US 20160040240A1

(19) **United States**

(12) **Patent Application Publication**

Gershon et al.

(10) **Pub. No.: US 2016/0040240 A1**

(43) **Pub. Date: Feb. 11, 2016**

(54) **CACNA1C ALLELE AND TREATMENT OF MOOD DISORDERS**

(71) Applicant: **THE UNIVERSITY OF CHICAGO**, Chicago, IL (US)

(72) Inventors: **Elliot Gershon**, Chicago, IL (US); **Chunyu Liu**, Chicago, IL (US); **Judith Badner**, Chicago, IL (US)

(21) Appl. No.: **14/823,973**

(22) Filed: **Aug. 11, 2015**

Related U.S. Application Data

(60) Provisional application No. 62/035,970, filed on Aug. 11, 2014.

Publication Classification

(51) **Int. Cl.**

C12Q 1/68	(2006.01)
A61K 31/4439	(2006.01)
A61K 31/4418	(2006.01)
A61K 31/554	(2006.01)
A61K 31/277	(2006.01)
A61K 45/06	(2006.01)

(52) **U.S. Cl.**

CPC ***C12Q 1/6883*** (2013.01); ***A61K 31/277*** (2013.01); ***A61K 45/06*** (2013.01); ***A61K 31/4418*** (2013.01); ***A61K 31/554*** (2013.01); ***A61K 31/4439*** (2013.01); *C12Q 2600/106* (2013.01); *C12Q 2600/156* (2013.01)

(57) **ABSTRACT**

Provided herein are methods of determining a treatment regimen for a subject with a mood disorder and methods of identifying a patient with a mood disorder as amenable to treatment with a calcium channel blocker (CCB). In exemplary embodiments, the methods comprise (a) analyzing a sample obtained from a subject with a mood disorder for the presence of allele [A] of CACNA1C, wherein allele [A] comprises the sequence of the polymorphic marker rs1006737.

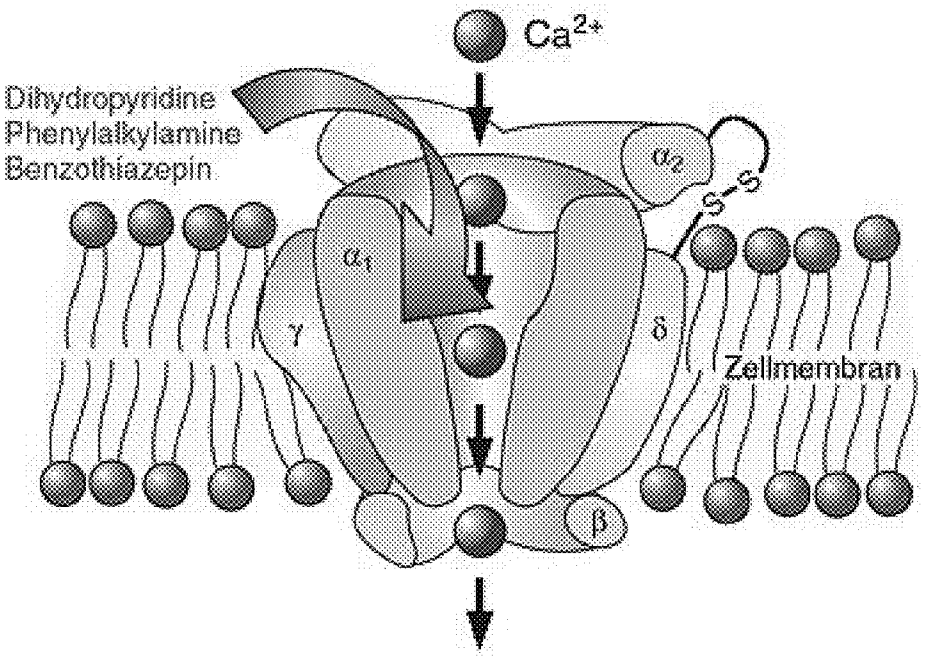

FIGURE 1

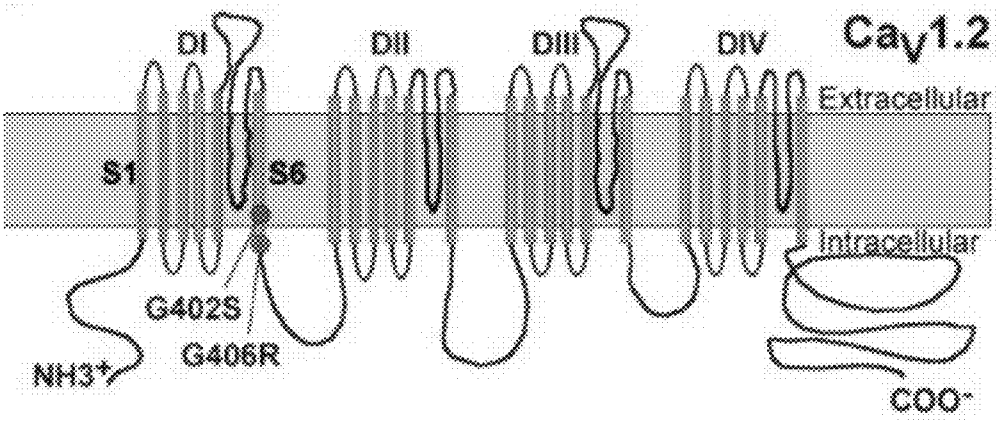

FIGURE 2

CACNA1C ALLELE AND TREATMENT OF MOOD DISORDERS

GRANT FUNDING

[0001] This invention was made with government support under Grant No. 1R01MH080425 awarded by the National Institutes of Health, and Grant No. 1R01MH094483-01 awarded by the National Institute of Mental Health. The government has certain rights in the invention.

INCORPORATION BY REFERENCE OF MATERIAL SUBMITTED ELECTRONICALLY

[0002] Incorporated by reference in its entirety is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: 1,810, 321 byte ACII (Text) file named "48562A_SeqListing.txt" created on Aug. 11, 2015.

BACKGROUND

[0003] Bipolar I disorder (BD) is a serious mental illness with life threatening psychiatric morbidity and mortality. BD affects 1-2% of the general population and consumes a substantial portion of mental healthcare resources worldwide. It typically has a remitting and relapsing course that cycles between the mood extremes of mania and depression. Psychosis is common and 10-20% of patients become suicides.

[0004] Recent genetic association studies have shown a strong genetic association between BD and CACNA1C, one of the four possible L-type Calcium Channel alpha-1 subunit genes (see FIG. **1**). The CACNA1C genetic risk allele is a functional regulator of expression of this subunit in one region in human brain [Gershon et al., *Mol Psychiatry* 19(8): 890-4 (2013)]. Calcium channels are ubiquitous in synapses between excitable cells, including neurons and cardiac muscle cells (myocytes).

[0005] Calcium Channel Blockers (CCBs) were first discovered in 1964. CCBs affecting the L-type calcium channel continue to be used for their effects on the heart, as treatment for high blood pressure and for heart rhythm abnormalities. Clinicians soon noted that a substantial proportion of Bipolar patients treated with CCBs for cardiovascular disorder appeared to have improvement in their mood disorder. Published reports on treatment of BD with CCBs first appeared in 1982 [Caillard and Masse, *Encephale* 8:587-594 (1982)], and there were numerous reports over the following two decades, as reviewed by Cassamassima [Casamassima et al., *Am J Med Genet B Neuropsychiatr Genet* 153B: 1373-1393 (2010)].

[0006] While there have been multiple reports of improvement in manic patients treated with Verapamil and other CCBs, systematic trials demonstrating statistically significant effectiveness of CCBs in BD patients are lacking [Casamassima et al., 2010, supra].

SUMMARY

[0007] The data from previous studies support that response to CCB therapy in BD patients varies. As supported by data presented herein, variability in patient response to CCB treatment is due to genetic differences among BD patients. More specifically, BD patients with the CACNA1C risk allele demonstrate reduced expression of the calcium channel gene and, BD patients who do not have the CACNA1C risk allele or have only one copy of the CACNA1C risk allele are, therefore, better responders to CCB treatment.

[0008] Provided herein are methods of treating a mood disorder in a subject. In exemplary embodiments, the method comprises (a) analyzing a sample obtained from the subject for the presence of an allele [A] of CACNA1C, wherein allele [A] comprises the sequence of polymorphic marker rs1006737; and (b) administering to the subject a calcium channel blocker (CCB) when no more than one copy of allele [A] is present in the cells of the sample.

[0009] Provided herein is a method of treating a mood disorder in a subject from which a sample was obtained, wherein the copy number of allele [A] of CACNA1C, comprising the sequence of polymorphic marker rs1006737, in the sample has been analyzed. Such a method comprises the step of administering to the subject an effective amount of a calcium channel blocker (CCB) when no more than one copy of the [A] allele is present in the cells of the sample.

[0010] A method of determining a treatment regimen for a subject with a mood disorder is further provided herein. In exemplary embodiments, the method comprises (a) analyzing a sample obtained from a subject with a mood disorder for the presence of allele [A] of CACNA1C, wherein allele [A] comprises the sequence of the polymorphic marker rs1006737; and (b) selecting a treatment regimen comprising administration of a calcium channel blocker (CCB), when no more than one copy of allele [A] is present in the cells of the sample.

[0011] A method of identifying a population of mood disorder patients amenable to treatment with a calcium channel blocker is also provided herein. In exemplary aspects, the method comprises (a) analyzing a sample obtained from a patient with a mood disorder for the presence of allele [A] of CACNA1C, wherein allele [A] comprises the sequence of the polymorphic marker rs1006737; and (b) identifying the patient as amenable to treatment with a calcium channel blocker when no more than one copy of allele [A] is present in the cells of the sample.

[0012] Related systems, e.g., computer systems, comprising a processor; a memory device coupled to the processor, and machine readable instructions stored on the memory device, are provided herein. In exemplary embodiments, the system comprises machine readable instructions that, when executed by the processor, cause the processor to: (a) receive a data value, a, that is a copy number determination of allele [A] of CACNA1C, wherein allele [A] comprises the sequence of polymorphic marker rs1006737, in the cells of a sample obtained from a subject; and (b) display an output relating to treating the subject for a mood disorder with a calcium channel blocker (CCB), when a is less than the diploid copy number of 2.

[0013] Related computer-readable storage media are also provided herein. In exemplary aspects, a computer-readable storage medium having stored thereon machine-readable instructions executable by a processor is provided. In exemplary aspects, the machine-readable instructions comprise: (a) instructions for receiving a data value, a, relating to the copy number of allele [A] of CACNA1C , wherein allele [A] comprises the sequence of the polymorphic marker rs1006737, in the cells of a sample obtained from a subject; and (b) instructions for displaying an output relating to treating the subject for a mood disorder with a calcium channel blocker (CCB), when a is less than the diploid copy number of 2.

[0014] Related methods implemented by a processor in a computer are provided herein. In exemplary embodiments, the method comprises (a) receiving a data value, a, relating to the copy number of allele [A] of CACNA1C, wherein allele [A] comprises the sequence of the polymorphic marker rs1006737, in the cells of a sample obtained from a subject; and (b) displaying an output relating to treating the subject for a mood disorder with a calcium channel blocker (CCB), when α is less than the diploid copy number of 2.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] FIG. **1** is an illustration of an L-type calcium channel in the cell membrane. The L-type calcium channel controls the inward flow of calcium, an essential process in cell signaling. (Diagram from Wikipedia.)

[0016] FIG. **2** is an illustration of Timothy Syndrome type 2, functional mutations in Cav1.2, the protein product of CACNA1C. The mutation of the patient described in Example 1 is G4025. (Figure taken from Splawski et al., 2005.)

DETAILED DESCRIPTION

[0017] Methods of Treating Mood Disorder

[0018] The invention provides methods of treating a mood disorder in a subject. In exemplary embodiments, the method comprises (a) analyzing a sample obtained from the subject for the presence of an allele [A] of CACNA1C, wherein allele [A] comprises the sequence of polymorphic marker rs1006737; and (b) administering to the subject a calcium channel blocker (CCB) when no more than one copy of allele [A] is present in the cells of the sample.

[0019] The invention also provides a method of treating a mood disorder in a subject from which a sample was obtained, wherein the copy number of allele [A] of CACNA1C, comprising the sequence of polymorphic marker rs1006737, in the sample has been analyzed. Such a method comprises the step of administering to the subject an effective amount of a calcium channel blocker (CCB) when no more than one copy of the [A] allele is present in the cells of the sample.

[0020] In exemplary aspects, the method of treating a mood disorder comprises administering to the subject a CCB when the subject is heterozygous for allele [A]. In exemplary aspects, the method of treating a mood disorder comprises administering to the subject a CCB when only one copy of the [A] allele is present in the cells of the sample. In exemplary aspects, the method of treating a mood disorder comprises administering to the subject a CCB when allele [A] is absent from the cells of the sample.

[0021] As used herein, the term "treat" as well as words stemming therefrom, e.g., "treating" and "treatment" do not necessarily imply 100% or complete treatment. Rather, there are varying degrees of treatment of which one of ordinary skill in the art recognizes as having a potential benefit or therapeutic effect. In this respect, the inventive methods can provide any amount of any level of treatment of the mood disorder in a subject. Furthermore, the treatment provided by the inventive method can include treatment of one or more conditions or symptoms of the disease, e.g., mood disorder, being treated.

[0022] Methods of Determining a Treatment Regimen for a Subject with Mood Disorder

[0023] The invention provides a method of determining a treatment regimen for a subject with a mood disorder is further provided herein. In exemplary embodiments, the method comprises (a) analyzing a sample obtained from a subject with a mood disorder for the presence of allele [A] of CACNA1C, wherein allele [A] comprises the sequence of the polymorphic marker rs1006737; and (b) selecting a treatment regimen comprising administration of a calcium channel blocker (CCB), when no more than one copy of allele [A] is present in the cells of the sample.

[0024] In exemplary aspects, the method of determining a treatment regimen for a subject with a mood disorder comprises selecting a treatment regimen comprising administration of a CCB, when the subject is heterozygous for the [A] allele. In exemplary aspects, the method of determining a treatment regimen for a subject with a mood disorder comprises selecting a treatment regimen comprising administration of a CCB, when only one copy of the [A] allele is present in the cells of the sample. In exemplary embodiments, the method of treating a mood disorder comprises selecting a treatment regimen comprising administration of a CCB, when allele [A] is absent from the sample.

[0025] Methods of Identifying a Population of Mood Disorder Patients Amenable to Treatment with a Calcium Channel Blocker

[0026] The invention also provides a method of identifying a population of mood disorder patients amenable to treatment with a calcium channel blocker is also provided herein. In exemplary aspects, the method comprises (a) analyzing a sample obtained from a patient with a mood disorder for the presence of allele [A] of CACNA1C, wherein allele [A] comprises the sequence of the polymorphic marker rs1006737; and (b) identifying the patient as amenable to treatment with a calcium channel blocker when no more than one copy of allele [A] is present in the cells of the sample.

[0027] The invention further provides a method of identifying a patient with a mood disorder as amenable to treatment with a calcium channel blocker is also provided herein. In exemplary aspects, the method comprises (a) analyzing a sample obtained from a patient with a mood disorder for the presence of allele [A] of CACNA1C, wherein allele [A] comprises the sequence of the polymorphic marker rs1006737; and (b) identifying the patient as amenable to treatment with a calcium channel blocker when no more than one copy of allele [A] is present in the cells of the sample.

[0028] In exemplary aspects, the method of identifying a population or a patient as amenable to treatment with a calcium channel blocker comprises identifying the patient as amenable to treatment with a calcium channel blocker, when the subject is heterozygous for the [A] allele. In exemplary aspects, the method of identifying a population or a patient as amenable to treatment with a calcium channel blocker comprises identifying the patient as amenable to treatment with a calcium channel blocker, when only one copy of the [A] allele is present in the cells of the sample. In exemplary embodiments, the method of identifying a population or a patient as amenable to treatment with a calcium channel blocker comprises identifying the patient as amenable to treatment with a calcium channel blocker, when allele [A] is absent from the sample.

[0029] Biomarkers and Measurement Thereof

[0030] In certain methods of the invention, a sample obtained from the subject with a mood disorder is analyzed for the presence of allele [A] of CACNA1C, or the copy number of allele [A] of CACNA1C, wherein allele [A] comprises the sequence of the polymorphic marker rs1006737. The CACNA1C gene is provided herein as SEQ ID NO: 1 and

is publically available as National Center for Biotechnology Information (NCBI) Reference Sequence NG_008801.2. The sequence of the polymorphic marker rs1006737 is provided herein as SEQ ID NO: 2. In SEQ ID NO: 2, the nucleotide at position 2282 is represented as "R" and, when R at position 2282 is G, the wild-type allele is represented, and, when R is A, the mutant risk allele is represented. The mutant risk allele, also referred to herein as "the risk allele" or "allele [A] of CACNA1C" or "allele [A]" comprises the sequence of SEQ ID NO: 3. In SEQ ID NO: 1, the polymorphic site is located at position 270344. SEQ ID NO: 1 includes the wild-type G at this position.

[0031] The sample may be analyzed for the presence of allele [A] or the copy number of allele [A] of CACNA1C by methods known in the art. In exemplary embodiments, the sample is analyzed for the sequence of CACNA1C. For example, the sample comprises saliva or cells, e.g., blood cells, neuronal cells, or brain cells, obtained from the subject, and the sequence of the genomic DNA of the cells is determined. In more particular aspects, the sequence of the CACNA1C gene, or a region thereof comprising the polymorphic site (i.e., position 2282 of SEQ ID NO: 2), of the genomic DNA of the saliva or cells (e.g., blood or neuronal cells) of the sample obtained from the subject is determined.

[0032] Suitable techniques of obtaining genomic sequence information from cells are known in the art. For example, the sequence data may be obtained through direct analysis of the sequence of the allele of the polymorphic marker. Suitable methods, some of which are described herein, include, for instance, whole genome analysis using a whole genome SNP chip (e.g., Infinium HD BeadChip), cloning for polymorphisms, non-radioactive PCR-single strand conformation polymorphism analysis, denaturing high pressure liquid chromatography (DHPLC), DNA hybridization, computational analysis, single-stranded conformational polymorphism (SSCP), restriction fragment length polymorphism (RFLP), automated fluorescent sequencing; clamped denaturing gel electrophoresis (CDGE); denaturing gradient gel electrophoresis (DGGE), mobility shift analysis, restriction enzyme analysis; heteroduplex analysis, chemical mismatch cleavage (CMC), RNase protection assays, use of polypeptides that recognize nucleotide mismatches, such as *E. coli* mutS protein, allele-specific PCR, and direct manual sequencing. These and other methods are described in the art (see, for instance, Li et al., *Nucleic Acids Research,* 28(2): e1 (i-v) (2000); Liu et al., *Biochem Cell Bio* 80:17-22 (2000); and Burczak et al., *Polymorphism Detection and Analysis,* Eaton Publishing, 2000; Sheffield et al., *Proc. Natl. Acad. Sci. USA,* 86:232-236 (1989); Orita et al., *Proc. Natl. Acad. Sci. USA,* 86:2766-2770 (1989); Flavell et al., *Cell,* 15:25-41 (1978); Geever et al., *Proc. Natl. Acad. Sci. USA,* 78:5081-5085 (1981); Cotton et al., *Proc. Natl. Acad. Sci. USA,* 85:4397-4401 (1985); Myers et al., *Science* 230:1242-1246 (1985); *Church and Gilbert, Proc. Natl. Acad. Sci. USA,* 81:1991-1995 (1988); Sanger et al., *Proc. Natl. Acad. Sci. USA,* 74:5463-5467 (1977); and Beavis et al., U.S. Pat. No. 5,288,644).

[0033] In exemplary embodiments, a hybridization method (see *Current Protocols in Molecular Biology,* Ausubel et al., eds., John Wiley & Sons, including all supplements) is used to analyze the sample for the presence (or absence) of allele [A]. A sample of genomic DNA, RNA, or cDNA is obtained from a subject. The DNA, RNA, or cDNA sample is then examined by incubating a sequence-specific nucleic acid probe with the DNA, RNA, or cDNA. A "nucleic acid probe", as used herein, can be a DNA probe or an RNA probe that hybridizes to a complementary sequence. In exemplary aspects, the sequence-specific nucleic acid probe is designed to specifically hybridize to the sequence of allele [A]. One of skill in the art would know how to design such a probe so that sequence specific hybridization will occur only if a particular allele is present in a genomic sequence from a sample.

[0034] In exemplary aspects, the nucleic acid probe is conjugated to a detectable label. The detectable label, in exemplary aspects, is a radioisotope, a fluorophore, or an element particle. In a preferred embodiment, the DNA template containing the SNP polymorphism is amplified by Polymerase Chain Reaction (PCR) prior to detection.

[0035] Additional Steps

[0036] In exemplary aspects, the method may include additional steps. For example, the method may include repeating one or more of the recited step(s) of the method. In exemplary aspects, the methods comprises repeating the step of analyzing a sample obtained from the subject for the presence of an allele [A] of CACNA1C, wherein allele [A] comprises the sequence of polymorphic marker rs1006737. In alternative or additional aspects, the method of the invention comprises repeating the step of administering to the subject a CCB when no more than one copy of allele [A] is present in the cells of the sample.

[0037] In exemplary aspects, the repeated steps are carried out regularly. For example, the method may comprise analyzing a sample obtained from the subject for the presence of an allele [A] of CACNA1C daily, every 2 days, every 3 days, every 4 days, every 5 days, every 6 days, weekly, every 2 weeks, monthly, every 2 months, every 3 months, quarterly, bi-annually, or annually. Optionally, the sample is obtained from the subject at each instance.

[0038] In exemplary aspects, the method comprises analyzing the sample for CACNA1C expression. In exemplary aspects, the method comprises measuring the sample for a gene product encoded by CACNA1C. In exemplary aspects, the method comprises measuring the levels of RNA encoded by CACNA1C. In alternative or additional aspects, the method comprises measuring CACNA1C protein encoded by CACNA1C. In exemplary aspects, the method comprises measuring one or more CACNA1C isoforms, including but not limited to any of the following isoforms:

NCBI Reference Sequence for the mRNA → NCBI Reference Sequence for the protein sequence, isoform name
NM_000719.6 (SEQ ID NO: 4)→ NP_000710.5 (SEQ ID NO: 5) voltage-dependent L-type calcium channel subunit alpha-1C isoform 18
NM_001129827.1 (SEQ ID NO: 6)→ NP_001123299.1 (SEQ ID NO: 7) voltage-dependent L-type calcium channel subunit alpha-1C isoform 2
NM_001129829.1 (SEQ ID NO: 8)→ NP_001123301.1 (SEQ ID NO: 9) voltage-dependent L-type calcium channel subunit alpha-1C isoform 3
NM_001129830.2 (SEQ ID NO: 10)→ NP_001123302.2 (SEQ ID NO: 11) voltage-dependent L-type calcium channel subunit alpha-1C isoform 4
NM_001129831.1 (SEQ ID NO: 12)→ NP_001123303.1 (SEQ ID NO: 13) voltage-dependent L-type calcium channel subunit alpha-1C isoform 5

-continued

NCBI Reference Sequence for the mRNA → NCBI Reference Sequence for the protein sequence, isoform name
NM_001129832.1 (SEQ ID NO: 14)→ NP_001123304.1 (SEQ ID NO: 15) voltage-dependent L-type calcium channel subunit alpha-1C isoform 6
NM_001129833.1 (SEQ ID NO: 16)→ NP_001123305.1 (SEQ ID NO: 17) voltage-dependent L-type calcium channel subunit alpha-1C isoform 7
NM_001129834.1 (SEQ ID NO: 18)→ NP_001123306.1 (SEQ ID NO: 19) voltage-dependent L-type calcium channel subunit alpha-1C isoform 8
NM_001129835.1 (SEQ ID NO: 20)→ NP_001123307.1 (SEQ ID NO: 21) voltage-dependent L-type calcium channel subunit alpha-1C isoform 9
NM_001129836.1 (SEQ ID NO: 22)→ NP_001123308.1 (SEQ ID NO: 23) voltage-dependent L-type calcium channel subunit alpha-1C isoform 10
NM_001129837.1 (SEQ ID NO: 24)→ NP_001123309.1 (SEQ ID NO: 25) voltage-dependent L-type calcium channel subunit alpha-1C isoform 11
NM_001129838.1 (SEQ ID NO: 26)→ NP_001123310.1 (SEQ ID NO: 27) voltage-dependent L-type calcium channel subunit alpha-1C isoform 12
NM_001129839.1 (SEQ ID NO: 28)→ NP_001123311.1 (SEQ ID NO: 29) voltage-dependent L-type calcium channel subunit alpha-1C isoform 13
NM_001129840.1 (SEQ ID NO: 30)→ NP_001123312.1 (SEQ ID NO: 31) voltage-dependent L-type calcium channel subunit alpha-1C isoform 14
NM_001129841.1 (SEQ ID NO: 32)→ NP_001123313.1 (SEQ ID NO: 33) voltage-dependent L-type calcium channel subunit alpha-1C isoform 15
NM_001129842.1 (SEQ ID NO: 34)→ NP_001123314.1 (SEQ ID NO: 35) voltage-dependent L-type calcium channel subunit alpha-1C isoform 16
NM_001129843.1 (SEQ ID NO: 36)→ NP_001123315.1 (SEQ ID NO: 37) voltage-dependent L-type calcium channel subunit alpha-1C isoform 17
NM_001129844.1 (SEQ ID NO: 38)→ NP_001123316.1 (SEQ ID NO: 39) voltage-dependent L-type calcium channel subunit alpha-1C isoform 19
NM_001129846.1 (SEQ ID NO: 40)→ NP_001123318.1 (SEQ ID NO: 41) voltage-dependent L-type calcium channel subunit alpha-1C isoform 20
NM_001167623.1 (SEQ ID NO: 10)→ NP_001161095.1 (SEQ ID NO: 43) voltage-dependent L-type calcium channel subunit alpha-1C isoform 21
NM_001167624.2 (SEQ ID NO: 10)→ NP_001161096.2 (SEQ ID NO: 45) voltage-dependent L-type calcium channel subunit alpha-1C isoform 22
NM_001167625.1 (SEQ ID NO: 46)→ NP_001161097.1 (SEQ ID NO: 47) voltage-dependent L-type calcium channel subunit alpha-1C isoform 23
NM_199460.3 (SEQ ID NO: 48)→ NP_955630.3 (SEQ ID NO: 49) voltage-dependent L-type calcium channel subunit alpha-1C isoform 1

[0039] Methods of detecting RNA and proteins are known in the art and include, but not limited to, RT-PCR, qPCR, and RNA-Seq, Northern Blot, in situ hybridization, western blot, and ELISA. See, e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual* (*Fourth Edition*), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 2012.

[0040] In exemplary aspects, wherein the method comprises measuring expression levels by measuring nucleic acids, e.g., RNA, mRNA, encoded by CACNA1C, the method further comprises amplifying at least a fragment of the nucleic acids to be measured. In exemplary aspects, the amplification is carried out via PCR or RT-PCR.

[0041] In exemplary aspects, the methods described herein further comprise genotyping the sample for additional polymorphic markers. In exemplary aspects, the method comprises genotyping the sample for one or more of the polymorphic markers listed in Table A. The human DNA sequences associated with these polymorphic markers are known in the art.

TABLE A

SNP IDs	chr.	start	end	Located within CACNA1C Gene
rs1000823	chr12	3461461	3461462	No
rs1001127	chr12	6601742	6601743	No
rs1005375	chr12	3436758	3436759	No
rs1006696	chr12	3405104	3405105	No

TABLE A-continued

SNP IDs	chr.	start	end	Located within CACNA1C Gene
rs1006737	chr12	2345294	2345295	Yes
rs10153570	chr2	131708648	131708649	No
rs1015832	chr12	5690229	5690230	No
rs10160993	chr12	2499564	2499565	Yes
rs1016388	chr12	2321867	2321868	Yes
rs1017101	chr12	6574300	6574301	No
rs10219509	chr12	4300808	4300809	No
rs1024582	chr12	2402245	2402246	Yes
rs1034969	chr12	6573855	6573856	No
rs1043262	chr12	6639087	6639088	No
rs10437827	chr12	4473328	4473329	No
rs10459125	chr12	2309863	2309864	Yes
rs10459134	chr12	5879850	5879851	No
rs10466913	chr12	6022494	6022495	No
rs10491954	chr12	1354344	1354345	No
rs10491961	chr12	2115709	2115710	No
rs10491969	chr12	3734335	3734336	No
rs10492061	chr12	4991284	4991285	No
rs10492094	chr12	5478147	5478148	No
rs10492097	chr12	6394677	6394678	No
rs10492184	chr12	5699047	5699048	No
rs10505724	chr12	2782069	2782070	Yes
rs1056008	chr12	662837	662838	No
rs1060499	chr12	1020265	1020266	No
rs1063856	chr12	6153533	6153534	No
rs1063857	chr12	6153513	6153514	No
rs10735005	chr12	1995402	1995403	No
rs10735020	chr12	3414983	3414984	No
rs10735026	chr12	3738848	3738849	No

TABLE A-continued

SNP IDs	chr.	start	end	Located within CACNA1C Gene
rs10744559	chr12	2298297	2298298	Yes
rs10744560	chr12	2387098	2387099	Yes
rs10744601	chr12	3405901	3405902	No
rs10744641	chr12	4436832	4436833	No
rs10744648	chr12	586406	586407	No
rs10744675	chr12	5145121	5145122	No
rs10744700	chr12	6297862	6297863	No
rs1076344	chr12	2553987	2553988	Yes
rs1076346	chr12	2554277	2554278	Yes
rs10773979	chr12	1788863	1788864	No
rs10774029	chr12	2280806	2280807	Yes
rs10774030	chr12	2292689	2292690	Yes
rs10774033	chr12	2314425	2314426	Yes
rs10774034	chr12	2330457	2330458	Yes
rs10774035	chr12	2368673	2368674	Yes
rs10774036	chr12	2386947	2386948	Yes
rs10774037	chr12	2420525	2420526	Yes
rs10774117	chr12	3219859	3219860	No
rs10774120	chr12	3224985	3224986	No
rs10774140	chr12	3461601	3461602	No
rs10774148	chr12	3557319	3557320	No
rs10774152	chr12	495216	495217	No
rs10774156	chr12	3664703	3664704	No
rs10774167	chr12	3844380	3844381	No
rs10774168	chr12	3846298	3846299	No
rs10774169	chr12	516345	516346	No
rs10774224	chr12	4471634	4471635	No
rs10774232	chr12	4518168	4518169	No
rs10774250	chr12	4735427	4735428	No
rs10774324	chr12	5476396	5476397	No
rs10774325	chr12	5476904	5476905	No
rs10774333	chr12	5563166	5563167	No
rs10774334	chr12	5611798	5611799	No
rs10774353	chr12	5767173	5767174	No
rs10774376	chr12	5941323	5941324	No
rs10774403	chr12	6277310	6277311	No
rs10774405	chr12	6285390	6285391	No
rs10774466	chr12	939301	939302	No
rs10848438	chr12	1211575	1211576	No
rs10848476	chr12	1587159	1587160	No
rs10848587	chr12	2002361	2002362	No
rs10848596	chr12	2034886	2034887	No
rs10848600	chr12	2083927	2083928	No
rs10848622	chr12	2274050	2274051	Yes
rs10848623	chr12	359462	359463	No
rs10848627	chr12	2312407	2312408	Yes
rs10848628	chr12	2312488	2312489	Yes
rs10848629	chr12	2312896	2312897	Yes
rs10848632	chr12	2315992	2315993	Yes
rs10848633	chr12	2316018	2316019	Yes
rs10848634	chr12	2316126	2316127	Yes
rs10848635	chr12	2316194	2316195	Yes
rs10848636	chr12	2316492	2316493	Yes
rs10848637	chr12	2316553	2316554	Yes
rs10848642	chr12	2331571	2331572	Yes
rs10848644	chr12	365288	365289	No
rs10848645	chr12	2420243	2420244	Yes
rs10848649	chr12	2460085	2460086	Yes
rs10848683	chr12	2791129	2791130	Yes
rs10848703	chr12	2882249	2882250	No
rs10848784	chr12	3188513	3188514	No
rs10848789	chr12	3195201	3195202	No
rs10848803	chr12	3222755	3222756	No
rs10848818	chr12	3293243	3293244	No
rs10848821	chr12	3298030	3298031	No
rs10848863	chr12	3561809	3561810	No
rs10848895	chr12	3749311	3749312	No
rs10848905	chr12	507788	507789	No
rs10848914	chr12	3844094	3844095	No
rs10848918	chr12	3853328	3853329	No
rs10849017	chr12	4322050	4322051	No
rs10849038	chr12	4437378	4437379	No
rs10849059	chr12	4521663	4521664	No
rs10849087	chr12	4650064	4650065	No

TABLE A-continued

SNP IDs	chr.	start	end	Located within CACNA1C Gene
rs10849168	chr12	4986995	4986996	No
rs10849175	chr12	5030706	5030707	No
rs10849216	chr12	5322961	5322962	No
rs10849222	chr12	5369482	5369483	No
rs10849261	chr12	5522555	5522556	No
rs10849265	chr12	5532011	5532012	No
rs10849290	chr12	5663171	5663172	No
rs10849298	chr12	5691999	5692000	No
rs10849310	chr12	5752724	5752725	No
rs10849401	chr12	6273237	6273238	No
rs10849414	chr12	6286369	6286370	No
rs10849573	chr12	982320	982321	No
rs10849575	chr12	230403	230404	No
rs11061839	chr12	1655448	1655449	No
rs11062012	chr12	1982124	1982125	No
rs11062038	chr12	2089229	2089230	No
rs11062040	chr12	2091256	2091257	No
rs11062055	chr12	2107300	2107301	No
rs11062057	chr12	2114605	2114606	No
rs11062068	chr12	2121723	2121724	No
rs11062114	chr12	2198826	2198827	Yes
rs11062145	chr12	2297352	2297353	Yes
rs11062156	chr12	2317522	2317523	Yes
rs11062159	chr12	2326223	2326224	Yes
rs11062161	chr12	2329969	2329970	Yes
rs11062162	chr12	2332103	2332104	Yes
rs11062170	chr12	2348843	2348844	Yes
rs11062196	chr12	2460106	2460107	Yes
rs11062197	chr12	2460387	2460388	Yes
rs11062290	chr12	2745150	2745151	Yes
rs11062293	chr12	2748274	2748275	Yes
rs11062309	chr12	2784987	2784988	Yes
rs11062351	chr12	2881762	2881763	No
rs11062385	chr12	427574	427575	No
rs11062630	chr12	3474413	3474414	No
rs11062739	chr12	3711361	3711362	No
rs11062745	chr12	3724582	3724583	No
rs11062747	chr12	3750108	3750109	No
rs11062752	chr12	3757387	3757388	No
rs11062760	chr12	3788528	3788529	No
rs11062770	chr12	3822839	3822840	No
rs11062772	chr12	3826642	3826643	No
rs11062776	chr12	3831992	3831993	No
rs11062778	chr12	3834326	3834327	No
rs11062885	chr12	3978660	3978661	No
rs11062886	chr12	3980955	3980956	No
rs11062932	chr12	4064155	4064156	No
rs11063022	chr12	4296516	4296517	No
rs11063027	chr12	4299312	4299313	No
rs11063069	chr12	4374372	4374373	No
rs11063099	chr12	4462504	4462505	No
rs11063101	chr12	4466402	4466403	No
rs11063182	chr12	4581370	4581371	No
rs11063189	chr12	4588247	4588248	No
rs11063199	chr12	4591853	4591854	No
rs11063205	chr12	4597744	4597745	No
rs11063207	chr12	4603697	4603698	No
rs11063282	chr12	4760977	4760978	No
rs11063426	chr12	5065592	5065593	No
rs11063462	chr12	5121112	5121113	No
rs11063468	chr12	5135473	5135474	No
rs11063476	chr12	5140981	5140982	No
rs11063490	chr12	5191130	5191131	No
rs11063539	chr12	658113	658114	No
rs11063567	chr12	5322550	5322551	No
rs11063623	chr12	5453278	5453279	No
rs11063634	chr12	5470168	5470169	No
rs11063663	chr12	5525569	5525570	No
rs11063692	chr12	5571844	5571845	No
rs11063806	chr12	708596	708597	No
rs11063995	chr12	6136152	6136153	No
rs11064020	chr12	6196313	6196314	No
rs11064021	chr12	6196412	6196413	No
rs11064024	chr12	6202048	6202049	No

TABLE A-continued

SNP IDs	chr.	start	end	Located within CACNA1C Gene
rs11064153	chr12	6488449	6488450	No
rs11064294	chr12	805450	805451	No
rs11064562	chr12	945321	945322	No
rs1108073	chr12	2333637	2333638	Yes
rs1108074	chr12	2333483	2333484	Yes
rs1108221	chr12	2332794	2332795	Yes
rs1108222	chr12	2332855	2332856	Yes
rs1108385	chr12	2482329	2482330	Yes
rs11559856	chr12	5850903	5850904	No
rs11609462	chr12	1590068	1590069	No
rs11609728	chr12	6139691	6139692	No
rs11609815	chr12	6134230	6134231	No
rs11610204	chr12	3510916	3510917	No
rs11610629	chr12	6137455	6137456	No
rs11611163	chr12	4279482	4279483	No
rs11611543	chr12	5476043	5476044	No
rs11611917	chr12	6136633	6136634	No
rs11612401	chr12	6136967	6136968	No
rs11612864	chr12	2462222	2462223	Yes
rs11613331	chr12	351466	351467	No
rs11613469	chr12	2074021	2074022	No
rs11613749	chr12	3708498	3708499	No
rs11614030	chr12	4769875	4769876	No
rs11614912	chr12	6148554	6148555	No
rs11615941	chr12	3556798	3556799	No
rs11616050	chr12	783349	783350	No
rs11616055	chr12	3849592	3849593	No
rs11616162	chr12	4591080	4591081	No
rs11677224	chr2	88789814	88789815	No
rs11835708	chr12	3515553	3515554	No
rs12191018	chr6	153479725	153479726	No
rs12230555	chr12	4418783	4418784	No
rs12303498	chr12	3411437	3411438	No
rs12304321	chr12	5163047	5163048	No
rs12304385	chr12	5898503	5898504	No
rs12315711	chr12	2346829	2346830	Yes
rs12320409	chr12	3428427	3428428	No
rs12368779	chr12	1982150	1982151	No
rs12369414	chr12	915769	915770	No
rs12369484	chr12	6271972	6271973	No
rs12370980	chr12	3849483	3849484	No
rs12422231	chr12	3803565	3803566	No
rs12422554	chr12	2312619	2312620	Yes
rs12423086	chr12	1344140	1344141	No
rs12423234	chr12	4930359	4930360	No
rs12423277	chr12	2314318	2314319	Yes
rs12423361	chr12	3657685	3657686	No
rs12423920	chr12	5047775	5047776	No
rs12424245	chr12	2322512	2322513	Yes
rs12425157	chr12	1357859	1357860	No
rs12426185	chr12	5709634	5709635	No
rs12470817	chr2	131703693	131703694	No
rs12473388	chr2	45549304	45549305	No
rs12579294	chr12	3289944	3289945	No
rs12580433	chr12	5800575	5800576	No
rs12811453	chr12	4761010	4761011	No
rs12816718	chr12	969799	969800	No
rs12817188	chr12	5567618	5567619	No
rs12818111	chr12	3501260	3501261	No
rs12823931	chr12	4467920	4467921	No
rs12825233	chr12	5453776	5453777	No
rs12830185	chr12	5101463	5101464	No
rs13395344	chr2	88795167	88795168	No
rs1355685	chr3	145892710	145892711	No
rs1420402	chr12	5377547	5377548	No
rs1421181	chr18	43068785	43068786	No
rs1468765	chr12	4296893	4296894	No
rs1532609	chr12	232122	232123	No
rs1544502	chr12	2438809	2438810	Yes
rs1544514	chr12	2558185	2558186	Yes
rs1544608	chr12	5813533	5813534	No
rs1548904	chr12	372381	372382	No
rs1558142	chr12	2022410	2022411	No
rs1558321	chr12	2230319	2230320	Yes

TABLE A-continued

SNP IDs	chr.	start	end	Located within CACNA1C Gene
rs1558322	chr12	2230054	2230055	Yes
rs1558325	chr12	6289107	6289108	No
rs1558506	chr12	5750895	5750896	No
rs1558507	chr12	5747821	5747822	No
rs1558508	chr12	5743213	5743214	No
rs1610056	chr12	6195396	6195397	No
rs16928082	chr12	6396155	6396156	No
rs16928108	chr12	989396	989397	No
rs16930578	chr12	3691436	3691437	No
rs16931965	chr12	976486	976487	No
rs16932084	chr12	1080853	1080854	No
rs16933825	chr12	5842890	5842891	No
rs17178877	chr12	5175402	5175403	No
rs17179631	chr12	5295432	5295433	No
rs17179798	chr12	5314507	5314508	No
rs17722632	chr12	5571980	5571981	No
rs17754970	chr12	773261	773262	No
rs17769092	chr12	3464296	3464297	No
rs17769954	chr12	3699213	3699214	No
rs17770663	chr12	3791142	3791143	No
rs17778793	chr12	5444246	5444247	No
rs17778948	chr12	5478112	5478113	No
rs17835992	chr12	3668988	3668989	No
rs1800380	chr12	6138594	6138595	No
rs1808285	chr12	3852359	3852360	No
rs1860002	chr12	2413802	2413803	Yes
rs1860004	chr12	2477048	2477049	Yes
rs1860048	chr12	2058694	2058695	No
rs1860053	chr12	1964415	1964416	No
rs1860056	chr12	2311835	2311836	Yes
rs1860363	chr12	6276532	6276533	No
rs1860365	chr12	6147109	6147110	No
rs1860431	chr12	3183026	3183027	No
rs1860449	chr12	3674830	3674831	No
rs1861584	chr12	5707817	5707818	No
rs1972582	chr12	374301	374302	No
rs2007044	chr12	2344959	2344960	Yes
rs2008134	chr12	6588444	6588445	No
rs2010932	chr12	2085981	2085982	No
rs2013064	chr12	1998043	1998044	No
rs2013195	chr12	3840420	3840421	No
rs2016141	chr12	5146002	5146003	No
rs2017273	chr12	2100022	2100023	No
rs2041135	chr12	2101497	2101498	No
rs2058349	chr12	3844595	3844596	No
rs2058468	chr12	5819953	5819954	No
rs2072373	chr12	6631887	6631888	No
rs2072374	chr12	6637844	6637845	No
rs2075031	chr12	669037	669038	No
rs2075316	chr12	4492805	4492806	No
rs2075317	chr12	4492314	4492315	No
rs2079867	chr12	6622110	6622111	No
rs2079868	chr12	6622345	6622346	No
rs2080105	chr12	5780595	5780596	No
rs2107613	chr12	888427	888428	No
rs2108570	chr12	2421587	2421588	Yes
rs2108638	chr12	2065369	2065370	No
rs2108639	chr12	1973383	1973384	No
rs2109112	chr12	3987472	3987473	No
rs2109425	chr12	4977334	4977335	No
rs2109426	chr12	6589521	6589522	No
rs2158502	chr12	936467	936468	No
rs2159100	chr12	2346392	2346393	Yes
rs2159407	chr12	3186923	3186924	No
rs2159410	chr12	3112728	3112729	No
rs216011	chr12	2725617	2725618	Yes
rs216014	chr12	2730450	2730451	Yes
rs216043	chr12	2760343	2760344	Yes
rs216046	chr12	2764000	2764001	Yes
rs216325	chr12	6145528	6145529	No
rs216327	chr12	6146148	6146149	No
rs216329	chr12	6146506	6146507	No
rs216334	chr12	6147610	6147611	No
rs216855	chr12	6085512	6085513	No

TABLE A-continued

SNP IDs	chr.	start	end	Located within CACNA1C Gene
rs216856	chr12	6086264	6086265	No
rs216865	chr12	6090302	6090303	No
rs216867	chr12	6090999	6091000	No
rs216873	chr12	6095273	6095274	No
rs2189669	chr12	1586845	1586846	No
rs2190769	chr12	2008798	2008799	No
rs2190770	chr12	2014352	2014353	No
rs2191365	chr12	5032639	5032640	No
rs2191537	chr12	3851709	3851710	No
rs2215738	chr12	5784873	5784874	No
rs2229351	chr12	406291	406292	No
rs2238022	chr12	2186477	2186478	Yes
rs2238023	chr12	2202536	2202537	Yes
rs2238027	chr12	2216957	2216958	Yes
rs2238029	chr12	2218895	2218896	Yes
rs2238043	chr12	2275662	2275663	Yes
rs2238046	chr12	2299997	2299998	Yes
rs2238048	chr12	2300206	2300207	Yes
rs2238049	chr12	2306127	2306128	Yes
rs2238050	chr12	2306706	2306707	Yes
rs2238052	chr12	2307295	2307296	Yes
rs2238053	chr12	2317095	2317096	Yes
rs2238054	chr12	2317643	2317644	Yes
rs2238056	chr12	2327943	2327944	Yes
rs2238057	chr12	2384004	2384005	Yes
rs2238069	chr12	2456061	2456062	Yes
rs2238070	chr12	2456114	2456115	Yes
rs2238077	chr12	2466083	2466084	Yes
rs2238078	chr12	2472451	2472452	Yes
rs2238079	chr12	2473357	2473358	Yes
rs2238083	chr12	2487000	2487001	Yes
rs2238090	chr12	2683331	2683332	Yes
rs2238103	chr12	6194182	6194183	No
rs2238104	chr12	6187664	6187665	No
rs2239017	chr12	2289650	2289651	Yes
rs2239018	chr12	2304356	2304357	Yes
rs2239019	chr12	2310309	2310310	Yes
rs2239023	chr12	2310615	2310616	Yes
rs2239030	chr12	2335940	2335941	Yes
rs2239032	chr12	2337137	2337138	Yes
rs2239033	chr12	2337745	2337746	Yes
rs2239037	chr12	2363715	2363716	Yes
rs2239038	chr12	2374129	2374130	Yes
rs2239047	chr12	2435705	2435706	Yes
rs2239061	chr12	2502511	2502512	Yes
rs2239062	chr12	2502571	2502572	Yes
rs2239074	chr12	2538548	2538549	Yes
rs2239079	chr12	2550817	2550818	Yes
rs2239080	chr12	2554688	2554689	Yes
rs2239093	chr12	2609561	2609562	Yes
rs2239131	chr12	2229058	2229059	Yes
rs2239144	chr12	6196182	6196183	No
rs2239145	chr12	6195995	6195996	No
rs2239147	chr12	6195526	6195527	No
rs2240283	chr12	966123	966124	No
rs2240610	chr12	2057591	2057592	No
rs2240612	chr12	2058244	2058245	No
rs2255390	chr12	999761	999762	No
rs2270152	chr12	6061068	6061069	No
rs2283275	chr12	2184559	2184560	Yes
rs2283276	chr12	2184846	2184847	Yes
rs2283287	chr12	2298723	2298724	Yes
rs2283288	chr12	2299047	2299048	Yes
rs2283291	chr12	2337459	2337460	Yes
rs2283294	chr12	2423619	2423620	Yes
rs2283301	chr12	2446805	2446806	Yes
rs2283304	chr12	2473970	2473971	Yes
rs2283306	chr12	2489389	2489390	Yes
rs2286006	chr12	968488	968489	No
rs2286374	chr12	1962758	1962759	No
rs2286646	chr12	6061490	6061491	No
rs2291094	chr12	5294805	5294806	No
rs2291095	chr12	5294346	5294347	No
rs2291919	chr12	280348	280349	No

TABLE A-continued

SNP IDs	chr.	start	end	Located within CACNA1C Gene
rs2291920	chr12	278375	278376	No
rs2291922	chr12	275064	275065	No
rs2299656	chr12	2165146	2165147	Yes
rs2299664	chr12	2226044	2226045	Yes
rs2300134	chr12	478854	478855	No
rs2301880	chr12	1003836	1003837	No
rs2302729	chr12	2783971	2783972	Yes
rs2302840	chr18	43072986	43072987	No
rs2335817	chr12	3294235	3294236	No
rs2361590	chr12	5775386	5775387	No
rs2363877	chr12	6292460	6292461	No
rs2363878	chr12	6292974	6292975	No
rs2363880	chr12	6302008	6302009	No
rs2369276	chr12	486172	486173	No
rs2369280	chr12	508858	508859	No
rs2369703	chr12	1333716	1333717	No
rs2370413	chr12	2354869	2354870	Yes
rs2370414	chr12	2368395	2368396	Yes
rs2370515	chr12	2511161	2511162	Yes
rs2370596	chr12	2666347	2666348	Yes
rs240826	chr12	5324763	5324764	No
rs241966	chr12	3839964	3839965	No
rs241970	chr12	3838416	3838417	No
rs241975	chr12	3836655	3836656	No
rs241978	chr12	3834823	3834824	No
rs241982	chr12	3831610	3831611	No
rs241983	chr12	3831159	3831160	No
rs242012	chr12	3790146	3790147	No
rs2429123	chr12	2113146	2113147	No
rs2429127	chr12	2116767	2116768	No
rs2429135	chr12	2124954	2124955	No
rs2429159	chr12	2016321	2016322	No
rs2429163	chr12	2022500	2022501	No
rs2429175	chr12	2045084	2045085	No
rs2470395	chr12	2145297	2145298	No
rs2470404	chr12	2049448	2049449	No
rs2470425	chr12	2077896	2077897	No
rs2534715	chr12	6573145	6573146	No
rs2534717	chr12	6573748	6573749	No
rs2534721	chr12	6580143	6580144	No
rs2607916	chr12	716508	716509	No
rs2887533	chr12	1201545	1201546	No
rs2887571	chr12	1638170	1638171	No
rs2887780	chr12	2499625	2499626	Yes
rs2906892	chr12	1995621	1995622	No
rs2906893	chr12	1995698	1995699	No
rs2907494	chr12	4642183	4642184	No
rs2907495	chr12	4638163	4638164	No
rs2907499	chr12	4616900	4616901	No
rs2970808	chr12	4640361	4640362	No
rs2970821	chr12	4519122	4519123	No
rs3217830	chr12	4392529	4392530	No
rs3217840	chr12	4394876	4394877	No
rs3217896	chr12	4404157	4404158	No
rs3217898	chr12	4404375	4404376	No
rs3217933	chr12	4412999	4413000	No
rs35452680	chr12	4277661	4277662	No
rs367206	chr12	5757028	5757029	No
rs367978	chr12	5756823	5756824	No
rs369858	chr12	5801347	5801348	No
rs3739127	chr2	131674284	131674285	No
rs3741935	chr12	3701389	3701390	No
rs3759371	chr12	464253	464254	No
rs376708	chr12	5762979	5762980	No
rs3782586	chr12	5690884	5690885	No
rs3782614	chr12	5775102	5775103	No
rs3782642	chr12	5850146	5850147	No
rs3782645	chr12	5888252	5888253	No
rs3782751	chr12	3673498	3673499	No
rs3782752	chr12	3670150	3670151	No
rs3782753	chr12	3670038	3670039	No
rs3782761	chr12	3652625	3652626	No
rs3782803	chr12	3348436	3348437	No
rs3782805	chr12	3345978	3345979	No

TABLE A-continued

SNP IDs	chr.	start	end	Located within CACNA1C Gene
rs3782843	chr12	3113579	3113580	No
rs3782860	chr12	361995	361996	No
rs3794297	chr12	2338395	2338396	Yes
rs380709	chr12	5762089	5762090	No
rs3809257	chr12	3864403	3864404	No
rs3809263	chr12	773455	773456	No
rs381373	chr12	5755326	5755327	No
rs3819526	chr12	2436521	2436522	Yes
rs3819532	chr12	2436836	2436837	Yes
rs3819535	chr12	2436883	2436884	Yes
rs3819537	chr12	6193095	6193096	No
rs3825369	chr12	3109640	3109641	No
rs3851333	chr2	45545406	45545407	No
rs3858698	chr12	2115760	2115761	No
rs3858703	chr12	863516	863517	No
rs387896	chr12	5795450	5795451	No
rs406430	chr12	5753919	5753920	No
rs4126711	chr12	2227310	2227311	Yes
rs4147666	chr12	4757354	4757355	No
rs4147667	chr12	4757392	4757393	No
rs4147672	chr12	4764136	4764137	No
rs417642	chr12	5763771	5763772	No
rs4238022	chr12	5482395	5482396	No
rs4238023	chr12	5524561	5524562	No
rs4283041	chr12	1637912	1637913	No
rs4298967	chr12	2408193	2408194	Yes
rs4370987	chr12	2494925	2494926	Yes
rs4417359	chr12	6293321	6293322	No
rs4437002	chr2	131717890	131717891	No
rs4441076	chr12	2502057	2502058	Yes
rs444834	chr12	5756794	5756795	No
rs445467	chr12	5756322	5756323	No
rs4477507	chr12	4373927	4373928	No
rs4530408	chr2	131693108	131693109	No
rs453385	chr12	5759608	5759609	No
rs454704	chr12	5758661	5758662	No
rs454736	chr12	5758619	5758620	No
rs4631963	chr12	4966213	4966214	No
rs4764487	chr12	6332837	6332838	No
rs4764519	chr12	5937957	5937958	No
rs4764589	chr12	6532281	6532282	No
rs4764605	chr12	6623388	6623389	No
rs4765670	chr12	2313125	2313126	Yes
rs4765676	chr12	2489313	2489314	Yes
rs4765680	chr12	2557098	2557099	Yes
rs4765743	chr12	3727524	3727525	No
rs4765746	chr12	3729882	3729883	No
rs4765747	chr12	3735619	3735620	No
rs4765804	chr12	5190351	5190352	No
rs4765829	chr12	1720793	1720794	No
rs4765830	chr12	1721253	1721254	No
rs4765870	chr12	2090875	2090876	No
rs4765902	chr12	2312964	2312965	Yes
rs4765904	chr12	2332392	2332393	Yes
rs4765905	chr12	2349583	2349584	Yes
rs4765913	chr12	2419895	2419896	Yes
rs4765914	chr12	2420376	2420377	Yes
rs4765960	chr12	2667929	2667930	Yes
rs4766046	chr12	3222713	3222714	No
rs4766096	chr12	3403998	3403999	No
rs4766108	chr12	3460878	3460879	No
rs4766120	chr12	3555525	3555526	No
rs4766156	chr12	3761921	3761922	No
rs4766255	chr12	4684230	4684231	No
rs4766257	chr12	4689012	4689013	No
rs4766312	chr12	5031589	5031590	No
rs4766335	chr12	5168848	5168849	No
rs482514	chr12	396966	396967	No
rs492955	chr12	5241914	5241915	No
rs4930739	chr12	5712477	5712478	No
rs4930764	chr12	5702444	5702445	No
rs4930766	chr12	5712163	5712164	No
rs4980804	chr12	261928	261929	No
rs4980833	chr12	632239	632240	No

TABLE A-continued

SNP IDs	chr.	start	end	Located within CACNA1C Gene
rs4980836	chr12	675440	675441	No
rs4980877	chr12	418915	418916	No
rs4980885	chr12	442619	442620	No
rs4980968	chr12	883177	883178	No
rs4980976	chr12	232703	232704	No
rs524468	chr12	371785	371786	No
rs529446	chr12	5221318	5221319	No
rs550011	chr12	5240225	5240226	No
rs555044	chr12	335921	335922	No
rs564292	chr12	5235861	5235862	No
rs576159	chr12	382875	382876	No
rs579526	chr12	373119	373120	No
rs611652	chr12	5239768	5239769	No
rs614616	chr12	3365072	3365073	No
rs622513	chr12	4071237	4071238	No
rs6430431	chr2	131684662	131684663	No
rs6430441	chr2	131695641	131695642	No
rs6489338	chr12	2060579	2060580	No
rs6489341	chr12	2104467	2104468	No
rs6489353	chr12	2338857	2338858	Yes
rs6489367	chr12	2475675	2475676	Yes
rs6489375	chr12	2777767	2777768	Yes
rs6489439	chr12	3227202	3227203	No
rs6489454	chr12	475793	475794	No
rs6489482	chr12	3709764	3709765	No
rs6489500	chr12	3993627	3993628	No
rs6489501	chr12	3993808	3993809	No
rs6489568	chr12	4930099	4930100	No
rs6489589	chr12	5100436	5100437	No
rs6489630	chr12	5604623	5604624	No
rs6489662	chr12	726014	726015	No
rs6489746	chr12	865969	865970	No
rs6547780	chr2	88811786	88811787	No
rs6547781	chr2	88831690	88831691	No
rs6718310	chr2	131688178	131688179	No
rs6718816	chr2	131688586	131688587	No
rs7131705	chr12	2186579	2186580	Yes
rs7132154	chr12	2461222	2461223	Yes
rs7132763	chr12	487334	487335	No
rs7133350	chr12	3743474	3743475	No
rs7134353	chr12	425501	425502	No
rs7134570	chr12	1202357	1202358	No
rs7135976	chr12	6186115	6186116	No
rs7137113	chr12	3226697	3226698	No
rs7137875	chr12	3697838	3697839	No
rs7138047	chr12	5418537	5418538	No
rs714775	chr12	6619401	6619402	No
rs715230	chr12	461597	461598	No
rs717596	chr12	3841342	3841343	No
rs720721	chr12	2667743	2667744	Yes
rs721159	chr12	1948976	1948977	No
rs724709	chr12	898399	898400	No
rs7294326	chr12	594173	594174	No
rs7295590	chr12	2442788	2442789	Yes
rs7295704	chr12	884888	884889	No
rs7296925	chr12	3715460	3715461	No
rs7297582	chr12	2355805	2355806	Yes
rs7297784	chr12	5143053	5143054	No
rs7297853	chr12	3751045	3751046	No
rs7298053	chr12	6619053	6619054	No
rs7298357	chr12	6000125	6000126	No
rs7298570	chr12	6581481	6581482	No
rs7298766	chr12	661655	661656	No
rs7300043	chr12	3958712	3958713	No
rs7300338	chr12	4139899	4139900	No
rs7300444	chr12	993929	993930	No
rs7301134	chr12	3508718	3508719	No
rs7301422	chr12	447750	447751	No
rs7302743	chr12	2269587	2269588	Yes
rs7303991	chr12	1956289	1956290	No
rs7304949	chr12	4609624	4609625	No
rs7304958	chr12	3225938	3225939	No
rs7305265	chr12	2032112	2032113	No
rs7305676	chr12	5706126	5706127	No

TABLE A-continued

SNP IDs	chr.	start	end	Located within CACNA1C Gene
rs7307214	chr12	3851048	3851049	No
rs7308641	chr12	4667909	4667910	No
rs7309847	chr12	3841651	3841652	No
rs7312402	chr12	4755516	4755517	No
rs7314661	chr12	779905	779906	No
rs7314691	chr12	661980	661981	No
rs7315460	chr12	5235996	5235997	No
rs7315852	chr12	417632	417633	No
rs7316135	chr12	1718073	1718074	No
rs7342306	chr12	6291092	6291093	No
rs735295	chr12	547682	547683	No
rs740355	chr12	1723227	1723228	No
rs740416	chr12	2499891	2499892	Yes
rs740417	chr12	2499848	2499849	Yes
rs740458	chr12	1989413	1989414	No
rs740897	chr12	5441266	5441267	No
rs740898	chr12	5441311	5441312	No
rs740901	chr12	5444139	5444140	No
rs7485896	chr12	5938445	5938446	No
rs7486388	chr12	5766337	5766338	No
rs7488279	chr12	5568219	5568220	No
rs7488316	chr12	5606371	5606372	No
rs753076	chr12	2499167	2499168	Yes
rs7579148	chr2	131706882	131706883	No
rs758162	chr12	1966288	1966289	No
rs758170	chr12	2361459	2361460	Yes
rs758173	chr12	2315227	2315228	Yes
rs758174	chr12	2315705	2315706	Yes
rs758563	chr12	2737058	2737059	Yes
rs758739	chr12	6626368	6626369	No
rs758798	chr12	5441540	5441541	No
rs7595875	chr2	88817091	88817092	No
rs763385	chr12	2087044	2087045	No
rs763580	chr12	6193536	6193537	No
rs7645622	chr3	145887758	145887759	No
rs764614	chr12	430651	430652	No
rs765124	chr12	2156144	2156145	No
rs765125	chr12	2156206	2156207	No
rs765891	chr12	966992	966993	No
rs769087	chr12	2344643	2344644	Yes
rs7953137	chr12	486832	486833	No
rs7954351	chr12	6163704	6163705	No
rs7954694	chr12	3989666	3989667	No
rs7955352	chr12	4946014	4946015	No
rs7957013	chr12	3425576	3425577	No
rs7957545	chr12	2324041	2324042	Yes
rs7958182	chr12	4768436	4768437	No
rs7961089	chr12	2463053	2463054	Yes
rs7961557	chr12	2493590	2493591	Yes
rs7961826	chr12	4973358	4973359	No
rs7963651	chr12	4297830	4297831	No
rs7965755	chr12	4669739	4669740	No
rs7966355	chr12	2075651	2075652	No
rs7967032	chr12	2046098	2046099	No
rs7968633	chr12	2734449	2734450	Yes
rs7968680	chr12	2500202	2500203	Yes
rs7968928	chr12	5411035	5411036	No
rs7969171	chr12	1679783	1679784	No
rs7969761	chr12	355841	355842	No
rs7970204	chr12	3429755	3429756	No
rs7972490	chr12	1009055	1009056	No
rs7972545	chr12	3840771	3840772	No
rs7972667	chr12	863832	863833	No
rs7972920	chr12	4768618	4768619	No
rs7975360	chr12	6605154	6605155	No
rs7976678	chr12	6537543	6537544	No
rs7976964	chr12	887925	887926	No
rs7977039	chr12	2615133	2615134	Yes
rs797765	chr12	372437	372438	No
rs7978349	chr12	3694487	3694488	No
rs7978411	chr12	5415849	5415850	No
rs7978603	chr12	6598072	6598073	No
rs7979389	chr12	2441461	2441462	Yes
rs7980163	chr12	955507	955508	No

TABLE A-continued

SNP IDs	chr.	start	end	Located within CACNA1C Gene
rs8181786	chr12	2019321	2019322	No
rs82602	chr12	2760002	2760003	Yes
rs867167	chr12	5259442	5259443	No
rs876503	chr12	2797178	2797179	Yes
rs877478	chr12	229946	229947	No
rs880342	chr12	2481606	2481607	Yes
rs882194	chr12	2350451	2350452	Yes
rs882195	chr12	2350400	2350401	Yes
rs886540	chr12	1590757	1590758	No
rs886541	chr12	1590898	1590899	No
rs886898	chr12	2481935	2481936	Yes
rs886941	chr12	2026914	2026915	No
rs887357	chr12	3474644	3474645	No
rs917367	chr12	1967525	1967526	No
rs917668	chr12	5452772	5452773	No
rs936577	chr12	5263803	5263804	No
rs959940	chr3	65148430	65148431	No
rs959941	chr3	65148831	65148832	No
rs9651889	chr12	257059	257060	No
rs9669580	chr12	5811468	5811469	No
rs979878	chr12	4757473	4757474	No

SNP IDs listed in the above table correspond to the Reference SNP (refSNP) Cluster Report No. of the NCBI dbSNP database located at http://www.ncbi.nlm.nih.gov/snp. dbSNP is a database of single nucleotide polymorphisms (SNPs) and multiple small-scale variations

[0042] In exemplary aspects, the method further comprises administering a therapeutic compound other than a CCB, such as a mood stabilizer. As used herein, the term "mood stabilizer" refers to a psychiatric medication used to treat mood disorders. The mood stabilizer may be include, but are not limited to, Lithium, Valproic acid, Lamotrigine, Carbamazepine, Divalproex sodium, Sodium valproate, Lithium carbonate, Lithium hydroxidelithium. In exemplary aspects, the mood disorder is an anticonvulsant or an atypical antipsychotic.

[0043] In exemplary aspects, the method comprises sample preparation steps. DNA can be extracted from whole blood or saliva sample obtained from the subject. Genotyping can be performed on the DNA using PsychChip or TaqMan method, or other methods known in the art, to determine the subject's genotype, including for the allele [A] of CACNA1C, wherein allele [A] comprises the sequence of polymorphic marker rs1006737.

[0044] For example, in some aspects, the method comprises selecting a specific cell population from the sample obtained from the subject. The selection step may be carried out by any means known in the art, including, but not limited to FACS or chromatography. In order to assess gene expression level, e.g., RNA levels or protein levels, in neuronal cells, fibroblast cells can be obtained from the subject and used to construct induced pluripotent stem cells (iPSCs). Then, iPSCs can be induced into neuronal cells in culture. Methods for obtaining iPSCs and inducing them to become neuronal cells in culture are known in the art. Gene expression of CACNA1C can be assessed in the cultured neuronal cells using methods of detecting RNA or protein that are known and used routinely in the art and described herein. In exemplary aspects, wherein RNA expression levels are measured, the method may further comprise a step to extract or isolate the RNA from the cells of the sample.

[0045] Any and all possible combinations of the steps described herein are contemplated for purposes of the inventive methods

[0046] Mood Disorders

[0047] As used herein, the term "mood disorder" refers to a mental disorder wherein a disturbance in a subject's mood is thought to be the main underlying feature. Mood disorders are

classified in the Diagnostic and Statistical Manual(s) of Mental Disorders, DSM-IV and DSM5. In exemplary embodiments, the mood disorder is a depressive disorder, including, but not limited to, atypical depression, melancholic depression, psychotic major depression, catatonic depression, postpartum depression, seasonal affective disorder, dysthymia, double depression, depressive disorder not otherwise specified, depressive personality disorder, recurrent brief depression, and mino depressive disorder. In exemplary embodiments, the mood disorder is a bipolar disorder (BD). In exemplary aspects, the bipolar disorder is mania, hypomania, bipolar I, bipolar II, cyclothymia, or biopolar disorder not otherwise specified.

[0048] Samples

[0049] With regard to the methods disclosed herein, in exemplary embodiments, the sample obtained from the subject comprises a bodily fluid, including, but not limited to, blood, plasma, serum, lymph, breast milk, saliva, mucous, semen, vaginal secretions, cellular extracts, inflammatory fluids, cerebrospinal fluid, feces, vitreous humor, or urine obtained from the subject. In some aspects, the sample is a composite panel of at least two of the foregoing samples. In exemplary aspects, the sample comprises DNA obtained from one or more blood cells of the subject. In exemplary aspects, the sample comprises DNA obtained from saliva of the subject. In exemplary aspects, the sample comprises brain or neuronal cells from the subject. In exemplary aspects, the sample contains neuronal cells derived from iPSCs induced from fibroblasts collected from the subject. In exemplary aspects, the sample comprises RNA from neuronal cells derived from such iPSCs.

[0050] Subjects

[0051] With regard to the methods disclosed herein, the subject in exemplary aspects is a mammal, preferably a human. In exemplary aspects, the subject is an adult. In exemplary aspects, the subject is a female. In exemplary aspects, the subject is a male. In exemplary aspects, the subject is a subject with a mood disorder. In exemplary aspects, the mood disorder is any of those mentioned herein. In exemplary aspects, the subject is one who suffers from a bipolar disorder. In exemplary aspects, the subject has been treated with a CCB. In exemplary aspects, the subject has not been treated with a CCB.

[0052] Calcium Channel Blockers

[0053] As used herein, the term "Calcium Channel Blocker" or CCB" refers to any compound, e.g., any drug, that blocks the action of a calcium channel. In exemplary embodiments, the CCB is selected from the group consisting of: amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nisoldipine and verapamil. In exemplary aspects, the calcium channel blocker is nicardipine.

[0054] Formulations and Routes of Administration

[0055] With regard to the administration of a therapeutic agent, e.g., a CCB, the agent may be administered through any suitable means, compositions and routes known in the art.

[0056] Kits

[0057] The invention further provides kits which in exemplary embodiments are useful in the methods described herein. In exemplary embodiments, the kit comprises one or more binding agents to the CACNA1C gene or a gene product thereof. In exemplary aspects, the binding agent is a nucleic acid molecule which is about 5, about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45 or about 50 nucleotides in length. In exemplary aspects, the nucleic acid molecule is about 15 to about 30 nucleotides in length or about 20 to 30 nucleotides in length or about 25 to 30 nucleotides in length. In exemplary aspects, the nucleic acid molecule is about 25 nucleotides in length.

[0058] In exemplary aspects, the binding agent, e.g., the nucleic acid molecule, is conjugated to a detectable label. The detectable label, in exemplary aspects, is a radioisotope, a fluorophore, or an element particle.

[0059] In exemplary embodiments, the binding agent is a nucleic acid molecule, e.g., a nucleic acid probe, which specifically binds to the CACNA1C gene or a gene product thereof. In exemplary embodiments, the nucleic acid molecule hybridizes to or specifically binds to SEQ ID NO: 1, and in exemplary aspects, the nucleic acid molecule hybridizes to or specifically binds to a region of SEQ ID NO: 1 which is about 20 basepairs (bp) to about 1000 bp (e.g., about 30 bp, about 40 bp, about 50 bp, about 60 bp, about 70 bp, about 80 bp, about 90 bp, about 100 bp, about 200 bp, about 300 bp, about 400 bp, about 500 bp, about 600 bp, about 700 bp, about 800 bp, about 900 bp, about 1000 bp) upstream or downstream of position 270344 of SEQ ID NO: 1, which is the polymorphic site of rs1006737. In exemplary aspects, the nucleic acid molecule hybridizes to or specifically binds to a region of SEQ ID NO: 1 which is about 50 bp to about 500 bp upstream or downstream of position 270344 of SEQ ID NO: 1. In exemplary aspects, the nucleic acid molecule hybridizes to or specifically binds to a region of SEQ ID NO: 1 which is about 50 bp to about 400 bp upstream or downstream of position 270344 of SEQ ID NO: 1. In exemplary aspects, the nucleic acid molecule hybridizes to or specifically binds to a region of SEQ ID NO: 1 which is about 50 bp to about 300 bp upstream or downstream of position 270344 of SEQ ID NO: 1. In exemplary aspects, the nucleic acid molecule hybridizes to or specifically binds to a region of SEQ ID NO: 1 which is about 50 bp to about 200 bp upstream or downstream of position 270344 of SEQ ID NO: 1. In exemplary aspects, the nucleic acid molecule hybridizes to or specifically binds to a region of SEQ ID NO: 1 which is about 50 bp to about 100 bp upstream or downstream of position 270344 of SEQ ID NO: 1. In exemplary aspects, the nucleic acid molecule hybridizes to or specifically binds to a region of SEQ ID NO: 1 which is about 100 bp to about 500 bp upstream or downstream of position 270344 of SEQ ID NO: 1. In exemplary aspects, the nucleic acid molecule hybridizes to or specifically binds to a region of SEQ ID NO: 1 which is about 200 bp to about 500 bp upstream or downstream of position 270344 of SEQ ID NO: 1. In exemplary aspects, the nucleic acid molecule hybridizes to or specifically binds to a region of SEQ ID NO: 1 which is about 300 bp to about 500 bp upstream or downstream of position 270344 of SEQ ID NO: 1. In exemplary aspects, the nucleic acid molecule hybridizes to or specifically binds to a region of SEQ ID NO: 1 which is about 400 bp to about 500 bp upstream or downstream of position 270344 of SEQ ID NO: 1.

[0060] In exemplary aspects, the kit comprises a pair of primers suitable for, e.g., amplification of a region of the CACNA1C gene of a given sample. In exemplary aspects, the pair comprises two nucleic acid molecules which work together to amplify (e.g., via a polymerase chain reaction (PCR)) a region of the CACNA1C gene. In exemplary aspects, at least one primer of the pair is a nucleic acid described above.

[0061] In exemplary aspects, the binding agent is a set of oligonucleotides that specifically bind to the CACNA1C

gene, and flank the sequence comprising position 2282 of SEQ ID NO: 2. In exemplary aspects, the kit comprises a primer pair, wherein the forward primer is CCACTTGGCTCTATCAAAGTCT and the reverse primer is CCTGAGAGACACTGTGAGGT (SEQ ID NO: 50 and 51, respectively). In exemplary aspects, the kit comprises the primer pairs attached to a solid support. In exemplary aspects, the solid support is a multi-well plate and the primer pairs are attached to a well of the multi-well plate.

[0062] In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises one or more non-naturally-occurring nucleotides and/or non-naturally-occurring internucleotide linkages (e.g., phosphoroamidate linkages, phosphorothioate linkages). In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises at least one non-naturally-occurring nucleotide and/or non-naturally-occurring internucleotide linkage. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises one or more modified nucleotides, including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl)uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueuosine, inosine, N^6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N -substituted adenine, 7-methylguanine, 5-methylammomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueuosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N^6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queuosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, 3-(3-amino-3-N-2-carboxypropyl) uracil, and 2,6-diaminopurine.

[0063] In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises non-naturally-occurring nucleotides which differ from naturally occurring nucleotides by comprising a chemical group in place of the phosphate group. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises or is a methylphosphonate oligonucleotide, which are noncharged oligomers in which a non-bridging oxygen atom, e.g., alpha oxygen of the phosphate, is replaced by a methyl group. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises or is a phosphorothioate, wherein at least one of the non-bridging oxygen atom, e.g., alpha oxygen of the phosphate, is replaced by a sulfur. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises or is a boranophosphate olignucleotide, wherein at least one of the non-bridging oxygen atom, e.g., alpha oxygen of the phosphate, is replaced by —BH_3.

[0064] In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises at least one non-naturally-occurring nucleotide which differs from naturally occurring nucleotides by comprising a ring structure other than ribose or 2-deoxyribose. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit is an analog comprising a replacement of the hydroxyl at the 2'-position of ribose with an O-alkyl group, e.g., —O—CH_3, —OCH_2CH_3. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises a modified ribonucleotide wherein the 2' hydroxyl of ribose is modified to methoxy (OMe) or methoxy-ethyl (MOE) group. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises a modified ribonucleotide wherein the 2' hydroxyl of ribose is replaced with allyl, amino, azido, halo, thio, O-allyl, O—C_1-C_{10} alkyl, O—C_1-C_{10} substituted alkyl, O—C_1-C_{10} alkoxy, O—C_1-C_{10} substituted alkoxy, OCF_3, $O(CH_2)_2SCH_3$, $O(CH_2)_2$—O—$N(R^1)(R^2)$, or $O(CH_2)$—C(=O)—$N(R^1)(R^2)$, wherein each of R^1 and R^2 is independently selected from the group consisting of H, an amino protecting group or substituted or unsubstituted C_1-C_{10} alkyl. In exemplary aspects, the antisense nucleic acid analog comprises a modified ribonucleotide wherein the 2' hydroxyl of ribose is replaced with 2'F, SH, CN, OCN, CF_3, O-alkyl, S-Alkyl, $N(R^1)$alkyl, O-alkenyl, S-alkenyl, or $N(R^1)$-alkenyl, O-alkynyl, S-alkynyl, $N(R^1)$-alkynyl, O-alkylenyl, O-Alkyl, alknyyl, alkaryl, aralkyl, O-alkaryl, or O-aralkyl. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit is an analog comprising a replacement of the hydrogen at the 2'-position of ribose with halo, e.g., F. In exemplary aspects, the antisense nucleic acid analog comprises a fluorine derivative nucleic acid.

[0065] In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises a substituted ring. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit is or comprises a hexitol nucleic acid. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit is or comprises a nucleotide with a bicyclic or tricyclic sugar moiety. In exemplary aspects, the bicyclic sugar moiety comprises a bridge between the 4' and 2' furanose ring atoms. Examplary moieties include, but are not limited to: —$[C(R_a)(R_b)]_n$—, —$[C(R_a)(R_b)]_n$-0-, —$C(R_aR_b)$-N(R)-0- or, —$C(R_aR_b)$-0-N(R)—; 4'-CH_2-2',4'-$(CH_2)_2$-2',4'- $(CH_2)_3$-2',4'-(CH_2)-0-2' (LNA); 4'-(CH_2)—S-2'; 4'-$(CH_2)_2$-0-2' (ENA); 4'-$CH(CH_3)$-0-2' (cEt) and 4'-$CH(CH_2OCH_3)$-0-2',4'-$C(CH_3)(CH_3)$-0-2',4'-CH_2—N(OCH_3)-2',4'-CH_2-0-N(CH_3)-2'4'-CH_2-0-N(R)-2', and 4'-CH_2—N(R)-0-2'-, wherein each R is, independently, H, a protecting group, or C_1C_{12} alkyl; 4'-CH_2—N(R)-0-2', wherein R is H, C1-C12 alkyl, or a protecting group, 4'-CH_2—C(H)(CH_3)-2',4'-CH_2—C(=CH_2)-2'. Such molecules are known in the art. See, e.g., International Application Publication No. WO 2008/154401, U.S. Pat. No. 7,399,845, International Application Publication No. WO2009/006478, International Application Publication No. WO2008/150729, U.S. Application Publication No. US2004/0171570, U.S. Pat. No. 7,427,672, and Chattopadhyaya, et al, J. Org. Chem., 2009, 74, 118-134). In exemplary aspects, the the nucleic acid molecule, primer and/or probe of the kit comprises a nucleoside comprising a bicyclic sugar moiety, or a bicyclic nucleoside (BNA). In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises a BNA selected from the group consisting of: α-L-Methyleneoxy (4'-CH_2-0-2') BNA, Aminooxy (4'-CH_2-0-N(R)-2') BNA, β-D-Methyleneoxy (4'-CH_2-0-2') BNA, Ethyleneoxy (4'-$(CH_2)_2$-0-2') BNA, methylene-amino (4'-CH2-N(R)-2') BNA, methyl carbocyclic (4'-CH_2—$CH(CH_3)$-2') BNA, Methyl(methyleneoxy) (4'-$CH(CH_3)$-0-2') BNA (also known as constrained ethyl or cEt), methylene-thio (4'-CH_2-S-2') BNA, Oxyamino (4'-CH_2—N(R)-0-2') BNA, and propylene carbocyclic (4'-$(CH_2)_3$-2') BNA. Such BNAs are described in the art. See, e.g., International Patent Publication No. WO 2014/071078.

[0066] In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises a modified back-

bone. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit is or comprises a peptide nucleic acid (PNA) containing an uncharged flexible polyamide backbone comprising repeating N-(2-aminoethyl)glycine units to which the nucleobases are attached via methylene carbonyl linkers. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises a backbone substitution. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit is or comprises an N3'→P5' phosphoramidate, which results from the replacement of the oxygen at the 3' position on ribose by an amine group. Such nucleic acid analogs are further described in Dias and Stein, *Molec Cancer Ther* 1: 347-355 (2002). In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises a nucleotide comprising a conformational lock. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit is or comprises a locked nucleic acid.

[0067] In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises a 6-membered morpholine ring, in place of the ribose or 2-deoxyribose ring found in RNA or DNA. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises non-ionic phophorodiamidate intersubunit linkages in place of anionic phophodiester linkages found in RNA and DNA. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit comprises nucleobases (e.g., adenine (A), cytosine (C), guanine (G), thymine, thymine (T), uracil (U)) found in RNA and DNA. In exemplary aspects, the nucleic acid molecule, primer and/or probe of the kit is a Morpholino oligomer comprising a polymer of subunits, each subunit of which comprises a 6-membered morpholine ring and a nucleobase (e.g., A, C, G, T, U), wherein the units are linked via non-ionic phophorodiamidate intersubunit linkages. For purposes herein, when referring to the sequence of a Morpholino oligomer, the conventional single-letter nucleobase codes (e.g., A, C, G, T, U) are used to refer to the nucleobase attached to the morpholine ring.

[0068] In exemplary aspects, the kit comprises reagents for measuring the expression level of the CACNA1C gene. For example, antibodies that bind to the CACNA1C protein $CA_v1.2$ may be included in the kit of the invention. The antibody may be any type of immunoglobulin, fragment of an immunoglobulin, or nonantibody scaffold known in the art. In exemplary embodiments, the antibody is an antibody of isotype IgA, IgD, IgE, IgG, or IgM. Also, the antibody in some embodiments is a monoclonal antibody. In other embodiments, the antibody is a polyclonal antibody. In some embodiments, the antibody is a naturally-occurring antibody, e.g., an antibody isolated and/or purified from a mammal, or produced by a hybridoma generated from a mammalian cell. Methods of producing antibodies are well known in the art. In some embodiments, the antibody is a genetically-engineered antibody, e.g., a single chain antibody, a humanized antibody, a chimeric antibody, a CDR-grafted antibody, a humaneered antibody, a bispecific antibody, a trispecific antibody, a recombinant antibody, and the like. Genetic engineering techniques also provide the ability to make fully human antibodies in a non-human source. In some aspects, the antibody is in polymeric, oligomeric, or multimeric form. In certain embodiments in which the antibody comprises two or more distinct antigen binding regions fragments, the antibody is considered bispecific, trispecific, or multi-specific, or bivalent, trivalent, or multivalent, depending on the number of distinct epitopes that are recognized and bound by the antibody.

[0069] In some aspects of the invention, the binding agent is an antigen binding fragment of an antibody. The antigen binding fragment (also referred to herein as "antigen binding portion") may be an antigen binding fragment of any of the antibodies described herein. The antigen binding fragment can be any part of an antibody that has at least one antigen binding site, including, but not limited to, Fab, $F(ab')_2$, dsFv, sFv, scFvs, diabodies, triabodies, bis-scFvs, fragments expressed by a Fab expression library, domain antibodies, VhH domains, V-NAR domains, VH domains, VL domains, and the like.

[0070] In exemplary aspects, the kit comprises a CCB, including but not limited to any of the CCBs described herein. In exemplary aspects, the kit comprises a container suitable for holding a sample obtained from the subject. In exemplary aspects, the kit comprises a vial, a tube, a microtiter plate, a dish, a flask, or the like. In exemplary aspects, the kit comprises reagents suitable for isolating DNA, RNA or proteins from the sample.

[0071] In exemplary aspects, the nonantibody scaffold is a nanobody, affibody, affilin, anticalin (lipocalin), fynomer, Kunitz variant, fibronectin type III (FN3) domain (monobody, and related binding protein systems using the FN3 domain), ankyrin repeat (DARPin), disulfide-constrained peptide, or other nonantibody scaffolds.

[0072] Computer Related Inventions

[0073] Related systems, e.g., computer systems, comprising a processor; a memory device coupled to the processor, and machine readable instructions stored on the memory device, are provided herein. In exemplary embodiments, the system comprises machine readable instructions that, when executed by the processor, cause the processor to: (a) receive a data value, α, that is a copy number determination of allele [A] of CACNA1C, wherein allele [A] comprises the sequence of polymorphic marker rs1006737, in the cells of a sample obtained from a subject; and (b) display an output relating to treating the subject for a mood disorder with a calcium channel blocker (CCB), when a is less than the diploid copy number of 2.

[0074] Related computer-readable storage media are also provided herein. In exemplary aspects, a computer-readable storage medium having stored thereon machine-readable instructions executable by a processor is provided. In exemplary aspects, the machine-readable instructions comprise: (a) instructions for receiving a data value, a, relating to the copy number of allele [A] of CACNA1C , wherein allele [A] comprises the sequence of the polymorphic marker rs1006737, in the cells of a sample obtained from a subject; and (b) instructions for displaying an output relating to treating the subject for a mood disorder with a calcium channel blocker (CCB), when a is less than the diploid copy number of 2.

[0075] Related methods implemented by a processor in a computer are provided herein. In exemplary embodiments, the method comprises (a) receiving a data value, α, relating to the copy number of allele [A] of CACNA1C, wherein allele [A] comprises the sequence of the polymorphic marker rs1006737, in the cells of a sample obtained from a subject; and (b) displaying an output relating to treating the subject for a mood disorder with a calcium channel blocker (CCB), when α is less than the diploid copy number of 2.

[0076] The following examples further illustrate the disclosure but, of course, should not be construed as in any way limiting its scope.

EXAMPLES

Example 1

[0077] This example demonstrates that an intronic SNP within the CACNA1C gene is a cis-expression quantitative trait locus for CACNA1C. This example also demonstrates that the risk allele is associated with decreased expression of this gene.

[0078] Abstract

[0079] Timothy Syndrome (TS) is caused by very rare exonic mutations of the CACNA1C gene that produce delayed inactivation of Cav1.2voltage-gated calcium channels during cellular action potentials, with greatly increased influx of calcium into the activated cells. The major clinical feature of this syndrome is a long QT interval that results in cardiac arrhythmias. However, TS also includes cognitive impairment, autism, and major developmental delays in many of the patients. We observed the appearance of Bipolar Disorder (BD) in a patient with a previously reported case of TS, who is one of the very few patients to survive childhood. This is most interesting because the common SNP most highly associated with BD is rs1006737, which we show here is a cis-expression quantitative trait locus (eQTL) for CACNA1C in human cerebellum, and the risk allele (A) is associated with decreased expression. To combine the CACNA1C perturbations in the presence of BD in this patient and in patients with the common CACNA1C SNP risk allele, we would propose that either increase or decrease in calcium influx in excitable cells can be associated with BD. In treatment of BD with calcium channel blocking drugs (CCBs), we would predict better response in patients without the risk allele, because they have increased CACNA1C expression.

[0080] Case Summary

[0081] The patient is a European-American male with TS Type 2 (see below) diagnosed in childhood. At age 28, the patient was referred for research evaluation after diagnosis of BD by one of us (FO). This was confirmed by interview with the patient and his mother, using the Diagnostic Interview for Genetic Studies (DIGS), version 3.0.

[0082] The patient was born full-term in good health, and had an uneventful history during his first three years. At age 4, he suffered a cardiac arrest during a trampoline class[1,5]. Diagnostic work-up identified long QT syndrome, with a QT interval of 550-600 ms. In molecular investigation of his case and one other, TS was described as a severe variant of TS, as discussed below[1] (See FIG. **2**).

[0083] No neurological sequelae were observed after this episode of cardiac arrest. He later had other arrests, and a cardiac pacemaker was implanted when he was 8 years old. He suffered his most complicated arrest at age 10, which led to a prolonged hospitalization complicated by liver failure, coma, and anoxic brain injury. After this illness, he received an implanted cardioverter-defibrillator (ICD).

[0084] His cognitive abilities declined after this episode. He became more socially withdrawn and began attending special education classes with full-time aides. He showed left hemiparesis, which persisted, although not severely. He completed high school and worked for one year as a cleaner at a gym. He has never had a seizure.

[0085] At age 19, he had his first episode of major depression, and at 21 he had an episode of mania. Shortly afterwards[6], TS was described as a mutation in the voltage-gated calcium channel gene CACNA1C. A molecular diagnosis was made when he was 22, and he was treated with a calcium channel blocker (CCB) verapamil at 250 mg/d, which continues to the present time. Theoretically, this would counteract the effects of his mutation, which causes increased Ca^{++} cellular influx during its extended activation[5]. He had a marked decrease in the number of ventricular fibrillation episodes, but no change in QT interval, and continued to have some episodes of a trial fibrillation.

[0086] Ten months after starting the medication, he was referred to a neurologist, who found depression and prescribed citalopram. The patient then had significant improvement in mood and behavior.

[0087] By age 30 he had experienced 10 manic episodes and 3 hypomanic episodes. These were characterized by periods of up to two weeks duration when his sleep decreased markedly, and he would become aggressive with his siblings and would start fights and verbal altercations that were a departure from his usual behavior. Restlessness, talkativeness and difficult-to-follow speech were also present. Ability to focus was impaired. At age 27, the most extreme manic episode occurred, when, along with the usual symptoms, there were hallucinations and paranoid delusions.

[0088] Lithium was then given for mood stabilization, but was not well tolerated, with complaints of increased lethargy and irritability. He was restarted on his antidepressant and has been stable for the three years of observation since then. We note that this is not a typical course of BD, and that further observation will be needed to fully define his course.

[0089] Timothy Syndrome (TS) Molecular Pathophysiology

[0090] TS is caused by missense mutations in the CACNA1C gene, which encodes the alpha-1 subunit of the L-type calcium channel $Ca_v1.2$. All these mutations occur in one of the pore-forming S6 trans-membrane helix segments of the protein. The G406R mutation in exon 8A causes TS1[6], while TS2 is produced by one of two mutations in the alternate splice form exon 8, G406R or G402S (as in this patient)[1], and a recently reported mutation in exon 38 causes TS3[7]. Our patient is the only known living carrier of the exon 8 G402S mutation, for which he is a mosaic[1]. We confirmed his reported mutation by sequencing in our own lab (data not shown).

[0091] It is still not completely clear how TS mutations lead to altered function of CaV1.2 channels, but it is known that multiple aspects of channel function are affected. Voltage-dependent inactivation is decreased[8], action potentials are longer, and calcium flux through Cav1.2 channels is increased[9-11]. It is also not known how the delayed inactivation leads to long QT intervals, ventricular fibrillation, or any of the neurological traits associated with the syndrome. In neuronal induced pluripotent stem cells (iPSCs) derived from TS patients, there are multiple changes in gene expression, including increased tyrosine hydroxylase (TH) activity and increased production of norepinephrine and dopamine[12]. These changes are most likely related to the role of calcium influx as a second messenger indirectly regulating transcription. Conceivably, these changes in catecholamines are related to the observed arrhythmias and neuropsychiatric changes.

[0092] The L-type channel blocker nimodipine failed to reverse excess expression of TH in these neuronal cells[12]. However, treatment of the cells with roscovitine, an experimental drug in cancer treatment that inhibits cyclin-dependent kinases and also blocks the calcium channel, specifically enhanced (normalized) inactivation of the L-type channel of the Cav1.2 protein[13], and caused a 68% reduction in the proportion of TH-positive neurons.

[0093] CACNA1C Knockout Mice Cardiac Effects

[0094] Two studies of transgenic mice with knockout (KO) of CACNA1C reported opposite effects on heart function. Rosati et al.'s heterozygous KO mouse showed a 58% reduction of CACNA1C mRNA and a 21% reduction in CACNA1C protein, but no change in L-type calcium channel (LTCC) current or in gross cardiac phenotype[14]. The Goonasekera study[15] had a graded knockdown heterozygote with cardiac protein levels of CACNA1C reduced by approximately 40%, and roughly 25% less whole-cell LTCC current measured in freshly isolated adult ventricular myocytes. These mice had a pronounced cardiac stress-induced phenotype, but the effects of verapamil were actually detrimental to cardiac function, despite a reduced LTCC current[15]. The differences are difficult to resolve. Both studies had a KO cassette maintained on a C57BL/6 background, but there were some differences in the cassette construction. Another mouse study, in which LTCC activity was increased by over-expressing the β2a subunit of the LTCC, found that increased LTCC activity produced a phenotype similar to that of the Goonasekera, leading to cardiac hypertrophy and early death[16]. This suggests that it may be a perturbation in calcium influx, rather than specifically an increase or decrease, that leads to a disease phenotype in the mouse models.

[0095] CAC1NAC in Bipolar Disorder

[0096] The marker most significantly associated with BD in a recent meta-analysis of genome-wide association studies is an intronic SNP within CACNA1C, rs1006737[17]. Although the variant with biological effect is not necessarily the associated SNP, it must be in LD with the functional variant, so the biology of the associated SNP is of some interest. One of us (CL) is leading an ongoing study of expression Quantitative Trait Loci (eQTLs) in brain, using the Stanley Medical Research Institute postmortem brain collections. For the current paper, we tested rs1006737 for association with CACNA1C expression levels in human brain tissue.

[0097] Materials and Methods for CACNA1C Expression Study

[0098] Samples

[0099] In our ongoing study, we obtained 164 cerebellum and parietal cortex brain samples from two collections of the Stanley Medical Research Institute (SMRI)[18-20]. We used the Norgen DNA purification kit to extract high molecular weight DNA from tissue blocks. The DNA was resuspended in low EDTA TE buffer. The DNA concentration and A260/A280 ratio were determined on a NanoDrop ND-1000 spectrophotometer (NanoDrop Technologies, Wilmington, Del.). Only intact DNA samples showing a major band at approximately 10-20 kb on a 1% agarose gel were genotyped.

[0100] RNA Preparation and QC

[0101] We used the RN easy Mini kit (Qiagen, Valencia, Calif.) to extract total RNA from brain tissue blocks. The ratio of 28S to 18S rRNA and RNA Integrity Number (RIN) were measured using an RNA LabChip kit on the Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, Calif.). To avoid use of seriously degraded samples, only RNA samples with a RIN>7 were used for expression profiling.

[0102] Genotyping was performed using Affymetrix GeneChip Mapping 500K Array at TGen by Dr. David Craig (www.tgen.org). Genotypes were called using the BRLMM-p algorithm (Affymetrix). SNPs with call rates ≥99%, Hardy-Weinberg equilibrium (HWE) p values≥0.001 and minor allele frequencies (MAF)≥10% were included in the association tests. Pairwise identity-by-state was calculated using PLINK to verify unrelatedness. We used MACH (http://www.sph.umich.edu/csg/abecasis/MACH/index.html) to impute 852,963 SNPs.

[0103] Gene expression profiling was performed using Affymetrix's GeneChip Human Gene 1.0 ST Array, by the NIH Neuroscience Microarray Consortium at Yale University. Raw data in CEL files were summarized by Affymetrix Expression Console software EC1.1, using our customized library files to remove probes that have cross-hybridization to multiple genomic regions, or contain common SNPs. Batch effects were removed by ComBat[21]. All covariates were removed by SVA[22] before the SNP-expression association tests.

[0104] SNP-expression association tests were performed for cis-regulation. Cis-association refers to correlation of genes and SNPs within 1 Mb of before or after those genes. We used mach2qtl to perform the association tests, and permutation correction. Permutation was used to correct for multiple testing: region-wide significance corrected for the number of SNPs tested; phenotype-wide significance corrected for the number of phenotypes tested as well. No trans-associations (with SNPs outside this region) were found with CACNA1C.

[0105] Results of CACNA1C Expression Study

[0106] We detect a significant cis-association of CACNA1C expression in cerebellum for SNP rs1006737 that survives correction for region-wide multiple tests, where the risk allele (A) is associated with reduced expression (Table 1). The association is present in multiple exons as well as transcripts of this gene in cerebellum but not in parietal cortex (see Table 2). This finding is also present for rs1024582, the CACNA1C SNP recently associated by Smoller et al.[3] with multiple psychiatric disorders. rs1024582 is in nearly complete LD with rs1006737 (R^2=0.94), and its risk allele (A) is also associated with significantly decreased cerebellar expression of the same CACNA1C probes (data not shown).

TABLE 1

Association of SNP rs1006737 bipolar risk allele (A) with decreased expression of CACNA1C in human cerebellum

Probe type	Probe ID	Frequency (A allele)	Effect	CHISQ	P-value	Corr_p
exon	7953041	0.36	−0.47	14.67	1.28E−04	0.026
exon	7953044	0.36	−0.52	17.65	2.66E−05	0.006
exon	7953049	0.36	−0.61	24.46	7.59E−07	0.001
exon	7953050	0.36	−0.52	17.67	2.63E−05	0.004
exon	7953066	0.36	−0.54	19.73	8.91E−06	0.004
exon	7953068	0.36	−0.55	20.18	7.04E−06	0.002
exon	7953075	0.36	−0.61	24.50	7.43E−07	0.001
exon	7953076	0.36	−0.52	17.73	2.54E−05	0.004
exon	7953079	0.36	−0.50	16.30	5.41E−05	0.014
exon	7953081	0.36	−0.49	16.10	6.00E−05	0.026
exon	7953093	0.36	−0.67	29.47	5.67E−08	0.001
exon	7953095	0.36	−0.55	19.84	8.43E−06	0.004
transcript	7953040	0.36	−0.60	23.73	1.11E−06	0.001

TABLE 1-continued

Association of SNP rs1006737 bipolar risk allele (A) with decreased expression of CACNA1C in human cerebellum

Probe type	Probe ID	Frequency (A allele)	Effect	CHISQ	P-value	Corr_p
transcript	7953094	0.36	−0.46	14.28	1.58E−04	0.048

Notes:

EFFECT: Beta regression coefficient of expression on SNP after correcting for covariates; CHISQ: Test statistic; P-value for test statistic; Corr_p: regionwide-corrected p-value. Computation by MACHqtl (http://www.sph.umich.edu/csg/abecasis/MACH/download/).

TABLE 2

No association of Bipolar SNP rs1006737 risk allele (A) with expression of CACNA1C in human parietal cortex

Probe type	Probe ID	Frequency (A allele)	Effect	CHISQ	P-value	Corr_p
exon	7953041	0.36	0.08	0.48	0.49	1
exon	7953044	0.36	−0.04	0.15	0.71	1
exon	7953049	0.36	−0.02	0.03	0.89	1
exon	7953050	0.36	0.03	0.07	0.80	1
exon	7953066	0.36	0.09	0.57	0.45	1
exon	7953068	0.36	0.16	1.95	0.16	1
exon	7953075	0.36	0.03	0.08	0.77	1
exon	7953076	0.36	0.32	8.07	0.01	1
exon	7953079	0.36	0.06	0.31	0.58	1
exon	7953081	0.36	0.05	0.19	0.66	1
exon	7953093	0.36	0.05	0.21	0.64	1
exon	7953095	0.36	0.23	4.08	0.04	1
transcript	7953040	0.36	0.21	3.46	0.06	1
transcript	7953094	0.36	0.06	0.27	0.60	1

Notes:

The Bipolar disorder risk allele is the minor allele (A), but the analysis program reports on the major allele (G); EFFECT: Beta regression coefficient of expression on SNP after correcting for covariates; CHISQ: Test statistic; P-value for test statistic; Corr_p: region-wide-corrected p-value

[0107] Discussion

[0108] Cerebellum and Psychiatric Disorders

[0109] In a landmark review in 2005, Konarski et al.[23] advanced the paradigm-shifting hypothesis that, based on functional associations evident through cerebellar stimulation, lesions, and functional and morphometric imaging, cerebellar abnormalities play a crucial role in several psychiatric disorders, including schizophrenia, depression, and bipolar disorder. In a 2008 review, Andreasen and Pierson[24] remark that "The tentorium was once the Maginot Line of the brain. Supratentorial regions governed "higher cortical functions," while the humble subtentorial cerebellum performed "lower" functions unrelated to cognition." They then summarize evidence cortical circuitry connecting the cerebellum and cortex, and conclude that through its role modulating cognition the cerebellum appears to play a crucial role in Schizophrenia. More recent evidence showed, and changes in gene expression of NMDA receptor subunits in cerebellum in Schizophrenia[25], and differential expression of genes encoding neuronal ion-channel subunits in cerebellum in several psychiatric disorders including bipolar disorder[26]. In a whole-genome expression analysis, Chen et al.[27] demonstrated two gene co-expression modules associated with Bipolar Disorder and Schizophrenia in multiple data sets. One of the modules was associated with these diagnoses in both cerebral cortex and cerebellum. This module included metallothioneins (MT) and metal binding site functions, which are involved in oxidative stress and other cellular processes. In a related finding, myelination and oxidative stress alterations were observed in the cerebellum of the G72/G30 transgenic schizophrenia mouse model[28]. In view of all these findings, we would conclude that it is no longer valid to consider the cerebellum as a brain region that cannot play a decisive role in a mental disorder.

[0110] Role of Common SNPs in Brain Expression of CACNA1C

[0111] It is logical to test for an association between the CACNA1C SNP rs1006737 genotype and CACNA1C expression levels, given the strength and scope of the associations between that SNP and risks of multiple psychiatric diseases, as well as numerous behavioral and cognitive endophenotypes. We report such an association in human cerebellum, but not in parietal cortex. These findings have not yet been replicated in a second dataset; while similar genotype-expression datasets exist, they differ from the current data in multiple ways (See Table 3 for summary). In particular, none included parietal cortex and only one included cerebellum.

TABLE 3

Brain eQTL data: brain regions covered by gene expression and SNP microarrays in different studies

Authors	N	Brain regions	Gene expression microarray*	SNP genotype microarray	CB results	PC results
Gibbs JR et al.[22]	150	CB, FC, PONS, TC	GSE15745, Illumina Human Ref-8 v2.0 Expression BeadChip	HumanHap550 beadchips, 2,545,178 SNPs imputed	n.s.	n/a
Colantuoni C et al.[25] (Bigos et al.[24] reported on a subset of data from this study).	269	PFC	GSE30272, Illumina Human 49K Oligo Array	Illumina Infinium II 650K or Illumina Infinium HD Gemini 1M Duo BeadChips	n/a	n/a
Kang HJ et al.[23]	57	16 brain regions	GSE25219, Affymetrix GeneChip Human Exon 1.0 ST Array	Illumina Omni-2.5 Array	n/a	n/a

TABLE 3-continued

Brain eQTL data: brain regions covered by gene expression and SNP microarrays in different studies

Authors	N	Brain regions	Gene expression microarray*	SNP genotype microarray	CB results	PC results
Liu C et al. (this study)	130-150	PC, CB	Affymetrix GeneChip Human Gene 1.0 ST Array	Affymetrix Genome-Wide Human SNP Array 500K, 852,963 SNPs imputed.	rs1006737 associated with down-regulation of CACNA1C expression	n.s.

Brain regions: PFC prefrontal cortex, PC parietal cortex, CB cerebellum, FC frontal cortex, PFC prefrontal cortex, PONS pons, TC temporal cortex.

*The Affymetrix GeneChip Human Gene 1.0 ST Array probe sets 7953049 and 7953050 are near exons 8 and 8a. Illumina's HumanRef-8 BeadChip has one CACNA1C probe, ILMN_1666775, which maps to a region 187 Kb away from exon 8 and 8a. Illumina's Human 49K Oligo Array has probe HEEBO-098-HCA98N4 near exon 8a. In BrainCloud, the corresponding probe is labeled as 37564. The Affymetrix GeneChip Human Exon 1.0 has two probe sets, 3400806 and 3400807, near exon 8 and 8a.

[0112] For the CACNA1C, there is reason to expect different results from different brain regions, because there are differences in relative expression of L-type calcium channels across brain regions. In a mouse model, Schlick et al. found that the ratio of CaV1.2 to CaV1.3 expression was about 1:1 in cortex and hippocampus, while in cerebellum it was 4:1[29]. Detection of expression differences in CaV 1.2 may thus be more feasible in cerebellum than in cortical regions.

[0113] The genome-wide mapping of brain expression and methylation QTLS by Gibbs et al.[30] is the one comparable study that included cerebellum. They reported no association between CACNA1C expression and rs1006737 genotype in cerebellum or in the other three regions tested. However, the Illumina expression platform they used had one probe for all of CACNA1C. Our study and Kang et al.'s[31] QTL mapping of human brain both used an Affymetrix platform with much better CACNA1C coverage. The increased number of probes and regions studied dramatically increased the multiple testing burden in the Kang study, which, combined with the Kang study's small sample size (N=57), left it with low statistical power. None of the probes studied met their criteria for statistical significance of association of SNPs with a gene (gene-wide Bonferroni correction followed by genome-wide Q<0. 1) in any of the 16 brain regions they tested, which did not include cerebellum or parietal cortex.

[0114] Bigos et al.[32] studied the association between CACNA1C genotype and expression in dorsolateral prefrontal cortex, with data that are also included in a later and broader publication by the same group[33]. Using another SNP rs2159100 as proxy for rs1006737, since the two are in complete LD (R^2=1.0), they reported that that the risk allele is associated with increased CACNA1C expression as measured by probe 28032. To review the group's findings, we used BrainCloud (http://braincloud.jhmi.edu/) to retrieve their cis-eQTL data for CACNA1C. There were actually six expression probes for this gene. Two (28032, 36147) showed nominally significant association with rs2159100 (P=0.022 and 0.028 respectively), with the risk allele (A) having increased expression relative to the non-risk allele. However, the expression probe near exon 8a (37564) and the other three probes were not even nominally associated with rs2159100 genotype. In addition, when the Bonferroni correction for multiple testing is applied (0.05/6 tests=0.008), none of the probes reach gene-wide signficance.

[0115] BD in Timothy Syndrome

[0116] TS includes a range of neurological, cognitive and psychiatric symptoms, including autism[1,6,34], and it would appear from this case that BD is one of them. A possible "confluence of rare/uncommon and common genetic variation on the same genetic [disease] loci" has been noted in GWASs[35], which would fit variations in CACNA1C associated with BD. However, we must consider other possibilities: the patient's anoxic brain injury might be considered as an alternative causes. Also, if his symptoms are due to a gain-of-function calcium channel defect, verapamil might be expected to have prevented or treated this defect, as it partially did in his cardiovascular system. Third, BD is a common disease, and could occur in the same patient independently of a rare disease.

[0117] Mania can arise after traumatic brain injury (TBI), but has only rarely been reported after anoxic brain injury[36]. Jorge et al. found a 9.1% incidence of mania after TBI within the first 12 months in 66 patients; but there is little data showing association of mania with a very long interval after head injury, such as the 11 years in this case[37,38]. Most experts conclude that the longer the latency, the more the attribution of mania to the TBI may be questioned.

[0118] If the patient's CACNA1C mutation is responsible for his BD, one might expect that verapamil would also have prevented or treated that condition, as it succeeded in treating his heart condition. However, as noted above, verapamil does not correct the depolarization deficit in TS, or change the intracellular neurotransmitter abnormalities of TS in iPSC cells.[12] Also, the doses used for the management of cardiac conditions are lower than those needed to attain effects in the brain[39], because verapamil has low penetration into the brain, particularly in males

[0119] Implications for BD

[0120] If the same disease is produced by the TS gain-of-function CACNA1C mutation (increased Ca^{++} flux) as is associated with the common CACNA1C BD risk polymorphism, and there is loss of function from the risk allele of the common polymorphism (decreased Ca^{++} flux from reduced gene expression), this would suggest that Ca^{++} flux that strays in either direction from normal can produce deficits in CNS function in humans, possibly as a result of changes in monoamine neurotransmitter synthesis and release. Our own human brain data, with the largest number of CANA1C expression probes so far examined, demonstrates that individuals with the common polymorphic risk allele have decreased CACNA1C expression in at least one brain region (Table 1). These patients may have a degree of decreased Ca^{++}flux due to haploin sufficency, by analogy with the CACNA1C heterozygous graded KO mice of Goonasekera.[15]

[0121] This would suggest that efficacy of CCB treatment in BD patients would differ in patients with and without the risk allele. Because the CACNA1C risk allele is expected to produce loss of calcium channel function, we would expect

BD patients without the risk allele to preferentially respond to CCB treatment. A 2000 review of treatment studies of CCBs in BD[41] concluded that CCBs had not been adequately evaluated as a BD treatment, but evidence that they were generally effective was not present. The reviewed trials had treated BD patients as a single population, but now patient groups can be subdivided according to CACNA1C genotype.

[0122] There is already evidence that CACNA1C genotype can affect response to CCBs in treatment of hypertension[42, 43]. A CCB medication which has less of a blood-brain gradient than verapamil, and which, like roscovitine, succeeds in reversing the TH abnormality in TS iPSC cells might be the preferred choice for a clinical trial.

[0123] These data indicate that patients with bipolar disorder who do not have the risk allele have increased CACNA1C expression, relative to patients with bipolar disorder who have one or two copies of the risk allele. Accordingly, these data indicate that patients with bipolar disorder who do not have the risk allele respond better to treatment with calcium channel blocking drugs.

Example 2

[0124] This example demonstrates a clinical study on the use of calcium channel blockers (CCB) as an augmentation therapy for patients with mania (including schizoaffective manic patients).

[0125] Response to CCB as an augmentation therapy is tested in a series of 90 patients (total for three collaborating centers). Bipolar I or Schizoaffective-manic patients between ages 18 and 50, who are not currently treated with a CCB, do not have a medical contraindication to CCB treatment, and are currently manic and hospitalized, are treated with CCB as an add-on to Treatment As Usual (TAU). Each patient is followed until mania ratings have subsided to <4 on YMRS or two weeks have passed. At the end of the study of 90 patients, genome-wide association genotyping is performed on all patients, and calcium channel gene polymorphisms are tested for correlation with clinical response to CCB treatment.

[0126] Patients for the study are selected as follows:

[0127] Clinical evaluation: At the time of hospital admission or as soon as possible afterward, the patient is invited to consent to the study. They then have a baseline examination to confirm the diagnosis of acute mania, and to obtain a medication history. This includes a clinical examination, review of medical records and treatment history, and interview with relatives and any significant other person who may know the patient's history.

[0128] Mania is diagnosed by satisfying DSM-V criteria for a manic epdisode (DSM-V Bipolar I description), Young Mania Rating Scale [7] (YMRS) score >15, and lifetime history of at least one previous episode of mania (based on medical records or history provided by a reliable source).

[0129] The criteria for excluding an individual from the study are as follows:

[0130] 1) Unwilling or unable to comply with study requirements.

[0131] 2) History of CCB-related toxicity or hypersensitivity.

[0132] 3) Currently treated with a CCB.

[0133] 3) Previous cardiac surgery. Previous diagnosis of certain cardiac (heart) or vascular disorders, including cardiac arrhythmia (heart rhythm problem), atherosclerosis (blockage of blood vessels), congestive heart failure, myocardial infarction, angina, cerebrovascular disease.

[0134] 4) High blood pressure, renal failure.

[0135] 5) Clinically significant hypotension (low blood pressure)

[0136] 6) Women who are pregnant, breastfeeding, or of child-bearing potential and aren't able to agree to medically acceptable contraception.

[0137] 7) Currently active substance abuse or dependence.

[0138] The following treatment protocol is followed:

[0139] Prior to entering the treatment protocol, each participant receives an EKG and comprehensive metabolic panel. Patients with evidence of clinically significant abnormalities in cardiac, hepatic, or renal function, based on these tests or other clinical examination, are excluded.

[0140] Treatment as Usual: The guidelines for treatment as usual (TAU) are well accepted [8], and indicate that the foundation of treatment as usual is to maintain treatment with at least one FDA approved mood stabilizer (including Lithium, certain anticonvulsants, and certain atypical antipsychotics) and to follow the recommendations summarized in the evidence-based stages of Texas Implementation of Medication Algorithm (TIMA) revised guidelines. For all patients in this protocol, TAU requires the presence of at least one FDA-approved mood stabilizer and antidepressant medications are only prescribed in combination with a mood stabilizing drug, as described in the TIMA guidelines.

[0141] All participants receive TAU for manic episode bipolar or schizoaffective disorder [8] either provided by the principal investigator or by co-investigator clinical psychiatrists or psychiatry residents trained and supervised in optimal treatment practices for bipolar disorder within inpatient hospital settings.

[0142] CCB treatment: Nicardipine satisfactorily crosses the blood-brain barrier, and has a long history of clinical use for cardiac arrhythmias, hypertension, and Reynaud phenomenon. The initial dosage is 20 mg po three times daily (60 mg per day). After 3 days, re-evaluation of dosage is made. If clinical state of mania has not improved, and there is not significant reduction in resting and standing blood pressure, dosage is increased to up to 120 mg per day.

[0143] Patient ratings: CGI-S-BP for Mania and for Depression and Young Mania Rating Scale are completed daily by the treating psychiatrist or by a designated collaborating resident or other professionally qualified trained rater.

[0144] Genetic test: The PsychChip under development by Illumina for genome-wide association studies has over 200,000 common SNPs on it, including the CACNA1C risk SNPs and all the SNPs of calcium channel genes that have suggestive association in the literature or have been of interest in psychiatric disorders. All patients with clinical data on their manic episode are genotyped using this PscyhChip.

[0145] Response analysis: The endpoint is either scored on YMRS <4 or 2 weeks in the trial [9]. Survival analysis is performed using the Kaplan-Meier method [10] for the main hypothesis of CACNA1C risk allele. For an exploratory analysis, the Cox proportional hazards model [11] is used, incorporating as covariates all genotypes of Calcium channel genes with $p<0.001$ in meta-analyes of genome-wide association tests of Bipolar disorder.

[0146] Statistical power: This is a preliminary trial, and we may not have enough data on treatment response to estimate power to discriminate two groups of patients.

[0147] Risks/Benefits: The potential benefit of this protocol is improved treatment of mania, a disorder that can be life-threatening to the patient because of risky behavior and because of manic exhaustion, and is difficult to manage with current medication. Common side effects of nicardipine include headache, peripheral edema, dizziness, flushing, asthenia, angina, hypotension, nausea/vomiting, tachycardia, and palpitations. Serious reactions include angina exacerbation, AV block, myocardial infarction, pericarditis, ventricular tachycardia, deep vein thrombosis, thrombocytopenia, and hypersensitivity reaction. The probability of serious reactions is minimized by not including patients with history of cardiovascular disorder or with abnormal measured risk factors for cardiovascular disorder, such as extreme obesity or abnormal LDL cholesterol. Patients with compromised renal or hepatic function, which can be associated with adverse effects of nicardipine, are excluded from the study.

[0148] Clinical Evaluation Protocol:

[0149] Symptom Severity

[0150] Each day, symptom raters examine patient and review nursing and medical records. Based on all this information, mania is rated using CGI-S-BP for Mania and for Depression, and the Young Mania Rating Scale (implemented in integrated version with CARS-M (see below)). The raters are attending or resident doctors on the inpatient service, nurses, or research assistants.

[0151] Clinical Global Impressions of Severity Scale-Bipolar Version (CGI-BP) [12]. The CGI-BP is a modified version of the original CGI designed specifically for use in assessing global illness severity and/or change in patients with bipolar disorder and assesses overall bipolar illness, depression, and mania. While the original CGI has been criticized for lack of reliability, the CGI-BP has been shown to have excellent inter-rater reliability [12]. Not surprisingly, placebo response rates have been shown to be lower with the CGI-BP, compared to the HAM-D or MADRS in bipolar disorder [13]. In contrast to symptom-severity scales, the CGI-BP is an integrated measure of illness severity. In contrast to the MADRS and HAM-D, it is not encumbered by the inability to distinguish improved somatic function (appetite and sleep) from medication-induced adverse events, which is important when studying medications that cause weight gain or somnolence.

[0152] Young Mania Rating Scale (YMRS). An 11-item, clinician-rated measure that queries symptoms of mania.

[0153] Clinician Administered Rating Scale for Mania (CARS-M) [14]. The CARS-M is a reliable and valid 15 item, clinician rated measure of mania The CARS-M incorporates a number of methodological improvements in comparison to more frequently utilized mania rating scales, such as the YMRS. For example, the CARS-M separately assesses the presence of psychotic symptoms (e.g., delusions and hallucinations). Given the overlap in symptoms assessed on the YMRS and CARS-M, an integrated version will be developed and utilized for the current study, minimizing patient burden, yet allowing full scale scores to be derived for each measure.

[0154] When it is clinically feasible, patients undergo a detailed interview scale (Diagnostic Interview for Genetic Studies (DIGS). Data are collected on course of illness including age of onset for bipolar disorder, number of prior episodes, past treatment response, childhood abuse (emotional, physical, sexual), medical conditions, psychoactive substance use, and family history, prior treatment and prior suicide attempt history, including lethality.

[0155] The following references are cited in the above example.

[0156] 1. Gershon E S, Grennan K, Busnello J, Badner J A, Ovsiew F, Memon S et al.: A rare mutation of CACNA1C in a patient with bipolar disorder, and decreased gene expression associated with a bipolar-associated common SNP of CACNA1C in brain. *Mol Psychiatry* 19(8):890-4 (2013).

[0157] 2. Caillard V, Masse G: Treatment of mania by a calcium inhibitor. Preliminary study. *Encephale* 1982, 8: 587-594.

[0158] 3. Casamassima F, Hay A C, Benedetti A, Lattanzi L, Cassano G B, Perlis RH: L-type calcium channels and psychiatric disorders: A brief review. *Am J Med Genet B Neuropsychiatr Genet* 2010, 153B: 1373-1390.

[0159] 4. Pazzaglia P J, Post R M, Ketter T A, Callahan A M, Marangell L B, Frye M A et al.: Nimodipine monotherapy and carbamazepine augmentation in patients with refractory recurrent affective illness. *J Clin Psychopharmacol* 1998, 18: 404-413.

[0160] 5. Bachmeier C, Beaulieu-Abdelahad D, Mullan M, Paris D: Selective dihydropyiridine compounds facilitate the clearance of beta-amyloid across the blood-brain barrier. *Eur J Pharmacol* 2011, 659: 124-129.

[0161] 6. Paris D, Bachmeier C, Patel N, Quadros A, Volmar C H, Laporte V et al.: Selective antihypertensive dihydropyridines lower Abeta accumulation by targeting both the production and the clearance of Abeta across the blood-brain barrier. *Mol Med* 2011, 17: 149-162.

[0162] 7. Young R C, Biggs J T, Ziegler V E, Meyer D A: A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 1978, 133: 429-435.

[0163] 8. Suppes T, Dennehy E B, Hirschfeld R M, Altshuler L L, Bowden C L, Calabrese J R et al.: The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder. *J Clin Psychiatry* 2005, 66: 870-886.

[0164] 9. Berk M, Ng F, Wang W V, Calabrese J R, Mitchell P B, Malhi G S et al.: The empirical redefinition of the psychometric criteria for remission in bipolar disorder. *J Affect Disord* 2008, 106: 153-158.

[0165] 10. Kaplan E L, Meier P: Nonparametric Estimation from Incomplete Observations. *Journal of the American Statistical Association* 1958, 53: 457-481.

[0166] 11. Cox D R, Oakes D: *Analysis of Survival Data.* Chapman & Hall; 1998.

[0167] 12. Spearing M K, Post R M, Leverich G S, Brandt D, Nolen W: Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. *Psychiatry Res* 1997, 73: 159-171.

[0168] 13. Calabrese J R, Bowden C L, Sachs G S, Ascher J A, Monaghan E, Rudd G D: A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J Clin Psychiatry* 1999, 60: 79-88.

[0169] 14. Altman E G, Hedeker D R, Janicak P G, Peterson J L, Davis J M: The Clinician-Administered Rating Scale for Mania (CARS-M): development, reliability, and validity. *Biol Psychiatry* 1994, 36: 124-134.

Example 3

[0170] This example demonstrates the testing of additional SNPs.

[0171] SNPs in Table A are tested for predictive power of response to CCB treatment in patients undergoing the protocol in Example 2, and in other clinical protocols studying treatment response in other affective disorder diagnoses, which are described above in the section entitled "Mood Disorders."

Example 4

[0172] This example demonstrates a method of determining a treatment regimen for a subject with a mood disorder.

[0173] DNA is extracted from whole blood of the subject using known methods. Presence of allele [A] is determined by Sanger sequencing, or by microarray methods, or by PscyhChip, or other known DNA polymorphism detection methods. If Sanger sequencing is used, the primers used are: Forward primer: CCACTTGGCTCTATCAAAGTCT (SEQ ID NO: 50) and Reverse primer: CCTGAGAGACACTGTGAGG (SEQ ID NO: 51). This amplifies a fragment of 100 bp, which contains the SNP rs1006737. Sequencing result can determine whether the subject has A or G allele. Subjects that have one or fewer copies of allele [A] of CACNA1C are treated with a calcium channel blocker.

[0174] The following represents a list of references cited in Example 1.

[0175] 1. Splawski I, et al. Severe arrhythmia disorder caused by cardiac L-type calcium channel mutations. Proceedings of the National Academy of Sciences of the United States of America. 2005; 102:8089-8096.

[0176] 2. Ferreira M A, et al. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. Nat Genet. 2008

[0177] 3. Cross-Disorder Group of the Psychiatric Genomics Consortium Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet. 2013

[0178] 4. Psychiatric GWAS Consortium Bipolar Disorder Working Group et al. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. Nat Genet. 2011

[0179] 5. Jacobs A, Knight B P, McDonald K T, Burke M C. Verapamil decreases ventricular tachyarrhythmias in a patient with Timothy syndrome (LQT8) Heart Rhythm. 2006; 3:967-970.

[0180] 6. Splawski I, et al. Ca(V)1.2 calcium channel dysfunction causes a multisystem disorder including arrhythmia and autism. Proc Natl Acad Sci USA. 2004; 119:19-31.

[0181] 7. Gillis J, et al. Long Q T, syndactyly, joint contractures, stroke and novel CACNA1C mutation: Expanding the spectrum of Timothy syndrome. Am J Med Genet A. 2012; 158A:182-187.

[0182] 8. Barrett C F, Tsien R W. The Timothy syndrome mutation differentially affects voltage- and calcium-dependent inactivation of CaV1.2 L-type calcium channels. 2008; 105:2157-2162.

[0183] 9. Thiel W H, et al. Proarrhythmic defects in Timothy syndrome require calmodulin kinase II. Circulation. 2008; 118:2225-2234.

[0184] 10. Erxleben C, et al. Cyclosporin and Timothy syndrome increase mode 2 gating of CaV1.2 calcium channels through aberrant phosphorylation of S6 helices. Proceedings of the National Academy of Sciences of the United States of America. 2006; 103:3932-3937.

[0185] 11. Depil K, et al. Timothy mutation disrupts the link between activation and inactivation in Ca(V)1.2 protein. J Biol Chem. 2011; 286:31557-31564.

[0186] 12. Pasca S P, et al. Using iPSC-derived neurons to uncover cellular phenotypes associated with Timothy syndrome. Nat Med. 2011; 17:1657-1662.

[0187] 13. Yarotskyy V, Gao G, Peterson B Z, Elmslie K S. The Timothy syndrome mutation of cardiac CaV1.2 (L-type) channels: multiple altered gating mechanisms and pharmacological restoration of inactivation. J Physiol. 2009; 587: 551-565.

[0188] 14. Rosati B, et al. Robust L-type calcium current expression following heterozygous knockout of the Cav1.2 gene in adult mouse heart. J Physiol. 2011; 589:3275-3288.

[0189] 15. Goonasekera S A, et al. Decreased cardiac L-type Ca(2)(+) channel activity induces hypertrophy and heart failure in mice. J Clin Invest. 2012; 122:280-290.

[0190] 16. Nakayama H, et al. Ca2+- and mitochondrial-dependent cardiomyocyte necrosis as a primary mediator of heart failure. J Clin Invest. 2007; 117:2431-2444.

[0191] 17. Liu Y, et al. Meta-analysis of genome-wide association data of bipolar disorder and major depressive disorder. Mol Psychiatry. 2011; 16:2-4.

[0192] 18. Knable M B, Barci B M, Webster M J, Meador-Woodruff J, Torrey E F. Molecular abnormalities of the hippocampus in severe psychiatric illness: postmortem findings from the Stanley Neuropathology Consortium. Mol Psychiatry. 2004; 9544:609-20.

[0193] 19. Torrey E F, Webster M, Knable M, Johnston N, Yolken R H. The stanley foundation brain collection and neuropathology consortium. Schizophr Res. 2000; 44:151-155.

[0194] 20. Torrey E F, et al. Neurochemical markers for schizophrenia, bipolar disorder, and major depression in postmortem brains. Biol Psychiatry. 2005; 57:252-260.

[0195] 21. Johnson W E, Li C, Rabinovic A. Adjusting batch effects in microarray expression data using empirical Bayes methods. Biostatistics. 2007; 8:118-127.

[0196] 22. Leek J T, Storey J D. Capturing heterogeneity in gene expression studies by surrogate variable analysis. PLoS Genet. 2007; 3:1724-1735.

[0197] 23. Konarski J Z, McIntyre R S, Grupp L A, Kennedy S H. Is the cerebellum relevant in the circuitry of neuropsychiatric disorders? J Psychiatry Neurosci. 2005; 30:178-186.

[0198] 24. Andreasen N C, Pierson R. The role of the cerebellum in schizophrenia. Biol Psychiatry. 2008; 64:81-88.

[0199] 25. Schmitt A, et al. Gene expression of NMDA receptor subunits in the cerebellum of elderly patients with schizophrenia. Eur Arch Psychiatry Clin Neurosci. 2010; 260:101-111.

[0200] 26. Smolin B, Karry R, Gal-Ben-Ari S, Ben-Shachar D. Differential expression of genes encoding neuronal ion-channel subunits in major depression, bipolar disorder and schizophrenia: implications for pathophysiology. Int J Neuropsychopharmacol. 2012; 15:869-882.

[0201] 27. Chen C, et al. Two Gene Co-expression Modules Differentiate Psychotics and Controls. Molecular Psychiatry. 2012 Ref Type: In Press.

[0202] 28. Filiou M D, Teplytska L, Otte D M, Zimmer A, Turck C W. Myelination and oxidative stress alterations in the

cerebellum of the G72/G30 transgenic schizophrenia mouse model. J Psychiatr Res. 2012; 46:1359-1365.

[0203] 29. Schlick B, Flucher B E, Obermair G J. Voltage-activated calcium channel expression profiles in mouse brain and cultured hippocampal neurons. Neuroscience. 2010; 167: 786-798.

[0204] 30. Gibbs J R, et al. Abundant quantitative trait loci exist for DNA methylation and gene expression in human brain. PLoS Genet. 2010; 6:e1000952.

[0205] 31. Kang H J, et al. Spatio-temporal transcriptome of the human brain. Nature. 2011; 478:483-489.

[0206] 32. Bigos K L, et al. Genetic variation in CACNA1C affects brain circuitries related to mental illness. Arch Gen Psychiatry. 2010; 67:939-945.

[0207] 33. Colantuoni C, et al. Temporal dynamics and genetic control of transcription in the human prefrontal cortex. Nature. 2011; 478:519-523.

[0208] 34. Bader P L, et al. Mouse model of Timothy syndrome recapitulates triad of autistic traits. Proceedings of the National Academy of Sciences of the United States of America. 2011; 108:15432-15437.

[0209] 35. Panagiotou O A, Evangelou E, Ioannidis J P. Genome-wide significant associations for variants with minor allele frequency of 5% or less—an overview: A HuGE review. Am J Epidemiol. 2010; 172:869-889.

[0210] 36. Calache M J, Bourgeois M. Bipolar affective disorder and anoxic brain damage. Br J Psychiatry. 1990; 157:458-459.

[0211] 37. Jorge R, Robinson R G. Mood disorders following traumatic brain injury. Int Rev Psychiatry. 2003; 15:317-327.

[0212] 38. Shukla D, Devi B I, Agrawal A. Outcome measures for traumatic brain injury. Clin Neurol Neurosurg. 2011; 113:435-441.

[0213] 39. May A. The importance of the heart in cluster headache treatment. Nat Clin Pract Neurol. 2008;4:182-183.

[0214] 40. van Assema D M, et al. P-glycoprotein function at the blood-brain barrier: effects of age and gender. Mol Imaging Biol. 2012; 14:771-776.

[0215] 41. Levy N A, Janicak P G. Calcium channel antagonists for the treatment of bipolar disorder. Bipolar Disord. 2000; 2:108-119.

[0216] 42. Kamide K, et al. Genetic polymorphisms of L-type calcium channel alpha1C and alpha1D subunit genes are associated with sensitivity to the antihypertensive effects of L-type dihydropyridine calcium-channel blockers. Circ J. 2009; 73:732-740.

[0217] 43. Bremer T, Man A, Kask K, Diamond C. CACNA1C polymorphisms are associated with the efficacy of calcium channel blockers in the treatment of hypertension. Pharmacogenomics. 2006; 7:271-279

[0218] 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.

[0219] 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.

[0220] 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 and each endpoint, unless otherwise indicated herein, and each separate value and endpoint is incorporated into the specification as if it were individually recited herein.

[0221] 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.

[0222] Preferred embodiments of this invention are described herein, including the best mode known to the inventors 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 inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend 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.

SEQUENCE LISTING

The patent application contains a lengthy "Sequence Listing" section. A copy of the "Sequence Listing" is available in electronic form from the USPTO web site (http://seqdata.uspto.gov/?pageRequest=docDetail&DocID=US20160040240A1). An electronic copy of the "Sequence Listing" will also be available from the USPTO upon request and payment of the fee set forth in 37 CFR 1.19(b)(3).

1. A method of treating a mood disorder in a subject, comprising

administering to the subject a calcium channel blocker (CCB) when no more than one copy of allele [A] is present in the cells of the sample;

wherein the method comprises the step of analyzing a sample obtained from the subject for the presence of an allele [A] of CACNA1C, wherein allele [A] comprises the sequence of polymorphic marker rs1006737 before the step of administering the CCB,

or

wherein the subject is a subject from which a sample was obtained, wherein the copy number of allele [A] of CACNA1C, comprising the sequence of polymorphic marker rs1006737, in the sample has been analyzed.

2. (canceled)

3. A method of determining a treatment regimen for a subject with a mood disorder, comprising:

a) analyzing a sample obtained from a subject with a mood disorder for the presence of allele [A] of CACNA1C, wherein allele [A] comprises the sequence of the polymorphic marker rs1006737; and

b) selecting a treatment regimen comprising administration of a calcium channel blocker (CCB), when no more than one copy of allele [A] is present in the cells of the sample.

4. The method of claim **1**, wherein the subject is heterozygous for allele [A].

5. (canceled)

6. The method of claim **1**, comprising administering to the subject a CCB when allele [A] is absent from the cells of the sample, and optionally, comprising selecting a treatment regimen comprising administration of a CCB, when allele [A] is absent from the sample.

7. (canceled)

8. The method of claim **1**, wherein the CCB is selected from the group consisting of amlodipine, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nisoldipine and verapamil.

9. (canceled)

10. The method of claim **1**, wherein the mood disorder is a depressive disorder, optionally, a bipolar disorder.

11. (canceled)

12. The method of claim **10**, wherein the bipolar disorder is bipolar I, bipolar II, cyclothymia, or biopolar disorder not otherwise specified.

13. The method of claim **1**, wherein the sample comprises DNA from a blood cell of the subject or comprises DNA from the saliva of the subject.

14. (canceled)

15. The method of claim **1**, further comprising analyzing the sample for CACNA1C expression.

16. The method of claim **1**, further comprising genotyping the sample for one or more of the polymorphic markers listed in Table A.

17. The method of claim **1**, further comprising administering a therapeutic compound other than a CCB.

18. The method of claim **17**, wherein the therapeutic compound is a mood stabilizer.

19. The method of claim **18**, wherein the mood stabilizer is lithium, an anticonvulsant, or an atypical antipsychotic.

20. The method of claim **3**, wherein the treatment regimen further comprises administration of a therapeutic compound other than a CCB.

21. The method of claim **20**, wherein the therapeutic compound is a mood stabilizer.

22. The method of claim **21**, wherein the mood stabilizer is lithium, an anticonvulsant, or an atypical antipsychotic.

23.-**26**. (canceled)

27. A kit comprising a nucleic acid molecule which hybridizes to or specifically binds to a region of SEQ ID NO: 1 which is about 20 basepairs (bp) to about 1000 bp upstream or downstream of position 270344 of SEQ ID NO: 1.

28. The kit of claim **27**, comprising a nucleic acid molecule of SEQ ID NO: 50 and a nucleic acid molecule of SEQ ID NO: 51.

* * * * *