 to about 0.85, from about 0.55 to 0.8, from about 0.55 to about 0.75, from about 0.55 to about 0.7, from about 0.55 to about 0.65, from about 0.55 to about 0.6, from about 0.6 to about 0.95, from about 0.6 to about 0.9, from about 0.6 to about 0.85, from about 0.6 to 0.8, from about 0.6 to about 0.75, from about 0.6 to about 0.7, from about 0.6 to about 0.65, from about 0.65 to about 0.95, from about 0.65 to about 0.9, from about 0.65 to about 0.85, from about 0.65 to 0.8, from about 0.65 to about 0.75, from about 0.65 to about 0.7, from about 0.7 to about 0.95, from about 0.7 to about 0.9, from about 0.7 to about 0.85, from about 0.7 to 0.8, from about 0.7 to about 0.75, from about 0.75 to about 0.95, from about 0.75 to about 0.9, from about 0.75 to about 0.85, from about 0.75 to 0.8, from about 0.8 to about 0.95, from about 0.8 to about 0.9, from about 0.8 to about 0.85, from about 0.85 to about 0.95, from about 0.85 to about 0.9, or from about 0.9 to about 0.95.

[000174] Positive predictive value is the probability that a patient has a disorder given a positive test result. The positive predictive value of the polymorphism associated with the outcome of treatment with antidepressant medication in the inventive method can be any suitable value. Preferably, the positive predictive value is about 0.05 or higher (e.g., about

0.1, about 0.2, about 0.25, about 0.3, about 0.4, about 0.5, about 0.55, about 0.6, about 0.65, about 0.7, about 0.75, about 0.8, about 0.85, about 0.9, or about 0.95). In some embodiments, the positive predictive value is from about 0.05 to about 0.95, from about 0.05 to about 0.9, from about 0.05 to about 0.85, from about 0.05 to about 0.8, from about 0.05 to about 0.75, from about 0.05 to about 0.7, from about 0.05 to about 0.65, from about 0.05 to about 0.65, from about 0.05 to about 0.6, from about 0.05 to about 0.55, from about 0.05 to about 0.5, from about 0.05 to about 0.4, from about 0.05 to about 0.3, from about 0.05 to about 0.25, from about 0.05 to about 0.2, from about 0.05 to about 0.1, from about 0.1 to about 0.95, from about 0.1 to about 0.9, from about 0.1 to about 0.85, from about 0.1 to about 0.8, from about 0.1 to about 0.75, from about 0.1 to about 0.7, from about 0.1 to about 0.65, from about 0.1 to about 0.65, from about 0.1 to about 0.6, from about 0.1 to about 0.55, from about 0.1 to about 0.5, from about 0.1 to about 0.4, from about 0.1 to about 0.3, from about 0.1 to about 0.25, from about 0.1 to about 0.2, from about 0.2 to about 0.95, from about 0.2 to about 0.9, from about 0.2 to about 0.85, from about 0.2 to about 0.8, from about 0.2 to about 0.75, from about 0.2 to about 0.7, from about 0.2 to about 0.65, from about 0.2 to about 0.65, from about 0.2 to about 0.6, from about 0.2 to about 0.55, from about 0.2 to about 0.5, from about 0.2 to about 0.4, from about 0.2 to about 0.3, from about 0.2 to about 0.25, from about 0.25 to about 0.95, from about 0.25 to about 0.9, from about 0.25 to about 0.85, from about 0.25 to about 0.8, from about 0.25 to about 0.75, from about 0.25 to about 0.7, from about 0.25 to about 0.65, from about 0.25 to about 0.65, from about 0.25 to about 0.6, from about 0.25 to about 0.55, from about 0.25 to about 0.5, from about 0.25 to about 0.4, from about 0.25 to about 0.3, from about 0.3 to about 0.95, from about 0.3 to about 0.9, from about 0.3 to about 0.85, from about 0.3 to about 0.8, from about 0.3 to about 0.75, from about 0.3 to about 0.7, from about 0.3 to about 0.65, from about 0.3 to about 0.65, from about 0.3 to about 0.6, from about 0.3 to about 0.55, from about 0.3 to about 0.5, from about 0.3 to about 0.4, from about 0.4 to about 0.95, from about 0.4 to about 0.9, from about 0.4 to about 0.85, from about 0.4 to about 0.8, from about 0.4 to about 0.75, from about 0.4 to about 0.7, from about 0.4 to about 0.65, from about 0.4 to about 0.65, from about 0.4 to about 0.6, from about 0.4 to about 0.55, from about 0.4 to about 0.5, from about 0.5 to about 0.95, from about 0.5 to about 0.9, from about 0.5 to about 0.85, from about 0.5 to about 0.8, from about 0.5 to about 0.75, from about 0.5 to about 0.7, from about 0.5 to about 0.65, from about 0.5 to about 0.65, from about 0.5 to about 0.6, from about 0.5 to about 0.55, from about 0.55 to

about 0.95, from about 0.55 to about 0.9, from about 0.55 to about 0.85, from about 0.55 to about 0.8, from about 0.55 to about 0.75, from about 0.55 to about 0.7, from about 0.55 to about 0.65, from about 0.55 to about 0.65, from about 0.55 to about 0.6, from about 0.6 to about 0.95, from about 0.6 to about 0.9, from about 0.6 to about 0.85, from about 0.6 to about 0.8, from about 0.6 to about 0.75, from about 0.6 to about 0.7, from about 0.6 to about 0.65, from about 0.6 to about 0.65, from about 0.65 to about 0.95, from about 0.65 to about 0.9, from about 0.65 to about 0.85, from about 0.65 to about 0.8, from about 0.65 to about 0.75, from about 0.65 to about 0.7, from about 0.7 to about 0.95, from about 0.7 to about 0.9, from about 0.7 to about 0.85, from about 0.7 to about 0.8, from about 0.7 to about 0.75, from about 0.75 to about 0.95, from about 0.75 to about 0.9, from about 0.75 to about 0.85, from about 0.75 to about 0.8, from about 0.8 to about 0.95, from about 0.8 to about 0.9, from about 0.8 to about 0.85, from about 0.85 to about 0.95, from about 0.85 to about 0.9, or from about 0.9 to about 0.95.

[000175] Negative predictive value is the probability that a patient has the disorder given a negative test result. The negative predictive value of the polymorphism associated with the outcome of treatment with antidepressant medication in the inventive method can be any suitable value. Preferably, the negative predictive value is about 0.5 or higher (e.g., about 0.55, about 0.6, about 0.65, about 0.7, about 0.75, about 0.8, about 0.85, about 0.9, or about 0.95). In some embodiments, the negative predictive value is from about 0.5 to about 0.95, from about 0.5 to about 0.9, from about 0.5 to about 0.85, from about 0.5 to 0.8, from about 0.5 to about 0.75, from about 0.5 to about 0.7, from about 0.5 to about 0.65, from about 0.5 to about 0.6, from about 0.5 to about 0.55, from about 0.55 to about 0.95, from about 0.55 to about 0.9, from about 0.55 to about 0.85, from about 0.55 to 0.8, from about 0.55 to about 0.75, from about 0.55 to about 0.7, from about 0.55 to about 0.65, from about 0.55 to about 0.6, from about 0.6 to about 0.95, from about 0.6 to about 0.9, from about 0.6 to about 0.85, from about 0.6 to 0.8, from about 0.6 to about 0.75, from about 0.6 to about 0.7, from about 0.6 to about 0.65, from about 0.65 to about 0.95, from about 0.65 to about 0.9, from about 0.65 to about 0.85, from about 0.65 to 0.8, from about 0.65 to about 0.75, from about 0.65 to about 0.7, from about 0.7 to about 0.95, from about 0.7 to about 0.9, from about 0.7 to about 0.85, from about 0.7 to 0.8, from about 0.7 to about 0.75, from about 0.75 to about 0.95, from about 0.75 to about 0.9, from about 0.75 to about 0.85, from about 0.75 to 0.8, from about 0.8 to about 0.95, from about 0.8 to about

0.9, from about 0.8 to about 0.85, from about 0.85 to about 0.95, from about 0.85 to about 0.9, or from about 0.9 to about 0.95.

[000176] The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

VIII. Examples:

[000177] A. Experimental Design:

[000178] The experimental design and results are essentially as described in McMahon et al. (*Am. J. Hum. Genet.* 78: 804-814 (2006)). DNA samples were collected from a clinically-representative cohort of 1953 outpatients with major depressive disorder enrolled in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial. Outpatients 18-75 years of age with a baseline Hamilton Depression Rating Scale (see Hamilton et al., *J. Neurol. Neurosurg. Psychiatry*, 23: 56-62 (1960); and Hamilton, Br. *J. Soc. Clin. Psychol.*, 6(4): 278-296 (1967)) score of ≥14 who met the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for non-psychotic major depressive disorder (MDD) were eligible for the trial.

[000179] All participants received initial therapy with citalopram, typically starting at 20 mg/day, with dose increases following recommended procedures (see Trivedi et al., *Am. J Psychiatry*, 163(1): 28-40 (2006)). The patients were treated with citalopram under a standard protocol for up to 14 weeks. DNA was extracted from whole blood and genotyped on an Illumina Bead Array platform (see Gunderson et al., *Genome Res.*, 14(5): 870-877 (2004)) for 768 single nucleotide polymorphisms (SNPs) in 68 candidate genes. Gentoypic data was derived from the combined set of data produced by the STAR*D trial (e.g. discovery and validation genotyping data sets). Genetic markers were preselected based on drugs known, or in development, to be useful in treating depression. The identified genes selected prior to genotypic analysis were HTR2A, OPRM1, FREQ, SLC6A3, SLC6A2, RGS10, SLC6A4, CHRNA3, CHRM2, CACNA1C, S100A10, and GRM7.

[000180] Specific SNPs within each of these genes were preselected based upon literature which describes the chosen SNPs as involved in either depressive illness, mood disorders, bipolar disorder, post-traumatic stress disorder, addiction and attentional deficits.

[000181] The 16-item Clinician-Rated Quick Inventory of Depressive Symptomatology (QIDS-C_{16}) score was obtained at baseline at each treatment visit to measure symptom severity. Patients with a baseline QIDS-C_{16} score of greater than or equal to 18 were eligible if the treating clinician determined that outpatient treatment with an antidepressant medication was indicated and safe.

[000182] Patients were scored for treatment outcome in two ways: designated remission and response. In the absence of external validators, the choice of categorical phenotypes was guided (1) by work with the STAR*D clinicians (in advance of the genotyping) to develop distinctions that had face validity and took advantage of the large body of data available from the STAR*D trial; (2) by ensuring maximal contrast between the outcome groups to improve power, and creating "probable" groups that approximated the more narrowly defined categories to test their robustness; and (3) by paying special attention to full remission of symptoms, since this was the primary target outcome of treatment.

[000183] Possible outcomes of the treatment were "remission," defined by a QIDS-C_{16} score of ≤ 5 at the last treatment visit and an entry CIRS ≤ 6. Non-response was defined as an exit QIDS-C_{16} score greater than entry score, a CIRS index ≤ 6, or a QIDS-C_{16} score less than 50% reduced when comparing entry and exit test scores (e.g. at least 45%; at least 40%, at least 35%, at least 30%, at least 25%, at least 20%, at least 15%, at least 10% or at least 5% and ranges included).

[000184] In the present invention no subjects in the combined validation and discovery genotype data sets who were classified as "responders"(e.g. 50% or greater reduction of QIDS-C_{16} score on study exit) were included in the genotypic anlaysis described here in.

[000185] Since failure to consider tolerability could lead to misclassification of intolerant patients as non-responders, all subjects were scored as tolerant, probably tolerant, intolerant, or probably intolerant on the basis of an algorithm that considered study exit data and the Global Rating of Side Effect Burden (GRSEB). In brief, all subjects who elected to continue citalopram at the end of the treatment period were considered tolerant, whereas subjects who refused to continue citalopram or who left the study because of side effects were considered intolerant. The remaining subjects were classified on the basis of

GRSEB score into probably tolerant (no more than moderate side effects) or probably intolerant (more than moderate side effects). Subjects who were classified as "intolerant" or "probably intolerant" were removed from the analysis.

[000186] Relative change in QIDS-C_{16} score at the last visit (expressed as a percentage change from the initial score) was tested as a quantitative trait, after removal of intolerant, probably intolerant and non-adherant subjects.

[000187] B. Statistical Analysis:

[000188] The experiment was based on comparison of gene, allele and haplotype frequencies between subjects who remitted or did not respond to citalopram therapy. All polymorphism call rates were >0.98 when analyzed in a combined validation and discovery data set. Similarly, all polymorphisms in each data set which comprised the combined data set had call rates >98%. After establishing criteria for analytical inclusion based upon either remission or non-response, a total of 255 subjects whose genotypic data was available were analyzed. Of this sample of 255 subjects 66% were classified as non-resonders while 33% were classified as true remitters. The categorical outcomes were defined as 0 for non-response and 1 for response. For each analysis, Fisher's two-sided exact test (for allele-wise tests only), Pearson chi-square, and the likelihood ratio chi-square tests were used for all haplotype analyses comparing the remitters and non-responders in the combined data sets ($p < 0.05$). These analyses were conducted using a Golden Helix software suite (Bozeman, MT).

Each marker was tested for association with treatment non-response or remission in the combined discovery and validation sample set. A total of 39 markers met or exceeded the nominal significance level of $p < 0.05$ using a Fischer's exact comparison between remitters and non-responders.

[000189] C. Exemplary Embodiments:

[000190] TABLE 1: exemplary embodiment 1

SNP No.	Outcome	FREQ	
rs885345	0	1	Total
C_C	56	26	82
C_T	74	53	127
T_T	40	6	46

[000191] In patients with the neuronal calcium sensor 1 gene (FREQ) polymorphism rs885345, 0.33 have outcome 1(85/255) and .66 have outcome 0 (170/255). This distribution aligns with epidemiological evidence for symptomatic relief of major depressive disorder in that about 70% of patients do not achieve full symptomatic relief of their presenting depression

[000192] Outcome 1 is Sequenced Treatment Alternatives to Relieve Depression (STAR*D) remission which is defined as tolerant or probably tolerant to modulating serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission and who have achieved full symptomatic relief from their presenting major depressive disorder symptoms. This set of subjects included those classified as in remission and those classified as responders. Outcome 1 corresponds to an entry Quick Inventory Depression scale (QIDS) ≥18, an exit QIDS of ≤ 5, a CIRS total score ≤ 6 and tolerant/probably tolerant of drug therapy.

[000193] Outcome 0 is STAR*D non-responder which is defined as below.

[000194] Outcome 0 corresponds to an entry QIDS≥18 and a less than <50% reduction in exit QIDS, a tolerance/probable tolerance of drug therapy with a Cumulative Illness Rating Scale (CIRS) total score ≤ 6. Outcome 0 also corresponds to an exit QIDS score≥entry QIDS with a CIRS total score ≤ 6 and tolerant/probably tolerant of drug therapy.

[000195] TABLE 2: exemplary embodiment 2

SNP No.	Outcome	SLC6A3	
rs10052016	0	1	Total
A_A	96	45	141
A_G	67	26	93
G_G	7	14	21

[000196] People inheriting the DAT allele designated "G" from both parents (a recessive inheritance pattern) have a greater chance of outcome 1, namely 14/21 = 0.66. The other two genotypes have close to the population average. Therefore, rs10052016-G_G allele predicts a high probability of achieving remission in a recessive inheritance pattern.

[000197] TABLE 3: exemplary embodiment 3

SNP No.	Outcome	CHRM2	
rs2350786	0	1	Total
C_C	10	15	25
C_T	74	29	103
T_T	86	41	127

[000198] In patients with the cholinergic receptor, muscarinic 2 gene (CHRM2) polymorphism rs2350786, those that are rs2350786-C_C homozygous have a greater chance of outcome 1, namely 15/25 = 0.60. Therefore, rs2350786-C_C allele predicts a high probability of achieving remission in patients with this inheritance pattern. In contrast, rs2350786-C_T and rs2350786-T_T alleles predict an increased risk of non-response to treatment in patients that are rs2350786-C_T heterozygous and rs2350786-T_T homozygous, respectively 74/103 = 0.72 and 86/127 = 0.68.

[000199] TABLE 4: exemplary embodiment 4

SNP No.	Outcome	CACNA1C	
rs929492	0	1	Total
A_A	3	6	9
A_G	35	22	57
G_G	130	55	185
?_?	2	2	4

In patients with the calcium channel voltage-dependent, L type, alpha 1C subunit (CACNA1C) gene polymorphism rs929492, those that are rs929492-A_A homozygous have a greater chance of outcome 1, namely 6/9 = 0.67. Therefore, rs929492-A_A allele predicts a high probability of achieving remission in patients with this inheritance pattern. In contrast, CACNA1C gene polymorphism rs929492 predicts an increased risk of non-response to treatment, namely 130/185 = 0.70, in patients that are rs9294G_G homozygous.

[000200] TABLE 5: exemplary embodiment 5

SNP No.	Outcome	CHRM2	
rs2113545	0	1	Total
C_C	75	36	111
C_T	83	31	114
T_T	12	18	30

In patients with the cholinergic receptor, muscarinic 2 gene (CHRM2) polymorphismrs 2113545, those that arers 2113545-T_T homozygous have a greater chance of outcome 1, namely 18/30 = 0.60. Therefore, rs2113545-T_T allele predicts a high probability of achieving remission in patients with this inheritance pattern. In contrast CHRM2 polymorphismrs 2113545 predicts an increased risk of non-response to treatment, namely 83/114 = 0.73, in patients that are rs2113545-C_T heterozygous or rs2113545-C_C homozygous namely 75/111 = 0.68.

[000201] TABLE 6: exemplary embodiment 6

SNP No.	Outcome	OPRM1	
rs17275521	0	1	Total
A_A	4	0	4
A_G	57	17	74
G_G	109	68	177

In patients with the mu-opiod receptor gene (OPRM1) polymorphism rs17275521, those that are rs17275521-G_G homozygous have a greater chance of outcome 0, namely 109//177 = 0.62. Therefore, rs17275521-G_G allele predicts a high probability of failing antidepressant therapy in patients with this inheritance pattern. IThe

OPRM1 polymorphism rs17275521 predicts an increased risk, namely 57/74 = 0.77, of non-response to treatment in patients that are rs17275521-A_G heterozygous.

[000202] TABLE 7: exemplary embodiment 7

SNP No.	Outcome	CHRNA3	
rs6495308	0	1	Total
A_A	96	33	129
A_G	56	42	98
G_G	18	10	28

In patients with the cholinergic receptor, nicotinic alpha-3 gene (CHRNA3) polymorphism rs6495308, those that are rs6495308-A_G heterozygous have a greater chance of outcome 0, namely 18/28 = 0.64. Therefore, rs6495308-A_G allele predicts a high probability of non-response in patients with this inheritance pattern. The CHRNA3 polymorphism rs6495308 predicts an increased risk of non-response to treatment, namely 96/129 = 0.74, in patients that are rs6495308-A_A homozygous. In patients that are rs6495308-G_G homozygous there is an increased probability of non-response (18/28 = 0.64).

[000203] TABLE 8: exemplary embodiment 8

SNP No.	Outcome	SLC6A2	
rs1814270	0	1	Total
A_A	48	39	87
A_G	91	29	120
G_G	29	16	45
?_?	2	1	3

In patients with the solute carrier family 6 (neurotransmitter transporter, noradrenalin) member 2 (SLC6A2) polymorphism rs1814270. Those patients with the rs1814270-G_G (29/45 = 0.64)allele predicts a high probability of failing antidepressant therapy.. Patients with the SLC6A2 polymorphism rs1814270 have an increased risk of non-response to treatment, namely 91/120 =0.76 in patients that are rs1814270-A_G heterozygous.

[000204] TABLE 9: exemplary embodiment 9

SNP No.	Outcome	OPRM1	
rs3778149	0	1	Total
C_C	111	68	179
C_G	53	16	69
G_G	4	0	4
?_?	2	1	3

In patients with the mu-opiod receptor gene (OPRM1) polymorphism rs3778149, those that are rs3778149-C_C homozygous have a greater chance of outcome 0, namely 111/179 = 0.62. Therefore, rs3778149-C_C allele predicts a high probability of non-response to antidepressant therapy in patients with this inheritance pattern. Similarly, OPRM1 polymorphism rs3778149 predicts an increased risk of non-response to treatment, namely 53/69 = 0.77 in patients that are rs3778149-C_G heterozygous. Finally, patients that are G_G homozygous at rs3778149 are 4 times as likely to fail antidepressant therapy although these numbers may not be significant with a larger rs3778149-G_G haplotype.

[000205] TABLE 10: exemplary embodiment 10

SNP No.	Outcome	OPRM1	
rs3778146	0	1	Total
C_C	4	0	4
C_T	55	17	72
T_T	111	68	179

In patients with the mu-opiod receptor gene (OPRM1) polymorphism rs3778146, those that are rs3778146-C_C homozygous have a four fold greater chance of responding to antidepressant therapy. Therefore, rs3778146-C_C allele predicts a high probability of non-response in patients with this inheritance pattern. In patients with the OPRM1 polymorphism rs3778146 there is an increased risk of non-response to treatment, namely 55/72 = 0.76, in patients that are rs3778146-C_T heterozygous. Similarly, those patients who are rs3778146-T_T homozygous have an increased probability of non-response (111/179= 0.62).

[000206] TABLE 11: exemplary embodiment 11

SNP No.	Outcome	OPRM1	
rs7773995	0	1	Total
C_C	111	68	179
C_T	55	17	72
T_T	4	0	4

In patients with the mu-opiod receptor gene (OPRM1) polymorphism rs7773995, those that are rs7773995-T_T homozygous have a four fold greater chance of not responding to antidepressant therapy. Therefore, rs7773995-T_T allele predicts a high probability of failing antidepressant therapy in patients with this inheritance pattern. In contrast, OPRM1 polymorphism rs7773995 predicts an increased risk of non-response to treatment, namely 55/72 = 0.76, in patients that are rs7773995-C_T heterozygous or C-C homozygous (111/179 = 0.62).

[000207] TABLE 12: exemplary embodiment 12

SNP No.	Outcome	OPRM1	
rs3778145	0	1	Total
A_A	112	68	180
A_C	54	17	71
C_C	4	0	4

In patients with the mu-opiod receptor gene (OPRM1) polymorphism rs3778145, those that are rs3778145-A_A homozygous have a greater chance of failing antidepressant therapy, namely 112/180 = 0.62. Therefore, rs3778145-A_A allele predicts a high probability of non-response to treatment in patients with this inheritance pattern. Patients with rs3778145-A_C have an increased risk of not responding to antidepressant therapy (54/71 = 0.76). Subjects with rs3778145-C_C have a four fold greater probability of failing antidepressant therapy as do patients with rs3778145-A_A (112/180 = 0.62).

[000208] TABLE 13: exemplary embodiment 13

SNP No.	Outcome	CHRM2	
rs6960707	0	1	Total
A_A	74	32	106
A_G	81	33	114
G_G	15	20	35

In patients with the cholinergic receptor, muscarinic 2 gene (CHRM2) polymorphism rs6960707, those that are rs6960707-G_G homozygous have a greater chance of outcome 1, namely 20/35 = 0.57. Therefore, rs6960707-G_G allele predicts a high probability of achieving remission in patients with this inheritance pattern. In contrast, CHRM2 polymorphism rs6960707 predicts an increased chance of non-response to treatment, namely 74/106 = 0.70 and 81/114 = 0.71, in patients that are respectively rs6960707-A_A (homozygous) and rs6960707-A_G (heterozygous).

[000209] TABLE 14: exemplary embodiment 14

SNP No.	**Outcome**	**S100A10 p11 protein**	
rs6678672	0	1	Total
A_A	8	13	21
A_G	73	25	98
G_G	89	45	134

In patients with the S100 calcium binding protein A10 (S100A10) gene polymorphism rs6678672, those that are rs6678672-A_G heterozygous or rs6678672-G_G homozygous have a greater probability of failing antidepressant therapy, namely 73/98 = 0.74 and 89/134 = 0.66, respectively. In contrast, rs6678672-A_A predicts a high probability of achieving remission, namely 13/21= 0.62, in patients with this inheritance pattern.

[000210] TABLE 15: exemplary embodiment 15

SNP No.	Outcome	5HT2A	
rs666693	0	1	Total
C_C	112	51	163
C_T	54	24	78
T_T	4	10	14

In patients with the 5-hydroxytryptamine (serotonin) receptor 2A (HTR2A) polymorphism rs666693, those that are rs582385-T_T homozygous have a greater chance of outcome 1, namely 10/14 = 0.71. Therefore, rs582385-T_T allele predicts a high probability of achieving remission in patients with this inheritance pattern. Patients with rs666693-C_C (112/163 = 0.69) or rs666693-C_T (54/78 = 0.69) have a greater probability of non-response.

[000211] TABLE 16: exemplary embodiment 16

SNP No.	Outcome	5HT2A	
rs582385	0	1	Total
A_A	109	51	160
A_G	52	24	76
G_G	4	10	14
?_?	5	0	5

In patients with the 5-hydroxytryptamine (serotonin) receptor 2A (HTR2A) polymorphism rs582385, those that are rs582385-G_G homozygous have a greater chance of outcome 1, namely 10/14 = 0.71. Therefore, rs582385-G_G allele predicts a high probability of achieving remission in patients with this inheritance pattern. In contrast, rs582385-A_A allele predicts a high probability, 109/160 = 0.68, of non-response in patients that have this inheritance pattern. Patients with rs582385-A_G have an increased probability of non-response (52/76 = 0.68).

[000212] TABLE 17: exemplary embodiment 17

SNP No	Outcome	OPRM1	
rs17209711	0	1	Grand Total
A_A	4	0	4
A_T	56	17	73
T_T	110	67	177
?_?	0	1	1
Grand Total	170	85	255

In patients with the OPRM1 opiod gene, individuals who are rs17209711-A_A have a four fold greater probability of not responding to antidepressant therapy. Individuals that are rs17209711-T_T homozygous or rs17209711-A_T are 110/177 = 0.62 and 56/73 = 0.77 respectively have an increased risk of non-response.

[000213] TABLE 18: exemplary embodiment 18

SNP No	Outcome		
rs9316232	0	1	Grand Total
C_C	79	24	103
C_T	70	46	116
T_T	18	14	32
?_?	3	1	4
Grand Total	170	85	255

Individuals with the HTR2A gene are at high probability of failing antidepressant therapy when they are rs9316232-C_C homozygous (79/103 = 0.77) or rs9316232-C_T heterozygous (70/ 116 = 0.60).

[000214] TABLE 19: Gene And SNPs Associated With A High Probability Of Treatment Failure

Gene and SNPs associated with a high probability of treatment failure are listed in Table 19. All call rates for combined data sets (validation and discovery > 0.98) for the polymorphisms and genes listed.

	Gene	Fishers exact *p* value
rs17047279	GRM7	0.04
rs17047286	GRM7	0.04
rs9368881	FKBP5	0.03
rs4765933	CACNA1C	0.03
rs7782904	CHRM2	0.05
rs1455857	CHRM2	0.01
rs1378646	CHRM2	0.01
rs6960707	CHRM2	0.01
rs2350786	CHRM2	0.012
rs2113545	CHRM2	0.003
rs6587640	S100A10	0.01
rs6678672	S100A10	0.006
rs11862589	SLC6A2	0.02
rs4564560	SLC6A2	0.02
rs17841329	SLC6A2	0.02
rs879522	SLC6A2	0.02
rs1814270	SLC6A2	0.007
rs1002513	HTR2A	0.01
rs9567739	HTR2A	0.03
rs666693	HTR2A	0.01
rs582385	HTR2A	0.01
rs10053602	SLC6A3	0.004
rs1002513	HTR2A	0.01
rs10053602	SLC6A3	0.004
rs2113545	CHRM2	0.003
rs6900677	OPRM1	0.0001

	Gene	Fishers exact *p* value
rs17047321	GRM7	0.03
rs11198986	RGS10	0.02
rs6916787	OPRM1	0.04
rs16965623	SLC6A4	0.036
rs1861646	SLC6A2	0.001
rs929492	CACNA1C	0.045
rs3778145	OPRM1	0.038
rs7773995	OPRM1	0.036
rs3778146	OPRM1	0.036
rs9316232	HTR2A	0.013
rs6495308	CHRNA3	0.022
rs17209711	OPRM1	0.032
rs17275521	OPRM1	0.023

[000215] Genotyping patients for genes, SNPs and haplotype markers can help to determine the outcome of treatment with antidepressant medication. For example, genotyping and haplotype anlaysis of patients using HTR2A, OPRM1, SLC6A2, CHRNA3, GRM7, FKBP5, SLC6A3 markers, among others identified in the teachings of this patent, can identify patients with a high probability of non-response to treatment with antidepressant medication. In another example genotyping and haplotype analysis of CHRM2, CACNA1C, S100A10, HTR2A, GRM7, or SLC6A3 can identify patients with a high probability of responding to treatment with antidepressant medications. Additionally, absence of the alleles associated with decreased risk for non-response can be used to identify individuals who may suffer from treatment non-response, which patients could benefit from alternative treatment and/or could require closer monitoring. These findings suggest that at least some of theheterogeneity observed in treatment outcome has a genetic basis.

[000216] CHI SQUARE STAR*D DATASET (N = 27 SNPs)

[000217] TABLE 20: exemplary embodiment 20

Haplotypes for SNP	Outcome	Outcome	CHRM2	χ^2	*p* <
rs2113545	0	1	Total		
C_C	75	36	111	3.27	*n.s.*
C_T	83	31	114	0.02	*n.s.*
T_T	12	18	30	19.6	0.001
Grand Total	170	85	255	9.4444	0.01

For the SNP above, a haplotype of T_T indicates that outcome 1 (true remitter) has a statistically reliable probability ($p < 0.001$) of occurring when compared to outcome 0 (non-response). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p < 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000218] TABLE 21: exemplary embodiment 21

Haplotypes For SNP	Outcome	Outcome	CHRM2	χ^2	*p* <
rs2350786	0	1	Total		
C_C	10	15	25	16.333	0.001
C_T	74	29	103	0.546926	***n.s.***
T_T	86	41	127	3.5931	***n.s.***
Grand Total	170	85	255	9.4444	0.01

For the SNP above, a haplotype of C_C indicates that outcome 1 (true remitter) has a statistically reliable probability ($p < 0.001$) of occurring when compared to outcome 0 (non-response). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p < 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000219] TABLE 22: exemplary embodiment 22

Haplotypes for SNP	Outcome	Outcome	CACNA1C	X^2	*p* <
rs929492	0	1	Total		
A_A	3	6	9	8.3333	0.001
A_G	35	22	57	5.6198	0.05
G_G	130	55	185	2.207	***n.s.***
?_?	2	2	4	***n.s.***	***n.s.***
Grand Total	170	85	255	9.4444	0.01

For the SNP above, a haplotype of A_A indicates that outcome 1 (true remitter) has a statistically reliable probability ($p < 0.001$) of occurring when compared to outcome 0 (non-response). For the SNP a haplotype of A_G indicates that outcome 0 (non-response) has a statistically reliable probability ($p < 0.05$) of occurring when compared with outcome 1 (true remitter). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000220] TABLE 23: exemplary embodiment 23

Haplotypes for SNP	Outcome	Outcome	OPRM1	X^2	*p* <
rs17275521	0	1	Total		
A_A	4	0	4	***n.s.***	***n.s.***
A_G	57	17	103	8.281553	0.01
G_G	109	68	177	16.99623	0.001
Grand Total	170	85	255	9.4444	0.01

For the SNP a haplotype of A_G ($p < 0.01$) or G_G ($p < 0.001$) indicates that outcome 0 (non-response) has a statistically reliable probability of occurring when compared with outcome 1 (true remitter). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000221] TABLE 24: exemplary embodiment 24

Haplotypes for SNP	Outcome	Outcome	OPRM1	χ^2	*p* <
rs17209711	0	1	Total		
A_A	4	0	4	***n.s.***	***n.s.***
A_T	56	17	73	0.1144	***n.s.***
T_T	110	67	177	15.5951	0.001
?_?	0	1	1	***n.s.***	***n.s.***
Grand Total	170	85	255	9.4444	0.01

For the SNP a haplotype of T_T indicates that outcome 0 (non-response) has a statistically reliable probability ($p < 0.001$) of occurring when compared with outcome 1 (true remitter). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000222] TABLE 25: exemplary embodiment 25

Haplotypes for SNP	Outcome	Outcome	SLC6A2	χ^2	*p* <
rs1814270	0	1	Total		
A_A	48	39	87	18.24138	0.001
A_G	91	29	120	0.044444	***n.s.***
G_G	29	16	45	2.6745	***n.s.***
?_?	2	1	3	***n.s.***	***n.s.***
Grand Total	170	85	255	9.4444	0.01

For the SNP a haplotype of A_A indicates that outcome 0 (non-response) has a statistically reliable probability ($p < 0.001$) of occurring when compared with outcome 1 (true remitter). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000223] TABLE 26: exemplary embodiment 26

Haplotypes for SNP	Outcome	Outcome	CHRNA3	χ^2	*p* <
rs6495308	0	1	Total		
A_A	96	33	129	0.0232	***n.s.***
A_G	56	42	98	16.106	0.001
G_G	18	10	28	1.72	***n.s.***
Grand Total	170	85	255	9.4444	0.01

For the SNP a haplotype of A_G indicates that outcome 0 (non-response) has a statistically reliable probability ($p < 0.001$) of occurring when compared with outcome 1 (true remitter). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000224] TABLE 27: exemplary embodiment 27

Haplotypes for SNP	Outcome	Outcome	HTR2A	χ^2	*p* <
rs9316232	0	1	Total		
C_C	79	24	103	0.1587	***n.s.***
C_T	70	46	116	13.28736	0.001
T_T	18	14	32	6.00	0.05
?_?	3	1	4	***n.s.***	***n.s.***
Grand Total	170	85	255	9.4444	0.01

For the SNP a haplotype of C_T ($p < 0.001$) or T_T ($p < 0.05$) indicates that outcome 0 (non-response) has a statistically reliable probability of occurring when compared with outcome 1 (true remitter). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000225] TABLE 28: exemplary embodiment 28

Haplotypes for SNP	Outcome	Outcome	OPRM1	χ^2	*p* <
rs3778149	0	1	Total		
C_C	111	68	179	16.106	0.001
C_G	53	16	69	0.120	***n.s.***
G_G	4	0	4	***n.s.***	***n.s.***
?_?	2	1	3	***n.s.***	***n.s.***
Grand Total	170	85	255	9.4444	0.01

For the SNP a haplotype of C_C indicates that outcome 0 (non-response) has a statistically reliable probability ($p < 0.001$) of occurring when compared with outcome 1 (true remitter). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p < 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000226] TABLE 29: exemplary embodiment 29

Haplotypes for SNP	Outcome	Outcome	OPRM1	χ^2	*p* <
rs3778146	0	1	Total		
C_C	4	0	4	***n.s.***	***n.s.***
C_T	55	17	72	0.07	***n.s.***
T_T	111	68	179	6.00	0.05
Grand Total	170	85	255	9.4444	0.01

For the SNP a haplotype of T_T indicates that outcome 0 (non-response) has a statistically reliable probability ($p < 0.05$) of occurring when compared with outcome 1 (true remitter). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p < 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000227] TABLE 30: exemplary embodiment 30

Haplotypes for SNP	Outcome	Outcome	OPRM1	χ^2	*p* <
rs7773995	0	1	Total		
C_C	111	68	179	16.106	0.001
C_T	55	17	72	0.074	***n.s.***
T_T	4	0	4	***n.s.***	***n.s.***
Grand Total	170	85	255	9.4444	0.01

For the SNP a haplotype of C_C indicates that outcome 0 (non-response) has a statistically reliable probability ($p < 0.001$) of occurring when compared with outcome 1 (true remitter). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p < 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000228] TABLE 31: exemplary embodiment 31

Haplotypes for SNP	Outcome	Outcome	OPRM1	χ^2	*p* <
rs3778145	0	1	Total		
A_A	112	68	180	15.674	0.001
A_C	54	17	71	0.0425	***n.s.***
C_C	4	0	4	***n.s.***	***n.s.***
Grand Total	170	85	255	9.444	0.01

For the SNP a haplotype of A_A indicates that outcome 0 (non-response) has a statistically reliable probability ($p < 0.001$) of occurring when compared with outcome 1 (true remitter). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p < 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000229] TABLE 32: exemplary embodiment 32

Haplotypes for SNP	Outcome	Outcome	CHRM2	χ^2	*p* <
rs6960707	0	1	Total		
A_A	74	32	106	1.522	*n.s.*
A_G	81	33	114	0.947	*n.s.*
G_G	15	20	35	19.285	0.001
Grand Total	170	85	255	9.444	0.01

For the SNP a haplotype of G_G indicates that outcome 1 (true remitter) has a statistically reliable probability ($p < 0.001$) of occurring when compared with outcome 0 (non-responder). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p < 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000230] TABLE 33: exemplary embodiment 33

Haplotypes for SNP	Outcome	Outcome	S100A10	χ^2	*p* <
rs6678672	0	1	Total		
A_A	8	13	21	15.254	0.001
A_G	73	25	98	0.0137	*n.s.*
G_G	89	45	134	5.264	0.05
Grand Total	170	85	255	9.444	0.01

For the SNP a haplotype of G_G indicates that outcome 0 (non-response) has a statistically reliable probability ($p < 0.05$) of occurring when compared with outcome 1 (true remitter). A haplotype of A_A indicates a statistically reliable probability ($p < 0.001$) of outcome 1 (true remitter) when compared with outcome 0 (non-responder). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p < 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000231] TABLE 34: exemplary embodiment 34

Haplotypes for SNP	Outcome	Outcome	HTR2A	χ^2	*p* <
rs666693	0	1	Total		
C_C	112	51	163	3.478	***n.s.***
C_T	54	24	78	1.384	***n.s.***
T_T	4	10	14	16.095	0.001
Grand Total	170	85	255	9.444	0.01

For the SNP a haplotype of T_T indicates that outcome 1 (true remitter) has a statistically reliable probability ($p < 0.001$) of occurring when compared with outcome 0 (non-responder). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p < 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000232] TABLE 35: exemplary embodiment 35

Haplotypes for SNP	Outcome	Outcome	CACNA1C	χ^2	*p* <
rs4765933	0	1	Total		
C_C	94	50	144	7.25	0.01
C_T	67	27	94	0.695	***n.s.***
T_T	4	8	12	11.11	0.001
Grand Total	170	85	255	9.444	0.01

For the SNP a haplotype of C_C indicates that outcome 0 (non-response) has a statistically reliable probability ($p < 0.01$) of occurring when compared with outcome 1 (true remitter). A haplotype of T_T indicates a statistically reliable probability ($p < 0.001$) of outcome 1 (true remitter) of occurring when compared to outcome 0 (non-response). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability($p < 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000233] TABLE 36: exemplary embodiment 36

Haplotypes for SNP	Outcome	Outcome	HTR2A	χ^2	*p* <
rs9316232	0	1	Total		
C_C	79	24	103	0.16	***n.s.***
C_T	70	46	116	13.3	0.001
T_T	18	14	32	16.00	0.01
?_?	3	1	4	***n.s.***	***n.s.***
Grand Total	170	85	255	9.444	0.01

For the SNP a haplotype of C_T ($p < 0.001$) or T_T ($p < 0.01$) indicates that outcome 0 (non-response) has a statistically reliable probability of occurring when compared with outcome 1 (true remitter). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000234] TABLE 37: exemplary embodiment 37

Haplotypes for SNP	Outcome	Outcome	HTR2A	χ^2	*p* <
rs582385	0	1	Total		
A_A	109	51	160	4.033	0.05
A_G	52	24	76	1.754	***n.s.***
G_G	4	10	14	16.092	0.001
?_?	5	0	5	61.267	0.001
Grand Total	170	85	255	9.444	0.01

For the SNP a haplotype of A_A indicates that outcome 0 (non-response) has a statistically reliable probability ($p < 0.05$) of occurring when compared with outcome 1 (true remitter). A haplotype of G_G has a statistically reliable probability ($p < 0.001$) of outcome 1 (true remitter) of occurring when compared with outcome 0 (non-responder). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000235] TABLE 38: exemplary embodiment 38

Haplotypes for SNP	Outcome	Outcome	HTR2A	χ^2	*p* <
rs985934	0	1	Total		
A_A	65	42	107	11.59	0.001
A_G	85	30	115	0.072	***n.s.***
G_G	20	13	33	3.64	0.05
Grand Total	170	85	255	9.444	0.01

For the SNP a haplotype of A_A ($p < 0.001$) or G_G ($p < 0.05$) indicates that outcome 0 (non-response) has a statistically reliable probability of occurring when compared with outcome 1 (true remitter). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000236] TABLE 39: exemplary embodiment 39

Haplotypes for SNP	Outcome	Outcome	CHRM2	χ^2	*p* <
rs1455857	0	1	Total		
A_A	13	18	31	18.10	0.001
A_G	80	32	112	0.076	***n.s.***
G_G	77	35	112	2.33	***n.s.***
Grand Total	170	85	255	9.444	0.01

For the SNP a haplotype of A_A indicates that outcome 1 (true remitter) has a statistically reliable probability ($p < 0.001$) of occurring when compared with outcome 0 (non-response). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000237] TABLE 40: exemplary embodiment 40

Haplotypes for SNP	Outcome	Outcome	GRM7	χ^2	*p* <
rs17047279	0	1	Total		
G_G	0	0	0	***n.s***	***n.s.***
G_T	1	4	5	8.06	0.01
T_T	169	81	250	7.30	0.01
Grand Total	170	85	255	9.444	0.01

For the SNP a haplotype of T_T indicates that outcome 0 (non-response) has a statistically reliable probability ($p < 0.01$) of occurring when compared with outcome 1 (true remitter). A haplotype of G_T indicates that outcome 1 (true remitter) has a statically reliable probability ($p < 0.01$) of occurring when compared with outcome 0 (non-response). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000238] TABLE 41: exemplary embodiment 41

Haplotypes for SNP	Outcome	Outcome	CHRM2	χ^2	*p* <
rs7782904	0	1	Total		
A_A	76	34	110	2.048	***n.s.***
A_T	79	36	115	2.44	***n.s.***
T_T	10	13	23	12.2	0.001
?_?	5	2	7	0.048	***n.s.***
Grand Total	170	85	255	9.444	0.01

For the SNP a haplotype of T_T indicates that outcome 1 (true remitter) has a statistically reliable probability ($p < 0.001$) of occurring when compared with outcome 0 (non-response). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000239] TABLE 42: exemplary embodiment 42

Haplotypes for SNP	Outcome	Outcome	SLC6A3	χ^2	*p* <
rs10053602	0	1	Total		
A_A	100	41	144	8.957	0.01
A_G	64	26	90	0.726	***n.s.***
G_G	6	13	19	19.10	0.001
?_?	0	2	2	***n.s.***	***n.s.***
Grand Total	170	85	255	9.444	0.01

For the SNP a haplotype of A_A indicates that outcome 1 (true remitter) has a statistically reliable probability ($p < 0.001$) of occurring when compared with outcome 0 (non-response). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000240] TABLE 43: exemplary embodiment 43

Haplotypes for SNP	Outcome	Outcome	S100A10	χ^2	*p* <
rs6587640	0	1	Total		
A_A	10	14	24	14.22	0.001
A_G	80	30	110	0.303	***n.s.***
G_G	80	40	120	4.444	***n.s.***
Grand Total	170	85	255	9.444	0.01

For the SNP a haplotype of A_A indicates that outcome 0 (non-response) has a statistically reliable probability ($p < 0.01$) of occurring when compared with outcome 1 (true remitter). A haplotype of G_G indicates that outcome 1 (true remitter) has a statistically reliable probability ($p < 0.001$) of occurring when compared with outcome 0 (non-response). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000241] TABLE 44: exemplary embodiment 44

Haplotypes for SNP	Outcome	Outcome	FKBP5	χ^2	*p* <
rs9368881	0	1	Total		
C_C	62	45	107	16.62	0.001
C_T	83	33	116	0.736	***n.s.***
T_T	25	7	32	0.167	***n.s.***
Total	170	85	255	9.444	0.01

For the SNP a haplotype of C_C indicates that outcome 0 (non-response) has a statistically reliable probability ($p < 0.001$) of occurring when compared with outcome 1 (true remitter). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000242] TABLE 45: exemplary embodiment 45

Haplotypes for SNP	Outcome	Outcome	HTR2A	χ^2	*p* <
rs1002513	0	1	Total		
A_A	4	10	14	16.10	0.001
A_G	57	25	82	1.32	***n.s.***
G_G	108	50	158	3.72	***n.s.***
?_?	1	0	1	***n.s.***	***n.s.***
Grand Total	170	85	255	9.444	0.01

For the SNP a haplotype of A_A indicates that outcome 1 (true remitter) has a statistically reliable probability ($p < 0.001$) of occurring when compared with outcome 0 (non-response). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000243] TABLE 46: exemplary embodiment 46

Haplotypes for SNP	Outcome	Outcome	CHRM2	χ^2	*p* <
rs1378646	0	1	Total		
C_C	14	18	32	16.70	0.001
C_T	82	34	116	1.149	***n.s.***
T_T	74	33	107	1.95	***n.s.***
Grand Total	170	85	255	9.444	0.01

For the SNP a haplotype of C_C indicates that outcome 1 (true remitter) has a statistically reliable probability ($p < 0.001$) of occurring when compared with outcome 0 (non-responder). The Chi square analysis compares outcome 0 (non-response) with outcome 1 (response) as defined in disclosures. The Grand total Chi square value indicates that there is a statistically reliable probability ($p< 0.01$) of outcome 0 (non-response) when compared to outcome 1 (true remitter) for this gene.

[000244] TABLE 47: Haplotypes which predict true remission (N = 17 alleles)

rs929492	A_A	CACNA1C
rs2113545	T_T	CHRM2
rs10052016	G_G	SLC6A3
rs2350786	C_C	CHRM2
rs929492	A_A	CACNAC1
rs6960707	G_G	CHRM2
rs6678672	A_A	S100A10
rs666693	T_T	HTR2A
rs582385	G_G	HTR2A
rs17047279	G_T	GRM7
rs4765933	T_T	CACNA1C
rs10053602	G_G	SLC6A3
rs7782904	T_T	CHRM2
rs1455857	A_A	CHRM2
rs1378646	C_C	CHRM2
rs6587640	A_A	S100A10
rs1002513	C_T	HTR2A

[000217] TABLE 48: Haplotypes which predict Treatment Resistant Depression (TRD)

rs6495308	A_G	CHRNA3
rs9567739	C_G	HTR2A
rs17275521	A_G	OPRM1
rs17209711	A_T	OPRM1
rs3778149	C_G	OPRM1
rs3778146	A_C_G_T	OPRM1
rs7773995	C_T	OPRM1
rs3778145	A_G	OPRM1
rs6900677	C_G	OPRM1
rs6916787	A_G	OPRM1
rs6678672	C_T	S100A10
rs6587640	C_T	S100A10
rs929492	C_T	CACNA1C
rs4765933	A_G	CACNA1C
rs9316232	A_G	HTR2A
rs9567739	C_G	HTR2A
rs582385	C_T	HTR2A
rs1002513	C_T	HTR2A
rs666693	A_G	HTR2A
rs9368881	A_C_G_T	FKBP5
rs10053602	A_A	SLC6A3
rs10052016	A_G	SLC6A3

[000245] TABLE 48 (Continued): Haplotypes which predict Treatment Resistant Depression (TRD)

rs1861646	G_T	SLC6A2
rs17841329	A_G	SLC6A2
rs4564560	C_T	SLC6A2
rs879522	C_T	SLC6A2
rs11862589	C_T	SLC6A2
rs1814270	C_T	SLC6A2
rs17047321	A_G	GRM7
rs17047279	G_T	GRM7
rs17047286	A_G	GRM7
rs11198986	A_G	RGS10
rs6916787	A_G	OPRM1
rs16965623	A_G	SLC6A4
rs885345	C_T	FREQ/NCS
rs2350786	A_G	CHRM2
rs6960707	C_T	CHRM2
rs7782904	A_T	CHRM2
rs1455857	A_G	CHRM2
rs1378646	A_G	CHRM2

[000246] Table 49 provides Fischer's exact *p* values for the identified SNPs and genes. A statitistically significant association with non-response was found for all listed genes and SNPs ($p < 0.04$ or greater). The minor allele frequency refers to the frequency at which the less common allele occurs in a given population. In most cases genes and SNPs in this table have a minor allele frequency greater than 0.15 (15%). Hardy Weinberg equilibrium values indicate that both allele and genotype frequencies in a population remain constant. The Hardy Weinberg equilibrium value for each gene and SNP indicates that alleles from these genes are normally distributed between generations. That is, the frequency of each allele for the identified genes follows a normal distribution from generation to generation.

[000247] Table 49: Fischer's Exact *p* Values For the Identified SNPs and Genes.

SNP Number	Gene Name	Fishers *p* value	Minor allele frequency	HWE** value
rs885345	FREQ/NCS1	0.001	0.429	0.898
rs2113545	CHRM2	0.003	0.341	1.000
rs10052016	SLC6A3	0.003	0.264	0.334
rs2350786	CHRM2	0.01	0.300	0.551
rs929492	CACNA1C	0.04	0.149	0.130
rs17275521	OPRM1	0.02	0.160	0.350
rs17209711	OPRM1	0.03	0.159	0.349
rs1814270	SLC6A2	0.007	0.416	0.795
rs6495308	CHRNA3	0.02	0.301	0.180
rs9316232	HTR2A	0.01	0.358	1.000
rs3778149	OPRM1	0.03	0.152	0.469
rs3778146	OPRM1	0.03	0.156	0.350
rs7773995	OPRM1	0.03	0.156	0.350
rs3778145	OPRM1	0.03	0.154	0.470
rs6960707	CHRM2	0.007	0.360	0.683
rs985934	HTR2A	0.01	0.354	0.785
rs17047279	GRM7	0.04	0.352	0.830
rs17047286	GRM7	0.04	0.009	0.783
rs9368881	FKBP5	0.03	0.009	1.000
rs4765933	CACNA1C	0.03	0.236	0.599
rs6678672	S100A10	0.006	0.276	0.637
rs10053602	SLC6A3	0.004	0.252	0.404

SNP Number	Gene Name	Fishers *p* value	Minor allele frequency	HWE** value
rs7782904	CHRM2	0.05	0.324	0.468
rs1455857	CHRM2	0.01	0.341	0.780
rs6587640	S100A10	0.01	0.311	1.000
rs1378646	CHRM2	0.01	0.352	1.000
rs582385	HTR2A	0.01	0.208	0.247
rs1002513	HTR2A	0.01	0.216	0.459
rs17047321	GRM7	0.03	0.010	0.012#
rs11198986	RGS10	0.02	0.056	0.037#
rs6916787	OPRM1	0.04	0.014	0.045
rs16965623	SLC6A4	0.036	0.005	1.000
rs666693	HTR2A	0.012	0.207	0.255
rs1861646	SLC6A2	0.001	0.188	0.148
rs6900677	OPRM1	0.001	0.053	0.516
rs11862589	SLC6A2	0.02	0.453	0.043#
rs879522	SLC6A2	0.02	0.453	0.043#
rs4564560	SLC6A2	0.02	0.453	0.043#
rs17841329	SLC6A2	0.02	0.060	0.608

** Hardy Weinberg Equilibrium ($p > 0.05$); # HWE ($p < 0.05$); e.g. not in HWE

[000248] The foregoing examples demonstrate that genetic markers can be used to identify individuals with a major depressive disorder who have an increased risk of non-response to treatment with a SSRI, such as citalopram. They also demonstrate that genetic markers can be used to identify individuals with a major depressive disorder who have high probability of achieving remission. The DNA collected from the STAR*D consort, as set forth in tables 1-19, included 255 genotyped samples which met the

screening criteria for inclusion in the present data analysis. Individuals who self-reported as "black" were excluded and all remaining individuals who self-reported as "white, non-Hispanic or other" were included in the treatment outcome analyses. Thus, all treatment outcome comparisons were confined to patients who self-reported "white, non-Hispanic or other."

[000249] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[000250] The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[000251] Preferred embodiments of this invention are described herein, including the best mode known to the inventor for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such

variations as appropriate, and the inventor intends for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

What is claimed is:

1. Identification of the demised treatment resistant depression (TRD) in a patient who had been treated with an agent or agents that increase serotonin neurotransmission with or without changes in adrenergic neurotransmission by the determination of the presence of a genotype in a sample of genetic material obtained from the patient, wherein the genotype is characterized by a polymorphism in a gene having at least one marker, wherein the gene is selected from the group consisting of 5-hydroxytryptamine (serotonin) receptor 2A (HTR2A) and polymorphisms having reference sequence numbers rs666693, rs582385 and rs9316232,; the mu-opiod receptor gene (OPRM1) and polymorphisms having reference sequence numbers rs17275521, rs17209711, rs3778149, rs3778146, rs7773995, rs3778145 and rs690067; the neuronal calcium sensor 1 (FREQ) gene and a polymorphism having reference sequence number rs885345; the solute carrier family (neurotransmitter transporter, dopamine), member 3 gene (SLC6A3) and a polymorphism having reference sequence number rs10052016 and rs10053602; the norepinephrine transporter gene (SLC6A2) and a polymorphism having reference sequence number rs1814270 and rs1861646the solute carrier family 6 (neurotransmitter transporter, serotonin) member 4 (SLC6A4) and a polymorphisms reference number rs16965623, the cholinergic receptor, nicotinic alpha-3 gene (CHRNA3) and a polymorphism having reference sequence number rs6495308; the cholinergic receptor, muscarinic 2 gene (CHRM2) and polymorphisms having reference sequence numbers rs2113545, rs1378646, rs7782904, rs2350786, rs1455857, and rs6960707 the calcium channel voltage-dependent, L type, alpha 1C subunit (CACNA1C) gene and a polymorphism

having reference sequence number rs929492 and rs4765933 ; the A100 calcium binding protein A10 (S100A10) gene and a polymorphism having reference sequence number rs6678672, and rs6587640; the solute carrier family 6 (neurotransmitter transporter, noradrenalin) member 2 (SLC6A2) and polymorphisms having reference sequence numbers rs1861646, rs17841329, rs11862589, rs879522 and rs4564560 and rs1814270; the FK506 binding protein (FKBP5) and a polymorphism having reference sequence number rs9368881; and the glutamate receptor metabotropic 7 receptor (GRM7) and polymorphisms having reference sequence numbers rs17047279, rs17047321 and rs17047286; the gene OPRM1 having a reference number rs6916787; the gene RGS10 having a reference sequence number rs11198986.

2. A method of predicting the outcome of treatment with antidepressant medication in a patient receiving antidepressant therapy targeting increases in serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission (a) obtaining a sample of genetic material from the patient; (b) assaying the sample for the presence of a genotype in the patient which is associated with the outcome of treatment with antidepressant medication; and (c) predicting the outcome of treatment with antidepressant medication in the patient based on the presence of the genotype in the sample, wherein the genotype is characterized by a polymorphism in a gene having at least one marker, wherein the gene is selected from the group consisting of 5-hydroxytryptamine (serotonin) receptor 2A (HTR2A) and polymorphisms having reference sequence numbers rs666693, rs582385 and, rs9316232 and rs1002513 ; the mu-opiod receptor gene (OPRM1) and polymorphisms

having reference sequence numbers rs17275521, rs17209711, rs3778149, rs3778146, rs7773995, rs690067, rs3778145; the neuronal calcium sensor 1 (FREQ) gene and a polymorphism having reference sequence number rs885345; the solute carrier family 6 (neurotransmitter transporter, dopamine), member 3 gene (SLC6A3) and a polymorphism having reference sequence number rs10052016 and rs10053602; the norepinephrine transporter gene (SLC6A2) and a polymorphism having reference sequence number rs1814270, rs1861646, rs11862589, rs879522, rs4564560 and rs17841329; the solute carrier family 6 (neurotransmitter transporter, serotonin) member 4 (SLC6A4) having reference number rs16965623, the cholinergic receptor, nicotinic alpha-3 gene and a polymorphism having reference sequence number rs6495308; the cholinergic receptor, muscarinic 2 gene and polymorphisms having reference sequence numbers rs2113545,rs1378646, rs7782904, rs2350786 and rs1455857 and rs6960707; the calcium channel voltage-dependent, L type, alpha 1C subunit (CACNA1C) gene and a polymorphism having reference sequence number rs929492 and rs4765933; the A100 calcium binding protein A10 (S100A10) gene and a polymorphism having reference sequence number rs6678672, and rs6587640; the solute carrier family 6 (neurotransmitter transporter, noradrenalin) member 2 (SLC6A2) and polymorphisms having reference sequence numbers rs11862589, rs879522, rs4564560, rs17841329, rs879522, and rs1861646; the FK506 binding protein (FKBP5) and a polymorphism having reference sequence number rs9368881 and rs9462104; and the glutamate receptor metabotropic 7 receptor (GRM7) and polymorphisms having reference sequence numbers rs17047279, rs17047321 and

rs17047286; the gene OPRM1 having reference number rs6916787; the gene RGS10 having reference sequence number rs11198986.

3. A method comprising assaying for the presence of a genotype in patients receiving antidepressant therapy targeting increases in serotonergic neurotransmission with or without concomitant changes in adrenergic neurotransmission which is associated with a increased probability of response to treatment with antidepressant medication, wherein the genotype is characterized by a polymorphism in a gene selected from the group consisting of SLC6A3 and present as rs10052016-G_G homozygote and rs10053602-G_G homozygote genotype; CHRM2 present as a genotype selected from the group consisting of rs2113545--T_T homozygote, rs2350786–C_C homozygote, rs1455857-A_A homozygote, rs1378646- C_C homozygote, rs7782904-T_T homozygote, and rs6960707 -G_G homozygote ; HTR2A and present as a genotype selected from the group consisting of rs1002513-A_A homozygote rs666693 -T_T and rs582385-G_G homozygotes ; CACNA1C and present as rs4765933-T_T and rs929492-A_A homozygotes homozygote, GRM7 rs17047279-G_T heterozygote genotype; S100A10 and present as rs6678672-A_A homozygote and rs6587640-A_A homozygote genotype; and combinations thereof.

4. The method of claim 2, wherein assaying comprises detecting the polymorphism by allele specific hybridization, allele specific oligonucleotide ligation, primer extension, minisequencing, mass spectroscopy, heteroduplex analysis, single strand conformational polymorphism (SSCP), denaturing gradient gel electrophoresis (DGGE), oligonucleotide microarray analysis, temperature gradient gel electrophoresis (TGGE), and combinations thereof.

5. The method of claim 2, wherein the gene is HTR2A.

6. The method of claim 2, wherein the gene is FREQ.

7. The method in claim 2, wherein the gene is SLC6A3.

8. The method in claim 2, wherein the gene is FKBP5.

9. The method in claim 2, wherein the gene is GRM7.

10. The method in claim 2, wherein the gene is OPRM1.

11. The method in claim 2, wherein the gene is CACNA1C.

12. The method in claim 2, wherein the gene is CHRM2.

13. The method in claim 2, wherein the gene is SLC6A2.

14. The method in claim 2, wherein the gene is CHRNA3.

15. The method in claim 2, wherein the gene is S100A10.

16. The method in claim 2, wherein the gene is RGS10

17. The method in claim 2, wherein the gene is SLC6A4

18. The method in claim 2, wherein the gene is OPRM1

19. The method of claim 2, wherein the antidepressant medication is a selective serotonin reuptake inhibitor.

20. The method of claim 2, wherein the selective serotonin reuptake inhibitor is citalopram.

21. The method of claim 2, wherein assaying comprises detecting the polymorphism by allele specific hybridization, allele specific oligonucleotide ligation, primer extension, minisequencing, mass spectroscopy, heteroduplex analysis, single strand conformational polymorphism (SSCP), denaturing gradient gel electrophoresis

(DGGE), oligonucleotide microarray analysis, temperature gradient gel electrophoresis (TGGE), and combinations thereof.

22. The method in claim 2, wherein the gene is SLC6A3 present as rs10052016-A/G heterozygote and rs10053602-C/T heterozygote genotype.

23. The method in claim 2, wherein the gene is CHRM2 and present as a genotype selected from the group consisting of rs2113545-A/G heterozygote, rs2350786-A/G heterozygote, rs2350786-A/G heterozygote , rs1378646-A/G heterozygote, rs7782904-A/T heterozygote and rs1455857-A/G heterozygotes.

24. The method in claim 2, wherein the gene is OPRM1 and present as a genotype selected from the group consisting of, rs3778145-A/C heterozygote , rs7773995-C/T heterozygote, , rs3778146-A/C/G/T heterozygote, , rs3778149-C/G heterozygote , rs17275521-A/G homozygote, rs17209711-A/T heterozygote, and rs17275521-A/G homozygote.

25. The method in claim 2, wherein the gene is CACNA1C present as rs929492-G/G homozygote genotype rs4765933-T/T.

26. The method in claim 2, wherein the gene is selected from FREQ and present as a genotype selected from the group consisting of rs885345-T/T homozygote, rs885345-C/C homozygote and rs885345-C/T heterozygote.

27. The methnod in claim 2, where in the gene is SLC6A2 and present as a genotype selected from the group consisting of rs1814270-C/T heterozygote and, rs11862589-C/T heterozygote, rs879522-C/T heterozygote, rs4564560-C/T herterozygote, rs17841329-A/G herterozygote and rs1861646-G/T heterozygote.

28. The method in claim 2, wherein the gene is CHRNA3 and present as a genotype selected from the group consisting of rs6495308-A/A homozygote and rs6495308-G/G homozygote.

29. The method in claim 2, wherein the gene is HTR2A and present as a genotype selected from the group consisting of rs9316232-C/C homozygote, rs9316232-C/T heterozygote, rs666693-C/C homozygote, rs666693-C/T heterozygote, rs666693-A/G heterozygote, rs582385-A/A homozygote, and rs582385-A/G heterozygote.

30. The method in claim 2, wherein the gene is S100 calcium binding protein A10 (S100A10) and present as a genotype selected from the group consisting of rs6678672-A/G heterozygote and rs6678672-G/G homozygote.

31. The method in claim 2, wherein the gene is RGS10 and present as a genotype selected from rs11198986-A/G heterozygote

32. The method in claim 2, wherein the gene is OPRM1and present as a gentotype rs6916787-A/G heterozygote

33. The method in claim 2, wherein the gene is SLC6A4 and present as a gentotype rs16965623

34. The method in claim 3, wherein the genotype is characterized by a polymorphism in a gene selected from the group consisting of of SLC6A3 and present as rs10053602-G_G homozygote and rs10052016-G_G homozygote genotype; CHRM2 present as a genotype selected from the group consisting of rs2113545-T_T homozygote, rs2350786–C_C homozygote, rs1455857-A_A homozygote, rs1378646-C_C homozygote, rs7782904-T_T homozygote, and rs6960707 -G_G homozygote ;

HTR2A and present as a genotype selected from the group consisting of rs1002513-A_A homozygote, rs666693 -T_T and rs582385-G_G homozygotes ; CACNA1C and present as rs4765933-T_T and rs929492-A_A homozygotes, GRM7 rs17047279-G_T heterozygote genotype; S100A10 and present as rs6678672-A_A homozygote and rs6587640-A_A homozygote genotype; and combinations thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/024694

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68 (2012.01)
USPC - 435/6.11
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A01K 67/027; A61P 25/24; C12Q 1/68; G01N 33/50 (2012.01)
USPC - 435/6.11, 6.13, 16, 17, 18; 514/17.7, 18.1; 536/23.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google, PubMed, ProQuest, dbSNP

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 7,795,033 B2 (MCMAHON et al) 14 September 2010 (14.09.2010) entire document	1, 2, 4, 5, 10, 12-14, 18-21
Y	WO 2010/111080 A2 (DOWNING et al) 30 September 2010 (30.09.2010) entire document	1, 2, 4, 5, 10, 12-14, 18-21
Y	WO 2009/155585 A9 (KENNETH et al) 23 December 2009 (23.12.2009) entire document	10, 18
Y	US 2009/0253585 A1 (DIATCHENKO et al) 08 October 2009 (08.10.2009) entire document	12, 13
Y	US 2009/0176878 A1 (GOATE et al) 09 July 2009 (09.07.2009) entire document	14
A	US 2010/0304391 A1 (LOMBARD) 02 December 2010 (02.12.2010) entire document	1-34

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 May 2012	16 JUL 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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