METHODS OF DIAGNOSING AND TREATING TOURETTE SYNDROME

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority to the following four United States Provisional Patent Applications, each filed on September 8. 2015: 62/215,628; 62/215,633; 62/215,636; and 62/215,673, each of which is incorporated herein by reference in its entirety.

FIELD

[002] This application relates to the treatment of Tourette syndrome with nonselective activators of metabotropic glutamate receptors (mGluRs) and of diagnosis and treatment of Tourette syndrome in subjects having genetic alterations, such as copy number variations (CNVs), in one or more mGluR network genes.

BACKGROUND

[003] Tourette syndrome (TS) is a neurologic disorder that is characterized by tics, which are involuntary vocalizations or repetitive, purposeless movements. It is estimated that up to 200,000 Americans have the most severe form of TS, and as many as one in 100 Americans show milder and less complex TS symptoms that may include chronic motor or vocal tics, see NIH Handbook on Tourette Syndrome (2012). The prevalence of TS is estimated to be 0.3% in US children aged 6-17 years, although there are suggestions that this may be an underestimation of its prevalence, see Cohen S, et al. Neurosci Biobehav Rev. 37(6): 997–1007 (2013).

[004] The onset of symptoms of TS is usually between 3 and 9 years of age, with approximately 3-4 times more males affected than females. For many patients, TS is a chronic, lifetime disease with a peak of symptoms in the teen years. Simple tics in TS may include eye blinking, head jerking, or repetitive grunting, while complex tics involve several muscle groups and can include hopping, twisting, or vocalization of words or phrases. Tics can be disabling, such as those that involve hitting oneself, swearing, or repeating the words or phrases of others. It is estimated that 10%-15% of patients with TS have a progressive or disabling disease course that lasts into adulthood, see NIH Handbook on Tourette Syndrome (2012).

[005] In addition to tics, patients with TS often experience other neurobehavioral symptoms such as hyperactivity and impulsivity (such as attention deficit hyperactivity disorder [ADHD]), difficulties with reading and schoolwork, obsessive-compulsive thoughts, and repetitive behaviors. It has been estimated that 90% of patients with TS suffer from comorbid neuropsychiatric disorders, most commonly ADHD and obsessive-compulsive disorder (OCD) (Cohen 2013).

[006] Individuals affected by both TS and ADHD are at a much greater risk for academic and social impairment.

[007] Diagnosis of TS may be based on patient history and presence of tics for a sustained period. In children and adolescents, the Yale Global Tic Severity Scale may be used as a clinician rating of tic severity, which evaluates the number, frequency, intensity, complexity, and interference of motor and vocal tics, see Storch et al., Psychol. Assessment. 17(4):486-491. Because of the high incidence of OCD in patients with TS, the Children's Yale-Brown Obsessive Compulsive Scale may be used to evaluate

obsessive-compulsive symptoms severity in children and adolescents with TS, see Scahill et al, J Am. Acad. Child Adolesc. Psychiatry. 36(6):844-852 (1997).

[008] There is currently no medication that is helpful to all patients with TS. While neuroleptic drugs (i.e., antipsychotics) have been effective for treatment of tics in some patients, these medications are associated with significant side effects, and these medications do not entirely eliminate tic symptoms. In addition, treatment of neurobehavioral disorders associated with TS, such as ADHD, may be complicated as some medications used to treat ADHD are contraindicated in patients with TS (see Prescribing Information for Ritalin) (2013). Therefore, new treatments are needed to treat the spectrum of symptoms of TS, including tics and neurobehavioral disorders.

SUMMARY

[009] In accordance with the description, the inventors have studied the genotypes of over 90 patients diagnosed with Tourette syndrome (TS) and have found that these patients possess genetic alterations in one or more metabotropic glutamate receptor (mGluR) network genes at a significantly higher frequency than historical control patients. The frequency of genetic alterations in mGluR network genes was substantially higher in this TS population than in control populations that did not have other neuropsychological disorders.

[0010] Thus, provided herein are methods of treating TS in a subject comprising administering an effective amount of a nonselective activator of metabotropic glutamate receptors (mGluRs) to a subject, thereby treating TS. In some embodiments the subject has at least one genetic alteration in an mGluR network gene, such as a copy number variation (CNV). In some embodiments, the subject to be treated has been diagnosed with TS by any method known in the art for diagnosing TS, including meeting the criteria

in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) for a diagnosis of Tourette's Syndrome. In some embodiments, a diagnosis of TS is made when it is discovered that the subject has at least one genetic alteration in an mGluR network gene. In some embodiments, a diagnosis of TS is made when it is discovered that the subject has at least one genetic alteration in an mGluR network gene and when the subject has at least one symptom of TS including, but not limited to, a motor tic, a vocal tic, a motor and vocal tic.

[0011] Also provided herein are methods of treating TS comprising administering an effective amount of a nonselective activator of metabotropic glutamate receptors (mGluRs) to a subject that has at least one genetic alteration in an mGluR network gene, such as a CNV, thereby treating TS. In some embodiments, where the subject has a CNV in an mGluR network gene, the CNV is a duplication or deletion.

[0011a] In one aspect of the disclosure, there is provided a use of fasoracetam in the preparation of a medicament for treating Tourette syndrome (TS) in a subject,wherein an effective amount of fasoracetam is to be administered to the subject, thereby treating TS.

[0012] In some embodiments, the invention comprises a method a subject having a motor and/or vocal tic comprising administering an effective amount of a nonselective activator of metabotropic glutamate receptors (mGluRs), thereby treating TS. In some embodiments, the subject also has at least one genetic alteration in an mGluR network gene.

[0013] Also provided are methods of treating TS in a subject comprising obtaining results from a genetic screen that determines whether a subject has a genetic alteration in an mGluR network gene, and, if the results show that the subject has at least

one genetic alteration in an mGluR network gene, treating the subject by administering an effective amount of a nonselective activator of mGluRs.

[0014] In some embodiments of the above methods, the nonselective activator of mGluRs is fasoracetam, such as fasoracetam monohydrate (NS-105 or NFC-1). In some

embodiments the fasoracetam is administered at a dose of 50 mg, 100mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, or 400 mg, wherein the dose is administered once, twice, or three times daily. In some embodiments, fasoracetam is administered at a dose of 50-400 mg, 100-400 mg, or 200-400 mg, and administered once, twice, or three times daily. In some embodiments, the fasoracetam is administered at a dose of 200-400 mg, such as 200 mg, 300 mg, or 400 mg, and administered twice daily.

[0015] In some embodiments the method comprises considering results of a screen to determine whether the subject has a genetic alteration such as a CNV in an mGluR network gene. In some embodiments of the above methods, the subject has a CNV in at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 mGluR network genes. In some embodiments a CNV in an mGluR network gene is determined by obtaining a nucleic acid-comprising sample from the subject and subjecting the sample to a screen that assesses CNVs in at least 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, or all of Tier 1 mGluR network genes. In some embodiments a CNV in an mGluR network gene is determined by obtaining a nucleic acid-comprising sample from the subject and subjecting the sample to a screen that assesses CNVs in at least 50, at least 100, at least 150, at least 175, or all of Tier 2 mGluR network genes. In some embodiments a CNV in an mGluR network gene is determined by obtaining a nucleic acid sample from the subject and subjecting the sample to a screen that assesses CNVs in at least 50, at least 100, at least 200, at least 300, at least 400, at least 500, or all of Tier 3 mGluR network genes. In some embodiments the screen does not assess CNVs in one or more of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, or GRM8. In certain embodiments the subject does not have a CNV in one or more of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, or GRM8.

[0016] In some embodiments of the above methods, the TS is one or more of persistent (chronic) motor tic disorder, persistent (chronic) vocal tic disorder, or provisional tic disorder. In some embodiments, the methods reduce the frequency and/or severity of tics in the subject. In some embodiments, the methods reduce other behavioral symptoms such as inattentiveness, hyperactivity, and/or impulsiveness. In some embodiments, the methods also comprise assessing symptoms such as the frequency, type (e.g. verbal or motor), and/or severity of tics in the subject, as well as inattentiveness, hyperactivity, and/or impulsiveness during or after administration, for example, to determine if one or more of these symptoms has been reduced in the subject. In some methods, such assessment may be performed based on the Yale-Brown Pediatric Obsessive-Compulsive Scale and/or the Tourette's Clinical Rating Scale. In some embodiments, the methods further comprise obtaining a clinical global impression of severity or improvement for the subject during or after administration. In some embodiments, the methods may improve clinical global improvement (CGI) scores in the subject.

[0017] In some embodiments the subject is a pediatric or adolescent subject, such as between the ages of 5 and 17, 5 and 8, 8 and 17, 8 and 12, 12 to 18, 13 to 18, or 12 and 17. In other embodiments the subject is an adult.

[0018] In some embodiments of the above methods, the nonselective activator of mGluRs is administered in combination with another pharmaceutical, such as an antipsychotic agent, or non-pharmaceutical therapy. The non- pharmaceutical therapy may comprise brain stimulation, such as vagus nerve stimulation, repetitive transcranial magnetic stimulation, magnetic seizure therapy, or deep brain stimulation.

[0019] In some embodiments, tic symptoms in the TS subject, such as frequency of tics or degree of movement for movement-based tics or the intensity of language-based tics, are reduced in the subject. In some embodiments, symptoms of inattentiveness, hyperactivity, and/or impulsiveness are reduced in the subject.

[0020] Also provided herein are methods for diagnosing TS in a subject comprising isolating a nucleic-acid comprising sample from a subject, analyzing the sample for the presence or absence of a genetic alteration in at least one mGluR network genes, and diagnosing TS if the subject has at least one genetic alteration in a mGluR network gene. Also provided are methods for diagnosing TS in a subject comprising isolating a nucleic-acid comprising sample from a subject, isolating nucleic acid from the sample, analyzing the nucleic acid for the presence or absence of a genetic alteration in at least one mGluR network genes, and diagnosing TS if the subject has at least one genetic alteration in a mGluR network gene. Provided as well are methods for identifying a subject as having TS comprising obtaining a sample from a patient, optionally isolating nucleic acid from the sample, optionally amplifying the nucleic acid, and analyzing the nucleic acid in the sample for the presence or absence of a genetic alteration, such as a CNV, in at least one mGluR network gene, wherein the subject is identified as having TS if at least one genetic alteration, such as a CNV, in an mGluR network gene is detected. Additionally, provided are methods for diagnosing TS in a subject comprising analyzing genetic information about one or more mGluR network genes, comparing the subject's information to a control subject that does not have TS, and diagnosing TS if the genetic information suggests that the subject has at least one genetic alteration in an mGluR network gene.

[0020a] In another aspect of the disclosure, there is provided a method for diagnosing Tourette syndrome (TS) in a subject comprising analyzing a sample comprising nucleic acid which has been isolated from a subject, for the presence or absence of a copy number variation (CNV) in at least one metabotropic glutamate receptor (mGluR) network genes, and diagnosing TS if the subject has at least one CNV in an mGluR network gene.

[0021] Provided herein also are methods of confirming a diagnosis of TS in a subject comprising: obtaining a nucleic acid-comprising sample from a subject diagnosed with TS by a method that does not comprise detecting or analyzing genetic alterations in mGluR network genes; optionally amplifying the nucleic acid in the sample; and determining whether the subject has at least one genetic alteration, such as a CNV, in an mGluR network gene, and confirming a diagnosis of TS if the subject has at least one genetic alteration in an mGluR network gene.

[0022] In any of the above methods, the analysis for the presence or absence of at least one genetic alteration in an mGluR network gene may comprise microarrays, whole genome sequencing, exome sequencing, targeted sequencing, FISH, comparative genomic hybridization, genome mapping, or other methods using next-generation sequencing, Sanger sequencing, PCR, or TaqMan technologies.

[0023] In some embodiments, the subject has CNVs in one, two, or more mGluR network genes. In some embodiments, the methods comprise detecting CNVs in mGluR network genes by subjecting the sample to a screen that assesses CNVs in at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 mGluR network genes. In some embodiments, CNVs in mGluR network genes are determined by subjecting the sample to a screen that assesses CNVs in at least 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, or all of Tier 1 mGluR network genes. In some embodiments, CNVs in mGluR network genes are determined by subjecting the sample to a screen that assesses CNVs in at least 50, at least 100, at least 150, at least 175, or all of Tier 2 mGluR network genes. In some embodiments, CNVs in mGluR network genes are determined by subjecting the sample to a screen that assesses CNVs in at least 50, at least 100, at least 200, at least 300, at least 400, at least 500, or all of Tier 3 mGluR network genes.

[0024] In some embodiments of the above methods, the TS is one or more of persistent (chronic) motor tic disorder, persistent (chronic) vocal tic disorder, or provisional tic disorder. In some embodiments, the subject is a pediatric or adolescent subject, such as a subject between the ages of 5 and 17, 5 and 8, 8 and 17, 8 and 12, 12 to 18, 13 to 18, or 12 and 17. In other embodiments, the subject is an adult subject.

[0025] In some embodiments, the screening method for determining the presence or absence of at least one mGluR network gene genetic alteration comprises microarrays, whole genome sequencing, exome sequencing, targeted sequencing, FISH, comparative genomic hybridization, genome mapping, or other methods using next-generation sequencing, Sanger sequencing, PCR, or TaqMan technologies.

[0026] In some embodiments, the subject is not assessed for genetic alterations or CNVs in one or more of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, and GRM8. In some embodiments, the subject does not have CNVs in one or more of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, and GRM8. In some embodiments, the subject does not have CNVs in any of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, and GRM8.

[0027] In any of the methods and embodiments described in the preceding paragraphs of this Summary, the subject may have TS as well as one or more comorbid conditions such as attention-deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder, anxiety disorder, autism, a mood disorder, schizophrenia, obsessive compulsive disorder (OCD), difficulty controlling anger, disruptive behavior symptoms, dermatillomania, a developmental disorder, a co-morbid movement disorder, or depression. In other cases, the subject does not have one or more of ADHD, ODD, conduct disorder, anxiety disorder, phobia, autism, a mood disorder,

schizophrenia, or depression. In yet other cases, the subject does not have any of ADHD, ODD, conduct disorder, anxiety disorder, phobia, autism, a mood disorder, schizophrenia, obsessive compulsive disorder (OCD), difficulty controlling anger, disruptive behavior symptoms, dermatillomania, a developmental disorder, a co-morbid movement disorder, or depression.

[0028] In one embodiment, a method for diagnosing an mGluR-associated disorder is provided, wherein a subject is diagnosed with an mGluR-associated disorder if at least one genetic alteration in an mGluR network gene is detected.

[0029] Additional objects and advantages will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice. The objects and advantages will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims.

[0030] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the claims.

[0031] The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate one (several) embodiment(s) and together with the description, serve to explain the principles described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] **Figure 1** shows the mGluR network genes included in the Tier 1 gene set. These genes have 2 degrees of protein-protein interaction with mGluR genes (GRM1-8) based on the Cytoscape Human Interactome, which is software for integrating biomolecular interaction networks with high-throughput data (as described in Shannon P (2003) Genome Research 13:2498-2504). The Tier 1 gene set includes 76 genes. The

exact location for each gene in Tier 1 is listed in both the Human Genome version 18 (hg18) and Human Genome version 19 (hg19). In addition, the exact gene location plus 500 kilobase (i.e., the range from 500 kilobase before and 500 kilobase after the gene of interest) is listed for hg19. The start single nucleotide polymorphism (StartSNP) (i.e., the SNP located 500 kilobases before the gene of interest) and the EndSNP (i.e., the SNP located 500 kilobases after the gene of interest) are also listed. Genes of the mGluRs themselves are noted as "GRM." The expanded regions (i.e., 500kg up and down stream) frequently harbor regulatory elements and if impacted by a CNV, can have the same impact on the gene expression and function as a CNV residing in the gene sequence itself.

[0033] **Figure 2** shows the mGluR network genes included in the Tier 2 gene set. These genes have 2 degrees of protein-protein interaction with mGluR genes (GRM1-8) based on the Cytoscape Human Interactome but exclude genes from Tier 1. The Tier 2 gene set includes 197 genes. The exact location for each gene in Tier 2 is listed in both the Human Genome version 18 (hg18) and Human Genome version 19 (hg19). In addition, the exact gene location plus 500 kilobase (i.e., the range from 500 kilobase before and 500 kilobase after the gene of interest) is listed for hg19. The start single nucleotide polymorphism (StartSNP) (i.e., the SNP located 500 kilobases before the gene of interest) and the EndSNP (i.e., the SNP located 500 kilobases after the gene of interest) in hg19 are also listed.

[0034] **Figure 3** shows genes within the Tier 3 gene set. Genes with reciprocal gene querying with 2 degrees of protein-protein interaction with mGluR genes based on Cytoscape Human Interactome are included. Genes contained within Tiers 1 and 2 are excluded from Tier 3. The Tier 3 gene set includes 599 genes. The exact location for each

gene in Tier 3 is listed in both the Human Genome version 18 (hg18) and Human Genome version 19 (hg19). In addition, the exact gene location plus 500 kilobase (i.e., the range from 500 kilobase before and 500 kilobase after the gene of interest) is listed for hg19. The StartSNP (i.e., the SNP located 500 kilobases before the gene of interest) and the EndSNP (i.e., the SNP located 500 kilobases after the gene of interest) in hg19 are also listed.

[0035] **Figure 4** shows the number of copy number variation (CNV) calls containing an mGluR network gene within the samples from the 95 TS patients who were fully genotyped. Note that some patients had more than one CNV call that contained an mGluR network gene.

[0036] **Figure 5** shows the percentage of fully-genotyped patients with TS who had a CNV within Tier 1, Tiers 1 + 2, or Tiers 1 + 2 + 3 mGluR network gene sets.

DESCRIPTION OF THE EMBODIMENTS

I. Definitions

[0037] In addition to definitions included in this sub-section, further definitions of terms are interspersed throughout the text.

[0038] In this invention, "a" or "an" means "at least one" or "one or more," etc., unless clearly indicated otherwise by context. The term "or" means "and/or" unless stated otherwise. In the case of a multiple-dependent claim, however, use of the term "or" refers back to more than one preceding claim in the alternative only.

[0039] An "mGluR" or metabotropic glutamate receptor refers to one of eight glutamate receptors expressed in neural tissue named mGluR1, mGluR2, mGluR3, mGluR4, mGluR5, mGluR6, mGluR7, and mGluR8. Their genes are abbreviated GRM1 to GRM8. The mGluR proteins are G-protein-coupled receptors. They are typically

placed into three sub-groups, Group I receptors including mGluR1 and mGluR5 are classed as slow excitatory receptors. Group II includes mGluR2 and mGluR3. Group III includes mGluR4, mGluR6, mGluR7, and mGluR8. Groups II and III are classed as slow inhibitory receptors. The mGluRs are distinguished from the ionotropic GluRs or iGluRs, which are ion channel-associated glutamate receptors and are classed as fast excitatory receptors.

[0040] An "mGluR network gene," for purposes of this invention, comprises not only the mGluR genes GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, and GRM8, but also each of the other genes listed herein in Figs. 1-3 as well as the regions of DNA that regulate the genes listed in Figs 1-3. In addition, "mGluR network proteins" are the proteins encoded by the mGluR network genes.

[0041] The mGluR network genes are grouped into three subsets: Tier 1, Tier2, and Tier 3. (See Figs. 1-3.) Tier 1 mGluR network genes, shown in Fig. 1, comprise 76 genes, including some GRM genes themselves as well as a number of other genes. The Tier 2 mGluR network genes, shown in Fig. 2, comprise 197 genes, and exclude the Tier 1 genes.

[0042] Tiers 1 and 2 together are included in the "primary mGluR network." The "primary network" of mGluR genes also includes the genes 4-Sep, LOC642393, and LOC653098, for a total of 276 genes. There are presently technical difficulties in assessing the 4-Sep, LOC642393, and LOC653098 genes. Thus, they are not included in the genes of Tiers 1 and 2, although they are included in the primary network of genes of the present invention. The genes of Tier 1 and Tier 2 differ in that alterations in Tier 1 genes had been documented in previous genotyping studies of subjects suffering from mental disorders.

[0043] Tier 3 mGluR network genes, shown in Fig. 3, comprise 599 genes that are in the distal part of the mGluR network based on the merged human interactome provided by the Cytoscape Software (Shannon P et al. (2003) Genome Research 13:2498-2504), and exclude the Tier 1 and Tier 2 genes. The Tier 3 genes are thus part of the "distal mGluR network." In addition to the Tier 3 genes, the genes LOC285147, LOC147004, and LOC93444 are included in the "distal mGluR network," although they were not assessed in the present study and are not included in Tier 3 due to technical difficulties in assessing genetic alterations in these genes.

[0044] A "genetic alteration" as used herein means any alteration in the DNA of a gene, or in the DNA regulating a gene. A genetic alteration, for example, may result in a gene product that is functionally changed as compared to a gene product produced from a non-altered DNA. A functional change may be differing expression levels (up-regulation or down-regulation) or loss or change in one or more biological activities, for example. A genetic alteration includes without limitation, copy number variations (CNVs), single nucleotide variants (SNVs), also called single nucleotide polymorphisms (SNPs) herein, frame shift mutations, or any other base pair substitutions, insertions, and deletions or duplications.

[0045] A "copy number variation" or "CNV" is a duplication or deletion of a DNA segment encompassing a gene, genes, segment of a gene, or DNA region regulating a gene, as compared to a reference genome. In some embodiments, a CNV is determined based on variation from a normal diploid state. In some embodiments, a CNV represents a copy number change involving a DNA fragment that is 1 kilobase (kb) or larger. CNVs described herein do not include those variants that arise from the insertion/deletion of transposable elements (e.g., 6-kb KpnI repeats). The term CNV therefore encompasses

terms such as large-scale copy number variants (LCVs; Iafrate et al. 2004), copy number polymorphisms (CNPs; Sebat et al. 2004), and intermediate-sized variants (ISVs; Tuzun et al. 2005), but not retrotransposon insertions.

[0046] A "CNV deletion" or "deletion CNV" or similar terms refer to a CNV in which a gene, DNA segment regulating a gene, or gene segment is deleted. A "CNV duplication" or "duplication CNV" or similar terms refer to a CNV in which a gene, DNA segment regulating a gene, or gene segment is present in at least two, and possibly more than two, copies in comparison with the single copy found in a normal reference genome.

[0047] A "sample" refers to a sample from a subject that may be tested, for example, for presence of a CNV in one or more mGluR network proteins, as described herein. The sample may comprise cells, and it may comprise body fluids, such as blood, serum, plasma, cerebral spinal fluid, urine, saliva, tears, pleural fluid, and the like.

[0048] Tourette syndrome is described in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5 2013) as a disorder characterized by the presence of both multiple motor and one or more vocal tics with symptoms that have persisted for more than one year. Tics are sudden, rapid, recurrent, nonrhythmic motor movement or vocalization. Typically, symptoms appear before age 18. The term "Tourette syndrome" as used herein includes each of: "persistent (chronic) motor tic disorder," "persistent (chronic) vocal tic disorder," "provisional tic disorder," and "tic disorder." A Tourette syndrome patient may have both motor and vocal tic symptoms that have been present for at least a year. A patient with a "tic disorder," however, may have only motor or only vocal tics. A patient with "persistent (chronic) motor tic disorder" may have only motor tics. A patient with "persistent (chronic) vocal tic

disorder" may have only vocal tics. A patient with "provisional tic disorder" may have symptoms for less than one year.

[0049] Patients with TS may also have inattention, hyperactivity, anxiety, mood, and sleep disturbances. Currently, TS may be diagnosed using one or more rating scales, such as, Yale Global Tic Severity Scale, as described in Storch 2005.

[0050] The terms "subject" and "patient" are used interchangeably to refer to a human.

[0051] The terms "pediatric subject" or "pediatric patient" are used interchangeably to refer to a human less than 18 years of age. An "adult patient" or "adult subject" refers to a human 18 years of age or older. An "adolescent patient" or "adolescent subject" is a subject typically about 12 to 18, such as 12 to 17 or 13 to 18, years old.

II. Methods of Diagnosing Tourette's Syndrome

[0052] In some embodiments, the invention comprises a method of diagnosing TS in a subject comprising analyzing the genetic information of the subject to determine whether the subject has a genetic variation in at least one mGluR network gene, and diagnosing the subject as having TS if a genetic variation is found. In some embodiments, the subject has TS but does not have ADHD, oppositional defiant disorder (ODD), conduct disorder, anxiety disorder, phobia, autism, a mood disorder, schizophrenia, obsessive compulsive disorder (OCD), difficulty controlling anger, disruptive behavior symptoms, dermatillomania, another movement disorder, a developmental disorder, or depression. In some embodiments, the subject has TS and also one or more of ADHD, conduct disorder, anxiety disorder, phobia, autism, a mood disorder, schizophrenia, obsessive compulsive disorder (OCD), difficulty controlling anger, disruptive behavior

symptoms, dermatillomania, another movement disorder, a developmental disorder, and depression. In some embodiments, the subject has both TS and ADHD.

[0053] "Developmental disorders" herein include, for example, those classified under the International Classification of Diseases 9th Ed. (World Health Organization) under codes 299.80, 299.90, 315.2, 315.39, 315.4, 315.5, 315.8, and 315.9, and may affect behaviors such as learning, coordination, and speech. "Dermatillomania" is also called skin picking disorder or excoriation, and is a disorder involving excessive picking at one's own skin to the extent of causing damage, and includes picking at normal skin as well as at real or imagined skin defects such as moles, freckles, or acne.

[0054] In other embodiments, the invention encompasses confirming a diagnosis of TS in a subject. As used herein, "confirming a diagnosis of TS" means diagnosing a subject who has already been diagnosed with TS. In some embodiments, the method of confirming a diagnosis of TS comprises analyzing the genetic information of a subject that has been diagnosed as having TS by a method that does not comprise analyzing mGluR network genes, to determine whether the subject has a genetic variation in at least one mGluR network gene, and confirming the diagnosis of TS if a genetic variation in at least one mGluR network gene is found. In some embodiments, a screen for the presence of mGluR network gene variations is one of two or more tests or evaluations that are performed to confirm a diagnosis in a subject. In some embodiments, the subject has TS but does not have ADHD, ODD, conduct disorder, anxiety disorder, phobia, autism, a mood disorder, or depression. In some embodiments, the subject has TS and also one or more of ADHD, ODD, conduct disorder, anxiety disorder, autism, a mood disorder, phobia, and depression. In some embodiments the subject has both TS and ADHD.

[0055] In other embodiments, the invention comprises confirming a diagnosis of TS in a subject who does not have ADHD, ODD, conduct disorder, anxiety disorder, autism, a mood disorder, phobia, or depression, comprising analyzing the genetic information of a subject that has been diagnosed as having TS by a method that does not comprise analyzing mGluR network genes, to determine whether the subject has a genetic variation in at least one mGluR network gene, and confirming the diagnosis of TS if a genetic variation in at least one mGluR network gene is found.

[0056] In one embodiment, TS is diagnosed and/or confirmed if at least one CNV, SNV, frameshift mutation, or any other base pair substitution, insertion, deletion or duplication in an mGluR network gene is detected. In other embodiments, TS is diagnosed and/or confirmed if at least one CNV, SNV, frameshift mutation, or any other base pair substitution, insertion, or deletion in a Tier 1 mGluR network gene is detected. In another embodiment, TS is diagnosed and/or confirmed if at least one CNV, SNV, frameshift mutation, or any other base pair substitution, insertion, or deletion in a Tier 2 mGluR network gene is detected. In still other embodiments, TS is diagnosed and/or confirmed if at least one CNV, SNV, frameshift mutation, or any other base pair substitution, insertion, or deletion in a Tier 3 mGluR network gene is detected.

[0057] A diagnosis or confirmation of diagnosis of TS may be based or confirmed on finding a genetic alteration in a Tier 1, Tier 2, and/or Tier 3 mGluR network gene. The genetic alteration may be a CNV. The CNV may be a duplication or deletion of a region of DNA that contains some or all of the DNA encoding and controlling/regulating an mGluR network gene. In another embodiment, the diagnosis or confirmation of diagnosis of TS is made in a patient who does not have ADHD, ODD, conduct disorder, anxiety disorder, autism, a mood disorder, phobia, or depression. In

some embodiments, the diagnosis or confirmation of diagnosis of TS is made in a patient who has TS as well as one or more of ADHD, ODD, conduct disorder, anxiety disorder, autism, a mood disorder, autism, a mood disorder, phobia, and depression.

[0058] In some embodiments, the diagnosis or confirmation of diagnosis of TS is based on a finding that the copy number of an mGluR network gene deviates from the normal diploid state. In some embodiments, the diagnosis or confirmation of diagnosis of TS is based on a copy number of zero or one, which indicates a CNV deletion. In some embodiments, the diagnosis or confirmation of diagnosis of TS is based on a copy number of three or greater, which indicates a CNV duplication. In another embodiment, the diagnosis or confirmation of diagnosis of TS is made in a patient who does not have ADHD, ODD, conduct disorder, anxiety disorder, autism, a mood disorder, phobia, or depression by the presence of a copy number of zero or one, by a copy number of three or greater, or by any deviation from the diploid state.

[0059] In one embodiment, a more severe form of TS is diagnosed if at least two CNVs in mGluR network genes are detected. In one embodiment, a more severe form of TS in a patient who does not have ADHD, ODD, conduct disorder, anxiety disorder, autism, a mood disorder, phobia, or depression is diagnosed if at least two CNVs in mGluR network genes are detected.

[0060] In one embodiment, a method of diagnosing and/or confirming TS comprises: obtaining a nucleic acid-containing sample from a subject; optionally amplifying the nucleic acid; optionally labeling the nucleic acid sample; applying the nucleic acid to a solid support that comprises one or more nucleic acids of mGluR network genes, wherein the nucleic acids optionally comprise SNVs of mGluR network genes; removing any unbound nucleic acid sample; and detecting any nucleic acid that has

bound to the nucleic acid on the solid support, wherein the subject is diagnosed or confirmed as having TS if bound nucleic acids are detected. In one embodiment the method further comprises comparing any bound nucleic acids to a standard or control and diagnosing or confirming TS if the analysis finds that the test sample is different from the control or standard. In another embodiment of this method, the patient with TS does not have ADHD, ODD, conduct disorder, anxiety disorder, autism, a mood disorder, autism, a mood disorder, phobia, or depression. In another embodiment, the TS patient also has one or more of ADHD, ODD, conduct disorder, anxiety disorder, autism, a mood disorder, phobia, or depression.

[0061] In each diagnostic, confirming, and treatment method of the invention, the disorder may be TS, persistent (chronic) vocal tic disorder, persistent (chronic) motor tic disorder, or provisional tic disorder. In each diagnostic, confirming, and treatment method of the invention, the subject has TS but not any of ADHD, ODD, conduct disorder, anxiety disorder, autism, a mood disorder, phobia, or depression. In other diagnostic, confirming, and treatment methods of the invention, the subject has TS and one or more additional disorders such as ADHD, conduct disorder, anxiety disorder, autism, a mood disorder, phobia, or depression. In some methods, the subject has both TS and ADHD.

III. Methods and Uses for Treating Tourette's Syndrome

[0062] Encompassed herein are methods of treating TS in a subject comprising administering an effective amount of a nonselective mGluR activator. The term "treatment," as used herein, includes any administration or application of a therapeutic for a disease or disorder in a subject, and includes inhibiting the disease, arresting its

development, relieving the symptoms of the disease, or preventing occurrence or reoccurrence of the disease or symptoms of the disease.

[0063] The mGluR proteins are typically placed into three sub-groups, group I receptors including mGluR1 and mGluR5 are classed as slow excitatory receptors. Group II includes mGluR2 and mGluR3. Group III includes mGluR4, mGluR6, mGluR7, and mGluR8. Groups II and III are classed as slow inhibitory receptors.

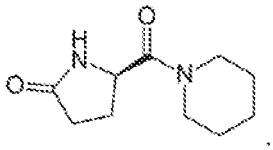
[0064] The mGluRs are distinguished from the ionotropic GluRs or iGluRs, which are ion channel-associated glutamate receptors and are classed as fast excitatory receptors.

[0065] A "nonselective activator of mGluRs" refers to a molecule that activates mGluRs from more than one of the group I, II, and III categories. Thus, a nonselective activator of mGluRs may provide for a general stimulation of the mGluR networks. This is in contrast to specific mGluR activators that may only significantly activate a single mGluR, such as mGluR5, for example. Nonselective mGluR activators include, for example, nonselective mGluR agonists.

[0066] In some embodiments, the nonselective mGluR activator is fasoracetam. Fasoracetam is a nootropic (i.e., cognitive-enhancing) drug that can stimulate both group I and group II/III mGluRs in in vitro studies. (See Hirouchi M, et al. (2000) European Journal of Pharmacology 387:9–17.) Fasoracetam may stimulate adenylate cyclase activity through activation of group I mGluRs, while it may also inhibit adenylate cyclase activity by stimulating group II and III mGluRs. (Oka M, et al (1997) Brain Research 754:121–130.) Fasoracetam has been observed to be highly bioavailable (79%-97%) with a half-life of 5-6.5 hours in prior human studies (see Malykh AG, et al. (2010) Drugs 70(3):287-

312). Fasoracetam is a member of the racetam family of chemicals that share a five-carbon oxopyrrolidone ring.

[0067] The structure of fasoracetam is:



[0068] The term "fasoracetam" as used herein encompasses pharmaceutically acceptable hydrates and any solid state, amorphous, or crystalline forms of the fasoracetam molecule. For example, the term fasoracetam herein includes forms such as NFC-1: fasoracetam monohydrate. In addition to NFC-1, fasoracetam is also known as C-NS-105, NS105, and LAM-105.

[0069] NFC-1 has been previously studied in Phase I-III clinical trials in dementia-related cognitive impairment but did not show sufficient efficacy in dementia in Phase III trials. These trials demonstrated that NFC-1 was generally safe and well tolerated for those indications. Phase III data indicated that NFC-1 showed beneficial effects on psychiatric symptoms in cerebral infarct patients and adult dementia patients with cerebrovascular diseases.

[0070] In each of the method of treatment embodiments, a metabotropic glutamate receptor positive allosteric modulator, a metabotropic glutamate receptor negative allosteric modulator, or a tachykinin-3/neurokinin-3 receptor (TACR- 3/NK3R) antagonist may be administered alone or in combination with a nonselective activator of mGluRs to a subject, for example, having an alteration in an mGluR network gene. In some embodiments, the treatment agent comprises ADX63365, ADX50938, ADX71149,

AMN082, a 1-(hetero)aryl-3-amino-pyrrolidine derivative, LY341495, ADX48621, GSK1144814, or SB223412.

[0071] Also encompassed herein are methods of treating TS comprising administering fasoracetam to a subject that has a genetic alteration in at least one mGluR network gene. In some embodiments, this subject has TS but does not have ADHD, ODD, conduct disorder, anxiety disorder, autism, a mood disorder, phobia, schizophrenia, obsessive compulsive disorder (OCD), difficulty controlling anger, disruptive behavior symptoms, dermatillomania, another movement disorder, a developmental disorder, or depression, while in other embodiments, the subject has TS as well as at least one of ADHD, ODD, conduct disorder, anxiety disorder, autism, a mood disorder, phobia, schizophrenia, obsessive compulsive disorder (OCD), difficulty controlling anger, disruptive behavior symptoms, dermatillomania, another movement disorder, a developmental disorder, or depression. In some embodiments, the subject has both TS and ADHD.

[0072] In some embodiments, the treatment methods comprise identifying or diagnosing a subject as having a genetic alteration in at least one mGluR network gene, and administering a nonselective mGluR activator such as fasoracetam to the identified or diagnosed subject. In some of the embodiments, the subject has TS, but does not have ADHD, ODD, conduct disorder, anxiety disorder, autism, a mood disorder, phobia, or depression. In other embodiments, the subject has TS, as well as one or more neuropsychological disorders such as ADHD, ODD, conduct disorder, anxiety disorder, autism, a mood disorder, phobia, and depression.

[0073] In each method of the treating embodiments of the invention, the disorder may be TS, persistent (chronic) vocal tic disorder, persistent (chronic) motor tic disorder,

or provisional tic disorder. In each method of treating, the nonselective mGluR activator, such as fasoracetam, may lessen the frequency or the degree of motion in the subject's tics, and/or it may improve symptoms of inattention, hyperactivity, anxiety, mood, and sleep disturbances that may be seen in patients with TS or a tic disorder. For example, these symptoms may be lessened after 1 week of treatment with the activator, such as after 2 weeks, after 3 weeks, or after 4 weeks of treatment.

[0074] In some embodiments, the subject has co-morbid symptoms of anxiety and in some cases, the method reduces anxiety symptoms. In some embodiments, the subject has OCD and in some cases, the method reduces OCD symptoms. In some cases, the subject has co-morbid symptoms of dermatillomania, such as excessive skin picking, and the method reduces those symptoms. In some embodiments, the subject has one or more co-morbid developmental disorders, and in some cases, the method reduces the severity of symptoms related to the developmental disorders.

[0075] In some embodiments, the subject may have one or more of the following changes in symptoms after at least one, two, three, or four weeks of treatment with the activator: (a) the subject has symptoms of anger control and the anger control symptoms are reduced; (b) the subject has symptoms of disruptive behavior and the disruptive behavior symptoms are reduced; (c) the subject's CGI-I is reduced by at least 1 or by at least 2; (d) the subject's CGI-I score after one, two, three, or four weeks of treatment is 1 or 2; (e) the subject's CGI-S score after one, two, three, or four weeks of treatment is 1; (f) the subject has ADHD and the subject's ADHD Rating Scale score is reduced by at least 25%, such as at least 30%, at least 35%, or at least 40%; (g) the subject has symptoms of inattentiveness and the inattentiveness symptoms are reduced; (h) the subject has symptoms of hyperactivity and the hyperactivity symptoms are reduced; (i)

the subject has symptoms of impulsiveness and the impulsiveness symptoms are reduced; (j) the subject has symptoms of ODD such as anger and irritability, argumentation and defiance, and/or vindictiveness and the ODD symptoms are reduced; (k) the subject has symptoms of conduct disorder and the conduct disorder symptoms are reduced; (l) the subject has symptoms of anxiety and the anxiety symptoms are reduced; (m) the subject has symptoms of OCD, and the OCD symptoms are reduced; (n) the subject has symptoms of autism, and the autism symptoms are reduced; and (o) the subject has symptoms of a movement disorder other than Tourette's and the movement disorder symptoms are reduced.

[0076] In one embodiment, the nonselective mGluR activator, such as fasoracetam, is administered to a subject that has TS and has been confirmed as having at least one genetic alteration in an mGluR network gene. The genetic alteration may be in a Tier 1 mGluR network gene. The genetic alteration may be in a Tier 2 mGluR network gene. The genetic alteration may be in a Tier 3 mGluR network gene. The genetic alteration may be more than one genetic alteration, and the more than one alteration may be in one of Tiers 1, 2, or 3, or in any combination of Tiers.

[0077] Some embodiments include a method of treating TS comprising obtaining genetic information about a subject's mGluR network genes, and administering a nonselective mGluR activator, such as fasoracetam, if the subject has at least one genetic alteration, such as a CNV, in an mGluR network gene. Other embodiments encompass a method of treating TS comprising obtaining genetic information about a subject's mGluR network genes, and administering a nonselective mGluR activator, such as fasoracetam, if the subject has least one genetic alteration, such as a CNV, in a Tier 1 mGluR network gene.

[0078] Other embodiments include a method of treating TS comprising obtaining genetic information about a subject's mGluR network genes, and administering a nonselective mGluR activator, such as fasoracetam, if the subject has at least one genetic alteration, such as a CNV, in a Tier 2 mGluR network gene.

[0079] Still other embodiments encompass a method of treating TS comprising obtaining genetic information about a subject's mGluR network genes, and administering a nonselective mGluR activator, such as fasoracetam, if the subject has at least one genetic alteration, such as a CNV, in a Tier 3 mGluR network gene.

[0080] Subjects having more than one CNV in any one Tier, or in a combination of any of the three Tiers, may be treated by administering a nonselective mGluR activator, such as fasoracetam.

[0081] In some embodiments, subjects having TS, but not having ADHD, ODD, conduct disorder, anxiety disorder, autism, a mood disorder, phobia, schizophrenia, difficulty controlling anger, disruptive behavior, symptoms, obsessive compulsive disorder (OCD), dermatillomania, a developmental disorder, another movement disorder other than TS, or depression, may be treated. In other method of treatment embodiments of the invention, the subject has one or more neuropsychological disorders such as ADHD, ODD, conduct disorder, anxiety disorder, autism, a mood disorder, phobia, schizophrenia, difficulty controlling anger, disruptive behavior, symptoms, obsessive compulsive disorder (OCD), dermatillomania, a developmental disorder, another movement disorder other than TS, and depression in addition to TS.

IV. Methods for Determining the Presence or Absence of Genetic Alterations

[0082] Any biological sample may be used to determine the presence or absence of mGluR network gene alterations, including, but not limited to, blood, urine, serum,

gastric lavage, CNS fluid, any type of cell (such as brain cells, white blood cells, mononuclear cells) or body tissue. Any biological sample whereby DNA can be extracted may be used to determine the presence or absence of mGluR network gene alterations. Samples may be freshly collected, or samples may have been previously collected for any use/purpose and stored until the time of testing for genetic alterations. DNA that was previously purified for a different purpose may also be used.

[0083] Various methods for determining genetic alterations are known, including the following:

A. Single Nucleotide Variant (SNV) / Single Nucleotide Polymorphism (SNP) Genotyping

[0084] Determining whether a patient has a genetic alteration, such as a CNV, in an mGluR network gene may be done by SNP/SNV Genotyping. A "single nucleotide variant (SNV)," also called a "single nucleotide polymorphism (SNP)" herein, refers to a change in which a single base in the DNA differs from the usual base at that position. Millions of SNVs have been cataloged in the human genome. Some SNVs are normal variations in the genome, while others are associated with disease. While specific SNVs may be associated with disease states or susceptibility, high-density SNV genotyping can also be undertaken, whereby sequencing information on SNVs is used to determine the unique genetic makeup of an individual.

[0085] In SNV genotyping, SNVs can be determined by hybridizing complementary DNA probes to the SNV site. A wide range of platforms can be used with SNV genotyping tools to accommodate varying sample throughputs, multiplexing capabilities, and chemistries. In high-density SNV arrays, hundreds of thousands of probes are arrayed on a small chip, such that many SNVs can be interrogated

simultaneously when target DNA is processed on the chip. By determining the amount of hybridization of target DNA in a sample to a probe (or redundant probes) on the array, specific SNV alleles can be determined. Use of arrays for SNV genotyping allows the large-scale interrogation of SNVs.

[0086] When analyzing CNVs, after SNVs have been analyzed, a computer program can be used to manipulate the SNV data to arrive at CNV data. PennCNV or a similar program, can then be used to detect signal patterns across the genome and identify consecutive genetic markers with copy number changes. (See Wang K, et al. (June 2008) Cold Spring Harb Protoc). PennCNV allows for kilobase-resolution detection of CNVs. (See Wang K, et al. (Nov 2007) Genome Res. 17(11):1665-74).

[0087] In CNV analysis, the SNV genotyping data is compared with the behavior of normal diploid DNA. The software uses SNV genotyping data to determine the signal intensity data and SNV allelic ratio distribution and to then use these data to determine when there is deviation from the normal diploid condition of DNA that indicates a CNV. This is done in part by using the log R Ratio (LRR), which is a normalized measure of the total signal intensity for the two alleles of the SNV (Wang 2008). If the software detects regions of contiguous SNVs with intensity (LRR) trending below 0, this indicates a CNV deletion. If the software instead detects regions of contiguous SNVs with intensity (LRR) trending above 0, this indicates a CNV duplication. If no change in LRR is observed compared to the behavior of diploid DNA, the sequence is in the normal diploid state with no CNV present. The software also uses B allele frequency (BAF), a normalized measure of the allelic intensity ratio of two alleles that changes when alleles are lost or gained as with a CNV deletion or duplication. For example, a CNV deletion is indicated by both a decrease in LRR values and a lack of heterozygotes in BAF values. In contrast,

a CNV duplication is indicated by both an increase in LRR values and a splitting of the heterozygous genotype BAF clusters into two distinct clusters. The software automates the calculation of LRR and BAF to detect CNV deletions and duplications for whole-genome SNV data. The simultaneous analysis of intensity and genotype data accurately defines the normal diploid state and determines CNVs.

[0088] Array platforms such as those from Illumina, Affymetrix, and Agilent may be used in SNV Genotyping. Custom arrays may also be designed and used based on the data described herein.

B. Comparative Genomic Hybridization

[0089] Comparative genomic hybridization (CGH) is another method that may be used to evaluate genetic alterations such as CNVs. CGH is a molecular cytogenetic method for analyzing genetic alterations such as CNVs in comparison to a reference sample using competitive fluorescence in situ hybridization (FISH). DNA is isolated from a patient and a reference source and independently labeled with fluorescent molecules (i.e., fluorophores) after denaturation of the DNA. Hybridization of the fluorophores to the resultant samples are compared along the length of each chromosome to identify chromosomal differences between the two sources. A mismatch of colors indicates a gain or loss of material in the test sample in a specific region, while a match of the colors indicates no difference in genetic alterations such as copy number between the test and reference samples at a particular region.

C. Comparative Genomic Hybridization

[0090] Whole genome sequencing, whole exome sequencing, or targeted sequencing may also be used to analyze genetic alterations such as CNVs. Whole genome sequencing (also known as full genome sequencing, complete genome sequencing, or

entire genome sequencing) involves sequencing of the full genome of a species, including genes that do or do not code for proteins. Whole exome sequencing, in contrast, is sequencing of only the protein-coding genes in the genome (approximately 1% of the genome). Targeted sequencing involves sequencing of only selected parts of the genome.

[0091] A wide range of techniques would be known to those skilled in the art to perform whole genome, whole exome, or targeted sequencing with DNA purified from a subject. Similar techniques could be used for different types of sequencing.

[0092] Techniques used for whole genome sequencing include nanopore technology, fluorophore technology, DNA nanoball technology, and pyrosequencing (i.e., sequencing by synthesis). In particular, next-generation sequencing (NGS) involves sequencing of millions of small fragments of DNA in parallel followed by use of bioinformatics analyses to piece together sequencing data from the fragments.

[0093] As whole exome sequencing does not need to sequence as large an amount of DNA as whole genome sequencing, a wider range of techniques are may be used. Methods for whole exome sequencing include polymerase chain reaction methods, NGS methods, molecular inversion probes, hybrid capture using microarrays, in-solution capture, and classical Sanger sequencing. Targeted sequencing allows for providing sequence data for specific genes rather than whole genomes and can use any of the techniques used for other types of sequencing, including specialized microarrays containing materials for sequencing genes of interest.

D. Other Methods for Determining Genetic Alterations

[0094] Proprietary methodologies, such as those from BioNano or OpGen, using genome mapping technology can also be used to evaluate genetic alterations such as CNVs.

[0095] Standard molecular biology methodologies such as quantitative polymerase chain reaction (PCR), droplet PCR, and TaqMan probes (i.e., hydrolysis probes designed to increase the specificity of quantitative PCR) can be used to assess genetic alterations such as CNVs. Fluorescent in situ hybridization (FISH) probes may also be used to evaluate genetic alterations such as CNVs. The analysis of genetic alterations such as CNVs present in patients with TS is not limited by the precise methods whereby the genetic alterations such as CNVs are determined.

V. Methods for Diagnosing TS Based on CNV Data

[0096] In some embodiments, the genetic alteration is a SNV or CNV. The SNV(s) or CNV(s) associated with TS are found in an mGluR network gene, such as a gene listed in Tier1, Tier2, or Tier3 as shown in Figs. 1-3 or a set or panel of such genes.

[0097] In some embodiments, gene sets of mGluR network genes are used for analyzing samples from patients with or suspected of having TS. In some embodiments, the presence of CNV duplications or deletions within these gene sets or panels is determined. In some embodiments, CNVs in the Tier 1 genes shown in Fig. 1 are determined. In some embodiments a panel of at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, or all 76 of the Tier 1 genes is evaluated for the presence of CNVs. Within any such panel of genes, individual, specific Tier 1 genes may be excluded from the analysis set. Any or all of GRM1-8 may be excluded from the panel, for example.

[0098] In some embodiments, the Tier 2 genes as shown in Figure 2 are analyzed for the presence of genetic alterations such as CNVs. Tier 2 genes are those that are tightly associated with mGluRs, but which are not contained within Tier 1.

[0099] In some embodiments, the Tier 2 genes are evaluated together with Tier 1 genes. In some embodiments, at least 100 Tier 2 genes are evaluated, while in some embodiments, at least 150, or 197 of the Tier 2 genes are evaluated. Individual, specific Tier 2 genes may be excluded from the gene set for evaluation in some embodiments.

[00100] In some embodiments, the 599 Tier 3 genes shown in Figure 3 are evaluated for genetic alterations such as CNVs. In some embodiments, the Tier 3 genes are evaluated together with Tier 1 and/or Tier 2 genes. In some embodiments, at least 100 Tier 3 genes are evaluated, while in some embodiments, at least 150, 200, 250, 300, 350, 400, 450, or 599 of the Tier 3 genes are evaluated. Individual, specific Tier 3 genes may be excluded from the gene set for evaluation in some embodiments.

VI. Methods of Administration and Combination Therapy

[00101] In some embodiments, the agent that modulates mGluR signaling is fasoracetam or fasoracetam monohydrate (also known as C-NS-105, NFC1, NS105, or LAM-105).

A. Dosing

[00102] In some embodiments, fasoracetam may be administered as fasoracetam monohydrate (NFC-1). In some embodiments, fasoracetam may be administered by mouth (i.e., per os). In some embodiments, fasoracetam may be administered as capsules. In some embodiments, fasoracetam capsules may contain 50, 60, 70, 80, 90, 100, 110, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, or 200 mg of fasoracetam monohydrate. In some embodiments, fasoracetam may be dosed once daily or twice daily. In some embodiments, the daily dose of fasoracetam may be 50 mg once-daily, 100 mg once-daily, 200 mg once-daily, 400 mg once-daily, 50 mg twice-daily, 100 mg twice-daily, 200 mg twice-daily, or 400 mg twice-

daily. In some embodiments, fasoracetam dosing may be adjusted using a series of dose escalations. In some embodiments, pharmacokinetic data on drug level or clinical response is used to determine changes in dosing. In some embodiments, dose escalation of fasoracetam is not used. In some embodiments, subjects are treated at a dose of fasoracetam expected to be clinically efficacious without a dose- escalation protocol.

B. Combination Therapies

[00103] In some embodiments, fasoracetam is used in combination with other agents for the treatment of TS. The other agent used in combination with fasoracetam may be an antipsychotic, including haloperidol, chlorpromazine, amisulpride, aripiprazole, asenapine, blonaserin, clozapine, iloperidone, lurasidone, melperone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, sulpiride, ziprasidone, or zotepine.

[00104] In some embodiments, fasoracetam may be used in combination with a non-pharmacologic treatment, such as psychotherapy or brain stimulation therapies. In some embodiments, fasoracetam is used in combination with brain stimulation, which may be vagus nerve stimulation, repetitive transcranial magnetic stimulation, magnetic seizure therapy, deep brain stimulation, or any other therapies involving modulation of brain function by electricity, magnets, or implants.

VII. Articles of Manufacture

[00105] In some embodiments, the invention comprises articles of manufacture that may be used in the methods and treatments described herein. In one embodiment, the manufacture is a solid support or microarray for use in detecting genetic alterations in some or all of the mGluR network genes listed in Figs. 1-3 (i.e., Tiers 1-3). (See also Tables 1-3 herein providing start and stop locations for different

mGluR network-related SNPs. This information may be useful in constructing a microarray.) In some embodiments, genes contained in multiple Tiers are assessed within the same solid support or microarray. In some embodiments, certain mGluR network genes are excluded. In some embodiments, the GRM genes are excluded.

[00106] Thus, for example, in some embodiments in which mGluR network genes are assayed to determine if there is a genetic alteration in one or more of the genes, such as a CNV, a solid support or microarray, such as on a chip, is used that contains appropriate probes for determining the presence of genetic alterations in 10, 20, 30, 40, 50, 60, 70 or all of the Tier 1 genes. In certain embodiments, the detectable labels are non-naturally occurring. In some embodiments, the solid support or microarray may also include appropriate probes for determining the presence of genetic alterations in at least 10, 20, 30, 50, 100, 150, or all of the Tier 2 genes. In some embodiments, it may further include appropriate probes for determining the presence of genetic alterations in at least 10, 20, 50, 100, 200, 300, 400, 500 or all of the Tier 3 genes. For example, such a solid support, microarray, or chip may be used to determine the presence of genetic alterations such as CNVs or SNVs in the Tier 1, Tier 1+2, or Tier 1+2+3 mGluR gene networks as part of a method of treating an ADHD or 22q deletion and/or duplication patient.

[00107] In some embodiments, the manufacture is a set of probes for mGluR network genes of interest from Tiers 1, 2, and/or 3. In some embodiments the probes are labelled. Similarly, sets of probes may be manufactured for determining the presence of genetic alterations in 10, 20, 30, 40, 50, 60, 70 or all of the Tier 1 genes. In some embodiments, probes may be manufactured for determining the presence of genetic alterations in at least 10, 20, 30, 50, 100, 150, or all of the Tier 2 genes. In some embodiments, probes may further include those for determining the presence of genetic

alterations in at least 10, 20, 50, 100, 200, 300, 400, 500 or all of the Tier 3 genes. These various probe sets may be used in methods of determining the presence of genetic alterations, such as CNVs and SNVs in the Tier 1, Tier 1+2, or Tier 1+2+3 mGluR gene networks as part of a method of treating an ADHD or 22q deletion and/or duplication patient.

EXAMPLES

Example 1. Enrichment of CNV calls containing mGluR network genes in samples from patients with TS

[00108] Previously, a large-scale genome association study for copy-number variations enriched in patients with ADHD was performed, as described in Elia et al., Nature Genetics, 44(1): 78-84 (2012)). Elia's study included about 2,493 patients with ADHD and about 9,222 controls, all of whom were of European ancestry and were between the ages of 6 to 18 years of age. This study noted that the rate of CNVs that contained an mGluR network gene was 1.2% in the control group, and that this rate increased to 11.3% in ADHD patients.

[00109] The study revealed that rare, recurring CNVs impacting specific mGluR network genes (i.e. GRM1, GRM5, GRM7, and GRM8) encoding for metabotropic glutamate receptors (mGluRs) were found in ADHD patients at significantly higher frequencies compared to healthy controls. The large effect sizes (with odds-ratios of >15) suggest that these mutations likely are highly penetrant for their effects on ADHD. Single cases with GRM2 and GRM6 deletions were also observed that were not found in controls. When genes in the signaling pathway of mGluR network genes were assessed, significant enrichment of CNVs was found to reside within this network in ADHD cases compared to controls.

[00110] We have identified a total of 279 mGluR primary network genes based on the merged human interactome provided by the Cytoscape Software. A network analysis of the mGluR pathway found that in a population of approximately 1,000 cases and 4,000 controls from subjects of European ancestry, genes involved with mGluR signaling or their interactors are significantly enriched for CNVs in cases ($P = 4.38x10^{-10}$), collectively impacting ~20% of the ADHD cases, corrected for control occurrence. These data suggest that mGluR network genes may serve as critical hubs that coordinate highly-connected modules of interacting genes, many of which may harbor CNVs and are enriched for synaptic and neuronal biological functions. Thus, several rare, recurrent CNVs were identified that are overrepresented in multiple independent ADHD cohorts that impact genes involved in glutamatergic neurotransmission.

[00111] TS frequently coexists in children with ADHD. Specifically, about two thirds of pediatric TS patients also have ADHD. In addition, as much as 10% of ADHD patients may have tics. Thus, we examined if mGluR gene alterations would also be enriched in children with TS.

[00112] Samples for the present study were selected based on ICP-9 codes for diagnoses of children and adolescents from electronic health records that were treated at the Children's Hospital of Philadelphia (CHOP). All 95 subjects had been evaluated by a pediatric psychiatrist who had entered a diagnosis of TS. All subjects had recurrent tics of sufficient duration to meet diagnostic criteria for Tourette syndrome. Certain patients in the study had a diagnosis of both schizophrenia and TS.

[00113] Single nucleotide variant (SNV) / single nucleotide polymorphism (SNP) genotype data were used to determine CNVs. SNV genotyping provides a genetic fingerprint of an individual using a large number of SNV markers to provide high-density

SNV genotyping data (see Wang K, et al. (Nov 2007) Genome Res.17(11):1665-74). HumanHap550 Genotyping BeadChip™ (Illumina) or Human610- Quad v1.0 BeadChip™ (Illumina) were used in this study. For both chips, the same 520 SNVs were analyzed; therefore, data from these two chips are interchangeable. Standard manufacturer protocols were used for all genotyping assays. Illumina readers were used for all experiments.

[00114] SNV genotyping data from each fully genotyped patient sample were analyzed with the PennCNV software to determine the signal intensity data and SNV allelic ratio distribution. These data were then used to determine CNVs via simultaneous analysis of intensity and genotype data (as previously described in Wang 2008). Using this analysis, data indicating a region of loss of contiguous SNVs lead to a call of a CNV deletion. Data indicating a region of gain of contiguous SNVs lead to a call of a CNV duplication. A single individual may have multiple CNV deletions/duplications or may not have any CNVs.

[00115] As discussed previously, three tiers of mGluR network genes were developed. Figures 1-3 show the genes that are included in the three gene sets – Tier 1 (76 genes) in Figure 1, Tier 2 (197 genes) in Figure 2, and Tier 3 (599 genes) in Figure 3. Note that these gene sets were non-inclusive, so a single gene was only contained in a single Tier.

[00116] Figure 4 shows data on the number of CNV calls in each mGluR gene Tier for the TS patients. CNVs are either duplications or deletions. The data indicate that a relatively high number of CNV calls were seen for each gene set of mGluR network genes in the samples from patients with TS.

[00117] The percentage of patients who had a CNV call (either duplication or deletion) in each gene set of mGluR network genes is shown in Figure 5. Among 95 genotyped children with TS, 20 (~21%) had mutations in the Tier 1 genes that were found to be most significant in ADHD and we have labelled as Tier 1 (all are genes in the mGluR primary network). A total of 28 children had mutations within the full mGluR primary network genes assessed (Tiers 1 + 2) or ~29%. About 52% of the children had mutations in either the primary or secondary (Tiers 1 + 2 + 3) mGluR networks, suggesting that up to 50% of patients with TS might have this pathway disrupted and may be responsive to therapy that reverses the consequences of these mutations.

[00118] These data also indicate that a substantially higher percentage of patients with TS had a CNV call within each of the mGluR network gene sets compared with the previously reported frequency of CNV calls in a control population. The control frequency of patients with CNVs in mGluR network genes was previously estimated to be 1.2% (see Elia), supporting the specificity of the enrichment of mGluR network genes within CNVs in patients with TS.

[00119] As indicated in Figures 4-5, there was a significant enrichment of mGluR network gene alterations in the patients with TS. Therefore, diagnostics and treatments focused on modulation of mGluR gene networks may be of particular use in patients with TS.

Example 2. Analysis of mGluR network genes contained within CNVs from samples of patients with TS

[00120] We next analyzed genotyping data from the 95 fully genotyped patients with TS to identify the genes associated with the CNVs.

[00121] Table 1 shows data of representative CNVs from patients with TS wherein a Tier 1 mGluR network gene was located within, or in the vicinity of, a CNV in the patient's sample. CNVs can lead to structural changes that affect the transcription of genes located outside of, but in the vicinity of, the CNV. As such, mGluR network genes within one of the Tiers that were located within 500,000 base pairs of a CNV were included in the analysis. When an mGluR network gene is contained within the listed CNV, this is noted with a "distance from gene" value of 0. When an mGluR network gene is contained in close proximity to a CNV but not within it, this is presented with a "distance from gene" value of greater than 0.

[00122] Table 1 lists the chromosome wherein the CNV was located, with its start and stop location in relation to the Human Genome version 19 (hg19). The number of SNVs (SNPs) located within the CNV is noted as "Num SNP," and the length of the CNV is noted in base pairs. The StartSNP and EndSNP of the CNV are also provided.

[00123] The "State, CN" column indicates the copy number resulting from the CNV. As normal human DNA (i.e. with no CNV) should be diploid and would have a "State, CN" of 2. CNVs with a "State, CN" of 0 or 1 indicate a copy number deletion. In contrast, CNVs with a "State, CN" of three or greater indicate a copy number duplication.

[00124] The confidence value indicates the relative confidence that the call of the CNV is correct. All CNVs included in this analysis had a positive confidence value, indicating a high likelihood that the CNV call is correct. A value of 15 or greater was seen for most CNVs and is considered extremely high confidence in the CNV call based on qPCR and Taqman genotyping validation.

[00125] In Table 1, the "mGluR gene" column lists the specific mGluR network gene within Tier 1 contained within the listed CNV. Table 1 is sorted to show all of the CNVs that included a given Tier 1 mGluR network gene. Some Tier 1 genes may be represented in multiple CNVs from different patients in the study, leading to multiple rows for those particular mGluR network genes. Some Tier 1 genes may not have been represented in a CNV from this particular patient population.

[00126] Table 2 shows data from specific CNVs that contained a Tier 1 or Tier 2 mGluR network gene. The organization of Table 2 follows that of Table 1. The "mGluR gene" column lists the specific mGluR network gene within Tier 1 or Tier 2 contained within the listed CNV. Table 2 is sorted to show all of the CNVs that included a given Tier 1 or Tier 2 mGluR network gene. Some Tier 1 or Tier 2 genes may be represented in multiple CNVs from different patients in the study, leading to multiple rows for those particular genes. Some Tier 1 or Tier 2 genes may not have been represented in a CNV from this particular patient population.

[00127] Table 3 shows data from specific CNVs that contained a Tier 1, 2, or 3 mGluR network gene. The organization of Table 3 follows that of Tables 1 and 2. The "mGluR gene" column lists the specific mGluR network gene within Tier 1, Tier 2, or Tier 3 contained within the listed CNV. Table 3 is sorted to show all the CNVs that included a given Tier 1, 2, or 3 mGluR network gene. Some Tier 1, 2, or 3 genes may be represented in multiple CNVs from different patients in the study, leading to multiple rows for those particular mGluR network genes. Some Tier 1, 2, or 3 genes may not have been represented in a CNV from this particular patient population.

[00128] Together, the data in Tables 1-3 indicate that a wide variety of mGluR network genes contained within each Tier are present in CNVs from patients

with TS. If a larger patient cohort with TS was genotyped, all the genes in Tier 1, Tier 2, and Tier 3 would show enrichment for CNVs in patients with TS.

Example 3. Treatment with Fasoracetam Monohydrate (NFC-1) of ADHD Patients with CNVs in mGluR Network Genes and Impact on Tic Symptoms

[00129] An open-label Phase Ib clinical trial was conducted to investigate the safety, pharmacokinetics and efficacy of NFC-1 (fasoracetam monohydrate) in adolescent subjects between the ages of 12 and 17 previously diagnosed with ADHD who also had at least one genetic alteration in an mGluR network gene.

[00130] The study included 30 ADHD subjects who were between ages 12 and 17, of any ancestry or race, of weight within the 5th to 95th percentile for their age, and otherwise judged to be in good medical health. Subjects were genotyped and included in the trial if they possess at least one genetic alteration in the form of at least one copy number variation (deletion or duplication) in a mGluR network gene that potentially disrupts the function of the gene. Seventeen of the 30 subjects have a CNV in a tier 1 mGluR network gene, while 7 subjects have a CNV in a tier 2 gene and 6 in a tier 3 gene. At enrollment, several trial subjects showed evidence of co-morbid phenotypes, including two subjects having recurrent tics.

[00131] Exclusion criteria comprised subjects suffering from a clinically significant illness, either mental or physical, that, in the investigator's opinion, might confound the results of the study or that might prevent them from completing the study, subjects that are pregnant or nursing, subjects that test positive for illicit drugs of that have a history of drug abuse, subjects that consume alcoholic beverages, or subjects for which the investigator is otherwise concerned regarding their compliance or suitability.

[00132] NFC-1 capsules of either 50 mg or 200 mg comprising fasoracetam monohydrate as active ingredient and placebo capsules comprising microcellulose were used for the study. The design of the trial was a phone screening (1 day), enrollment phase (1 to 2 days), a wash-out phase for subjects currently on ADHD medications (1-14 days), pharmacokinetic (PK) assessment (2 days), followed by a dose-escalation phase (35 days) and a follow-up phone visit approximately four weeks after the last dose, for a maximum of 127 days. All ADHD medications were discontinued during the wash-out phase prior to the study. The wash-out period for stimulants was 2-3 days and that for atomoxetine or noradrenergic agonists was 10-12 days. No new ADHD medications were started during the study.

[00133] A dose-escalation phase of the trial ran over a 5-week period, after the initial wash-out period and the PK and initial safety assessments. During week 1, all subjects were administered placebo capsules twice daily. After one week of placebo treatment, patients were started on 50 mg bid NFC-1 for 1 week. If safety and responsiveness data from prior dose level of fasoracetam indicated it was appropriate, subjects were then escalated to the next higher dose (100, 200, or 400 mg). Subjects who showed tolerance to the 50 mg bid dose as well as response to the drug were to be maintained at that level for the remaining 3 weeks of the trial.

[00134] Subjects who showed tolerance but lack of response or partial response to the 50 mg bid dose were to be moved up to the next higher dose of 100 mg during the following week. Subjects who showed tolerance at 100 mg but lack of response or partial response were to be moved up to the 200 mg dose the following week while those who showed both tolerance and response at 100 mg were to be kept at 100 mg bid for the remainder of the trial. Similarly, subjects moved up to the 200 mg dose

who showed both tolerance and response were to be kept at 200 mg for the final week of the trial while those showing tolerance but lack of response or partial response were moved to a 400 mg dose for the final week. Of the 30 trial subjects, 3 received a maximum dose of 100 mg, 9 received a maximum dose of 200 mg, and the remaining 18 received a maximum dose of 400 mg.

[00135] While this study was not specifically directed at measuring tics or TS, the two individuals with history of recurrent tics did not demonstrate tics during the therapy with NFC-1.

Example 4. Treatment with Fasoracetam Monohydrate (NFC-1) of ADHD Patients with CNVs in mGluR Network Genes and Impact on Obsessive Compulsive Symptoms

[00136] Among the 30 ADHD subjects tested in the open-label Phase Ib clinical trial described in Example 2, eight had symptoms of obsessive compulsive-disorder (OCD). One of the subjects with tics also had symptoms of OCD. In all eight subjects, OCD symptoms improved during therapy with NFC-1.

[00137] One subject with OCD also had a history of ear scratching (i.e., dermatillomania), leading to a bleeding ulcer. The bleeding ulcer healed during therapy with NFC-1, indicating that the subject's dermatillomania symptoms had reduced during NFC-1 therapy.

Example 5. Study of Phenotypes Associated with mGluR Network CNVs

[00138] A total of 1,000 ADHD patients aged 6-17 years were enrolled in a trial to consider phenotypes that may be associated with CNVs in Tier 1 or 2 mGluR network genes. Study sites collected saliva for a DNA sample. Each DNA sample was then subjected to DNA extraction, genetic sequencing, and biobanking of DNA.

[00139] Genetic sequencing results together with medical history were used to evaluate genotype (based on genetic sequencing) and phenotype (based on interviews conducted by a clinician with the subject's parent(s)/guardian(s)). Subjects had ADHD as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V).

[00140] A single clinician posed a series of questions related to potential behavioral or health phenotypes to the parent(s) or legal guardian(s) of the subjects. For each individual phenotype, the parent/guardian was asked: "Is this a current concern" and a Yes or No answer was collected. The clinician determined the frequency of Yes and No responses to generate phenotype data.

[00141] The study found that prevalence of anger control as a current concern for parents was 58.9% in ADHD subjects with a Tier 1 or 2 mGluR network gene CNV but only 47.4% in ADHD subjects without such an mGluR network gene CNV. This difference was statistically significant (odds ratio of 1.59, $P = 0.003$). This odds ratio of greater than 1 implies a higher prevalence of current anger control concerns in parents in ADHD subjects who had a Tier 1 or 2 mGluR network gene CNV versus those without such a CNV.

[00142] The prevalence of disruptive behavior as a current concern for parents was 57.1% in ADHD subjects with a Tier 1 or 2 mGluR network gene CNV and 43.9% in ADHD subjects without such an mGluR network gene CNV. This difference was also statistically significant (odds ratio of 1.70, $P < 0.001$), indicating a higher prevalence of current disruptive behavior concerns in parents in ADHD subjects who also had an mGluR network gene mutation versus those without a mutation.

Example 6: Copy Number Variation in mGluR Network Genes in ADHD Subjects with Co-Morbid Disorders

[00143] Samples from 2707 known ADHD pediatric subjects (mean age of about 10-10.5 years) were genotyped on 550/610 Illumina chips to determine if they have one or more CNVs in Tier 1 or Tier 2 genes. The 2707 subjects included 759 females and 1778 males of African American or white ethnicity (1063 and 1483, respectively). 430 of the 2707 subjects (16.9%) had at least one CNV in an mGluR Tier 1 or Tier 2 gene.

[00144] The 2707 subjects' records were also checked to determine if they had co-morbid diagnoses according to the World Health Organization International Classification of Diseases 9th Edition (ICD-9). Of the 2707 subjects, 1902 (about 70%) had comorbidities while 805 did not. Of those 1902 subjects with comorbidities, about 30% had more than one comorbidity, and about 20% had two or more, while smaller percentages had larger numbers of comorbidities.

[00145] The most prevalent comorbidities, each occurring in more than 100 of the subjects, are listed in Table 4. The table lists the comorbidities by ICD-9 code and provides the number of cases among the 2707 subjects (column titled "N") and name for each co-morbid condition or disorder.

Table 4

ICD-9 Code	N	Name
N_299.00	342	Autistic disorder, current or active state
N_299.80	267	Other specified pervasive developmental disorders, current or active state
N_299.90	179	Unspecified pervasive developmental disorder, current or active state
N_300.00	407	Anxiety state unspecified
N_311	244	Depressive disorder not elsewhere classified

ICD-9 Code	N	Name
N_312.9	568	Unspecified disturbance of conduct
N_313.81	313	Oppositional defiant disorder (ODD)
N_314.9	120	Unspecified hyperkinetic syndrome of childhood
N_315.2	320	Other specific developmental learning difficulties
N_315.31	189	Expressive language disorder
N_315.32	157	Mixed receptive-expressive language disorder
N_315.39	327	Other developmental speech disorder
N_315.4	116	Developmental coordination disorder
N_315.5	160	Mixed development disorder
N_315.8	398	Other specified delays in development
N_315.9	479	Unspecified delay in development
N_319	110	Unspecified intellectual disabilities

[00146] The comorbidies in Table 4 tend to cluster into a few different groups: disorders related to anxiety, depression, or mood; prevalent developmental disorders; less prevalent developmental disorders; and autism and related disorders.

[00147] The genotype data and the comorbidity data were then combined to determine how many of the subjects with CNVs in Tier 1 or 2 mGluR network genes also had comorbidities. It was found that 316 of the subjects with such a CNV also had at least one comorbidity (about 18% of the CNV-positive subjects or about 12% of the total subjects) while 114 of the subjects without a Tier 1 or 2 mGluR network gene CNV had at least one comorbidity (about 15% of the CNV-negative subjects or about 4% of the total subjects). This difference showed a P value of 0.118. Thus, comorbidities tended to be more common in CNV-positive than in CNV-negative subjects overall. When only subjects identifying as white ethnicity are considered, there was a highly significant correlation between mGluR CNVs and ADHD comorbidities. Specifically, 218 of 1483 subjects had at least one CNV in a Tier 1 or 2 mGluR network gene, and, of

those 218 subjects, 169 also had a comorbidity whereas 49 did not. That difference showed a P value of 0.004.

[00148] The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the embodiments. The foregoing description and Examples detail certain embodiments and describes the best mode contemplated by the inventors. It will be appreciated, however, that no matter how detailed the foregoing may appear in text, the embodiment may be practiced in many ways and should be construed in accordance with the appended claims and any equivalents thereof.

[00149] As used herein, the term about refers to a numeric value, including, for example, whole numbers, fractions, and percentages, whether or not explicitly indicated. The term about generally refers to a range of numerical values (e.g., +/-5-10% of the recited range) that one of ordinary skill in the art would consider equivalent to the recited value (e.g., having the same function or result). When terms such as at least and about precede a list of numerical values or ranges, the terms modify all of the values or ranges provided in the list. In some instances, the term about may include numerical values that are rounded to the nearest significant figure.

Table 1

Chr:Start-Stop(hg19)	NumSNP	Length	State, CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	ACTR2
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	ALDOA
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	APP
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	APP
chr14:96684770-96688669	4	3,900	1	rs4905466	rs4905469	14.379	0	BDKRB2
chr8:60997355-61008986	10	11,632	1	rs1464327	rs2611360	12.59	92437	CA8
chr8:60654261-60775727	18	121,467	1	rs1949102	rs7822560	11.681	325696	CA8
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	CIC
chr3:2189641-2223722	19	34,082	1	rs2729015	rs7613165	52.462	0	CNTN4
chr3:234726-6328081	2293	6,093,356	3	rs7632811	rs1595039	106.207	0	CNTN4
chr17:43657921-43728376	4	70,456	1	rs9898857	rs417968	10.243	0	CRHR1
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	CTNNA2
chr7:153331061-153608121	32	277,061	3	rs4595033	rs12673076	37.54	0	DPP6
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	FPR1
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	GNAO1
chr16:56362725-56384720	13	21,996	1	rs2241952	rs3790113	20.256	0	GNAO1
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	GNAQ
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	GRIK1
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	GRIK1
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	GRM1
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	GRM1
chr7:85774549-86281198	56	506,650	3	rs41440	rs1024516	24.091	0	GRM3
chr11:88696662-88744425	11	47,764	3	rs477399	rs7932640	10.213	0	GRM5
chr11:88696662-88744425	11	47,764	3	rs477399	rs7932640	10.213	0	GRM5
chr3:7405044-7411730	3	6,687	1	rs13091584	rs7647001	16.073	0	GRM7
chr3:7405044-7411730	3	6,687	1	rs13091584	rs7647001	16.073	0	GRM7
chr7:125999649-126219766	52	220,118	1	rs714237	rs2299470	25.109	0	GRM8

Chr:Start-Stop(hg19)	NumSNP	Length	State, CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr7:125999649-126219766	52	220,118	1	rs714237	rs2299470	25.109	0	GRM8
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	GSN
chr5:78629346-78765405	28	136,060	1	rs9293769	rs7710089	19.586	0	HOMER1
chr5:78661854-78673236	5	11,383	1	rs7732902	rs12187625	11.269	0	HOMER1
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	LARP7
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	MX1
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	MX1
chr2:152065396-152499580	79	434,185	3	rs289871	rs4664494	89.838	0	NMI
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	PCBP3
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	PCBP3
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	PPP2R1A
chr11:198510-244552	23	46,043	1	rs3802985	rs2272566	13.271	0	PSMD13
chr2:152065396-152499580	79	434,185	3	rs289871	rs4664494	89.838	0	RIF1
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	RUVBL2
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	RYR1
chr6:1171596-29895228	43	28,723,633	0	rs3128994	rs9259831	43.568	0	SERPINB9
chr6:2585208-31281876	-2	28,696,669	1	rs1634746	rs1634747	31.615	0	SERPINB9
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	SETD4
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	SETD4
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	SHANK1
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	SLC7A10
chr3:171220708-171220919	3	212	1	cnvi0011707	cnvi0011705	9.195	42511	TNIK

Table 2

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	ACAT2
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	ACTR2
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	ADD2
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	ADRA2A
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	ALDOA
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	ANXA2
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	APP
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	APP
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	APTX
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	ARHGAP24
chr14:96684770-96688669	4	3,900	1	rs4905466	rs4905469	14.379	0	BDKRB2
chr8:60997355-61008986	10	11,632	1	rs1464327	rs2611360	12.59	92437	CA8
chr8:60654261-60775727	18	121,467	1	rs1949102	rs7822560	11.681	325696	CA8
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	CALB2
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	CALM2
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	CALM3
chr7:44376785-44388619	4	11,835	1	rs12535537	rs10257749	12.04	11555	CAMK2B
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	CIC
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	CNR1
chr17:43657921-43728376	4	70,456	1	rs9898857	rs417968	10.243	0	CRHR1
chr12:84152210-113464649	5560	29,312,440	1	rs10862748	rs16942470	28.181	0	DCN
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	FPR1
chr15:73186518-94501564	4223	21,315,047	1	rs1947219	rs4344687	34.841	0	FURIN
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	FYN
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	GLP1R
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	GNAO1
chr16:56362725-56384720	13	21,996	1	rs2241952	rs3790113	20.256	0	GNAO1
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	GNAQ

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	GOT1
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	GRIK1
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	GRIK1
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	GRM1
chr7:85774549-86281198	56	506,650	3	rs41440	rs1024516	24.091	0	GRM3
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	GRM4
chr11:88696662-88744425	11	47,764	3	rs477399	rs7932640	10.213	0	GRM5
chr3:7405044-7411730	3	6,687	1	rs13091584	rs7647001	16.073	0	GRM7
chr7:125999649-126219766	52	220,118	1	rs714237	rs2299470	25.109	0	GRM8
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	GSN
chr5:78661854-78673236	5	11,383	1	rs7732902	rs12187625	11.269	0	HOMER1
chr5:78629346-78765405	28	136,060	1	rs9293769	rs7710089	19.586	0	HOMER1
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	HSP90AB1
chr3:234726-6328081	2293	6,093,356	3	rs7632811	rs1595039	106.207	0	ITPR1
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	LAMA4
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	LRP2BP
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	LTA
chr6:31281438-31878433	-8677	596,996	1	cnvi0006173	rs519417	56.15	0	LTA
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	MARK4
chr18:58316345-58573151	29	256,807	1	rs9964060	rs7233420	16.278	276344	MC4R
chr18:58267843-58310343	9	42,501	3	rs7240781	rs1346831	19.841	227842	MC4R
chr18:58117122-58120972	5	3,851	1	rs9967057	rs2000778	14.81	77121	MC4R
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	MRPL14
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	MRPS16
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	MX1
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	MX1
chr8:84037048-138506934	11020	54,469,887	1	rs13265895	rs1849692	72.228	0	MYC
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	MYO6
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	NANS

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr2:152065396-152499580	79	434,185	3	rs289871	rs4664494	89.838	0	NMI
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	NPY2R
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	PAFAH1B3
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	PCBP1
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	PCBP3
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	PCBP3
chr5:140225908-140233387	8	7,480	1	rs7730895	rs10054866	22.285	0	PCDHA4
chr5:140227999-140232346	3	4,348	0	rs4151689	rs17119246	10.222	0	PCDHA4
chr5:140227999-140232346	3	4,348	1	rs4151689	rs17119246	14.695	0	PCDHA4
chr5:140225908-140233387	8	7,480	1	rs7730895	rs10054866	18.25	0	PCDHA4
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	PCMT1
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	PDCD5
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	PHKB
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	PHKG2
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	PLA2G7
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	PLCG2
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	PPP2R1A
chr17:64287309-64288738	4	1,430	1	cnvi0008597	cnvi0008599	18.218	10188	PRKCA
chr17:64287309-64288738	4	1,430	1	cnvi0008597	cnvi0008599	15.126	10188	PRKCA
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	PRLHR
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	PRMT1
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	PSAT1
chr9:81429567-81443855	7	14,289	3	rs12345239	rs6559415	5.259	484558	PSAT1
chr11:198510-244552	23	46,043	1	rs3802985	rs2272566	13.271	0	PSMD13
chr14:22513116-32242747	1997	9,729,632	1	rs4982546	rs17098165	31.673	0	PSME1
chr1:188802542-196412070	1346	7,609,529	1	rs10158341	rs12075206	61.486	0	RGS2
chr2:152065396-152499580	79	434,185	3	rs289871	rs4664494	89.838	0	RIF1
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	RUVBL2
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	RYR1

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	SCTR
chr6:1171596-29895228	43	28,723,633	0	rs3128994	rs9259831	43.568	0	SERPINB9
chr6:2585208-31281876	-2	28,696,669	1	rs1634746	rs1634747	31.615	0	SERPINB9
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	SET
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	SETD4
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	SETD4
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	SHANK1
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	SIAH1
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	SNCA
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	SYK
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	TCP1
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	TEAD3
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	TFAM
chr15:27740007-30366247	464	2,626,241	1	rs6497213	rs10152753	44.251	0	TJP1
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	TLR10
chr3:171220708-171220919	3	212	1	cnvi0011707	cnvi0011705	9.195	42511	TNIK
chr6:19044000-31286381	-6774	12,242,382	0	rs6922929	rs9265057	32.224	0	TUBB
chr6:2585208-31281876	-2	28,696,669	1	rs1634746	rs1634747	31.615	0	TUBB
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	TXN
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	UCHL1
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	ZAP70

Table 3

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	ACAT2
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	ACTR2
chr8:84037048-138506934	11020	54,469,887	1	rs13265895	rs1849692	72.228	0	ADCY8
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	ADD2
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	ADD3
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	ADRA2A
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	AKAP12
chr15:73186518-94501564	4223	21,315,047	1	rs1947219	rs4344687	34.841	0	AKAP13
chr14:105163532-105268228	14	104,697	3	rs7140154	rs4983387	15.629	0	AKT1
chr14:105126354-105277209	20	150,856	3	rs4074077	rs4983559	14.395	0	AKT1
chr14:105154105-105268228	15	114,124	1	rs3809456	rs4983387	16.554	0	AKT1
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	ALDOA
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	ANK2
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	ANXA2
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	ANXA7
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	APP
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	APP
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	APTX
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	ARHGAP24
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	ARHGEF1
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	ARL3
chr3:234726-6328081	2293	6,093,356	3	rs7632811	rs1595039	106.207	0	ARL8B
chr12:84152210-113464649	5560	29,312,440	1	rs10862748	rs16942470	28.181	0	ATP2B1
chr6:1171596-29895228	43	28,723,633	0	rs3128994	rs9259831	43.568	0	ATXN1
chr6:2585208-31281876	-2	28,696,669	1	rs1634746	rs1634747	31.615	0	ATXN1
chr12:63538458-63630987	15	92,530	1	rs10747983	rs1456040	22.29	0	AVPR1A

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	B4GALT1
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	BANK1
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	BCAR1
chr14:96684770-96688669	4	3,900	1	rs4905466	rs4905469	14.379	0	BDKRB2
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	BRD7
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	C4orf17
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	C9orf25
chr8:60997355-61008986	10	11,632	1	rs1464327	rs2611360	12.59	92437	CA8
chr8:60654261-60775727	18	121,467	1	rs1949102	rs7822560	11.681	325696	CA8
chr12:2245636-2252924	7	7,289	1	rs12579529	rs4765899	11.807	0	CACNA1C
chr12:2245636-2252924	7	7,289	0	rs12579529	rs4765899	41.646	0	CACNA1C
chr12:2245636-2252924	7	7,289	1	rs12579529	rs4765899	19.469	0	CACNA1C
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	CALB2
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	CALM2
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	CALM3
chr7:44376785-44388619	4	11,835	1	rs12535537	rs10257749	12.04	11555	CAMK2B
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	CAMK2G
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	CASP3
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	CASP6
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	CASP7
chr7:115525876-115956129	68	430,254	1	rs6948855	rs12667497	28.379	0	CAV1
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	CCNE1
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	CHAT
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	CHUK
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	CIC
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	CMIP
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	CNR1
chr3:118926656-121160369	362	2,233,714	1	rs4591498	rs4676677	42.841	0	COX17

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	CPE
chr12:84152210-113464649	5560	29,312,440	1	rs10862748	rs16942470	28.181	0	CRADD
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	CREM
chr17:43657921-43728376	4	70,456	1	rs9898857	rs417968	10.243	0	CRHR1
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	CRIPT
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	CSNK2A2
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	CSNK2B
chr6:31281438-31878433	-8677	596,996	1	cnvi0006173	rs519417	56.15	0	CSNK2B
chr12:84152210-113464649	5560	29,312,440	1	rs10862748	rs16942470	28.181	0	DCN
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	DDIT4
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	DIRAS2
chr17:7088923-7385454	57	296,532	3	rs11650232	rs3760422	2.875	0	DLG4
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	DNM1
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	DST
chr1:1227897-1273116	14	45,220	3	rs3737721	rs307371	16.779	0	DVL1
chr1:1163804-1314172	-103	150,369	3	rs7515488	rs2477777	25.97	0	DVL1
chr1:1191870-1314172	-109	122,303	3	rs3818646	rs2477777	21.258	0	DVL1
chr1:1239339-1307872	-123	68,534	3	rs11260584	rs2477774	18.526	0	DVL1
chr17:7088923-7385454	57	296,532	3	rs11650232	rs3760422	2.875	0	DVL2
chr8:144656187-144687092	17	30,906	3	rs12546272	rs896962	17.039	0	EEF1D
chr13:100580353-112257226	3428	11,676,874	1	rs10851110	rs1341154	52.726	0	EFNB2
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	EPB41L2
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	ESR1
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	ETHE1
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	FAS
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	FFAR1
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	FFAR2
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	FPR1

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr12:69925695-70075933	47	150,239	1	rs518634	rs775474	15.726	0	FRS2
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	FSHR
chr2:49533498-49537795	4	4,298	1	rs2350017	rs1991387	15.685	151832	FSHR
chr15:73186518-94501564	4223	21,315,047	1	rs1947219	rs4344687	34.841	0	FURIN
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	FXN
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	FYN
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	GABRR1
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	GABRR2
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	GC
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	GFI1B
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	GFPT1
chr12:84152210-113464649	5560	29,312,440	1	rs10862748	rs16942470	28.181	0	GIT2
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	GJA1
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	GLP1R
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	GNAO1
chr16:56362725-56384720	13	21,996	1	rs2241952	rs3790113	20.256	0	GNAO1
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	GNAQ
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	GOT1
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	GPM6A
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	GRIA2
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	GRIK1
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	GRIK1
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	GRM1
chr7:85774549-86281198	56	506,650	3	rs41440	rs1024516	24.091	0	GRM3
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	GRM4
chr11:88696662-88744425	11	47,764	3	rs477399	rs7932640	10.213	0	GRM5
chr3:7405044-7411730	3	6,687	1	rs13091584	rs7647001	16.073	0	GRM7
chr7:125999649-126219766	52	220,118	1	rs714237	rs2299470	25.109	0	GRM8

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	GSK3A
chr3:118926656-121160369	362	2,233,714	1	rs4591498	rs4676677	42.841	0	GSK3B
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	GSN
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	HABP4
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	HAND2
chr6:19044000-31286381	-6774	12,242,382	0	rs6922929	rs9265057	32.224	0	HLA-A
chr6:2585208-31281876	-2	28,696,669	1	rs1634746	rs1634747	31.615	0	HLA-A
chr6:19044000-31286381	-6774	12,242,382	0	rs6922929	rs9265057	32.224	0	HLA-C
chr6:2585208-31281876	-2	28,696,669	1	rs1634746	rs1634747	31.615	0	HLA-C
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	HLA-DQA2
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	HMGN1
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	HMGN1
chr5:162867195-162958461	20	91,267	1	rs2069347	rs7722476	13.271	0	HMMR
chr5:78661854-78673236	5	11,383	1	rs7732902	rs12187625	11.269	0	HOMER1
chr5:78629346-78765405	28	136,060	1	rs9293769	rs7710089	19.586	0	HOMER1
chr15:73186518-94501564	4223	21,315,047	1	rs1947219	rs4344687	34.841	0	HOMER2
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	HSP90AB1
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	HSPA1A
chr6:31281438-31878433	-8677	596,996	1	cnvi0006173	rs519417	56.15	0	HSPA1A
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	HSPA1B
chr6:31281438-31878433	-8677	596,996	1	cnvi0006173	rs519417	56.15	0	HSPA1B
chr7:75337644-77143217	201	1,805,574	1	rs10954377	rs6976567	29.447	0	HSPB1
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	IL4R
chr3:234726-6328081	2293	6,093,356	3	rs7632811	rs1595039	106.207	0	IL5RA
chr15:73186518-94501564	4223	21,315,047	1	rs1947219	rs4344687	34.841	0	IQGAP1
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	ITGB2
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	ITGB2
chr3:234726-6328081	2293	6,093,356	3	rs7632811	rs1595039	106.207	0	ITPR1

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	ITPR3
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	KCNE1
chr21:35726698-35904697	53	178,000	3	rs4817646	rs7280739	93.548	0	KCNE1
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	KCNE1
chr17:68408395-68506682	20	98,288	1	rs12601221	rs7218368	15.131	232212	KCNJ2
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	KCNN4
chr20:62038277-62053754	7	15,478	3	rs1801475	rs3893041	7.196	0	KCNQ2
chr20:62045709-62053754	4	8,046	3	rs2281570	rs3893041	7.185	0	KCNQ2
chr8:84037048-138506934	11020	54,469,887	1	rs13265895	rs1849692	72.228	0	KCNQ3
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	KCNQ5
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	KDR
chr5:132036252-132114847	11	78,596	1	rs1468216	rs30514	12.981	0	KIF3A
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	KIT
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	KLK10
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	LAMA4
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	LOC154092
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	LRP2BP
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	LTA
chr6:31281438-31878433	-8677	596,996	1	cnvi0006173	rs519417	56.15	0	LTA
chr14:22513116-32242747	1997	9,729,632	1	rs4982546	rs17098165	31.673	0	LTB4R
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	MAD2L1BP
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	MAP3K10
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	MAP3K7
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	MAPK14
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	MAPK3
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	MARCKS
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	MARK4
chr18:58316345-58573151	29	256,807	1	rs9964060	rs7233420	16.278	276344	MC4R

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr18:58267843-58310343	9	42,501	3	rs7240781	rs1346831	19.841	227842	MC4R
chr18:58117122-58120972	5	3,851	1	rs9967057	rs2000778	14.81	77121	MC4R
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	MLLT3
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	MPHOSPH6
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	MRPL14
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	MRPS12
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	MRPS16
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	MRPS6
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	MRPS6
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	MX1
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	MX1
chr8:84037048-138506934	11020	54,469,887	1	rs13265895	rs1849692	72.228	0	MYC
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	MYO6
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	NANS
chr8:84037048-138506934	11020	54,469,887	1	rs13265895	rs1849692	72.228	0	NCALD
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	NFKB2
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	NFKBIB
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	NFKBIE
chr2:152065396-152499580	79	434,185	3	rs289871	rs4664494	89.838	0	NMI
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	NPHP1
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	NPY2R
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	NUCB1
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	OPRM1
chr6:154379152-154393884	5	14,733	1	rs3823010	rs3778153	18.342	0	OPRM1
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	PAFAH1B3
chr5:101558083-102529401	120	971,319	1	rs4323206	rs26819	39.848	0	PAM
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	PARD6A
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	PCBP1

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	PCBP3
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	PCBP3
chr5:140225908-140233387	8	7,480	1	rs7730895	rs10054866	22.285	0	PCDHA4
chr5:140227999-140232346	3	4,348	0	rs4151689	rs17119246	10.222	0	PCDHA4
chr5:140227999-140232346	3	4,348	1	rs4151689	rs17119246	14.695	0	PCDHA4
chr5:140225908-140233387	8	7,480	1	rs7730895	rs10054866	18.25	0	PCDHA4
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	PCMT1
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	PCNT
chr21:47836122-47856106	5	19,985	1	rs2839245	rs2236616	11.082	0	PCNT
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	PCNT
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	PCP4
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	PCP4
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	PDCD5
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	PDCL
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	PHKB
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	PHKG2
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	PLA2G7
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	PLCG2
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	PLEKHA4
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	PLK1
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	POLR2C
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	PPEF2
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	PPP1R14A
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	PPP2R1A
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	PPP3CA
chr10:46961667-47748912	104	787,246	3	rs506372	rs3013867	193.838	0	PPYR1
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	PPYR1
chr10:46961667-47748912	104	787,246	3	rs506372	rs3013867	112.468	0	PPYR1

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr10:46961667-47149117	12	187,451	3	rs506372	rs4979753	13.078	0	PPYR1
chr10:46961667-47703613	102	741,947	3	rs506372	rs4128664	75.136	0	PPYR1
chr17:64287309-64288738	4	1,430	1	cnvi0008597	cnvi0008599	18.218	10188	PRKCA
chr17:64287309-64288738	4	1,430	1	cnvi0008597	cnvi0008599	15.126	10188	PRKCA
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	PRKCG
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	PRKG1
chr10:53388223-53399900	4	11,678	1	rs7915186	rs4486574	14.875	0	PRKG1
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	PRLHR
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	PRMT1
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	PSAT1
chr9:81429567-81443855	7	14,289	3	rs12345239	rs6559415	5.259	484558	PSAT1
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	PSG9
chr11:198510-244552	23	46,043	1	rs3802985	rs2272566	13.271	0	PSMD13
chr14:22513116-32242747	1997	9,729,632	1	rs4982546	rs17098165	31.673	0	PSME1
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	PTGIR
chr12:84152210-113464649	5560	29,312,440	1	rs10862748	rs16942470	28.181	0	PTPN11
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	RABAC1
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	RALB
chr14:22513116-32242747	1997	9,729,632	1	rs4982546	rs17098165	31.673	0	RBM23
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	REL
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	RELB
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	RGS10
chr1:188802542-196412070	1346	7,609,529	1	rs10158341	rs12075206	61.486	0	RGS13
chr1:191836316-191875752	12	39,437	1	rs2211195	rs9427811	47.094	251840	RGS18
chr1:188802542-196412070	1346	7,609,529	1	rs10158341	rs12075206	61.486	0	RGS18
chr1:191836316-191875752	12	39,437	1	rs2211195	rs9427811	47.13	251840	RGS18
chr1:188802542-196412070	1346	7,609,529	1	rs10158341	rs12075206	61.486	0	RGS2
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	RHOH

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr11:198510-244552	23	46,043	1	rs3802985	rs2272566	13.271	0	RIC8A
chr12:84152210-113464649	5560	29,312,440	1	rs10862748	rs16942470	28.181	0	RIC8B
chr2:152065396-152499580	79	434,185	3	rs289871	rs4664494	89.838	0	RIF1
chr6:1171596-29895228	43	28,723,633	0	rs3128994	rs9259831	43.568	0	RIPK1
chr6:2585208-31281876	-2	28,696,669	1	rs1634746	rs1634747	31.615	0	RIPK1
chr8:84037048-138506934	11020	54,469,887	1	rs13265895	rs1849692	72.228	0	RIPK2
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	RPL12
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	RRAD
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	RTN4
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	RUVBL2
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	RYR1
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	SCTR
chr8:84037048-138506934	11020	54,469,887	1	rs13265895	rs1849692	72.228	0	SDC2
chr6:1171596-29895228	43	28,723,633	0	rs3128994	rs9259831	43.568	0	SERPINB9
chr6:2585208-31281876	-2	28,696,669	1	rs1634746	rs1634747	31.615	0	SERPINB9
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	SET
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	SETD4
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	SETD4
chr12:84152210-113464649	5560	29,312,440	1	rs10862748	rs16942470	28.181	0	SH2B3
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	SHANK1
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	SIAH1
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	SIRT2
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	SLC1A1
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	SMPD3
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	SNAP91
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	SNCA
chr6:19044000-31286381	-6774	12,242,382	0	rs6922929	rs9265057	32.224	0	SOX4
chr6:1171596-29895228	43	28,723,633	0	rs3128994	rs9259831	43.568	0	SOX4

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr6:21599766-21623715	6	23,950	1	rs9295513	rs1744855	10.637	917	SOX4
chr6:2585208-31281876	-2	28,696,669	1	rs1634746	rs1634747	31.615	0	SOX4
chr8:84037048-138506934	11020	54,469,887	1	rs13265895	rs1849692	72.228	0	SPAG1
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	SPG7
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	SPP1
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	SPTBN1
chr13:34141695-34143447	3	1,753	1	cnvi0006685	rs9285097	14.343	0	STARD13
chr13:34141695-34143447	3	1,753	1	cnvi0006685	rs9285097	13.354	0	STARD13
chr13:34141695-34143447	3	1,753	0	cnvi0006685	rs9285097	14.964	0	STARD13
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	STRN4
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	STX4
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	STXBP1
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	SULT1E1
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	SUMO4
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	SYK
chr12:79441371-79473659	7	32,289	3	rs17273032	rs11838060	15.101	0	SYT1
chr2:160064395-160668661	110	604,267	1	rs6737837	rs1549579	37.853	0	TANC1
chr2:161901301-162018643	25	117,343	1	rs4664395	rs1267059	21.357	0	TANK
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	TAOK2
chr19:1114119-1876566	213	762,448	3	rs3746162	rs10414308	25.766	0	TCF3
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	TCP1
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	TEAD3
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	TFAM
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	TGFA
chr21:14601415-48084989	8249	33,483,575	3	rs2775537	rs2839378	6900.018	0	TIAM1
chr21:14901920-48084989	8239	33,183,070	3	rs12626247	rs2839378	11089.459	0	TIAM1
chr15:27740007-30366247	464	2,626,241	1	rs6497213	rs10152753	44.251	0	TJP1
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	TLR10

Chr:Start-Stop(hg19)	NumSNP	Length	State,CN	StartSNP	EndSNP	Confidence	Distance From Gene	mGluR Gene
chr3:171220708-171220919	3	212	1	cnvi0011707	cnvi0011705	9.195	42511	TNIK
chr4:2768630-2772530	3	3,901	1	rs6600766	rs7695151	12.121	10527	TNIP2
chr16:16348605-90291153	14331	73,942,549	4	rs2856546	rs12325137	10.397	0	TRADD
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	TRAF1
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	TRIM2
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	TRPC3
chr12:84152210-113464649	5560	29,312,440	1	rs10862748	rs16942470	28.181	0	TRPV4
chr6:31289284-56929863	15402	25,640,580	3	rs9265170	cnvi0015437	25.647	0	TTBK1
chr6:69900102-165298477	19424	95,398,376	1	rs779484	rs1511063	38.802	0	TTK
chr6:19044000-31286381	-6774	12,242,382	0	rs6922929	rs9265057	32.224	0	TUBB
chr6:2585208-31281876	-2	28,696,669	1	rs1634746	rs1634747	31.615	0	TUBB
chr9:1399761-136852891	25442	135,453,131	1	rs12341621	rs2789864	36.66	0	TXN
chr4:28602089-187390861	26883	158,788,773	1	rs16880825	rs1376534	32.409	0	UCHL1
chr10:33340331-123920784	17036	90,580,454	1	rs10430560	rs1885516	36.263	0	VCL
chr19:22609759-55294329	-4174	32,684,571	3	rs7251413	rs2569676	20.948	0	WDR62
chr7:75337644-77143217	201	1,805,574	1	rs10954377	rs6976567	29.447	0	YWHAG
chr8:84037048-138506934	11020	54,469,887	1	rs13265895	rs1849692	72.228	0	YWHAZ
chr2:38328178-128536280	15926	90,208,103	1	rs232542	rs7608627	30.628	0	ZAP70

What is Claimed is:

1. Use of fasoracetam in the preparation of a medicament for treating Tourette syndrome (TS) in a subject determined to have at least one copy number variation (CNV) in a metabotropic glutamate receptor (mGluR) network gene, wherein an effective amount of fasoracetam is to be administered to the subject, thereby treating TS.

2. The use according to claim 1, wherein the CNV is a duplication or deletion.

3. The use of any one of claims 1 or 2, wherein fasoracetam is to be administered at a dose of 50-400 mg, 100-400 mg, or 200-400 mg, and wherein the dose is to be administered once, twice, or three times daily.

4. The use according to any one of claims 1-3, wherein the TS is one or more of: persistent (chronic) motor tic disorder, persistent (chronic) vocal tic disorder, or provisional tic disorder.

5. The use according to any one of claims 1-4, wherein the subject is between the ages of 5 and 17, 5 and 8, 8 and 17, 8 and 12, or 12 and 17.

6. The use according to any one of claims 1-5, wherein the fasoracetam is to be administered in combination with another pharmaceutical or non-pharmaceutical therapy.

7. The use according to any one of claims 1-6, wherein tic symptoms are reduced in the subject following at least 1 week, such as at least 2 weeks, such as at least 3 weeks, such as at least 4 weeks of the treatment with fasoracetam.

8. The use according to claim 7, wherein the tic symptoms comprise frequency and/or degree of movement.

9. The use according to any one of claims 1-8, wherein symptoms of inattentiveness, hyperactivity, and/or impulsiveness are reduced in the subject following at least 1 week, such as at least 2 weeks, such as at least 3 weeks, such as at least 4 weeks of treatment with the activator.

10. The use according to any one of claims 1-9, wherein the subject also has obsessive compulsive disorder (OCD), and wherein symptoms of OCD are reduced in the subject following at least 1 week, such as at least 2 weeks, such as at least 3 weeks, such as at least 4 weeks of treatment with the activator.

11. The use according to claim 1, wherein the use comprises detecting CNVs in mGluR network genes by subjecting a sample isolated from said subject to a screen that assesses CNVs in at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 mGluR network genes.

12. The use according to claim 11, wherein CNVs in mGluR network genes are determined by subjecting the sample to a screen that assesses CNVs in at least 5, 6, 7, 8, 9, 10, 15, 20, 30, 40, 50, 60, 70, or all of Tier 1 mGluR network genes.

13. The use according to claim 11, wherein CNVs in mGluR network genes are determined by subjecting the sample to a screen that assesses CNVs in at least 50, at least 100, at least 150, at least 175, or all of Tier 2 mGluR network genes.

14. The use according to any one of claims 1-13, wherein the subject has TS as well as one or more of obsessive compulsive disorder (OCD), schizophrenia, and attention deficit hyperactivity disorder (ADHD).