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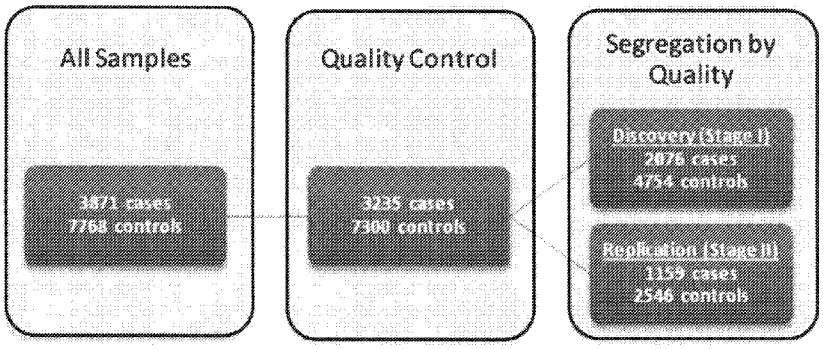


FIG. 1

(57) Abstract: Methods for diagnosing and treating autism spectral disorders are encompassed. In one embodiment, a patient is diagnosed as having autism spectral disorder if at least one CNV in an mGluR network gene is found in a patient sample. Patients with at least one mGluR network gene CNV are effectively treated with (+) - 5-oxo-Dprolinepiperidinamide monohydrate (NS-105) (also known as NFC-1 or fasoracetam).

WO 2016/205348 A1

METHODS OF DIAGNOSING AND TREATING AUTISM

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority to United States Nonprovisional Patent Application No. 14/740, 230, filed June 15, 2015, as well as to United States Provisional Patent Applications 62/215,628, 62/215,633, 62/215,636, and 62/215,673, all of which were filed September 8, 2015. All of the above-listed applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[002] Methods for diagnosing and treating autism spectrum disorders are provided.

BACKGROUND OF THE INVENTION

[003] Autism spectrum disorder (ASD) is a range of complex neurodevelopmental disorders characterized by mild to severe social impairments, communication difficulties, and restrictive or repetitive behaviors. ASD, previously known as pervasive developmental disorders (PDD), is an umbrella term that includes various conditions that used to be diagnosed separately such as autistic disorder (or classic autism), Asperger's syndrome, childhood disintegrative disorder, Rett's disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and social (pragmatic) communication disorder (SCD). (Vieux *et al.,* "Autism

Spectrum Disorder: DSM-5 Changes, Epidemiology & Outcomes," *The Carlat Report,* Vol. 11, Issue 6, June 2013.)

[004] ASD occurs in all racial, ethnic, and socioeconomic groups. (Durkin et al., "Socioeconomic inequality in the prevalence of autism spectrum disorder: evidence from a U.S. cross-sectional study," *PLOS One,* 5(7), July 2010.) In 2013, ASD was estimated to occur in 2% of children between the ages of 6 and 17, a significant increase from the estimate of 1.16% in 2007. (*see, e.g.,* Blumberg *et. al.*, *National Health Statistics Reports,* No. 65, March 20, 2013) While it is not known how many adults suffer from ASD, a British study reported that 1.8% adult men and 0.2% adult women have ASD. (Brugha *et al.*, "Epidemiology of autism spectrum disorders in adults in the community in England," *Arch. Gen. Psych.* 68: 459-66, 2011.)

[005] With the increased incidence of ASD comes increased costs to society. The CDC estimates that it costs between $17,000 -$21,000 more per year to care for a child diagnosed with ASD as compared to a child not diagnosed with ASD. Medical costs alone for children diagnosed with ASD can be elevated by $4,100-$6,200 per year, with behavioral interventions for children diagnosed with ASD costing $40,000 -$60,000 per year. It is estimated that total societal costs of caring for children diagnosed with ASD were over $9 billion in 2011.

[006] Some risk factors and patterns have emerged to assist in diagnosing ASD, and various treatment regimes are often used on a trial and error basis. While there have been improvements in diagnosis and treatment of ASD, there remains a need for consistent diagnosis and treatment of ASD using a genetic approach.

SUMMARY OF THE INVENTION

[007] In accordance with the description, a method for treating autism spectrum disorder (ASD) in patients having at least one CNV in a GRM/mGluR network gene, as shown in Figures 15A-D, comprising administering a therapeutically effective amount of fasoracetam (NS-105 or NFC-1), or member of the piracetam family of nootropic agents, is encompassed. CNVs in GRM/mGluR network genes are sensitive and specific biomarkers for diagnosing ASD. The inventors have identified drug candidates that specifically activate mGluRs, restoring normal neurophysiology in ASD patients having at least one CNV in any of the GRM/mGluR network genes shown in Figures 15A-D.

[008] In some embodiments, a CNV in at least one of the GRM/mGluR network genes recited in Tables 16-18 indicates a diagnosis of ASD. These genes include ACAT1, ACAT2, ACCN1, ACCN2, ACP1, ACTB, ACTR2, ADA, ADCY1, ADD1, ADD2, ADORA1, ADRA1B, ADRA2A, ADRA2C, ADRB2, ADRBK1, ALDOA, ANXA2, APP, APTX, AQP1, ARHGAP24, ARL15, ARRB1, ARRB2, ATXN7L3, BDKRB1, BDKRB2, BTBD2, BTG2, C17orf44, C1orf116, C7orf25, CA8, CACNA1B, CACYBP, CALB2, CALM1, CALM2, CALM3, CAMK1, CAMK2B, CAMK4, CCNB1, CDC42, CENTG1, CHGB, CHP, CHRM2, CHRM3, CIC, CMPK, CNP, CNR1, CNTN4, COPB2, CRHR1, CTNNA2, CYCS, DCN, DHCR7, DISC1, DLST, DPP6, DRD2, DRD3, DSTN, DYNLL1, ECHS1, EGFR, EIF3S3, ERBB2, F2R, F2RL2, F2RL3, F3, FKBP3, FPR1, FSCN1, FURIN, FYN, GAPDH, GLP1R, GLP2R, GNA15, GNAI1, GNAI2, GNAI3, GNAO1, GNAQ,

GNB2L1, GOT1, GP1BA, GPR26, GRB2, GRB7, GRIA1, GRIK1, GRIK3, GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, GRM8, GSN, HBXIP, HD, HNRPA3, HOMER1, HOMER3, HRPT2, HSP90AB1, HTR2A, IL8RB, IMPDH2, IQGAP2, ITGB1, ITGB7, ITPR1, KIAA0090, KIAA1683, LAMA4, LARP7, LRP2BP, LRRC59, LTA, LYAR, LYN, MAP4, MAPK1, MAPT, MARK4, MC4R, MGC11082, MRPL14, MRPS16, MTHFD1, MTNR1A, MTNR1B, MX1, MYC, MYO6, NANS, NARG1, NCK1, NEGR1, NFKBIA, NLN, NMI, NPY2R, NUDC, OPRD1, PAFAH1B3, PCBP1, PCBP3, PCDHA4, PCID1, PCMT1, PDCD5, PDE1B, PDE1C, PDE6G, PGM1, PHKB, PHKG2, PICK1, PIK3CA, PIK3R1, PLA2G7, PLCB1, PLCB3, PLCG2, PPIH, PPP2R1A, PRDX1, PRKCA, PRLHR, PRMT1, PRPSAP1, PSAT1, PSEN1, PSMA1, PSMC1, PSMD1, PSMD11, PSMD13, PSMD6, PSME1, PTHR2, PXN, PYGL, PYGM, QRICH2, RAB2, RALA, RANBP1, RAP2A, RCC1, RCC2, RGS12, RGS2, RHOA, RIF1, RPA2, RPLP2, RPN2, RPS14, RRM1, RUVBL2, RYR1, RYR2, S100A6, SACS, SARS, SCTR, SDC3, SELE, SERPINB9, SET, SETD4, SF3B14, SGTB, SHANK1, SHBG, SIAH1, SLC2A1, SLC6A3, SLC7A10, SNCA, SNRPB2, SOCS6, SOCS7, SORD, SRC, STAU1, STRAP, STX12, SYK, TBCA, TBXA2R, TCP1, TEAD3, TFAM, TGM2, TJP1, TK1, TLR10, TMEM4, TNIK, TPI1, TRAF2, TRMT112, TUBA1, TUBA1A, TUBA1B, TUBA2, TUBB, TUBG1, TXN, TXNDC4, TXNL2, TYMS, UBQLN4, UCHL1, USP24, VHL, VIPR1, YWHAQ, and ZAP70.

[009] Moreover, patients with at least one CNV in a GRM/mGluR network gene will see improvement in ASD upon administration of a therapeutically effective

amount of a member of the piracetam family of nootropic agents, as described in F. Gualtieri et al., Curr. Phann. Des., 8: 125-38 (2002). In one embodiment, the treating agent is a pyroglutamide. Details regarding the preparation and formulation of pyroglutamides, which may be used in the practice of this invention, are provided in U.S. Pat. No. 5,102,882 to Kimura et al. In one embodiment the nootropic agent for the treatment of ASD in patients determined to have one or more of the CNVs indicative as set forth in Figures 15A-D, is (+)-5-oxo-Dprolinepiperidinamide monohydrate (fasoracetam; NS-105).

[0010] In one embodiment, the patient has been diagnosed as having pervasive developmental disorder, or one or more conditions selected from autistic disorder (classic autism), Asperger's syndrome, childhood disintegrative disorder, Rett's disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), or social (pragmatic) communication disorder (SCD).

[0011] The CNV may be a duplication or deletion.

[0012] The ASD may be syndromic or non-syndromic.

[0013] In one embodiment, the ASD may be in a patient having 22q11.2 Deletion or Duplication Syndrome, Fetal Valproate Syndrome or Thalidomide Embryopathy.

[0014] In one embodiment, the patient has at least two CNVs in a gene selected from the group consisting of ACAT1, ACAT2, ACCN1, ACCN2, ACP1, ACTB, ACTR2, ADA, ADCY1, ADD1, ADD2, ADORA1, ADRA1B, ADRA2A, ADRA2C, ADRB2, ADRBK1, ALDOA, ANXA2, APP, APTX, AQP1,

ARHGAP24, ARL15, ARRB1, ARRB2, ATXN7L3, BDKRB1, BDKRB2, BTBD2, BTG2, C17orf44, C1orf116, C7orf25, CA8, CACNA1B, CACYBP, CALB2, CALM1, CALM2, CALM3, CAMK1, CAMK2B, CAMK4, CCNB1, CDC42, CENTG1, CHGB, CHP, CHRM2, CHRM3, CIC, CMPK, CNP, CNR1, CNTN4, COPB2, CRHR1, CTNNA2, CYCS, DCN, DHCR7, DISC1, DLST, DPP6, DRD2, DRD3, DSTN, DYNLL1, ECHS1, EGFR, EIF3S3, ERBB2, F2R, F2RL2, F2RL3, F3, FKBP3, FPR1, FSCN1, FURIN, FYN, GAPDH, GLP1R, GLP2R, GNA15, GNAI1, GNAI2, GNAI3, GNAO1, GNAQ, GNB2L1, GOT1, GP1BA, GPR26, GRB2, GRB7, GRIA1, GRIK1, GRIK3, GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, GRM8, GSN, HBXIP, HD, HNRPA3, HOMER1, HOMER3, HRPT2, HSP90AB1, HTR2A, IL8RB, IMPDH2, IQGAP2, ITGB1, ITGB7, ITPR1, KIAA0090, KIAA1683, LAMA4, LARP7, LRP2BP, LRRC59, LTA, LYAR, LYN, MAP4, MAPK1, MAPT, MARK4, MC4R, MGC11082, MRPL14, MRPS16, MTHFD1, MTNR1A, MTNR1B, MX1, MYC, MYO6, NANS, NARG1, NCK1, NEGR1, NFKBIA, NLN, NMI, NPY2R, NUDC, OPRD1, PAFAH1B3, PCBP1, PCBP3, PCDHA4, PCID1, PCMT1, PDCD5, PDE1B, PDE1C, PDE6G, PGM1, PHKB, PHKG2, PICK1, PIK3CA, PIK3R1, PLA2G7, PLCB1, PLCB3, PLCG2, PPIH, PPP2R1A, PRDX1, PRKCA, PRLHR, PRMT1, PRPSAP1, PSAT1, PSEN1, PSMA1, PSMC1, PSMD1, PSMD11, PSMD13, PSMD6, PSME1, PTHR2, PXN, PYGL, PYGM, QRICH2, RAB2, RALA, RANBP1, RAP2A, RCC1, RCC2, RGS12, RGS2, RHOA, RIF1, RPA2, RPLP2, RPN2, RPS14, RRM1, RUVBL2, RYR1, RYR2, S100A6, SACS, SARS, SCTR, SDC3, SELE, SERPINB9, SET, SETD4, SF3B14,

SGTB, SHANK1, SHBG, SIAH1, SLC2A1, SLC6A3, SLC7A10, SNCA, SNRPB2, SOCS6, SOCS7, SORD, SRC, STAU1, STRAP, STX12, SYK, TBCA, TBXA2R, TCP1, TEAD3, TFAM, TGM2, TJP1, TK1, TLR10, TMEM4, TNIK, TPI1, TRAF2, TRMT112, TUBA1, TUBA1A, TUBA1B, TUBA2, TUBB, TUBG1, TXN, TXNDC4, TXNL2, TYMS, UBQLN4, UCHL1, USP24, VHL, VIPR1, YWHAQ, and ZAP70.

[0015] In one embodiment, the CNVs are detected in any type of biological sample taken from a human patient, including but not limited to, body fluids (including blood, urine, serum, gastric lavage), any type of cell (such as brain cells, white blood cells, mononuclear cells) or body tissue.

[0016] Methods for determining whether a patient has a GRM/mGluR network gene CNV include, for example, analyzing the biological sample on a SNP-array, taking into account both LOG-R ratio (intensity data) and BAF (B allele frequency), which assesses allele states. SNP array platforms are commercially available from, for example, Illumina, Affymetrix, and Agilent.

[0017] Other methods for determining whether a patient has a GRM/mGluR network gene CNV include, for example, CGH (comparative genomic hybridization), which utilizes intensity data for evaluation of CNVs; whole exome or whole genome sequencing (or targeted sequencing); utilizing specific FISH probes; qPCR; droplet PCR; and taqman probes. Alternatively, certain companies that use proprietary methods for determining the presence or absence of CNVs may be provided samples

to be tested for presence of CNVs in GRM/mGluR network genes in accordance with the methods of the invention.

[0018] Some embodiments include methods of treating autism in a subject comprising administering an effective amount of a nonselective activator of metabotropic glutamate receptors (mGluRs) to a subject, thereby improving at least one symptom of autism. Some embodiments include treating autism in a subject 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 (e.g. as shown in Figures 16-18), thereby improving at least one symptom of autism. Some embodiments include methods of treating autism 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. In some such embodiments, the genetic alteration is a copy number variation (CNV) or single nucleotide variation (SNV). In some such embodiments, the nonselective activator of mGluRs is fasoracetam, such as fasoracetam monohydrate (NS-105 or NFC-1).

[0019] In methods comprising fasoracetam administration, the fasoracetam may be 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. For example, fasoracetam may be administered at a dose of 50-400 mg, 100-400 mg, or

200-400 mg, wherein the dose is administered once, twice, or three times daily. For example, the fasoracetam is administered at a dose of 200-400 mg, such as 200 mg, 300 mg, or 400 mg, wherein the dose is administered twice daily.

[0020] In some of the above embodiments, the subject has a CNV in at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 mGluR network genes. For example, the subject may have a CNV in an mGluR network gene, which is found 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 other cases, the subject may have a CNV in an mGluR network gene that 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 yet other cases the subject may have a CNV in an mGluR network gene that 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 some embodiments, the subject does not have a CNV in one or more of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, or GRM8.

[0021] In some of the above embodiments, the subject is a pediatric subject, for instance between the ages of 5 and 17, 5 and 8, 8 and 17, 8 and 12, or 12 and 17. In other embodiments the subject is an adult.

[0022] In some embodiments above, the nonselective activator of mGluRs is administered in combination with another pharmaceutical or non-pharmaceutical therapy.

[0023] In some of the above embodiments, the subject has been diagnosed with autism spectrum disorder, pervasive developmental disorder, or one or more conditions selected from autistic disorder (classic autism), Asperger's syndrome, childhood disintegrative disorder, Rett's disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and social (pragmatic) communication disorder (SCD). In some cases, the autism is syndromic ASD. In some cases, the patient has ASD and 22q11.2 Deletion or Duplication Syndrome, Fetal Valproate Syndrome or Thalidomide Embryopathy. In some embodiments, the patient does not have any of ADHD, ODD, conduct disorder, TS, anxiety disorder, phobia, or depression. In other cases, the autism patient also has one or more of ADHD, ODD, conduct disorder, TS, anxiety disorder, phobia, or depression.

[0024] Also encompassed herein are methods for diagnosing autism 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 autism if the subject has at least one genetic alteration in a mGluR network gene. Further encompassed are methods for diagnosing autism 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 autism if the

subject has at least one genetic alteration in a mGluR network gene. Additional embodiments include methods for identifying a subject as having autism 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 autism if at least one genetic alteration, such as a CNV, in an mGluR network gene is detected. Further encompassed are methods for diagnosing autism 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 autism, and diagnosing autism if the genetic information suggests that the subject has at least one genetic alteration in a mGluR network gene. Also encompassed are methods of confirming a diagnosis of autism in a subject comprising: obtaining a nucleic acid-comprising sample from a subject diagnosed with autism by a method that comprises 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 autism if the subject has at least one genetic alteration in an mGluR network gene. In any of those methods, the analysis for the presence or absence of at least one genetic alteration in an mGluR network gene can 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.

[0025] In some embodiments, the subject has CNVs in at least two mGluR network genes. In some embodiments, the method comprises 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.

[0026] In some of the above embodiments, the subject is a pediatric subject, such as a subject between the ages of 5 and 17, 5 and 8, 8 and 17, 8 and 12, or 12 and 17. In other embodiments, the subject is an adult subject.

[0027] 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.

[0028] In some embodiments, the 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.

[0029] In some of the above embodiments, the subject has been diagnosed with autism spectrum disorder, pervasive developmental disorder, or one or more conditions selected from autistic disorder (classic autism), Asperger's syndrome, childhood disintegrative disorder, Rett's disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and social (pragmatic) communication disorder (SCD). In some cases, the autism is syndromic ASD. In some cases, the patient has ASD and 22q11.2 Deletion or Duplication Syndrome, Fetal Valproate Syndrome or Thalidomide Embryopathy. In some embodiments, the patient does not have any of ADHD, ODD, conduct disorder, TS, anxiety disorder, phobia, or depression. In other cases, the autism patient also has one or more of ADHD, ODD, conduct disorder, TS, anxiety disorder, phobia, or depression. In some cases, the patient has both autism and ADHD.

[0030] 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.

[0031] 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.

[0032] The accompanying drawings, which are incorporated in and constitute a part of this specification, illustrate several embodiments and together with the description, serve to explain the principles described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] **Figure 1** provides the design of a clinical study. In this two-stage design, 2076 cases vs 4754 controls were used in the discovery cohort (Stage 1), and 1159 cases vs 2546 controls were used for a replication cohort (Stage 2). All samples used passed minimal quality control metrics, but the default quality calls of PennCNV were used to discriminate the discovery cohort (best quality) from the replication cohort (lesser quality.)

[0034] **Figure 2** is a graph showing certain classes of gene pathways, which are disrupted by the ASD-related CNVRs disclosed herein. All genes with exons disrupted by replicated CNVRs were submitted to Ingenuity to ascertain significance of pathway enrichment.

[0035] **Figures 3A-F** are a schematic of a first-degree interactome of the GABAR-A family highlighting copy number defects enriched in cases vs controls.

[0036] **Figure 4** shows a test and treat model for targeting therapeutics to specific pathways defective in disease. The generic test and treat model is shown in black where a molecular diagnostic is used to genetically define a population with

defective pathways that are likely to benefit from a targeted intervention. Examples of trastuzumab as a targeted intervention for HER2 specific breast cancer is shown as well as an extrapolation of behavioral programs and novel therapeutics that are being developed to target ASDs due to defective GABAR-A pathways.

[0037] **Figure 5** shows certain identified genetic marker CNVRs by GWAS predictive of ASDs in European-derived or African-derived populations. The Manhattan plots show the -log 10 transformed P value of association for each CNVR along the genome. Adjacent chromosomes are shown. The regions discovered in Europeans (P 0.0001) that replicated in Africans (P<=0.001) are highlighted with black arrows labeled by chromosome band. GWAS of 4,634 cases vs 4,726 controls in Europeans is shown on top and GWAS of 312 cases vs 4,173 controls in Africans is shown below.

[0038] **Figures 6A-D** show a representative enrichment of certain CNVRs across mGluR network of genes. Nodes of the network are labeled with their gene names, with red and green representing deletions and duplications respectively, while grey nodes lack CNV data. Dark and light colors represent enrichment in cases and controls respectively. The genes defining the network are showed as diamonds, while all other genes are shown as circles. Blue lines indicate evidence of interaction.

[0039] **Figure 7** shows a representative graph of enrichment of optimal CNVRs across the CALM1 network. The first degree directed interaction network defined by CALM1 is shown.

[0040] **Figure 8** shows a diagram of representative study design. Results from this study show that children with ASD and gene changes in mGluR network (mGluR+ASD) were more likely to have Syndromic ASD as compared to children with ASD without abnormalities of mGluR network genes (mGluR-ASD). $P<0.0001$. See US Patent application no. 14/292,480 incorporated herein by reference as though set forth in full.

[0041] **Figure 9** shows significant CNVRs in the mGluR network. The table shows the 10 most significant CNVRs for 189 genes with data in the GFIN for the GRM gene family across a European-derived population, as well as the most significant CNVRs harbored by the GRM mGluR receptors themselves.

[0042] **Figure 10** shows significant CNVRs across genes in the MXD network in European-derived populations. Where large CNVs span multiple genes, the component gene implicated within the MXD gene family interaction network is bolded.

[0043] **Figure 11** shows significant CNVRs across genes in the CALM1 network in European-derived populations.

[0044] **Figure 12** shows CNVRs distinguishing cases from controls significant across both European-derived populations ($P\leq 0.0001$ by Fisher's exact test) and African-derived populations ($P\leq 0.001$). CNVR=copy-number variable region; OR=odds ratio. For each CNVR, the table lists the type (del or dup), the closest gene impacted, the chromosomal band, the approximate size of the defect (Kb), the number of contributing SNPs, the numbers of affected cases and controls, as well as

P-value and odds ratio (OR) from Fisher's exact test for across all populations, and subsets of European-derived and African-derived populations. *Genes with an asterisk (*) harbor CNVRs that disrupt their exons of directly, while those without the asterisk are located in the genomic region around the intergenic CNVRs.

[0045] **Figures 13A-B** show significant gene family interaction networks (GFINs) by network permutation testing (Pperm≤0.05) enriched for CNV defects across at least 5% of cases. The table lists the name and size of gene family tested, the number and frequency of network genes enriched in the second degree gene interaction network, the number and frequency of cases harboring defects across the network, the number and frequency of controls harboring defects across the network, the significance of association by Fisher's exact test, the enrichment of CNV defects in cases, and the significance of that enrichment by 1,000 random network permutations.

[0046] **Figure 14** shows significant individual gene interaction networks ranked by permutation testing. Figure 14 lists the name and gene family member tested, the number and frequency of network genes enriched, the number and frequency of cases harbouring defects, the number and frequency of controls harbouring defects, and the significance of association by Fisher's exact test, the odds ratio of the effect size, and the significance of association by random permutation of network while controlling for number of genes tested. Among other highly ranked first degree gene interaction networks were the nuclear receptor co-repressor 1 (NCOR1; Pfisher ≤1.11E−06, enrichment=13.37, Pperm ≤0.004) and BCL2-

associated athanogene 1 (BAG1; Pfisher ≤2.18E−04, enrichment=15.40, Pperm ≤0.014) networks. NCOR1 is a transcriptional co-regulatory protein that appears to assist nuclear receptors in the downregulation of DNA expression through recruitment of histone deacetylases to DNA promoter regions; it is a principal regulator in neural stem cells. The oncogene BCL2 is a membrane protein that blocks the apoptosis pathway, and BAG1 forms a BCL2-associated athanogene and represents a link between growth factor receptors and antiapoptotic mechanisms. The BAG1 gene has been implicated in age-related neurodegenerative diseases, including Alzheimer's disease.

[0047] **Figures 15A-D** show the raw data described in Examples 1-4. Column A lists the GRM/mGluR network genes that are enriched in patients with ASD. Column B indicates whether the CNV is a duplication or deletion and the genetic start and stop locus. The odds ratio recited in column J recites "none" for any gene where no CNV was found in the control group. In column K, enrichment, the word "case" is indicative of enrichment in CNVs in the associated gene in ASD patients as compared to controls. Finding at least one CNV in any of the genes listed in Figures 15A-D, Column A, indicates a diagnosis of ASD and implicates treatment with NS-105.

[0048] **Figures 16A-D** show 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.

[0049] **Figures 17A-I** show 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 from500 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.

[0050] **Figures 18A-Y** 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.

DESCRIPTION OF PARTICULAR EMBODIMENTS

Definitions

[0051] 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.

[0052] "Autism" and "Autism Spectrum Disorder" (ASD) are used interchangeably herein. As noted earlier, autism or ASD comprises a range of complex neurodevelopmental disorders characterized by symptoms such as mild to severe social impairments, communication difficulties, and restrictive or repetitive behaviors. ASD, previously known as pervasive developmental disorders (PDD), is an umbrella term that includes various conditions that used to be diagnosed

separately such as autistic disorder (or classic autism), Asperger's syndrome, childhood disintegrative disorder, Rett's disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and social (pragmatic) communication disorder (SCD).

[0053] 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.

[0054] 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. 16-18 as well as the regions of DNA that regulate the genes listed in Figs 16-18. In addition, "mGluR network proteins" are the proteins encoded by the mGluR network genes.

[0055] The mGluR network genes are grouped into three subsets: Tier 1, Tier2, and Tier 3. (See Figs. 16-18.) Tier 1 mGluR network genes, shown in Figs. 16A-D, comprise 76 genes, including some GRM genes themselves as well as a

number of other genes. The Tier 2 mGluR network genes, shown in Figs. 17A-I, comprise 197 genes, and exclude the Tier 1 genes.

[0056] 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.

[0057] Tier 3 mGluR network genes, shown in Figs. 18A-Y, 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.

[0058] A "genetic alteration" as used herein means any alteration in the DNA of a gene, or in the DNA regulating a gene, that results 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.

[0059] A "copy number variation (CNV)" refers to the number of copies of a particular gene in the genotype of an individual. CNVs represent a major genetic component of human phenotypic diversity. Susceptibility to genetic disorders is known to be associated not only with single nucleotide polymorphisms (SNP), but also with structural and other genetic variations, including CNVs. A CNV represents a copy number change involving a DNA fragment that is ~1 kilobases (kb) or larger (Feuk et al. 2006a). CNVs described herein do not include those variants that arise from the insertion/deletion of transposable elements (e.g., .about.6-kb KpnI repeats) to minimize the complexity of future CNV analyses. The term CNV therefore encompasses previously introduced 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 retroposon insertions.

[0060] 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.

[0061] A "single nucleotide polymorphism (SNP)" refers to a change in which a single base in the DNA differs from the usual base at that position. These single base changes are called SNPs or "snips." Millions of SNP's have been cataloged in the human genome. Some SNPs such as that which causes sickle cell are responsible for disease. Other SNPs are normal variations in the genome.

[0062] 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.

[0063] The terms "subject" and "patient" are used interchangeably to refer to a human. The terms "pediatric subject" or "pediatric patient" are used interchangeably to refer to a human less than 18 years of age. An "adult patient" refers to a human 18 years of age or older.

[0064] "Target nucleic acid" as used herein refers to a previously defined region of a nucleic acid present in a complex nucleic acid mixture wherein the defined wild-type region contains at least one known nucleotide variation, which may or may not be associated with autism. The nucleic acid molecule may be isolated from a natural source by cDNA cloning or subtractive hybridization or synthesized manually. The nucleic acid molecule may be synthesized manually by the triester synthetic method or by using an automated DNA synthesizer.

[0065] With regard to nucleic acids used in the invention, the term "isolated nucleic acid" is sometimes employed. This term, when applied to DNA, refers to a DNA molecule that is separated from sequences with which it is immediately contiguous (in the 5' and 3' directions) in the naturally occurring genome of the organism from which it was derived. For example, the "isolated nucleic acid" may comprise a DNA molecule inserted into a vector, such as a plasmid or virus vector, or integrated into the genomic DNA of a prokaryote or eukaryote. An "isolated nucleic acid molecule" may also comprise a cDNA molecule. An isolated nucleic acid molecule inserted into a vector is also sometimes referred to herein as a recombinant nucleic acid molecule.

[0066] With respect to RNA molecules, the term "isolated nucleic acid" primarily refers to an RNA molecule encoded by an isolated DNA molecule as defined above. Alternatively, the term may refer to an RNA molecule that has been sufficiently separated from RNA molecules with which it would be associated in its natural state (i.e., in cells or tissues), such that it exists in a "substantially pure" form.

[0067] By the use of the term "enriched" in reference to nucleic acid it is meant that the specific DNA or RNA sequence constitutes a significantly higher fraction (2-5 fold) of the total DNA or RNA present in the cells or solution of interest than in normal cells or in the cells from which the sequence was taken. This could be caused by a person by preferential reduction in the amount of other DNA or RNA present, or by a preferential increase in the amount of the specific DNA or RNA sequence, or by a combination of the two. However, it should be noted that

"enriched" does not imply that there are no other DNA or RNA sequences present, just that the relative amount of the sequence of interest has been significantly increased.

[0068] It is also advantageous for some purposes that a nucleotide sequence be in purified form. The term "purified" in reference to nucleic acid does not require absolute purity (such as a homogeneous preparation); instead, it represents an indication that the sequence is relatively purer than in the natural environment (compared to the natural level, this level should be at least 2-5 fold greater, e.g., in terms of mg/ml). Individual clones isolated from a cDNA library may be purified to electrophoretic homogeneity. The claimed DNA molecules obtained from these clones can be obtained directly from total DNA or from total RNA. The cDNA clones are not naturally occurring, but rather are preferably obtained via manipulation of a partially purified naturally occurring substance (messenger RNA). The construction of a cDNA library from mRNA involves the creation of a synthetic substance (cDNA) and pure individual cDNA clones can be isolated from the synthetic library by clonal selection of the cells carrying the cDNA library. Thus, the process which includes the construction of a cDNA library from mRNA and isolation of distinct cDNA clones yields an approximately 10.sup.-6-fold purification of the native message. Thus, purification of at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.

[0069] The term "substantially pure" refers to a preparation comprising at least 50-60% by weight the compound of interest (e.g., nucleic acid, oligonucleotide, etc.). More preferably, the preparation comprises at least 75% by weight, and most preferably 90-99% by weight, the compound of interest. Purity is measured by methods appropriate for the compound of interest.

[0070] The term "complementary" describes two nucleotides that can form multiple favorable interactions with one another. For example, adenine is complementary to thymine as they can form two hydrogen bonds. Similarly, guanine and cytosine are complementary since they can form three hydrogen bonds. Thus if a nucleic acid sequence contains the following sequence of bases, thymine, adenine, guanine and cytosine, a "complement" of this nucleic acid molecule would be a molecule containing adenine in the place of thymine, thymine in the place of adenine, cytosine in the place of guanine, and guanine in the place of cytosine. Because the complement can contain a nucleic acid sequence that forms optimal interactions with the parent nucleic acid molecule, such a complement can bind with high affinity to its parent molecule.

[0071] With respect to single stranded nucleic acids, particularly oligonucleotides, the term "specifically hybridizing" refers to the association between two single-stranded nucleotide molecules of sufficiently complementary sequence to permit such hybridization under pre-determined conditions generally used in the art (sometimes termed "substantially complementary"). In particular, the term refers to hybridization of an oligonucleotide with a substantially complementary sequence

contained within a single-stranded DNA or RNA molecule of the invention, to the substantial exclusion of hybridization of the oligonucleotide with single-stranded nucleic acids of non-complementary sequence. For example, specific hybridization can refer to a sequence which hybridizes to any autism specific marker gene or nucleic acid, but does not hybridize to other nucleotides. Also polynucleotide which "specifically hybridizes" may hybridize only to a neurospecific specific marker, such an autism-specific marker shown in the Table contained herein. Appropriate conditions enabling specific hybridization of single stranded nucleic acid molecules of varying complementarity are well known in the art.

[0072] For instance, one common formula for calculating the stringency conditions required to achieve hybridization between nucleic acid molecules of a specified sequence homology is set forth below (Sambrook et al., Molecular Cloning, Cold Spring Harbor Laboratory (1989):

T_m=81.5 degrees C+16.6 Log [Na+]+0.41(% G+C)-0.63(% formamide)-600/#bp in duplex

[0073] As an illustration of the above formula, using [Na+]=[0.368] and 50% formamide, with GC content of 42% and an average probe size of 200 bases, the T_m is 57 degrees C. The T_m of a DNA duplex decreases by 1-1.5 degrees C with every 1% decrease in homology. Thus, targets with greater than about 75% sequence identity would be observed using a hybridization temperature of 42 degrees C.

[0074] The stringency of the hybridization and wash depend primarily on the salt concentration and temperature of the solutions. In general, to maximize the rate

of annealing of the probe with its target, the hybridization is usually carried out at salt and temperature conditions that are 20-25 degrees C below the calculated T_m of the hybrid.

[0075] Wash conditions should be as stringent as possible for the degree of identity of the probe for the target. In general, wash conditions are selected to be approximately 12-20 degrees C below the T_m of the hybrid. In regards to the nucleic acids of the current invention, a moderate stringency hybridization is defined as hybridization in 6xSSC, 5xDenhardt's solution, 0.5% SDS and 100 micro-gram/ml denatured salmon sperm DNA at 42 degree C, and washed in 2xSSC and 0.5% SDS at 55 degree C for 15 minutes. A high stringency hybridization is defined as hybridization in 6xSSC, 5x Denhardt's solution, 0.5% SDS and 100 micro-gram/ml denatured salmon sperm DNA at 42 degree C, and washed in 1xSSC and 0.5% SDS at 65 degree C for 15 minutes. A very high stringency hybridization is defined as hybridization in 6xSSC, 5x Denhardt's solution, 0.5% SDS and 100 micro-gram/ml denatured salmon sperm DNA at 42 degree C, and washed in 0.1xSSC and 0.5% SDS at 65 degrees C for 15 minutes.

[0076] The term "oligonucleotide," as used herein is defined as a nucleic acid molecule comprised of two or more ribo- or deoxyribonucleotides, preferably more than three. The exact size of the oligonucleotide will depend on various factors and on the particular application and use of the oligonucleotide. Oligonucleotides, which include probes and primers, can be any length from 3 nucleotides to the full length of the nucleic acid molecule, and explicitly include every possible number of contiguous

nucleic acids from 3 through the full length of the polynucleotide. Preferably, oligonucleotides are at least about 10 nucleotides in length, more preferably at least 15 nucleotides in length, more preferably at least about 20 nucleotides in length.

[0077] The term "probe" as used herein refers to an oligonucleotide, polynucleotide or nucleic acid, either RNA or DNA, whether occurring naturally as in a purified restriction enzyme digest or produced synthetically, which is capable of annealing with or specifically hybridizing to a nucleic acid with sequences complementary to the probe. A probe may be either single-stranded or double-stranded. The exact length of the probe will depend upon many factors, including temperature, source of probe and use of the method. For example, for diagnostic applications, depending on the complexity of the target sequence, the oligonucleotide probe typically contains 15-25 or more nucleotides, although it may contain fewer nucleotides. The probes herein are selected to be complementary to different strands of a particular target nucleic acid sequence. This means that the probes must be sufficiently complementary so as to be able to "specifically hybridize" or anneal with their respective target strands under a set of pre-determined conditions. Therefore, the probe sequence need not reflect the exact complementary sequence of the target. For example, a non-complementary nucleotide fragment may be attached to the 5' or 3' end of the probe, with the remainder of the probe sequence being complementary to the target strand. Alternatively, non-complementary bases or longer sequences can be interspersed into the probe, provided that the probe sequence has sufficient

complementarity with the sequence of the target nucleic acid to anneal therewith specifically.

[0078] The term "primer" as used herein refers to an oligonucleotide, either RNA or DNA, either single-stranded or double-stranded, either derived from a biological system, generated by restriction enzyme digestion, or produced synthetically which, when placed in the proper environment, is able to functionally act as an initiator of template-dependent nucleic acid synthesis. When presented with an appropriate nucleic acid template, suitable nucleoside triphosphate precursors of nucleic acids, a polymerase enzyme, suitable cofactors and conditions such as a suitable temperature and pH, the primer may be extended at its 3' terminus by the addition of nucleotides by the action of a polymerase or similar activity to yield a primer extension product. The primer may vary in length depending on the particular conditions and requirement of the application. For example, in diagnostic applications, the oligonucleotide primer is typically 15-25 or more nucleotides in length. The primer must be of sufficient complementarity to the desired template to prime the synthesis of the desired extension product, that is, to be able anneal with the desired template strand in a manner sufficient to provide the 3' hydroxyl moiety of the primer in appropriate juxtaposition for use in the initiation of synthesis by a polymerase or similar enzyme. It is not required that the primer sequence represent an exact complement of the desired template. For example, a non-complementary nucleotide sequence may be attached to the 5' end of an otherwise complementary primer. Alternatively, non-complementary bases may be interspersed within the

oligonucleotide primer sequence, provided that the primer sequence has sufficient complementarity with the sequence of the desired template strand to functionally provide a template-primer complex for the synthesis of the extension product. Probes and primers having the appropriate sequence homology which specifically hybridized to CNV containing nucleic acids are useful in the detecting the presence of such nucleic acids in biological samples.

[0079] Polymerase chain reaction (PCR) has been described in U.S. Pat. Nos. 4,683,195, 4,800,195, and 4,965,188, the entire disclosures of which are incorporated by reference herein.

[0080] The term "vector" relates to a single or double stranded circular nucleic acid molecule that can be infected, transfected or transformed into cells and replicate independently or within the host cell genome. A circular double stranded nucleic acid molecule can be cut and thereby linearized upon treatment with restriction enzymes. An assortment of vectors, restriction enzymes, and the knowledge of the nucleotide sequences that are targeted by restriction enzymes are readily available to those skilled in the art, and include any replicon, such as a plasmid, cosmid, bacmid, phage or virus, to which another genetic sequence or element (either DNA or RNA) may be attached so as to bring about the replication of the attached sequence or element. A nucleic acid molecule of the invention can be inserted into a vector by cutting the vector with restriction enzymes and ligating the two pieces together.

[0081] Those skilled in the art will recognize that a nucleic acid vector can contain nucleic acid elements other than the promoter element and the autism

specific marker gene nucleic acid molecule. These other nucleic acid elements include, but are not limited to, origins of replication, ribosomal binding sites, nucleic acid sequences encoding drug resistance enzymes or amino acid metabolic enzymes, and nucleic acid sequences encoding secretion signals, localization signals, or signals useful for polypeptide purification.

[0082] As used herein, the terms "reporter," "reporter system", "reporter gene," or "reporter gene product" shall mean an operative genetic system in which a nucleic acid comprises a gene that encodes a product that when expressed produces a reporter signal that is a readily measurable, e.g., by biological assay, immunoassay, radio immunoassay, or by colorimetric, fluorogenic, chemiluminescent or other methods. The nucleic acid may be either RNA or DNA, linear or circular, single or double stranded, antisense or sense polarity, and is operatively linked to the necessary control elements for the expression of the reporter gene product. The required control elements will vary according to the nature of the reporter system and whether the reporter gene is in the form of DNA or RNA, but may include, but not be limited to, such elements as promoters, enhancers, translational control sequences, poly A addition signals, transcriptional termination signals and the like.

Methods of Using Autism-Associated CNVs for Diagnosing a Propensity for the Development of Autism and Autistic Spectrum Disorders

[0083] Autism-related-CNV containing nucleic acids, including but not limited to those listed in the Tables and Figures provided herein, for example in Figures 15-18, may be used for a variety of purposes in accordance with the present invention.

Autism-associated CNV/SNP containing DNA, RNA, or fragments thereof may be used as probes to detect the presence of and/or expression of autism specific markers. Methods in which autism specific marker nucleic acids may be utilized as probes for such assays include, but are not limited to: (1) in situ hybridization; (2) Southern hybridization (3) northern hybridization; and (4) assorted amplification reactions such as polymerase chain reactions (PCR).

[0084] Further, assays for detecting autism-associated CNVs/SNPs may be conducted on any type of biological sample, including but not limited to body fluids (including blood, urine, serum, gastric lavage), any type of cell (such as brain cells, white blood cells, mononuclear cells) or body tissue. Such detection methods can include for example, southern and northern blotting, RFLP, direct sequencing and PCR amplification followed by hybridization of amplified products to a microarray comprising reference nucleic acid sequences.

[0085] Autism-associated CNV/SNP containing nucleic acids, vectors expressing the same, autism CNV/SNP containing marker proteins and anti-Autism specific marker antibodies of the invention can be used to detect autism associated CNVs/SNPs in body tissue, cells, or fluid, and alter autism SNP containing marker protein expression for purposes of assessing the genetic and protein interactions involved in the development of autism.

[0086] In some embodiments for screening for autism-associated CNVs, the autism-associated CNV containing nucleic acid in the sample will initially be amplified, e.g. using PCR, to increase the amount of the templates as compared to

other sequences present in the sample. This allows the target sequences to be detected with a high degree of sensitivity if they are present in the sample. This initial step may be avoided by using highly sensitive array techniques that are becoming increasingly important in the art. Alternatively, new detection technologies can overcome this limitation and enable analysis of small samples containing as little as 1 microgram of total RNA. Using Resonance Light Scattering (RLS) technology, as opposed to traditional fluorescence techniques, multiple reads can detect low quantities of mRNAs using biotin labeled hybridized targets and anti-biotin antibodies. Another alternative to PCR amplification involves planar wave guide technology (PWG) to increase signal-to-noise ratios and reduce background interference. Both techniques are commercially available from Qiagen Inc. (USA).

[0087] Thus any of the aforementioned techniques may be used to detect or quantify autism-associated CNV marker expression and accordingly, diagnose autism or an autism spectrum disorder.

Methods of Diagnosing Autism

[0088] In some embodiments, the invention comprises a method of diagnosing autism (including autism spectrum disorder) 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 autism if a genetic variation is found. In some embodiments, the subject has autism but does not have ADHD, oppositional defiant disorder (ODD), conduct disorder, Tourette's syndrome (TS), anxiety disorder, phobia, or depression. In some

embodiments, the subject has autism and also one or more of ADHD, conduct disorder, TS, anxiety disorder, phobia, and depression. In some embodiments, the subject has both autism and ADHD.

[0089] In other embodiments, the invention encompasses confirming a diagnosis of autism in a subject. As used herein, "confirming a diagnosis of autism" means diagnosing a subject who has already been diagnosed with autism. In some embodiments, the method of confirming a diagnosis of autism comprises analyzing the genetic information of a subject that has been diagnosed as having autism 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 autism 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 autism but does not have ADHD, ODD, conduct disorder, TS,anxiety disorder, phobia, or depression. In some embodiments, the subject has autism and also one or more of ADHD, ODD, conduct disorder, TS, anxiety disorder, phobia, and depression. In some embodiments the subject has both autism and ADHD.

[0090] In other embodiments, the invention comprises confirming a diagnosis of autism in a subject who does not have ADHD, ODD, conduct disorder, TS, anxiety disorder, phobia, or depression, comprising analyzing the genetic information of a subject that has been diagnosed as having autism 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 autism if a genetic variation in at least one mGluR network gene is found.

[0091] In one embodiment, autism 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, autism 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, autism 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, autism 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.

[0092] A diagnosis or confirmation of diagnosis of autism 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 autism is made in a patient who does not have ADHD, ODD, conduct disorder, TS, anxiety disorder, phobia, or depression. In some embodiments, the diagnosis or confirmation of diagnosis of autism is made in a patient

who has autism as well as one or more of ADHD, ODD, conduct disorder, TS, anxiety disorder, phobia, and depression.

[0093] In some embodiments, the diagnosis or confirmation of diagnosis of autism 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 autism 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 autism 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 autism is made in a patient who does not have ADHD, ODD, conduct disorder, TS, anxiety 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.

[0094] In one embodiment, a more severe form of autism is diagnosed if at least two CNVs in mGluR network genes are detected. In one embodiment, a more severe form of autism in a patient who does not have ADHD, ODD, conduct disorder, TS, anxiety disorder, phobia, or depression is diagnosed if at least two CNVs in mGluR network genes are detected.

[0095] In one embodiment, a method of diagnosing and/or confirming autism 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 autism 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 autism if the analysis finds that the test sample is different from the control or standard. In another embodiment of this method, the patient with autism does not have ADHD, ODD, conduct disorder, TS, anxiety disorder, phobia, or depression. In another embodiment, the autism patient also has one or more of ADHD, ODD, conduct disorder, TS, anxiety disorder, phobia, or depression.

[0096] In some diagnostic, confirming, and treatment method of the invention, the subject may have autism but not any of ADHD, ODD, conduct disorder, TS, anxiety disorder, phobia, or depression. In other diagnostic, confirming, and treatment methods of the invention, the subject may have autism and one or more additional disorders such as ADHD, conduct disorder, TS, anxiety disorder, phobia, or depression. In some methods, the subject has both autism and ADHD.

Methods of Treating Autism

[0097] Encompassed herein are methods of treating autism 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.

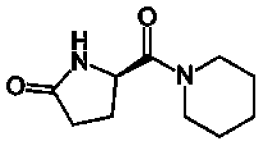
[0098] The mGluR proteins are typically placed into three sub-groups, group I receptors including mGluR1 and mGluR5 are classed as slow excitatory receptors.

[0099] Group II includes mGluR2 and mGluR3. Group III includes mGluR4, mGluR6, mGluR7, and mGluR8. Groups II and III are classed as slow inhibitory receptors.

[00100] The mGluRs are distinguished from the ionotropic GluRs or iGluRs, which are ion channel-associated glutamate receptors and are classed as fast excitatory receptors.

[00101] 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.

[00102] 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. The structure of fasoracetam is: .

[00103] 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.

[00104] 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.

[00105] 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.

[00106] Also encompassed herein are methods of treating autism comprising administering fasoracetam to a subject that has a genetic alteration in at least one mGluR network gene. In some embodiments, this subject has autism but does not have ADHD, ODD, conduct disorder, TS,anxiety disorder, phobia, or depression, while in other embodiments, the subject has autism as well as at least one of ADHD, ODD, conduct disorder, TS,anxiety disorder, phobia, or depression. In some embodiments, the subject has both autism and ADHD.

[00107] 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 autism, but does not have ADHD, ODD, conduct disorder, TS, anxiety disorder, phobia, or depression. In other embodiments, the subject has autism, as well as one or more neuropsychological disorders such as ADHD, ODD, conduct disorder, TS, anxiety disorder, phobia, and depression.

[00108] In one embodiment, the nonselective mGluR activator, such as fasoracetam, is administered to a subject that has autism 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.

[00109] Some embodiments include a method of treating autism 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 autism 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. Other embodiments include a method of treating autism 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. Still other embodiments encompass a method of treating autism 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. 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. In some embodiments, subjects having autism, but not having ADHD,

ODD, conduct disorder, TS, anxiety disorder, phobia, 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, TS, anxiety disorder, phobia, and depression in addition to autism.

Dosing

[00110] 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.

Combination Therapies

[00111] In some embodiments, fasoracetam is used in combination with other agents for the treatment of autism.

Kits and Articles of Manufacture

[00112] Any of the aforementioned products can be incorporated into a kit which may contain a autism-associated CNV/SNP specific marker polynucleotide or one or more such markers immobilized on a Gene Chip, an oligonucleotide, a polypeptide, a peptide, an antibody, a label, marker, or reporter, a pharmaceutically acceptable carrier, a physiologically acceptable carrier, instructions for use, a container, a vessel for administration, an assay substrate, or any combination thereof.

[00113] Vectors and probes comprising any of the autism-associated CNV/SNP specific marker polynucleotides or the Tier 1, 2, and/or 3 genes described in Figures 15-18 are encompassed.

[00114] Host cells expressing the autism-associated CNVs/SNPs of the present invention or functional fragments thereof are encompassed.

[00115] The following examples are provided to illustrate certain embodiments of the invention. They are not intended to limit the invention in any way.

EXAMPLES

Example 1

[00116] A large genome-wide association study (GWAS) of structural variants that disrupt gene family protein interaction networks in patients with autism

was performed. Multiple defective networks in the ASDs were found, most notably rare copy-number variants (CNVs) in the metabotropic glutamate receptor (mGluR) signaling pathway in 5.8% of patients with the ASDs. Defective mGluR signaling was found in both ADHD and schizophrenia, two common neuropsychiatric disorders that are highly coincident with the ASDs. Furthermore, other attractive candidates were found such as the MAX dimerization protein (MXD) network that is implicated in cancer, and a Calmodulin 1 (CALM1) gene interaction network that is active in neuronal tissues. The numerous defective gene family interactions found to underlie autism present many novel translational opportunities to explore for therapeutic interventions.

[00117] To identify and comprehensively characterize defective genetic networks underlying the ASDs, a large-scale genome association study for copy-number variation (CNVs) enriched in patients with autism was performed. By combining the affected cases from previously published large ASD studies with more recently recruited cases from the Children's Hospital of Philadelphia, one of the largest searches for rare pathogenic CNVs in ASDs to date was executed. In sum, 6,742 genotyped samples from patients with the ASDs were compared with those from 12,544 neurologically normal controls recruited at The Children's Hospital of Philadelphia (CHOP).

[00118] These cases were each screened by neurodevelopmental specialists to exclude patients with known syndromic causes for autism. Genotyping was performed for the vast majority of the ASD cases as well as all the controls. After

cleaning the data to remove sample duplicates and performing standard QC for CNVs, the continental ancestry of 5,627 affected cases and 9,644 disease-free controls was inferred using a training set defined by populations from HapMap 3 and the Human Genome Diversity Panel (Table 1). Using this QC criteria, it was estimated that the sensitivity and specificity of calling CNVs is ~70% and 100%, respectively, across 121 different genomic regions assayed by PCR. Across all ethnicities, there was an increased burden of CNVs in cases versus controls, a statistically significantly difference ($P \leq 0.001$) in the larger European (63.3 versus 54.5 Kb, respectively) and African-derived (70.4 versus 48.0 Kb, respectively) populations.

[00119] Table 1: Distribution of CNVs across samples and estimated ancestry.

Continental ancestry	Case	Control	Total
Europe			
Number of samples	4,602	4,722	9,324
CNV burden (Kb)	63.3	54.5	
Africa			
Number of samples	312	4,169	4,481
CNV burden (Kb)	70.4	48.0	
America			
Number of samples	485	276	761
CNV burden (Kb)	59.1	58.4	
Asia			
Number of samples	201	350	551
CNV burden (Kb)	56.1	54.1	
Other			
Number of samples	27	127	154
CNV burden (Kb)	51.5	49.4	

All Ethnicities			
Number of samples	5,627	9,644	15,271
*CNV burden (Kb)	63.0	51.7	

[00120] Referring to Table 1, CNV=copy-number variation. The table shows the distribution of cases, controls and CNV coverage across estimated continental ancestry. For groups of cases and controls across estimated ancestries, the table lists the numbers of subjects that passed quality control and their group-wise CNV burden, defined as the average span of CNVs in Kb for each group.

[00121] Referring to Table 1, *Statistically significant ($P \leq 0.01$ by PLINK permutation test) differences in CNV burden are marked with an asterisk(*).

Example 2

[00122] A search was performed for pan-ethnic CNV regions (CNVRs) discovered in the European-derived data set (4,602 cases versus 4,722 controls; $P \leq 0.0001$ by Fisher's exact test) and replicated in an independent ASD data set of African ancestry (312 cases versus 4,169 controls; $P \leq 0.001$ by Fisher's exact test) with subsequent measurement of overall significance across the entire multi-ethnic discovery cohort (5,627 cases versus 9,644 controls) for maximal power (Fig. 5, Fig. 10).

[00123] Figure 5 shows the significance of CNVRs by GWAS of ASDs in European-derived or African-derived populations. The Manhattan plots show the −log10 transformed P-value of association for each CNVR along the genome. Adjacent chromosomes are shown in alternating red and blue colors. The regions

discovered in Europeans ($P \leq 0.0001$) that replicated in Africans ($P \leq 0.001$) are highlighted with black arrows labeled by chromosome band. GWAS of 4,634 cases versus 4,726 controls in Europeans is shown on top and GWAS of 312 cases versus 4,173 controls in Africans is shown below.

[00124] On the basis of these selection criteria, two large well-known ASD risk loci emerged that harbored multiple duplications in the Prader Willi/Angelman syndrome (15q11–13) critical region, and multiple deletions were detected in the DiGeorge syndrome (22q11) critical region, albeit notably smaller than the 22q11 deletion syndrome. A third locus harboring deletions in poly ADP-ribose polymerase family 8 (PARP8) on chromosome 5q11 was also discovered. PARP8 has previously been identified as associated with the ASDs in a Dutch population but it has not previously been described for its pan ethnic distribution across European-derived and African-derived populations.

Example 3

[00125] The genetic interaction networks derived from gene families with members localized to the Prader Willi/Angelman syndrome (15q11-13) critical region, the DiGeorge syndrome (22q11) critical region, and the novel PARP8 (5q11) region were examined using a method previously applied to ADHD; however, hardly any of the most significant genes harboring significant CNVRs clustered within gene families. Consequently, the search for gene family interaction networks (GFINs) was broadened to search the entire genome for GFINs with CNVs enriched in autism. For every gene family, a GFIN was defined as the genetic interaction network

spawned by its multiple duplicated members. Standard HUGO gene names were used to define 1,732 GFINs across which were searched for enrichment of network defects associated with the ASDs. However, because there is an a priori excess of CNV burden in ASD cases over disease-free controls (Table 1), larger GFINs are expected to display significant enrichment of case defects by virtue solely of their increased size and complexity. Therefore, for each GFIN, a network permutation test of case enrichment was used across 1,000 random sets of networked genes to control for the GFIN size and complexity. With this approach, network defects associated with the ASDs were identified by minimizing statistical artifact derived from any a priori excessive CNV burden in cases over controls, as well as other unknown biases that may be inherent in the human interactome data that were mined.

[00126] Out of 1,732 GFINs, the network permutation test was used to rank 1,557 GFINs with defined CNVs for enrichment of genetic defects in the ASDs. Among the top GFINs (Figures 13A-B) was the metabotropic glutamate receptor (mGluR) pathway defined by the GRM family of genes that impacts glutamatergic neurotransmission. The GRM family contains eight members, all of which were defined in the human interactome to cumulatively spawn a GFIN of 279 genes (Figs. 6A-D). Across this GFIN for the GRM family of genes, we found CNV defects in 5.8% of European-derived ASD cases (265/4,602) versus only 3% of ethnically matched controls (153/4,722), a 1.8-fold enrichment of frequency (PFisher $\leq$2.40E−09). By 1,000 random network permutations, we found this excess of enrichment across cases in the mGluR pathway to also be statistically significant

(Pperm $\leq$ 0.05). In addition, 69.2% (124/181) of the informative genes within our mGluR network showed an excess of CNVs among cases. However, the component genes that harbor the most significant CNVRs contributing to this overall network significance reveal that the duplicated mGluR genes themselves (GRM1, GRM3, GRM4, GRM5, GRM6, GRM7 and GRM8) fail to achieve significance individually, although there is a trend for an excess of CNV defects across a specific subset of mGluR receptors (GRM1, GRM3, GRM5, GRM7, GRM8) that is unique to cases (Fig. 9).

[00127] Figures 6A-D shows enrichment of optimal CNVRs across mGluR network of genes. Nodes of the network are labeled with their gene names, with red and green representing deletions and duplications, respectively, while grey nodes lack CNV data. Dark and light colors represent enrichment in cases and controls, respectively. The genes defining the network are shown as diamonds, while all other genes are shown as circles. Blue lines indicate evidence of interaction.

Example 4

[00128] Many large studies of CNVs implicate genes within the glutamatergic signaling pathway in the etiology of the ASDs, and SNP and CNV duplications of GRM8 have been reported in association with the ASDs before in humans. Moreover, a recent functional study demonstrated that in mouse models of tuberous sclerosis and fragile X, two different forms of syndromic autism, the autistic phenotype was ameliorated by modulation of GRM5 in opposite directions for each syndrome, which suggests that GRM5 functional activity is central in defining the axis

of synaptopathophysiology in syndromic autism. The GRM network findings herein implicate rare defects in mGluR signalling also contribute to the ASDs outside of fragile X and tuberous sclerosis, and functional mGluR synaptopathophysiology may be initiated from many dozens if not hundreds of defective genes within the mGluR pathway that may account for as much as 6% of the endophenotypes of the ASDs (Figures 13A-B).

[00129] In addition, the importance of mGluRs in ADHD, a highly co-incident neuropsychiatric disorder within the autism spectrum, has been demonstrated. However, in contrast to ADHD where defects within the mGluR receptors themselves (GRMs) were among the most significant copy-number defects contributing to the overall network significance, it was found that in the ASDs defects of component GRMs contributed only modestly to the overall significance of the mGluR pathway. Nonetheless, the defects within GRM1, GRM3, GRM5, GRM7 and GRM8 that were identified as unique to cases and thus enriched are the same GRMs that were identified as being pathogenic in ADHD and may impact glutamatergic signaling.

[00130] Among the most highly ranked GFINs by permutation testing, the MAX dimerization protein (MXD) GFIN (PFisher $\leq$3.83E−23, enrichment=2.53, Pperm $\leq$0.042) was the most enriched. The MXD family of genes encode proteins that interact with MYC/MAX network of basic helix-loop-helix leucine zipper (bHLHZ) transcription factors that regulate cell proliferation, differentiation and apoptosis (MIM 600021); MXD genes are important candidate

tumour suppressor genes as the MXD-MYC-MAX network is dysregulated in various types of cancer. Interestingly an epidemiological link between autism and specific types of cancer has been reported, and anticancer therapeutics were recently shown to modulate ASD phenotypes in the mouse through regulation of synaptic NLGN protein levels. Within the component genes contributing to the MXD GFIN significance, duplications in PARP10 ($P \leq 4.06E-11$, OR=2.04) and UBE3A (1.50E−06, OR=inf) are the most significantly enriched (Figure 12). It is notable that PARP8 was found to be significant across ethnicities as described earlier (Figure 12), and the importance of structural defects in UBE3A in the ASDs was previously described.

[00131] Other notable significant GFINs uncovered were POU class 5 homeobox (POU5F) GIFN ($PFisher \leq 2.96E-17$, enrichment=2.3, $Pperm \leq 0.008$, and the SWI/SNF related, matrix associated, actin-dependent regulator of chromatin, subfamily c (SMARCC) GFIN ($PFisher \leq 1.22E-09$, enrichment=1.9, $Pperm \leq 0.035$). The POU5F family of genes encodes for transcription factors containing a POU homeodomain, and their role has been demonstrated in embryonic development, especially during early embryogenesis, and it is necessary for embryonic stem cell pluripotency. Component genes of the SMARCC gene family are members of the SWI/SNF family of proteins, whose members display helicase and ATPase activities and which are thought to regulate transcription of certain genes by altering the chromatin structure around those genes. Most interestingly, the KIAA family of genes ranked among the top GFINs ($PFisher \leq 3.12E-23$, enrichment=1.6, Pperm

≤0.040). KIAA genes have been identified in the Kazusa cDNA sequencing project and are predicted from novel large human cDNAs; however, they have no known function.

[00132] Some component members of gene families may contribute disproportionately to the significance of a GFIN because they are highly connected to interacting gene partners that are enriched for CNV defects in ASD. Therefore, the 1,732 gene families were decomposed into their 15,352 component duplicated genes of which 1,218 had defined networks with data to test for significance by genome-wide network permutation. The calmodulin 1 (CALM1) gene interaction network ranked highest by network permutation testing of case enrichment for CNV defects across 1,000 random gene networks (Figure 7, Figure 14) and represents a novel and attractive candidate gene for the ASDs. Across the CALM1 network, CNV defects were found in 14/4,618 cases versus only 1/4726 controls (Pfisher ≤4.16E−04, enrichment=14.37, Pperm ≤0.002), and these defects were distributed such that 90% (9/10) of genes that harbored CNVs in the CALM1 interactome were enriched in cases. Closer inspection of the most significant CNVR contributing to the CALM1 network significance (Figure 11) revealed that no single gene was significant on its own; instead, with the exception of only one gene (PTH2R), each contributing CNVR tagged highly penetrant rare defects unique to cases. Calmodulin is the archetype of the family of calcium-modulated proteins of which nearly 20 members have been found. Calmodulin contains 149 amino acids that define four calcium-binding domains used for Ca2+-mediated coordination of a large number of

enzymes, ion channels and other proteins including kinases and phosphatases; its functions include roles in growth and cell cycle regulation as well as in signal transduction and the synthesis and release of neurotransmitters [MIM 114180].

[00133] Figure 7 shows the enrichment of optimal CNVRs across CALM1 network. The first degree-directed interaction network defined by CALM1 is shown.

[00134] The comprehensive, unbiased analytical approach described herein has identified a diverse set of specific defective biological pathways that contribute to the underlying aetiology of the ASDs. Among GFINs robustly enriched for structural defects, the most enriched was that of the MXD family of genes that has been implicated in cancer pathogenesis, thereby providing concrete genetic defects to explore the reported coincidence of specific cancers with the ASDs. The most highly ranked component duplicated gene interaction network involves defects in CALM1 and its multiple interacting partners that are important in regulating voltage-independent calcium-activated action potentials at the neuronal synapse. Moreover, there was significant enrichment for defects within the GFIN for GRM that defines the mGluR pathway. While specific mGluR gene family members have been shown to underlie syndromic ASDs, these findings suggest that rare defects in mGluR signaling also contribute to idiopathic autism across the entire GFIN for GRM genes.

[00135] Given the unmet need for better treatment for neurodevelopmental diseases, the functionally diverse set of defective genetic

interaction networks reported herein presents attractive genetic biomarkers to consider for targeted therapeutic intervention in ASDs and across the neuropsychiatric disease spectrum.

Methods applicable to Examples 1-4

[00136] The majority of cases (5,049 of 6,742) and all controls (12,544) were genotyped with genome-wide coverage using the Infinium II platform across various iterations of the HumanHap BeadChip with 550 K, 610 K, 660 K and 1 M markers by the Center for Applied Genomics at The Children's Hospital of Philadelphia (CHOP). There were 1,693 cases genotyped by the AGP consortium. All cases and ~\n50% of controls were re-used from previously published large ASD studies. All cases were diagnosed by ADI-R/ADOS and fulfilled standard criteria for ASDs. Duplicate samples were removed by selecting unique samples with the best quality (based on genotyping statistics used to QC samples) from clusters defined by single linkage clustering of all pairs of samples with high pairwise identity by state measures (IBS $\geq$0.9) across 140 K non-correlated SNPs. Ethnicity of samples was inferred by a supervised k-means classification (k=3) of the first 10 eigenvectors estimated by principal component analysis across the same subset of 140 K non-correlated SNPs. We used HapMap 3 and the Human Genome Diversity Panel samples with known continental ancestry to train the k-means classifier implemented by the R Language for Statistical Computing.

CNV inference and association

[00137] CNVs with the PennCNV algorithm, which combines multiple values, including genotyping fluorescence intensity (Log R Ratio), population frequency of SNP minor alleles (B-allele frequency) and SNP spacing were called into a hidden Markov model. The term 'CNV' represents individual CNV calls, whereas 'CNVR' refers to population-level variation shared across subjects. Quality control thresholds for sample inclusion in CNV analysis included a high call rate (call rate ≥95%) across SNPs, low s.d. of normalized intensity (s.d. ≤0.3), low absolute genomic wave artifacts (|GCWF| ≤0.02) and low numbers of CNVs called (#CNVs ≤100). Genome-wide differences in CNV burden, defined as the average span of CNVs, between cases and controls and estimates of significance were computed using PLINK. CNVRs were defined based on the genomic boundaries of individual CNVs, and the significance of the difference in CNVR frequency between cases and controls was evaluated at each CNVR using Fisher's exact test.

Gene family interaction networks definition and association

[00138] Previous work on ADHD was extended here to rank all GFINs by a network permutation test. Specifically, using merged human interactome data from three different yeast two hybrid generated data sets accessed through the Human Interactome Database, the directed second-degree gene interaction network was defined for all gene families just as was done for the sole metabotropic glutamate receptor gene family network in ADHD. Specifically, GFIN was used to refer to these gene family-derived interaction networks. In sum, 2,611 gene families were

found with at least two members based on official HUGO gene nomenclature, and generated 1,732 GFINs using. For 1,557 GFINs with defined CNVs an odds ratio was calculated of cumulative network enrichment over all genes harboring CNVs within the network. Moreover, for each GFIN, its enrichment was quantified by a permutation test of 1,000 second-degree gene interaction networks derived from a random set of N genes, where N is the number of members of a given gene family. Because the CNVs focused on are so rare, there is relatively not enough power to achieve significance by permutation testing after correcting for multiple GFIN tests. However, all GFINs are reported in order of their nominal/marginal significance.

Experimental validation of CNVs

[00139] Significant CNVRs that were identified were validated using commercially available qPCR Taqman probes run on the ABI GeneAmp 9700 system from Life Technology. Figure 9 lists 251 reactions that were tested using 121 different genomic probes across 85 different samples for which DNA was available. For deletions, sensitivity=0.65, specificity=1.00, NPV=1.00 and PPV=0.88. For duplications, sensitivity=0.68, specificity=0.99, NPV=0.94 and PPV=0.91.

Conclusions

[00140] The data presented herein is evidence that ASD can be diagnosed after recognition of at least one CNV in an mGluR network gene selected from the group consisting of ACAT1, ACAT2, ACP1, ACTR2, ADCY1, ADD1, ADRA2C, ADRBK1, AGAP2, ALDOA, APTX, ARHGAP24, ARL15, BDKRB1, BDKRB2, C1orf116, C4orf3, C7orf25, CA8, CACNA1B, CALB2, CALM1,

CAMK2B, CHP, CHRM3, CNPY2, CNR1, COPB2, DCN, DHCR7, DISC1, DSTN, ECHS1, EGFR, ERBB2, ERP44, F2RL2, FKBP3, FURIN, GLP1R, GLP2R, GNA15, GNAI1, GNAI2, GNAI3, GNAO1, GNAQ, GNB2L1, GRB2, GRB7, GRIK1, GRM1, GRM3, GRM5, GRM7, GRM8, GSN, HNRNPA3, HOMER1, HOMER3, HTT, IMPDH2, IQGAP2, ITGB7, ITPR1, LAMA4, LRP2BP, LYAR, LYN, MAP4, MAPK1, MTHFD1, MTNR1A, MX1, MYO6, NAA15, NCK1, NPY2R, PCBP1, PCBP3, PCDHA4, PDE1C, PICK1, PIK3CA, PLA2G7, PLCB1, PRDX1, PRKCA, PRPSAP1, PSMC1, PSMD1, PSMD13, PSME1, PXN, RAB2A, RANBP1, RAP2A, RCC1, RGS12, RPA2, RPN2, RUVBL2, RYR2, S100A6, SACS, SDC3, SERPINB9, SLC6A3, SNRPB2, SRC, STRAP, STX12, SYK, TCP1, TEAD3, TFAM, TJP1, TRAF2, TUBA1A, TUBA3C, TXN, UBQLN4, VHL, and YWHAQ (also shown in Figures 15A-D).

[00141] The CNVs in these genes are sensitive and specific biomarkers for selecting and treating ADHD due to defective mGluR pathways. Furthermore, the present inventors have identified drug candidates that specifically activate the mGluRs, potentially restoring normal neurophysiology in ASD patients with mutations in any of the mGluR network genes, as shown in Figures 15A-D.

[00142] For example, compounds which may be administered in implementing the test and treat paradigm described herein include the piracetam family of nootropic agents, as described in F. Gualtieri et al., Curr. Phann. Des., 8: 125-38 (2002). More preferably, the treating agent is a pyroglutamide. Details regarding the preparation and formulation of pyroglutamides, which may be used in

the practice of this invention, are provided in U.S. Pat. No. 5,102,882 to Kimura et al. A particularly preferred agent for the treatment of ASD in patients determined to have one or more of the CNVs indicative as set forth in Figures 15A-D, is (+)-5-oxo-Dprolinepiperidinamide monohydrate (NS-105).

Example 5

The Role of mGluR Copy Number Variation in Genetic and Environmental Forms of Syndromic Autism Spectrum Disorder

[00143] Abnormal signaling mediated through mGluR5 is involved in the pathophysiology of Autism Spectrum Disorder (ASD) in Fragile X Syndrome and Tuberous Sclerosis. However, the role of other mGluR associated network/signaling genes in syndromic ASD is unknown. To determine whether copy number variants (CNV'S) are enriched in syndromic ASD, microarrays were used to identify mGluR network CNV's in children with ASD. We set out to determine 1) whether rate of syndromic features vary between children with ASD with and without CNV's in mGluR network genes; and 2) whether "second hits" in mGluR network genes occur more often in children with ASD in children with 22q11.2 Deletion Syndrome (who all have haplo insufficiency of RANBP1, an mGluR network gene in the 22q11.2 region.

[00144] Individuals in our biorepository with parental report of ASD (n=6,452) were screened for parental consent to access clinical evaluations in the Electronic Health Record at the Children's Hospital of Philadelphia (n=539). Our syndromic comparison cohort included children with 22q11.2 Deletion Syndrome

with full access to past medical and neuropsychological evaluations (n=75), including those with diagnosis of ASD (n=25) and those with no concern for ASD (n=50).

[00145] Patient categorization (syndromic vs nonsyndromic) was done via blinded medical chart review in all mGluR positive and 100 randomly selected mGluR negative cases.

[00146] Our results, explained further herein show that 11.5% of ASD had mGluR CNV's vs. 3.2% in healthy controls ($p<0.001$). Syndromic ASD was more prevalent in children with mGluR CNVs (72% vs 16%, $p<0.001$). A comparison cohort of children with 22q11.2 Deletion Syndrome (n=25 with ASD, n=50 without ASD), all haplo-insufficient for mGluR network gene RANBP1, was evaluated to determine whether "second hits" in mGluR network genes confer additional risk for ASD. 20% with 22q11.2DS+ASD had "second hits" in mGluR signaling genes vs 2% in 22q11.2DS-ASD ($p<0.014$). Conclusions: We propose that altered RANBP1 expression may provide a mechanistic link between ASD in 22q11.2DS, Thalidomide Embryopathy and Fetal Valproate Syndrome, providing a link for seemingly unrelated genetic and environmental forms of ASD.

[00147] The results suggest that CNV's in mGluR network genes, previously implicated in altered neurological development in Fragile X Syndrome and Tuberous Sclerosis, may link many other genetic and environmental forms of Autism Spectrum Disorder. As discussed in the previous examples, Autism Spectrum Disorder (ASD) occurs in approximately 1/88 individuals and is characterized by impairment in social communication and repetitive interests and activities.

Approximately 20% of cases occur in the context of an identifiable syndrome. Genetic syndromes with ASD are heterogeneous, including cytogenetically visible chromosomal alterations (e.g. Trisomy 21), microdeletion and microduplication syndromes (e.g. 22q11.2 deletion syndrome [22q11.2DS]; 22q11.2 duplication syndrome [22q11.2DupS]), and monogenic disorders (e.g. Fragile X Syndrome [FXS], Tuberous Sclerosis [TS]). In addition, prenatal exposure to thalidomide, valproic acid, misoprostol, ethanol and maternal rubella infection, have been associated with an elevated risk of ASD.

[00148] The mechanism for the development of ASD in most forms of idiopathic and syndromic forms of ASD remains elusive. Recently, signaling through metabotropic glutamate receptor 5 (mGluR5) has been implicated in the development of ASD in FXS and TS. In FXS, abnormal production of Fragile X Mental Retardation Protein (FMRP) removes normal inhibition of signaling through the mGluR pathway. Tuberous Sclerosis leads to over inhibition of signaling. Auerbach and colleagues (2011) demonstrated abnormal synaptic learning and atypical behavior in mouse models of FXS and TS, and reversed these effects by breeding the two strains together--mice harboring both mutations had normal mGluR signaling, and learning and behavior that was indistinguishable from control mice. Other studies have demonstrated normalization of learning and behavior in Fragile X mice by administration of an mGluR5 antagonist. In addition to elucidating the mechanism for cognitive and behavioral differences in FXS and TS, these studies suggest a promising avenue for pharmacological treatment. To determine whether additional

forms of syndromic ASD may share a similar mechanism (through disruption of the mGluR gene network), we analyzed DNA from 539 children with ASD (not filtered for comorbid genetic syndrome) followed at the Children's Hospital of Philadelphia.

[00149] The following materials and methods are provided to facilitate the practice of Example 5.

[00150] Participants: Phenotypic data for patients with ASD as reported on parental health questionnaires from our biorepository (n=6,452) were evaluated to identify patients who received clinical assessment at the Children's Hospital of Philadelphia and agreed to Electronic Health Record chart review. DNA from these cases (n=539) were selected for further phenotypic and genotypic analysis. Children were recruited for inclusion in the general Center for Applied Genomics biorepository when they were getting blood drawn for another purpose at The Children's Hospital of Philadelphia, so there is an overrepresentation of children with at least one medical problem in this patient cohort. The parents of all patients gave consent for participation in the study, which was approved by the Institutional Review Board at the Children's Hospital of Philadelphia (IRB 06-004886).

[00151] Chart Review: Subject selection and randomization process: All patients with an mGluR CNV (n=62) and 100 patients without mGluR CNV were randomly selected for chart review. This procedure was selected to ensure that all patients with mGluR CNV received detailed chart review with an adequately sized comparison cohort. A three-step process was done to ensure blinded chart review. The selection of the 162 charts was done by a geneticist with access to CNV data but

without access to the Electronic Health Record (CK). Another author who had no access to CNV data nor the Electronic Health Record blinded and randomized the patient ID's (RTS). Finally, a physician with access to the Electronic Health Record but blinded to mGluR status (TLW) reviewed charts for documentation of ASD diagnosis and presence of other medical comorbidities.

[00152] ASD: Charts were reviewed to confirm a diagnosis of ASD and also to determine medical comorbidities for each patient. Diagnosis of ASD was confirmed in the chart, but as this was a retrospective chart review, gold-standard research instruments (e.g. Autism).

[00153] Medical Comorbidities: Structural birth defects, genetic testing and medical conditions were recorded for each patient. Cases were categorized as "Syndromic ASD" if they had ASD and presence of a medical condition or structural birth defect (e.g. cleft palate) that occurs in less than 1% of the general population. This criteria was established to define a subset of patients whose ASD and other medical problems would be highly unlikely to occur coincidentally--With a baseline rate of ASD at 1/88 and a medical condition that occurs in <1% of the general population, the compound likelihood of both occurring by chance would be approximately 0.001%. See FIG. 8.

[00154] Genotyping Arrays and CNV Calling: DNA from subjects with ASD were each genotyped on the Human610-Quad or HumanHap550 SNP arrays from Illumina. For 22q11 DS cohorts, subjects were typed either on Illumina SNP arrays (Human610-Quad v1.0 or HumanHap550) or Affymetrix 6.0 SNP arrays.

Clustering and SNP calling was performed using GenomeStudio (Illumina) to generate normalized intensity (i.e. Log-R ratio, or LRR) and B-allele frequencies (BAF). CNV calling was performed using the PennCNV algorithm [PMID: 17921354] following waviness correction [PMID: 18784189]. In brief, PennCNV uses a hidden Markov model (HMM) that incorporates information from LRR, BAF, as well as features of the array (e.g. distance between neighboring SNPs) to detect CNVs.

[00155] CNV Quality Control: Samples with SNP arrays of poor quality were excluded from CNV calling, since typically the proportion of false positives increases considerably for these samples. Those samples where the genotyping call rate>96%, standard deviation of LRR (LRR sd)<0.4, GC-wave factor (GCWF) is between -0.2 and 0.2 after waviness correction, and total number of CNV calls for the sample <100 were included in analysis.

[00156] CNV Annotation: For syndromic ASD regions, genomic coordinates were those described by Betancur [PMID: 21129364]. The GRM/mGluR network generated by Cytoscape from the Human Interactome database was described by Elia et al. [PMID: 22138692] using UCSC Genome Browser definitions for gene coordinates (UCSC genes). This network from Cytoscape was used to define mGluR+ vs. mGluR-subsets. For 22q11 DS cohort analysis, additional GRM/mGluR network genes were identified based on 1st degree interaction network of the eight GRM genes using the program Ingenuity Pathway Analysis (Ingenuity Systems Inc./Qiagen; Redwood City, Calif.) as well as the genes encoding the group I

mGluR signaling pathway described in Kelleher et al. [PMID: 22558107]. CNV calls were analyzed for overlap to known syndromic regions and GRM network genes. All syndromic aberrations detected by clinical cytogenetic laboratory testing were confirmed on corresponding SNP arrays.

Results: mGluR Network Copy Number Variations (CNVs) are Prevalent in Syndromic ASD Compared to Nonsyndromic ASD

[00157] CNVs in the mGluR network genes were found in 74% of patients with syndromic ASD compared to 16% of patients with nonsyndromic ASD ($p<0.001$). Most of the mGluR CNV's in patients with syndromic ASD (75%) were included in larger clinically significant CNV's. As mGluR network genes are present in the 22q11.2 region (RANBP1) and on chromosome 21 (APP GRIK1 MX1 PCBP3 SETD4), patients with ASD in the presence of 22q11.2DS, 22q11.2DupS or Trisomy 21 accounted for 15 (33%) of the patients with Syndromic ASD+mGluR network changes. The remainder of observed cytogenetic changes had individual non-overlapping deletions or duplications. The analysis was repeated after exclusion of children with Trisomy 21, 22q11.2DS and 22q11.2DupS, (the syndromes in children in this study which have previously been associated with ASD). After their exclusion, the effect remained significant ($p<0.001$).

Autism Spectrum Disorder in 22q11.2 Deletion Syndrome is Associated with "Second Hit" in mGluR Pathway

[00158] As a comparison cohort, data from children with 22q11.2 DS with ASD (n=25) and without ASD (n=50) who had completed high density

microarray evaluation (either Affymetrix 6.0, Illumina 500K, and Illumina 610Q) and clinical developmental assessments (as enrolled through a parallel study, approved by the Children's Hospital of Philadelphia Institutional Review Board, IRB 07-005352) were examined for the presence of a second mGluR network hit outside of the 22q11.2 region. "Second hits", deletions of an mGluR network gene outside of the 22q11.2 region, were found in 20% (5/25) of patients with ASD and only 2% (1/50) without ASD ($p<0.014$).

[00159] Prior studies have demonstrated that abnormal signaling (either too much or too little) through mGluR5 could be the basis for abnormal neural development (and possibly ASD) in FXS and TS. Our data suggest that derangement of the mGluR network may be responsible for increased rates of ASD seen in cytogenetically distinct forms of syndromic ASD. mGluR network genes are found in the 22q11.2 region as well as on Chromosome 21, which may be involved in the increased prevalence of ASD in both Down Syndrome and 22q11.2 DS. However, all patients with Trisomy 21 or 22q11.2 DS harbor the change in the mGluR network suggesting a second hit outside of the region may be necessary for expression of the ASD phenotype.

Autism Spectrum Disorder in 22q11.2 Deletion Syndrome, 22q11.2 Duplication Syndrome, Thalidomide Embryopathy and Fetal Valproate Syndrome

[00160] The 22q11.2 DS is the most common microdeletion syndrome in humans, occurring in 1 in 4,000 individuals. The typical deletion spans approximately 3 Mb and includes approximately 45 genes, causing a variety of

medical and behavioral disorders. ASD occurs in approximately 20%, and psychosis in 25%. The 22q11.2DupS results in the same types of birth defects and medical comorbidities seen in 22q11.2 DS, but at a lower rate (among over 60 patients in our clinical cohort). There are no cases of psychosis in 22q11DupS in the literature.sup.29 or our cohort. Among our cases with documentation of developmental evaluation after the age of 4, the prevalence of ASD is 27%, which is slightly higher than the rate in children with 22q11.2DS.

[00161] Thalidomide exposure during pregnancy causes a variety of birth defects that have all been reported in 22q11.2DS, including some that are extremely rare (e.g. phocomelia, radial ray defects). Miller and Stromland reported an elevated risk of ASD following exposure to thalidomide during early embryogenesis. This study included prospective evaluation by a psychiatrist was done for adults who had been exposed to thalidomide during pregnancy and evaluation by a physician to document birth defects and associated features. All cases of ASD following thalidomide exposure had ear anomalies, suggesting exposure between days 24-28 post-fertilization. Among individuals exposed at this time, there was a 27% rate of ASD. Replications of this study in additional cohorts of children have not been possible because the use of thalidomide in pregnant women was widely restricted in the 1960's; therefore, additional cases are not available. Though several mechanisms for the cause of many of the birth defects in thalidomide embryopathy have been proposed, animal studies of the teratogenic effects of thalidomide have been limited due to significant species differences. One of the reasons thalidomide was used

widely in the 1960's was because of a lack of teratogenicity in animals at levels that are highly teratogenic in humans. This has resulted in significant limitation in the ability of researchers to determine the teratogenic mechanism of thalidomide, as studies have taken place in animals for which thalidomide is not particularly teratogenic, or using dosages which are much higher than that used in humans. Recent changes in legislation have allowed for a study to be completed in human embryonic stem cells--the first of its kind to use human cells and dosages which would have been analogous to that experienced by women taking thalidomide in the 1950's and 1960's.sup.30. This study, conducted by Meganathan and colleagues (2012) proposed that the teratogenic effects of thalidomide may be mediated through RANBP1. Valproic acid (VPA) is widely used as an anticonvulsant, mood stabilizer, and to prevent migraine headaches. Exposure to VPA during pregnancy causes an increased rate of several birth defects, all of which have been reported in 22q11.2DS, and most of which have been seen in Thalidomide Embryopathy. The comparison of all birth defects seen in 22q11.2 DS to the exposures syndromes was not made because 22q11.2 DS includes deletion of dozens of additional genes that we do not propose to be affected in Thalidomide Embryopathy or Fetal Valproate Syndrome. In addition to structural defects, children exposed to VPA in utero have an elevated risk of developing ASD. Rodent models of autism have used prenatal exposure to VPA to reproduce some of the neuroanatomic features of autism and abnormal behavior. Due to its action as a Histone Deacetylase Inhibitor, VPA affects expression of many genes. Based on homology, decreased expression of RanBP1 mRNA is predicted in VPA-treated rats.

Moreover, a recent study showed reversal of atypical behaviors in VPA-exposed mice with treatment with an mGluR antagonist.

CONCLUSIONS

[00162] Derangement of genes in the mGluR network are found at a high rate in patients with different forms of Syndromic ASD, including 22q11.2DS, 22q11.2DupS, Trisomy 21 and a large number of other seemingly-unrelated chromosomal alterations. Moreover, among children with 22q11.2DS, the presence of a "second hit" in the mGluR network was identified in 20% of children with ASD, and only 2% of those without ASD ($p<0.014$). Significantly, four children, all with autism phenotype, had a small deletion in the vicinity of the RANBP1 gene. While the expression level of RANBP1 was not affected in one individual available for testing (data not shown), these atypical deletions could impact gene function with resulting dysregulation of the RANBP1 protein.

[00163] Taken together, these data implicate dysregulation of the mGluR network as a likely permissive factor that increases the propensity to develop an ASD, including syndromic ASD, and ASD in individuals with 22q11.2 Deletion or Duplication Syndrome, Fetal Valproate Syndrome and Thalidomide Embryopathy. The striking increase in prevalence of ASD with a CNV affecting a second gene in the network suggests perturbations of mGluR signaling at multiple points is likely.

[00164] CNVs in the genes recited in Figures 15A-D are sensitive and specific biomarkers for selecting and treating ASD, syndromic ASD, and ASD in individuals with 22q11.2 Deletion or Duplication Syndrome, Fetal Valproate

Syndrome and Thalidomide Embryopathy. Furthermore, the present inventors have identified drug candidates that specifically activate the mGluRs, potentially restoring normal neurophysiology in patients with mutations in any of the mGluR network genes, as shown in Figures 15A-D.

[00165] For example, compounds which may be administered in implementing the test and treat paradigm described herein include the piracetam family of nootropic agents, as described in F. Gualtieri et al., Curr. Phann. Des., 8: 125-38 (2002). More preferably, the treating agent is a pyroglutamide. Details regarding the preparation and formulation of pyroglutamides, which may be used in the practice of this invention, are provided in U.S. Pat. No. 5,102,882 to Kimura et al. A particularly preferred agent for the treatment of ASD in patients determined to have one or more of the CNVs indicative as set forth in Figures 15A-D, is (+)-5-oxo-Dprolinepiperidinamide monohydrate (NS-105).

[00166] Therefore, in one embodiment, methods for treating an ASD, syndromic ASD, and ASD in patients with 22q11.2 Deletion or Duplication Syndrome, Fetal Valproate Syndrome or Thalidomide Embryopathy are encompassed comprising administering NS-105 to a patient having at least one CNV in an GRM/mGluR network gene selected from the group consisting of ACAT1, ACAT2, ACP1, ACTR2, ADCY1, ADD1, ADRA2C, ADRBK1, AGAP2, ALDOA, APTX, ARHGAP24, ARL15, BDKRB1, BDKRB2, C1orf116, C4orf3, C7orf25, CA8, CACNA1B, CALB2, CALM1, CAMK2B, CHP, CHRM3, CNPY2, CNR1, COPB2, DCN, DHCR7, DISC1, DSTN, ECHS1, EGFR, ERBB2, ERP44, F2RL2, FKBP3,

FURIN, GLP1R, GLP2R, GNA15, GNAI1, GNAI2, GNAI3, GNAO1, GNAQ, GNB2L1, GRB2, GRB7, GRIK1, GRM1, GRM3, GRM5, GRM7, GRM8, GSN, HNRNPA3, HOMER1, HOMER3, HTT, IMPDH2, IQGAP2, ITGB7, ITPR1, LAMA4, LRP2BP, LYAR, LYN, MAP4, MAPK1, MTHFD1, MTNR1A, MX1, MYO6, NAA15, NCK1, NPY2R, PCBP1, PCBP3, PCDHA4, PDE1C, PICK1, PIK3CA, PLA2G7, PLCB1, PRDX1, PRKCA, PRPSAP1, PSMC1, PSMD1, PSMD13, PSME1, PXN, RAB2A, RANBP1, RAP2A, RCC1, RGS12, RPA2, RPN2, RUVBL2, RYR2, S100A6, SACS, SDC3, SERPINB9, SLC6A3, SNRPB2, SRC, STRAP, STX12, SYK, TCP1, TEAD3, TFAM, TJP1, TRAF2, TUBA1A, TUBA3C, TXN, UBQLN4, VHL, and YWHAQ.

Example 6

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

[00167] 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.

[00168] The study included 30 ADHD subjects who were between ages 12 and 17, of any ancestry or race, and 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 an 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 a few subjects with symptoms related to autism.

[00169] 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.

[00170] 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.

[00171] 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.

[00172] 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.

[00173] While this study was not specifically directed at identifying autism sufferers or monitoring their symptoms, 7 of the 30 ADHD subjects showed certain signs of autism, particularly lack of social interactions or engagement, that appeared

to improve from the therapy with NFC-1. For example, two subjects showed increased social interactions after treatment. One of these two subjects, who had not communicated with a close relative for a long time, initiated contact with the relative. One subject went from not making eye contact to initiating conversation with clinicians. This same subject also had episodes of rapid repetitive movements, particularly when excited. These movements stopped while on the NFC-1 treatment and started again when the drug was discontinued. A teacher also commented during the trial that this subject also had increased social interactions. One subject went from not wanting to talk to peers to joining a school debating team. One subject was reported to be better able to relate to peers and to organize a peer get together. One subject was able to go to their locker at school without being fearful. And in a further subject, there was a decrease in self-talk. Thus, overall, in these seven subjects, social interactions appeared to improve while on NFC-1 medication.

EQUIVALENTS

[00174] 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.

[00175] 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.

What is Claimed is:

1. A method of treating autism in a human patient comprising administering a therapeutically effective amount of fasoracetam (NS-105 or NFC-1) to the patient, wherein the patient has at least one CNV in a gene selected from the group consisting of ACAT1, ACAT2, ACCN1, ACCN2, ACP1, ACTB, ACTR2, ADA, ADCY1, ADD1, ADD2, ADORA1, ADRA1B, ADRA2A, ADRA2C, ADRB2, ADRBK1, ALDOA, ANXA2, APP, APTX, AQP1, ARHGAP24, ARL15, ARRB1, ARRB2, ATXN7L3, BDKRB1, BDKRB2, BTBD2, BTG2, C17orf44, C1orf116, C7orf25, CA8, CACNA1B, CACYBP, CALB2, CALM1, CALM2, CALM3, CAMK1, CAMK2B, CAMK4, CCNB1, CDC42, CENTG1, CHGB, CHP, CHRM2, CHRM3, CIC, CMPK, CNP, CNR1, CNTN4, COPB2, CRHR1, CTNNA2, CYCS, DCN, DHCR7, DISC1, DLST, DPP6, DRD2, DRD3, DSTN, DYNLL1, ECHS1, EGFR, EIF3S3, ERBB2, F2R, F2RL2, F2RL3, F3, FKBP3, FPR1, FSCN1, FURIN, FYN, GAPDH, GLP1R, GLP2R, GNA15, GNAI1, GNAI2, GNAI3, GNAO1, GNAQ, GNB2L1, GOT1, GP1BA, GPR26, GRB2, GRB7, GRIA1, GRIK1, GRIK3, GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, GRM8, GSN, HBXIP, HD, HNRPA3, HOMER1, HOMER3, HRPT2, HSP90AB1, HTR2A, IL8RB, IMPDH2, IQGAP2, ITGB1, ITGB7, ITPR1, KIAA0090, KIAA1683, LAMA4, LARP7, LRP2BP, LRRC59, LTA, LYAR, LYN, MAP4, MAPK1, MAPT, MARK4, MC4R, MGC11082, MRPL14, MRPS16, MTHFD1, MTNR1A, MTNR1B, MX1, MYC, MYO6, NANS, NARG1, NCK1, NEGR1, NFKBIA, NLN, NMI, NPY2R, NUDC, OPRD1, PAFAH1B3, PCBP1, PCBP3, PCDHA4, PCID1, PCMT1, PDCD5,

PDE1B, PDE1C, PDE6G, PGM1, PHKB, PHKG2, PICK1, PIK3CA, PIK3R1, PLA2G7, PLCB1, PLCB3, PLCG2, PPIH, PPP2R1A, PRDX1, PRKCA, PRLHR, PRMT1, PRPSAP1, PSAT1, PSEN1, PSMA1, PSMC1, PSMD1, PSMD11, PSMD13, PSMD6, PSME1, PTHR2, PXN, PYGL, PYGM, QRICH2, RAB2, RALA, RANBP1, RAP2A, RCC1, RCC2, RGS12, RGS2, RHOA, RIF1, RPA2, RPLP2, RPN2, RPS14, RRM1, RUVBL2, RYR1, RYR2, S100A6, SACS, SARS, SCTR, SDC3, SELE, SERPINB9, SET, SETD4, SF3B14, SGTB, SHANK1, SHBG, SIAH1, SLC2A1, SLC6A3, SLC7A10, SNCA, SNRPB2, SOCS6, SOCS7, SORD, SRC, STAU1, STRAP, STX12, SYK, TBCA, TBXA2R, TCP1, TEAD3, TFAM, TGM2, TJP1, TK1, TLR10, TMEM4, TNIK, TPI1, TRAF2, TRMT112, TUBA1, TUBA1A, TUBA1B, TUBA2, TUBB, TUBG1, TXN, TXNDC4, TXNL2, TYMS, UBQLN4, UCHL1, USP24, VHL, VIPR1, YWHAQ, and ZAP70, thereby improving at least one symptom of autism in the patient.

2. The method of claim 1, wherein the patient has been diagnosed with autism spectrum disorder, pervasive developmental disorder, or one or more conditions selected from autistic disorder (classic autism), Asperger's syndrome, childhood disintegrative disorder, Rett's disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and social (pragmatic) communication disorder (SCD).

3. The method of claim 1 or claim 2, wherein the CNV is a duplication or deletion.

4. The method of claim 1 or 2, wherein the autism is syndromic ASD.

5. The method of claim 1 or 2, wherein the patient has ASD and 22q11.2 Deletion or Duplication Syndrome, Fetal Valproate Syndrome or Thalidomide Embryopathy.

6. The method of claim 1 or 2, wherein the patient has at least two CNVs in a gene selected from the group consisting of ACAT1, ACAT2, ACCN1, ACCN2, ACP1, ACTB, ACTR2, ADA, ADCY1, ADD1, ADD2, ADORA1, ADRA1B, ADRA2A, ADRA2C, ADRB2, ADRBK1, ALDOA, ANXA2, APP, APTX, AQP1, ARHGAP24, ARL15, ARRB1, ARRB2, ATXN7L3, BDKRB1, BDKRB2, BTBD2, BTG2, C17orf44, C1orf116, C7orf25, CA8, CACNA1B, CACYBP, CALB2, CALM1, CALM2, CALM3, CAMK1, CAMK2B, CAMK4, CCNB1, CDC42, CENTG1, CHGB, CHP, CHRM2, CHRM3, CIC, CMPK, CNP, CNR1, CNTN4, COPB2, CRHR1, CTNNA2, CYCS, DCN, DHCR7, DISC1, DLST, DPP6, DRD2, DRD3, DSTN, DYNLL1, ECHS1, EGFR, EIF3S3, ERBB2, F2R, F2RL2, F2RL3, F3, FKBP3, FPR1, FSCN1, FURIN, FYN, GAPDH, GLP1R, GLP2R, GNA15, GNAI1, GNAI2, GNAI3, GNAO1, GNAQ, GNB2L1, GOT1, GP1BA, GPR26, GRB2, GRB7, GRIA1, GRIK1, GRIK3, GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, GRM8, GSN, HBXIP, HD, HNRPA3, HOMER1, HOMER3, HRPT2, HSP90AB1, HTR2A, IL8RB, IMPDH2, IQGAP2, ITGB1, ITGB7, ITPR1, KIAA0090, KIAA1683, LAMA4, LARP7, LRP2BP, LRRC59, LTA, LYAR, LYN, MAP4, MAPK1, MAPT, MARK4, MC4R, MGC11082, MRPL14, MRPS16, MTHFD1, MTNR1A, MTNR1B, MX1, MYC, MYO6, NANS, NARG1, NCK1, NEGR1, NFKBIA, NLN, NMI, NPY2R, NUDC, OPRD1, PAFAH1B3, PCBP1,

PCBP3, PCDHA4, PCID1, PCMT1, PDCD5, PDE1B, PDE1C, PDE6G, PGM1, PHKB, PHKG2, PICK1, PIK3CA, PIK3R1, PLA2G7, PLCB1, PLCB3, PLCG2, PPIH, PPP2R1A, PRDX1, PRKCA, PRLHR, PRMT1, PRPSAP1, PSAT1, PSEN1, PSMA1, PSMC1, PSMD1, PSMD11, PSMD13, PSMD6, PSME1, PTHR2, PXN, PYGL, PYGM, QRICH2, RAB2, RALA, RANBP1, RAP2A, RCC1, RCC2, RGS12, RGS2, RHOA, RIF1, RPA2, RPLP2, RPN2, RPS14, RRM1, RUVBL2, RYR1, RYR2, S100A6, SACS, SARS, SCTR, SDC3, SELE, SERPINB9, SET, SETD4, SF3B14, SGTB, SHANK1, SHBG, SIAH1, SLC2A1, SLC6A3, SLC7A10, SNCA, SNRPB2, SOCS6, SOCS7, SORD, SRC, STAU1, STRAP, STX12, SYK, TBCA, TBXA2R, TCP1, TEAD3, TFAM, TGM2, TJP1, TK1, TLR10, TMEM4, TNIK, TPI1, TRAF2, TRMT112, TUBA1, TUBA1A, TUBA1B, TUBA2, TUBB, TUBG1, TXN, TXNDC4, TXNL2, TYMS, UBQLN4, UCHL1, USP24, VHL, VIPR1, YWHAQ, and ZAP70.

7. A method of treating autism in a subject comprising administering an effective amount of a nonselective activator of metabotropic glutamate receptors (mGluRs) to a subject, thereby improving at least one symptom of autism.

8. A method of treating autism in a subject 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, thereby improving at least one symptom of autism.

9. A method of treating autism 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.

10. The method of claim 8, wherein the genetic alteration is a copy number variation (CNV) or single nucleotide variation (SNV).

11. The method of any one of claims 7 to 10, wherein the nonselective activator of mGluRs is fasoracetam.

12. The method of claim 11, wherein fasoracetam is fasoracetam monohydrate (NS-105 or NFC-1).

13. The method of claim 11 or 12, wherein fasoracetam is administered at a dose of 50 mg, 100mg, 150 mg, 200 mg, 250 mg, 300 mg, 350 mg, or 400 mg, and wherein the dose is administered once, twice, or three times daily.

14. The method of claim 11 or 12, wherein fasoracetam is administered at a dose of 50-400 mg, 100-400 mg, or 200-400 mg, and wherein the dose is administered once, twice, or three times daily.

15. The method of claim 11 or 12, wherein the fasoracetam is administered at a dose of 200-400 mg, such as 200 mg, 300 mg, or 400 mg, and wherein the dose is administered twice daily.

16. The method of any one of claims 7-15, wherein the subject has a CNV in at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 mGluR network genes.

17. The method of any one of claims 10-16, wherein 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.

18. The method of any one of claims 10-17, wherein 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.

19. The method of any one of claims 10-18, wherein 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.

20. The method of claim 19, wherein the screen does not assess CNVs in one or more of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, or GRM8.

21. The method of any one of claims 1-20, wherein the subject does not have a CNV in one or more of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, or GRM8.

22. The method of any one of claims 1-21, wherein the subject is a pediatric subject.

23. The method of claim 22, wherein the pediatric subject is between the ages of 5 and 17, 5 and 8, 8 and 17, 8 and 12, or 12 and 17.

24. The method of any one of claims 1-21 wherein the subject is an adult.

25. The method of any one of claims 1-22, wherein the nonselective activator of mGluRs is administered in combination with another pharmaceutical or non-pharmaceutical therapy.

26. The method of any one of claims 7-25, wherein the patient has been diagnosed with autism spectrum disorder, pervasive developmental disorder, or one or more conditions selected from autistic disorder (classic autism), Asperger's syndrome, childhood disintegrative disorder, Rett's disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and social (pragmatic) communication disorder (SCD).

27. The method of claim 26, wherein the autism is syndromic ASD.

28. The method of claim 26 or 27, wherein the patient has ASD and 22q11.2 Deletion or Duplication Syndrome, Fetal Valproate Syndrome or Thalidomide Embryopathy.

29. A method for diagnosing autism 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 autism if the subject has at least one genetic alteration in a mGluR network gene.

30. A method for diagnosing autism 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 autism if the subject has at least one genetic alteration in a mGluR network gene.

31. A method for identifying a subject as having autism 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 autism if at least one genetic alteration, such as a CNV, in an mGluR network gene is detected.

32. A method for diagnosing autism 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 autism, and diagnosing autism if the genetic information suggests that the subject has at least one genetic alteration in a mGluR network gene.

33. A method of confirming a diagnosis of autism in a subject comprising: obtaining a nucleic acid-comprising sample from a subject diagnosed with autism by a method that comprises 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 autism if the subject has at least one genetic alteration in an mGluR network gene.

34. The method of any one of claims 29-33, wherein the analysis for the presence or absence of at least one genetic alteration in an mGluR network gene 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.

35. The method of any one of claims 29-34, wherein the subject has CNVs in at least two mGluR network genes.

36. The method of any one of claims 29-35, wherein the method comprises 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.

37. The method of any one of claims 29-36, 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.

38. The method of any one of claims 29-37, 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.

39. The method of any one of claims 29-38, 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 200, at least 300, at least 400, at least 500, or all of Tier 3 mGluR network genes.

40. The method of any one of claims 29-40, wherein the subject is a pediatric subject, such as a subject between the ages of 5 and 17, 5 and 8, 8 and 17, 8 and 12, or 12 and 17.

41. The method of any one of claims 29-40, wherein the subject is an adult subject.

42. The method of any one of claims 29-41, wherein the subject is not assessed for genetic alterations or CNVs in one or more of GRM1, GRM2, GRM3, GRM4, GRM5, GRM6, GRM7, and GRM8.

43. The method of any one of claims 29-42, wherein the 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.

44. The method of any one of claims 1-43, wherein the subject has autism as well as ADHD.

45. The method of any one of claims 1-43, wherein the subject does not have one or more of ADHD, schizophrenia, conduct disorder, TS, anxiety disorder, phobia, or depression.

46. The method of any one of claims 29-45, wherein the patient has autism spectrum disorder, pervasive developmental disorder, or one or more conditions selected from autistic disorder (classic autism), Asperger's syndrome, childhood disintegrative disorder, Rett's disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and social (pragmatic) communication disorder (SCD).

47. The method of claim 46, wherein the patient has syndromic ASD.

48. The method of claim 46 or 48, wherein the patient has ASD and 22q11.2 Deletion or Duplication Syndrome, Fetal Valproate Syndrome or Thalidomide Embryopathy.

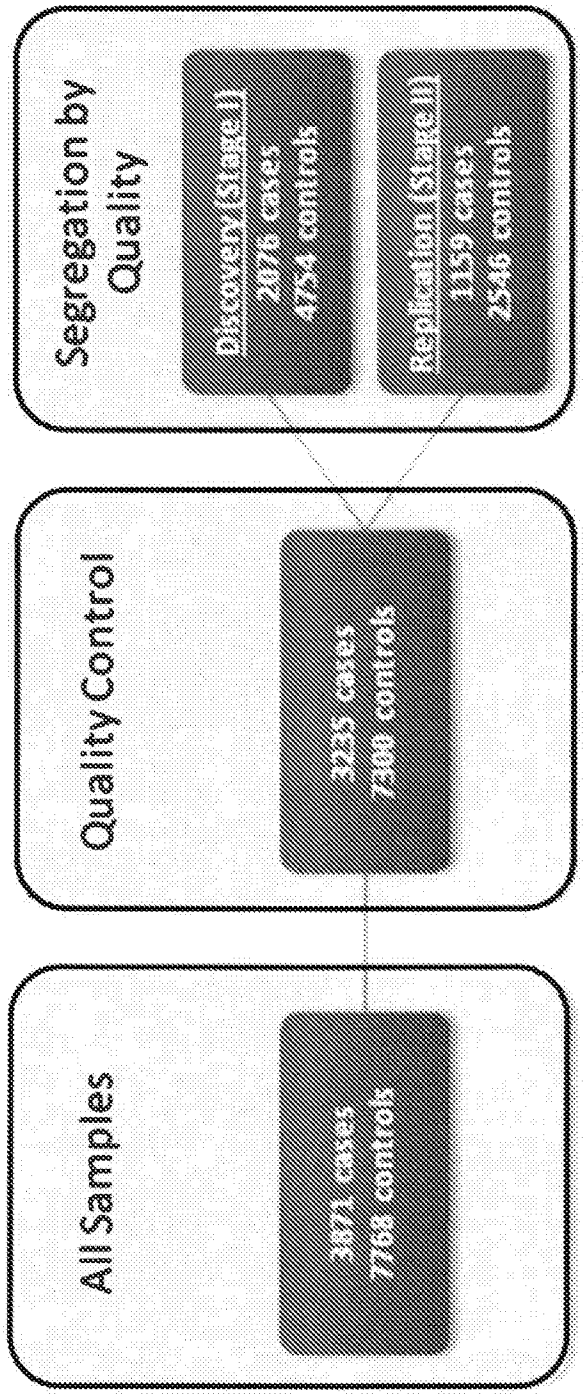

All Samples
3871 cases
7768 controls
Quality Control
3235 cases
7800 controls
Segregation by Quality
Discovery (Stage I)
2076 cases
4754 controls
Replication (Stage II)
1159 cases
2546 controls

FIG. 1

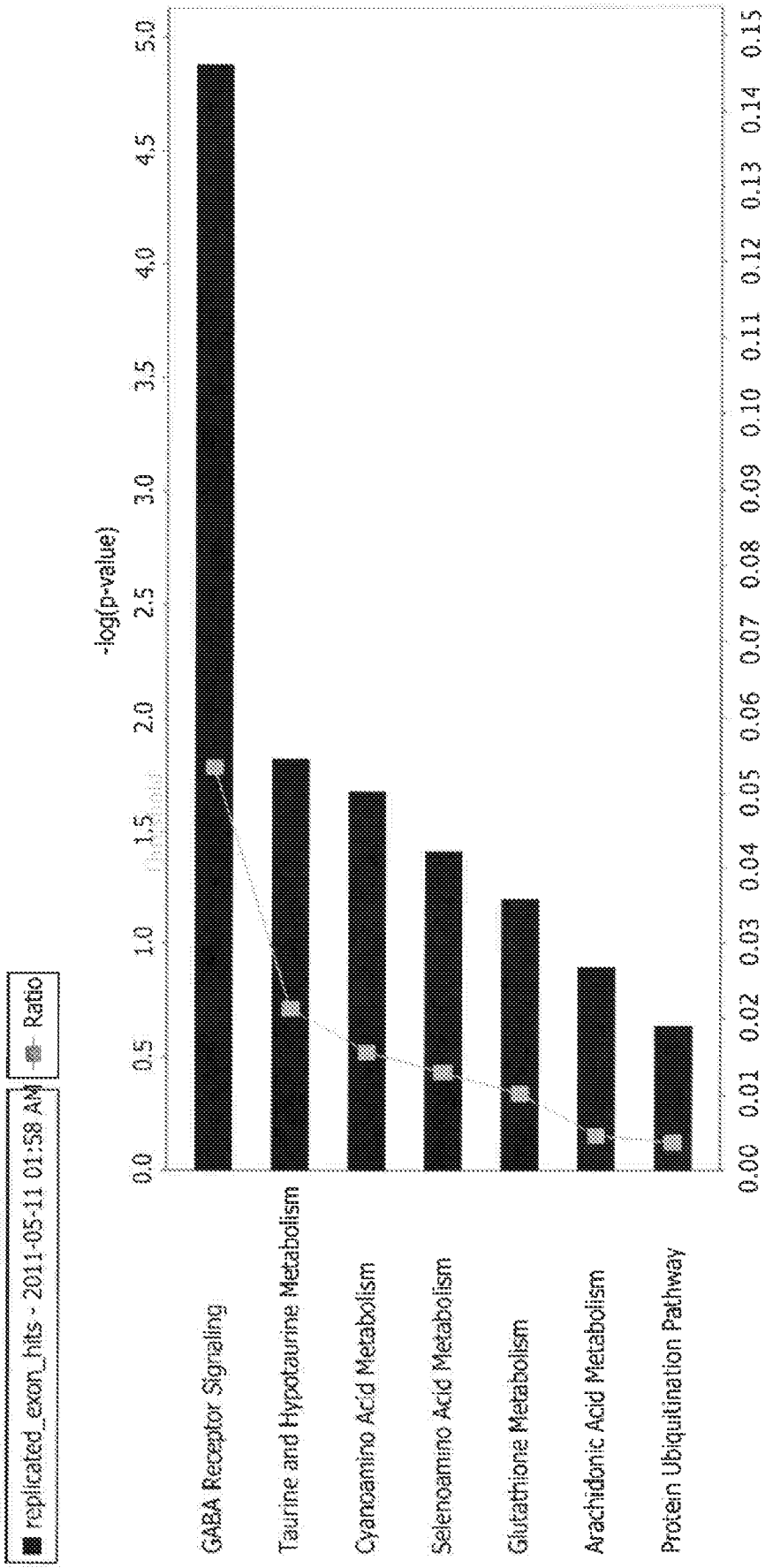

replicated_exon_hits - 2011-05-11 01:58 AM
Ratio
-log(p-value)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
0.00
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.09
0.10
0.11
0.12
0.13
0.14
0.15
Ratio
GABA Receptor Signaling
Taurine and Hypotaurine Metabolism
Cyanoamino Acid Metabolism
Selenoamino Acid Metabolism
Glutathione Metabolism
Arachidonic Acid Metabolism
Protein Ubiquitination Pathway

FIG. 2

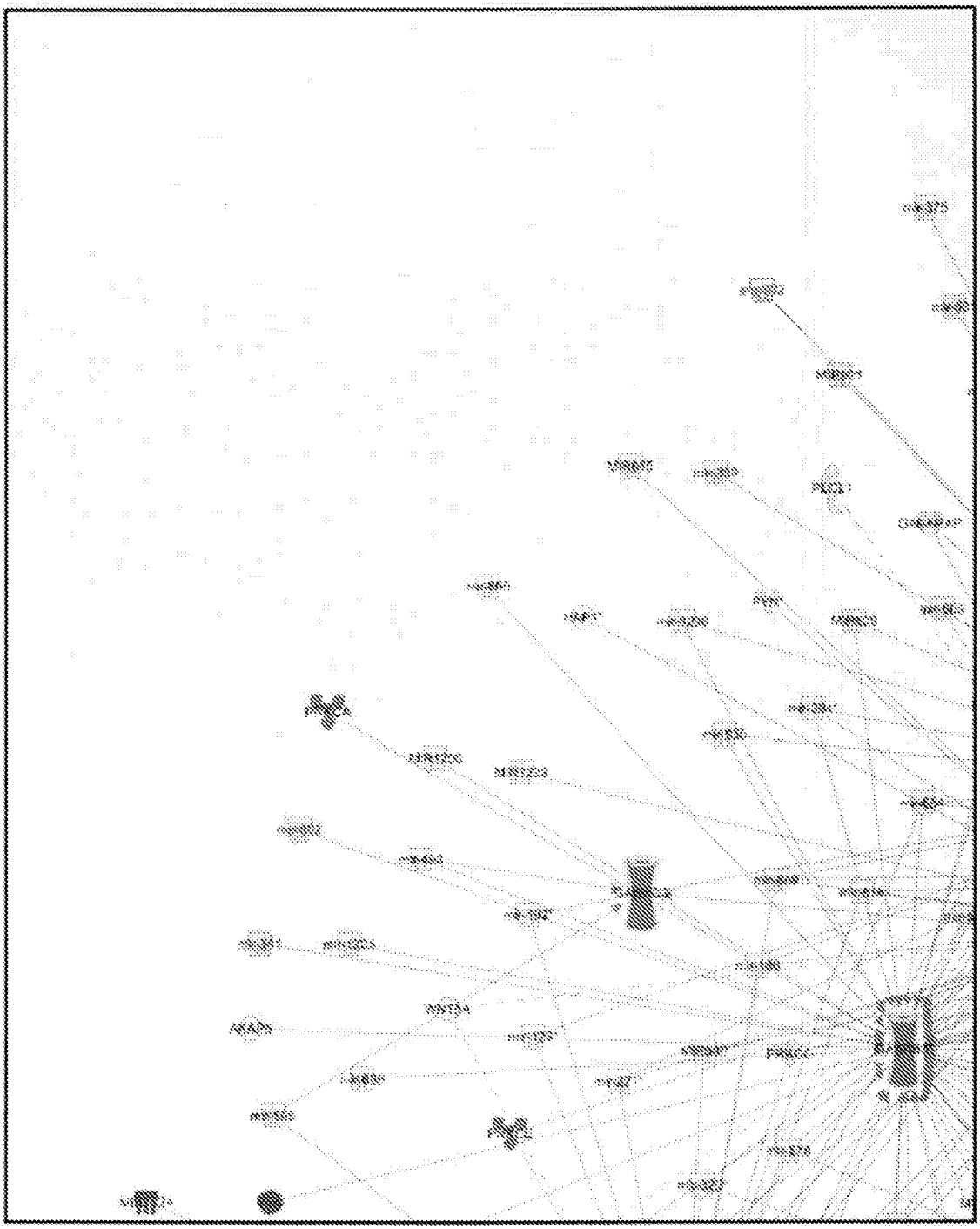


FIG. 3A (Top left)

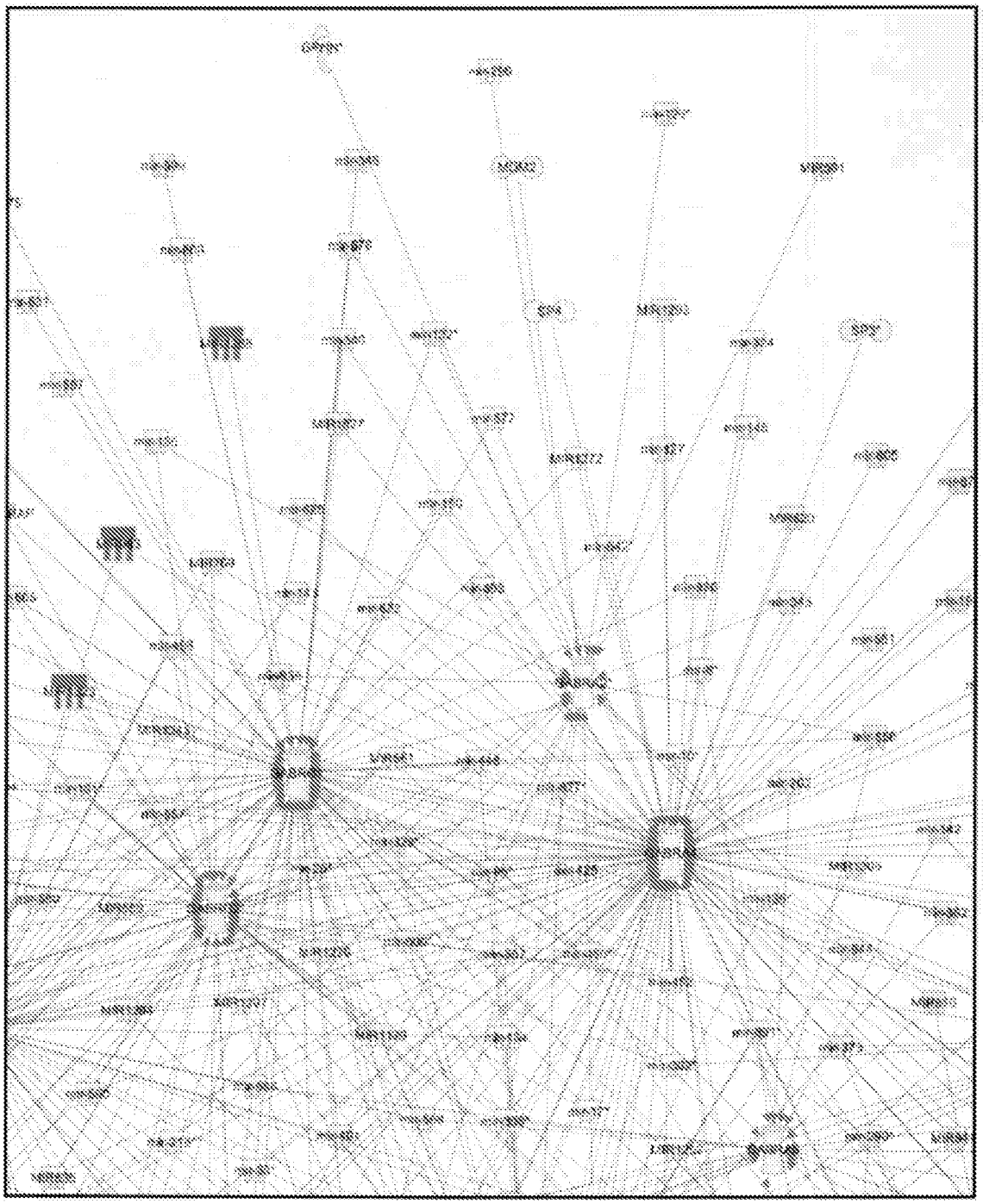


FIG. 3B (Top center)

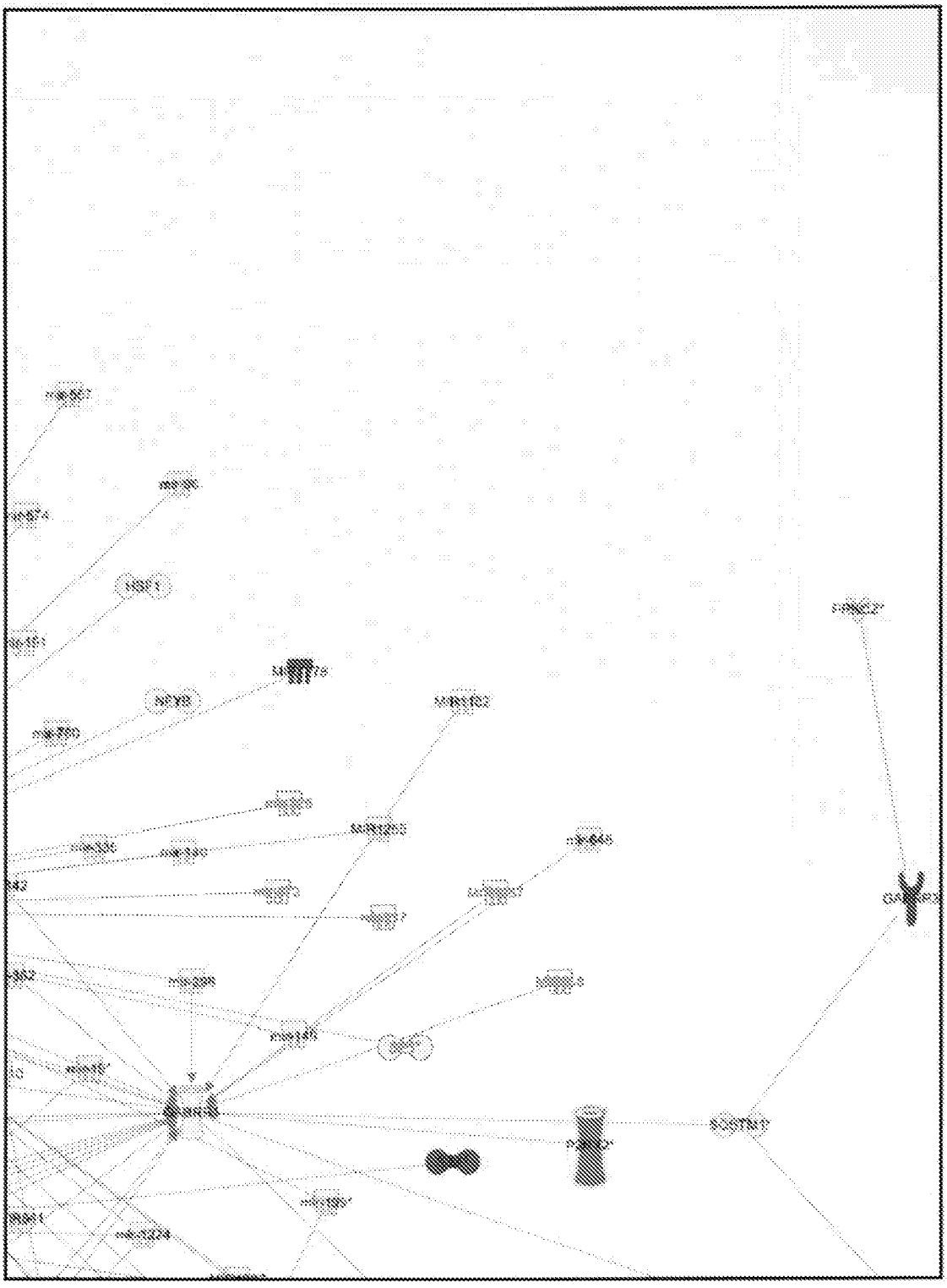


FIG. 3C (Top right)

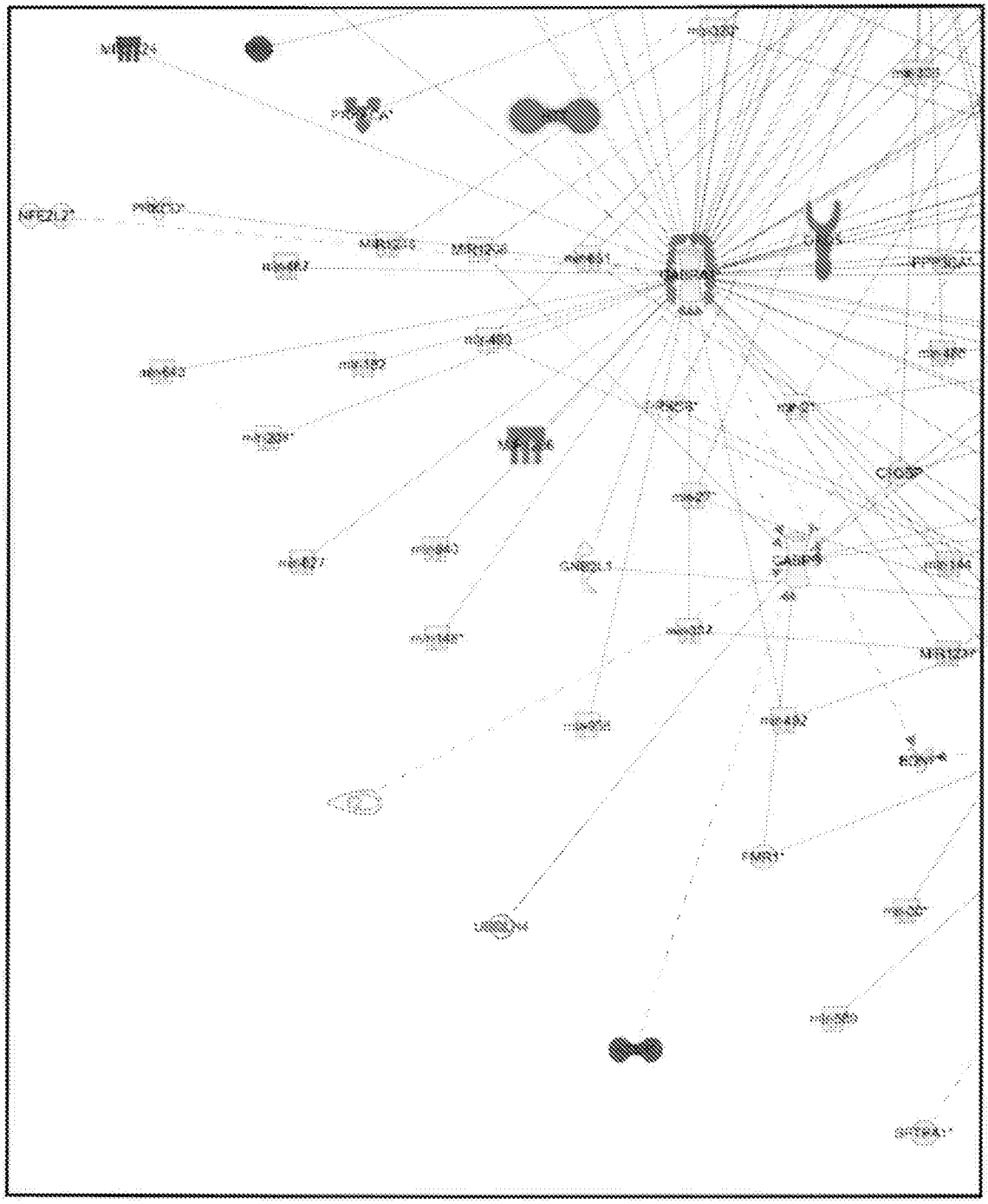


FIG. 3D (Bottom left)

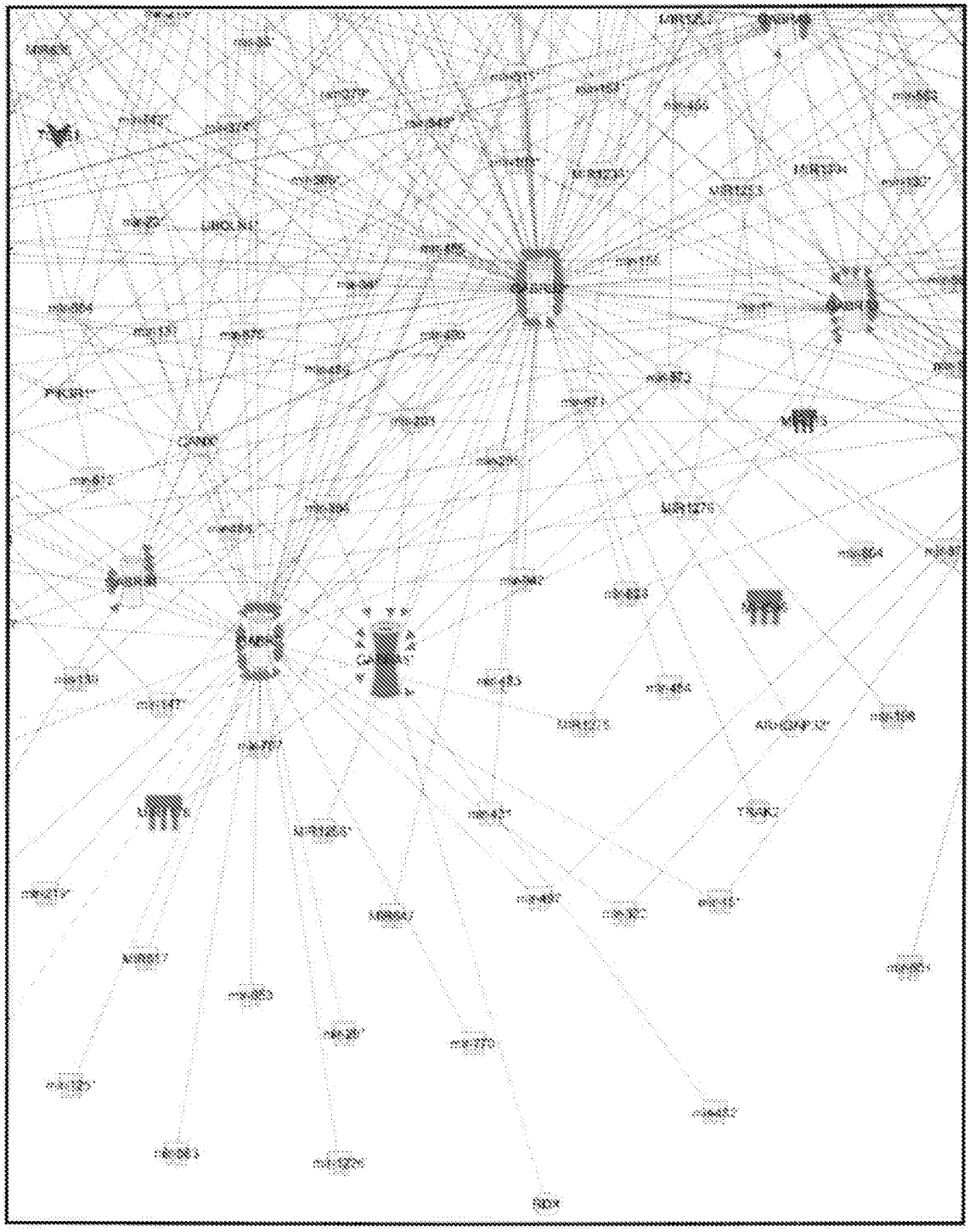


FIG. 3E (Bottom center)

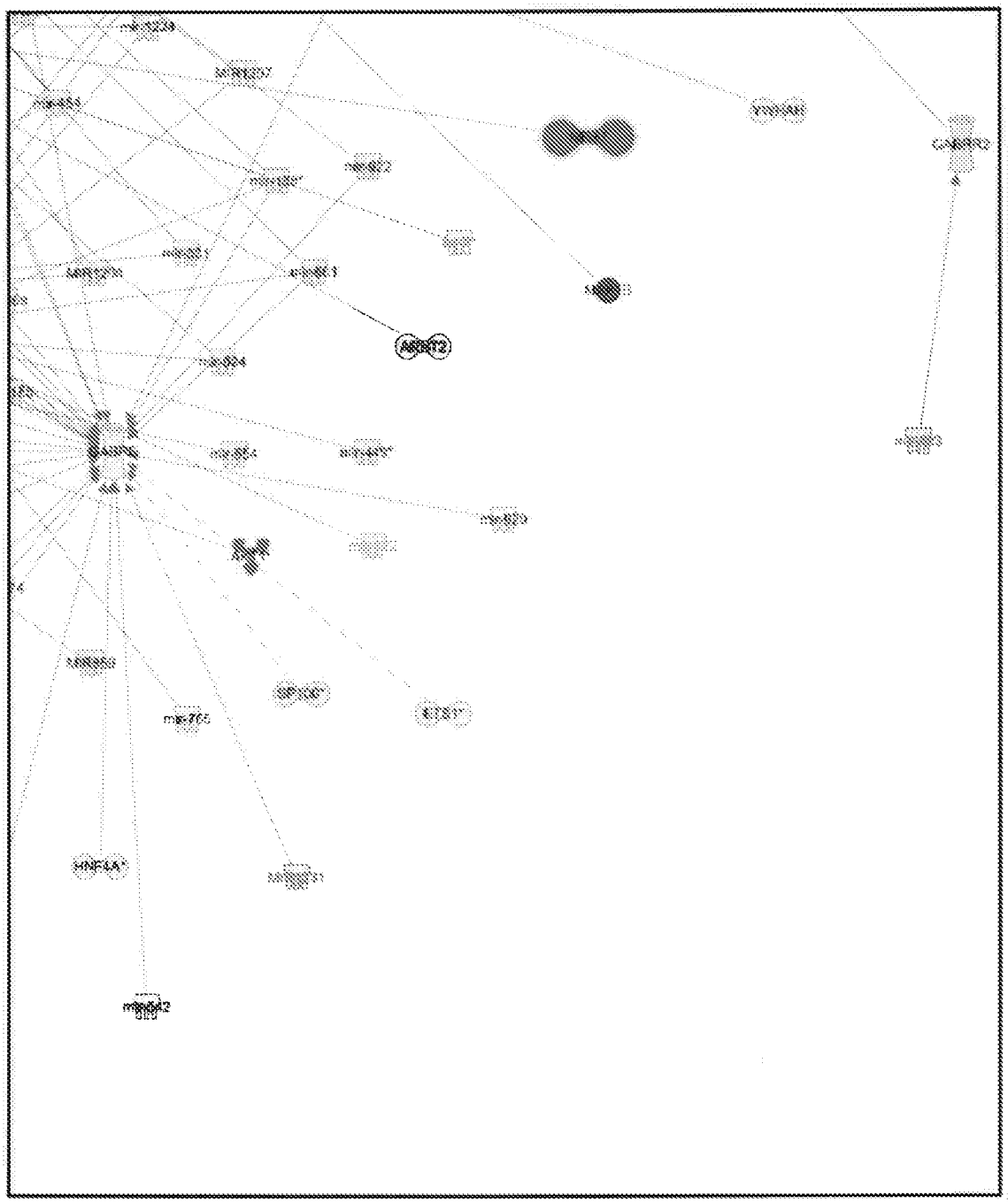


FIG. 3F (Bottom right)

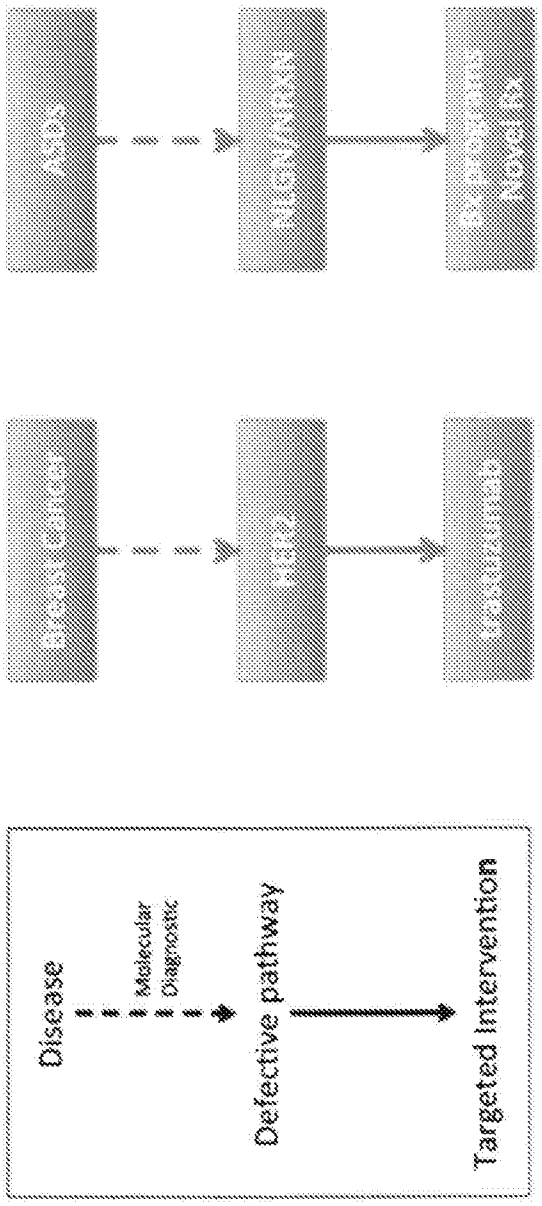

Disease
Molecular Diagnostic
Defective pathway
Targeted Intervention
Breast cancer
HER2
Trastuzumab
ABL1
BCR/ABL1
Therapeutic Modality

FIG. 4

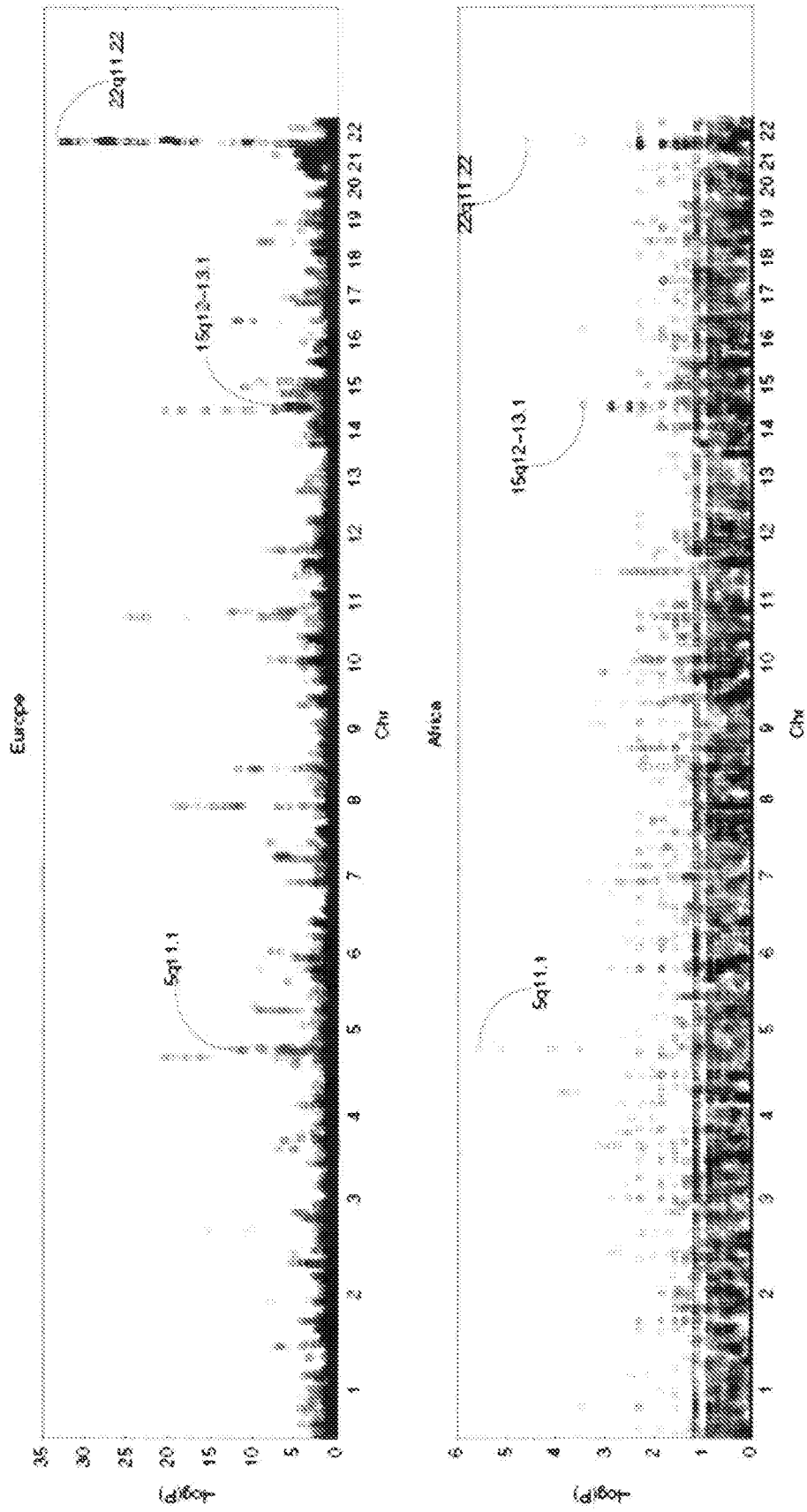

European
22q11.22
15q12-13.1
5q11.1
Chr
-log(P)
African
22q11.22
15q12-13.1
5q11.1
Chr
-log(P)

FIG. 5

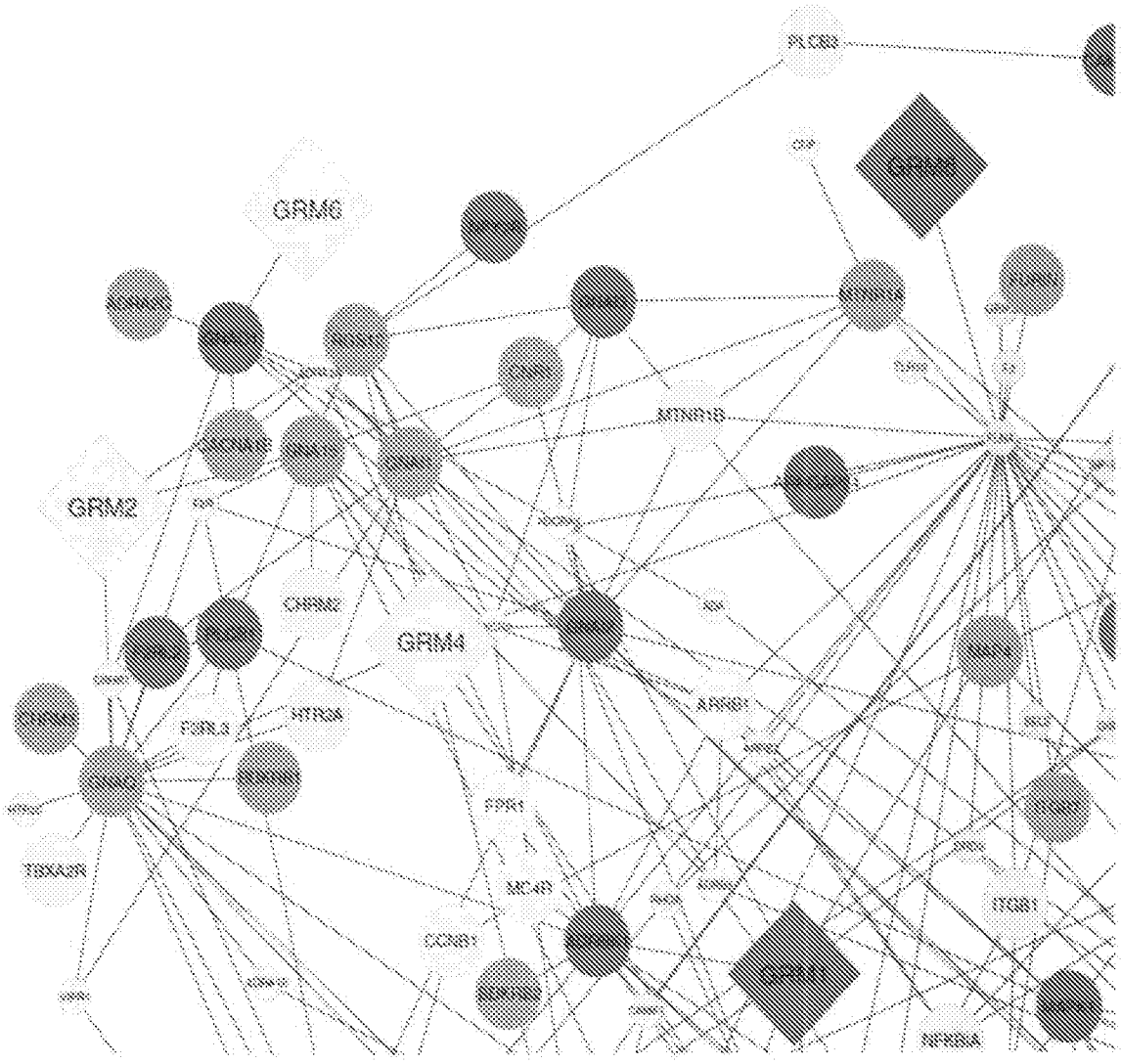


FIG. 6A (top left)

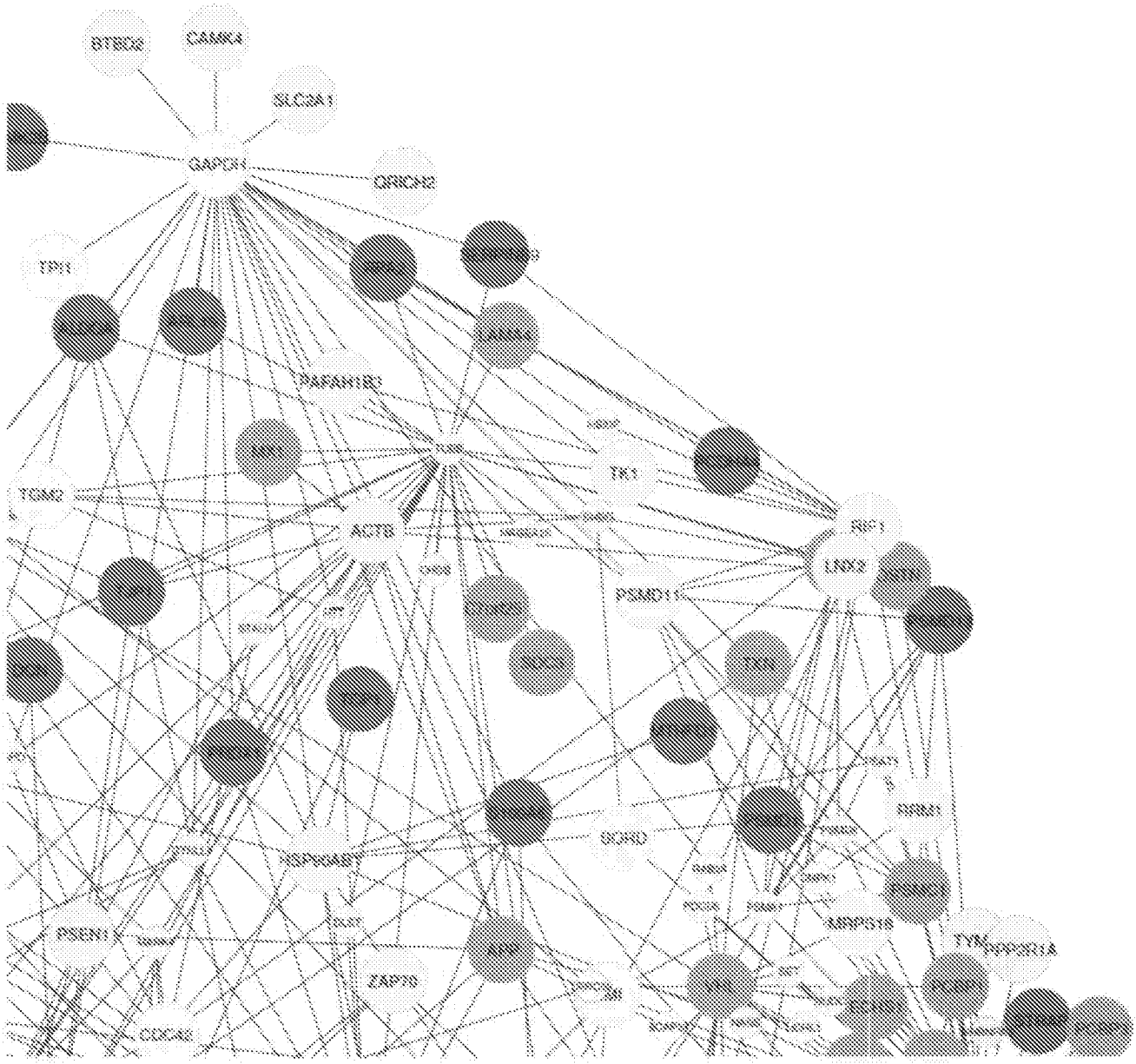


FIG. 6B (top right)

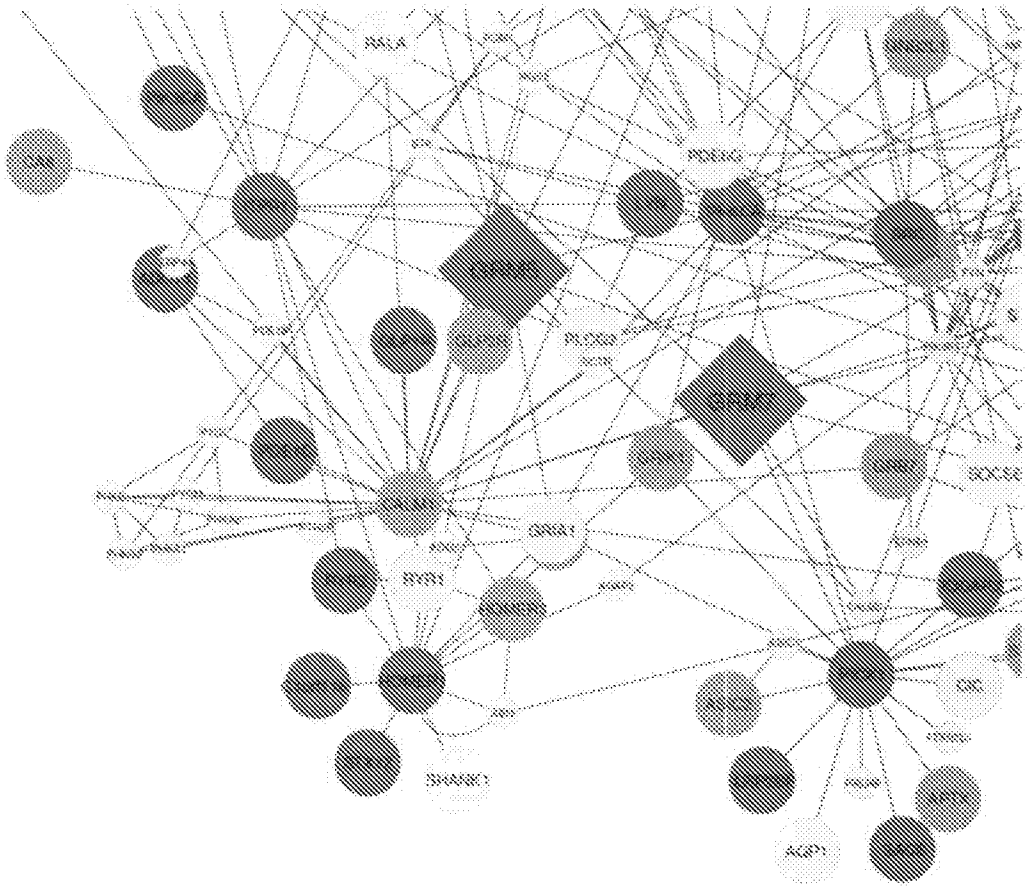


FIG. 6C (bottom left)

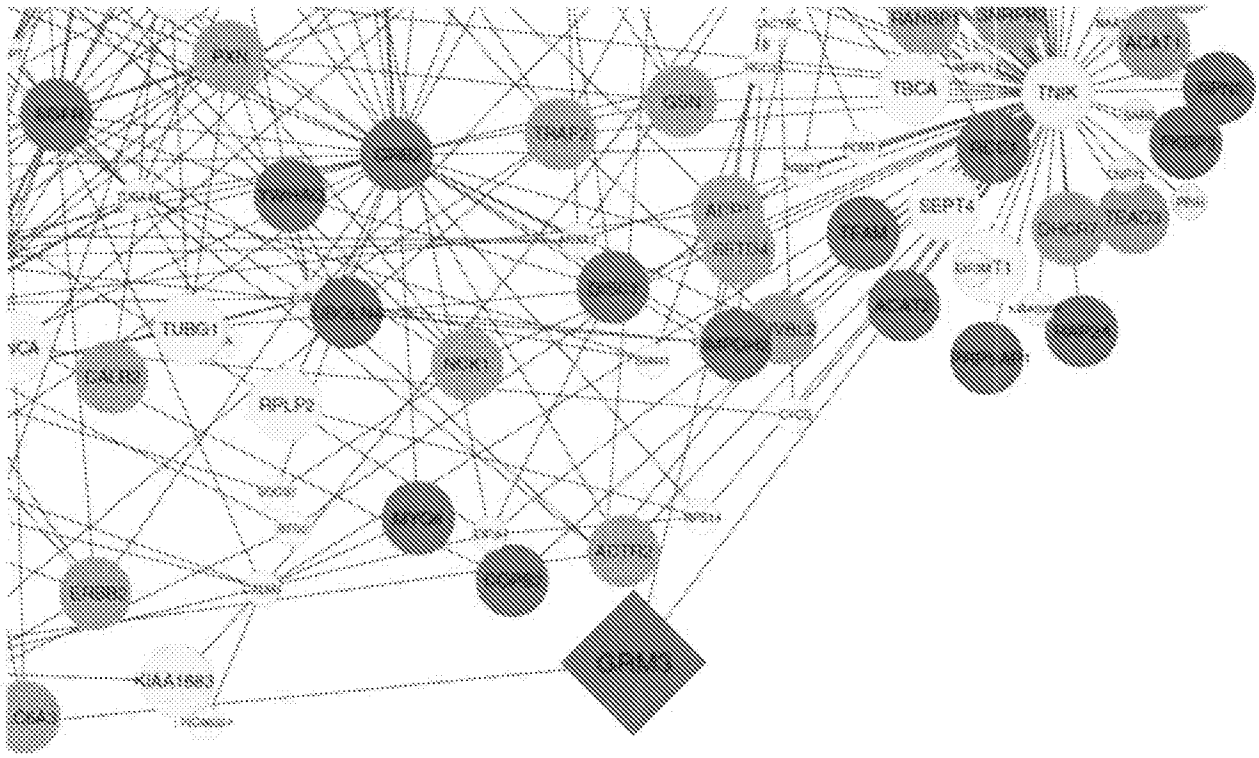


FIG. 6D (bottom right)

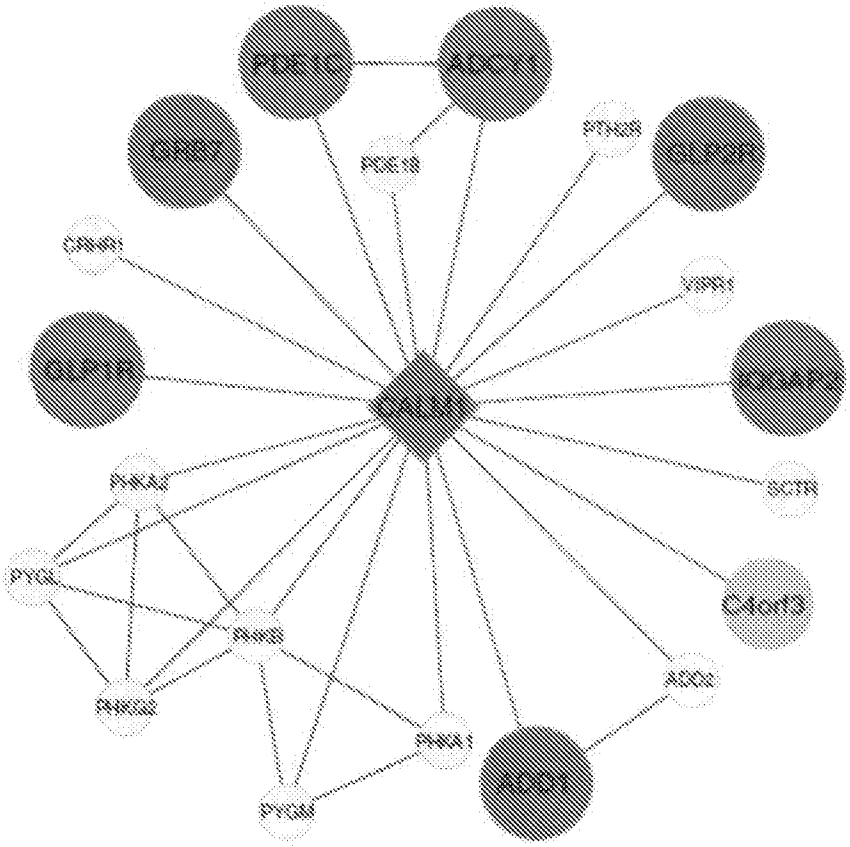

PDE11A
ADCY1
PDE1B
PTH2R
CNR1
VIPR1
PRKAR2B
PRKAR2A
SCTR
PTGIR
PRKCB
ADCY2
PRKCA2
PRKCA1
PTGIR

FIG. 7

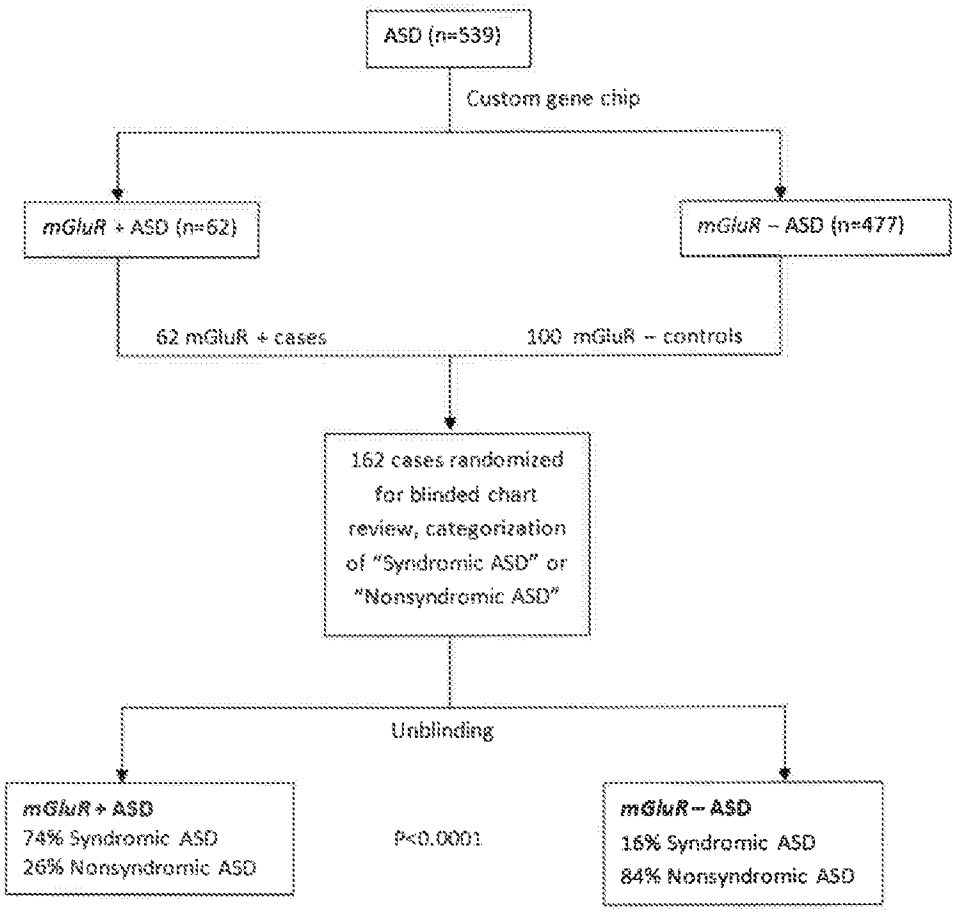

ASD (n=539)
Custom gene chip
mGluR + ASD (n=62)
mGluR – ASD (n=477)
62 mGluR + cases
100 mGluR – controls
162 cases randomized for blinded chart review, categorization of "Syndromic ASD" or "Nonsyndromic ASD"
Unblinding
mGluR + ASD
74% Syndromic ASD
26% Nonsyndromic ASD
P<0.0001
mGluR – ASD
16% Syndromic ASD
84% Nonsyndromic ASD

FIG. 8

CNV	gene	bands	locus	Size (Kb)	# SNP	# Case	# Ctrl	P	OR
Most significant CNVRs within genes across the mGluR GFIN									
dup	CACNA1B	9q34.3	chr9:140767745-140774721	6.98	2	11	0	4.21E-04	inf
dup	CNR1	6q15	chr6:88858724-88861698	2.98	1	15	8	9.39E-02	1.93
dup	ECHS1	10q26.3	chr10:135174203-135183094	8.89	2	10	0	8.54E-04	inf
dup	HOMER3	19p13.11	chr19:19050957-19054720	3.76	2	9	3	6.68E-02	3.08
del	PSMD1	2q37.1	chr2:232025285-232035793	10.51	1	14	2	1.77E-03	7.20
dup	RANBP1	22q11.21	chr22:20107729-20117344	9.62	1	13	3	9.24E-03	4.46
del	RYR2	1q43	chr1:237273380-237275393	2.01	1	4	0	5.93E-02	inf
del	TJP1	15q13.1	chr15:29812778-30178613	365.84	62	4	0	5.93E-02	inf
dup	TRAF2	9q34.3	chr9:139776401-139821067	44.67	3	6	1	5.83E-02	6.16
dup	TUBA3C	13q12.11	chr13:19743860-19748709	4.85	4	17	8	4.70E-02	2.18
Most significant CNVRs within GRM hubs of mGluR GFIN									
del	GRM1	6q24.3	chr6:146615383-146633818	18.44	3	2	0	2.44E-01	inf
del	GRM3	7q21.12	chr7:86410689-86455535	44.85	9	1	0	4.94E-01	inf
del	GRM4	6p21.31	chr6:33986091-34072561	86.47	26	0	1	1.00E+00	-inf
del	GRM5	11q14.3	chr11:88768276-88841459	73.18	7	4	0	5.96E-02	inf
dup	GRM6	5q35.3	chr5:178313079-178547566	234.49	51	0	2	5.00E-01	-inf
del	GRM7	3p26.1	chr3:7169454-7197715	28.26	11	2	0	2.44E-01	inf
del	GRM8	7q31.33	chr7:126405246-126457778	52.53	11	1	0	4.94E-01	inf

FIG. 9

CNV	gene(s)	bands	locus	Size (Kb)	# SNP	# Case	# Ctrl	P	OR
dup	SKI	1p36.33	chr1:2204755-2211849	7.10	3	6	1	5.87E-02	6.15
del	SMARCC1	3p21.31	chr3:47749708-47749708	0.00	1	10	2	1.74E-02	5.13
del	HDAC2	6q21	chr6:114260720-114273646	12.93	5	4	0	5.96E-02	inf
del	HDAC9	7p21.1	chr7:18375246-18384157	8.91	2	4	0	5.96E-02	inf
dup	PLEC **PARP10**	8q24.3	chr8:145046663-145059425	12.76	1	243	125	4.06E-11	2.04
del	HDAC7	12q13.11	chr12:48178513-48178604	0.09	2	7	1	3.26E-02	7.17
dup	SNORD115-43 SNORD115-42 **UBE3A** SNORD115-47 SNORD115-45 SNORD115-44 SNORD115-48 SNORD115-36 SNORD109A SNORD115-29 SNORD109B SNORD115-10 SNORD115-11	15q11.2	chr15:25491630-25606727	115.10	11	19	0	1.50E-06	inf
del	**PML** STOML1	15q24.1	chr15:74247944-74343330	95.39	20	6	0	1.45E-02	inf
del	PTPN9 **SIN3A**	15q24.2	chr15:75718670-75806911	88.24	4	7	0	7.19E-03	inf
	Most significant CNVRs within MXD hubs of MXD GFIN								
del	SNRNP27 **MXD1**	2p13.3	chr2:70112581-70173629	61.05	10	1	0	4.94E-01	inf
dup	ZFYVE28 **MXD4**	4p16.3	chr4:2256717-2287420	30.70	4	2	0	2.44E-01	inf
del	GPRIN1 RAB24 MIR4281 HK3 UNC5A TSPAN17 SNCB ZNF346 LMAN2 EIF4E1B NSD1 PRELID1 FGFR4 **MXD3** UIMC1	5q35.2 5q35.3	chr5:176024881-176780544	755.66	95	1	0	4.94E-01	inf

FIG. 10

CNV	gene	bands	locus	Size (Kb)	# SNP	# Case	# Ctrl	P	OR
del	ADCY1	7p12.3	chr7:45598469-45620959	22491	2	1	0	4.94E-01	inf
dup	ADD1	4p16.3	chr4:2906285-3080173	173889	28	3	0	1.21E-01	inf
del	C4orf3	4q26	chr4:120111190-120399505	288316	31	1	0	4.94E-01	inf
dup	CALM1	14q32.11	chr14:90843792-90868442	24651	4	2	0	2.44E-01	inf
del	GLP1R	6p21.2	chr6:39022698-39055516	32819	23	1	0	4.94E-01	inf
dup	GLP2R	17p13.1	chr17:9708956-9826778	117823	45	1	0	4.94E-01	inf
dup	GR87	17q12	chr17:37834542-37922259	87718	2	1	0	4.94E-01	inf
del	IQGAP2	5q13.3	chr5:75795407-75805105	9699	4	1	0	4.94E-01	inf
del	PDE1C	7p14.3	chr7:32225283-32228302	3020	5	3	0	1.21E-01	inf
del	PTH2R	2q34	chr2:209280931-209297026	16096	4	0	1	1.00E+00	0

FIG. 11

CNVR	Genes	Bands	Size (Kb)	No. of SNP	No. of Case	No. of Control	All		Europe		Africa	
							P-value	OR	*P*-value	OR	*P*-value	OR
del	*ZNF280B*	22q11.22	53.4	13	130	0	2.56E−57	Inf	1.94E−33	Inf	3.34E−04	Inf
del	*PARP8*	5q11.1	47.7	8	70	8	2.76E−22	15.11	3.84E−13	12.20	2.69E−06	40.9
dup	*GABRB3*	15q12	49.0	20	28	0	7.60E−13	Inf	1.50E−06	Inf	3.34E−04	Inf
dup	*GABRG3*	15q12	135.3	13	27	1	3.72E−11	Inf	1.60E−05	19.5	3.34E−04	Inf
dup	*HERC2*	15q13.1	84.4	2	24	0	4.12E−11	Inf	6.17E−06	Inf	3.34E−04	Inf

FIG. 12

Gene family		Enriched genes		Cases		Controls		Gene Network Association		
Name	Size	No.	Frequency	No.	Frequency	No.	Frequency	P fisher	Enrichment	P perm
BRF	2	242/326	0.742	567	0.123	370	0.079	3.30E-13	1.65	0.040
CCL	24	108/144	0.75	231	0.05	129	0.027	5.62E-09	1.88	0.008
CCNT	2	183/254	0.72	613	0.133	381	0.081	1.10E-16	1.75	0.007
ELAVL	4	108/156	0.692	327	0.071	152	0.032	6.87E-18	2.3	0.043
ERCC	7	263/369	0.713	836	0.182	360	0.119	7.67E-18	1.65	0.035
GRM	8	124/181	0.685	265	0.058	153	0.032	2.40E-09	1.82	0.043
GTF2H	5	152/223	0.682	391	0.085	233	0.049	3.21E-12	1.79	0.049
KIAA	106	268/373	0.718	988	0.215	647	0.137	3.12E-23	1.72	0.045
KPNA	7	256/367	0.698	560	0.122	369	0.078	1.26E-12	1.63	0.028
MYD	3	52/64	0.813	366	0.08	156	0.033	3.83E-23	2.53	0.042

FIG. 13A

POU5F	2	94/130	0.723	293	0.064	131	0.028	2.96E−17	2.38	0.041
RAD	7	218/309	0.706	535	0.116	339	0.072	9.68E−14	1.7	0.042
SAP	4	111/150	0.74	274	0.06	151	0.032	9.61E−11	1.92	0.040
SMAD	8	845/1,225	0.69	1,782	0.387	1,424	0.302	1.81E−18	1.46	0.039
SMARCC	3	106/147	0.721	239	0.052	131	0.028	1.22E−09	1.92	0.043
SMC	5	88/120	0.733	336	0.073	176	0.037	1.71E−14	2.03	0.034

FIG. 13B

Gene Family Member	Enriched Genes		Cases		Controls		Gene Network Association		
	No.	Frequency	No.	Frequency	#	Frequency	P_{fisher}	Enrichment	P_{perm}
AKAP13	7/7	1.00	16	0.0035	1	0.0002	1.14E-04	16.43	0.012
BAG1	7/7	1.00	15	0.0032	1	0.0002	2.18E-04	15.40	0.014
CALM1	9/10	0.90	14	0.0030	1	0.0002	4.16E-04	14.37	0.002
CASP6	16/17	0.94	46	0.0100	6	0.0013	2.96E-09	7.91	0.012
CTTN3	23/26	0.88	42	0.0091	8	0.0017	3.66E-07	5.41	0.009
MAPK8	11/12	0.92	34	0.0074	4	0.0008	2.02E-07	8.76	0.012
NCOR1	9/10	0.90	26	0.0056	2	0.0004	1.11E-06	13.37	0.004
PARP1	5/5	1.00	5	0.0011	0	0.0000	2.95E-02	inf	0.012
PTPN13	6/6	1.00	9	0.0019	0	0.0000	1.75E-03	inf	0.007
TCEA1	22/26	0.85	39	0.0084	7	0.0015	5.94E-07	5.74	0.009

FIG. 14

	A	B	C	D	E	F	G	H	I	J	K
1	sym	locus	numCases	totalCases	numControls	totalControls	fCase	fControl	pVal	oddsRatio	enrichment
2	ACAT1	dup:chr11:107957476-108034124	4	4602	1	4722	0.00086919	0.000211777	0.179493275	4.107803034	case
3	ACAT2	del:chr6:160152776-160207572	1	4602	0	4722	0.0002173	0	0.49356499	None	case
4	ACP1	dup:chr2:238975-272916	2	4602	0	4722	0.00043459	0	0.24357959	None	case
5	ACTR2	dup:chr2:65425014-65485283	1	4602	0	4722	0.0002173	0	0.49356499	None	case
6	ADCY1	del:chr7:45598469-45620959	1	4602	0	4722	0.0002173	0	0.49356499	None	case
7	ADD1	dup:chr4:2908385-3080173	3	4602	0	4722	0.00065189	0	0.12019589	None	case
8	ADRA2C	dup:chr4:3505449-3780071	3	4602	0	4722	0.00065189	0	0.12019589	None	case
9	ADRBK1	del:chr11:67033077-67164494	2	4602	0	4722	0.00043459	0	0.24357959	None	case
10	AGAP2	dup:chr12:5811190-56177292	2	4602	0	4722	0.00043459	0	0.24357959	None	case
11	ALDOA	del:chr16:30046843-30141257	8	4602	3	4722	0.00173837	0.000635532	0.10506275	2.739225008	case
12	APTX	dup:chr9:32954680-33083731	1	4602	0	4722	0.0002173	0	0.49356499	None	case
13	ARHGAP24	del:chr4:86517054-86532911	1	4602	0	4722	0.0002173	0	0.49356499	None	case
14	ARL13	del:chr5:53368171-53398717	1	4602	0	4722	0.0002173	0	0.49356499	None	case
15	BDKRB1	dup:chr14:96054262-96728753	1	4602	0	4722	0.0002173	0	0.49356499	None	case
16	BDKRB2	dup:chr14:96054262-96728753	1	4602	0	4722	0.0002173	0	0.49356499	None	case
17	C1orf135	del:chr1:207303757-207236524	1	4602	0	4722	0.0002173	0	0.49356499	None	case
18	C4orf3	del:chr4:120111190-120399505	1	4602	0	4722	0.0002173	0	0.49356499	None	case
19	C7orf25	dup:chr7:42869485-43178373	1	4602	0	4722	0.0002173	0	0.49356499	None	case
20	CA8	dup:chr8:60997356-61231164	1	4602	0	4722	0.0002173	0	0.49356499	None	case
21	CACNA1B	dup:chr9:140767745-140774733	11	4602	0	4722	0.00239027	0	0.00442089	None	case
22	CALB2	dup:chr16:70786633-71429523	2	4602	0	4722	0.00043459	0	0.24357959	None	case
23	CALM1	dup:chr14:90843792-90868442	2	4602	0	4722	0.00043459	0	0.24357959	None	case
24	CAMK2B	del:chr7:44235034-44334542	1	4602	0	4722	0.0002173	0	0.49356499	None	case
25	CHP	del:chr15:41486991-41529712	6	4602	3	4722	0.00130378	0.000635532	0.24179356	2.05255248	case
26	CHRM3	dup:chr1:239821058-239827726	2	4602	0	4722	0.00043459	0	0.24357959	None	case
27	CNPY2	dup:chr12:56325420-56948639	1	4602	0	4722	0.0002173	0	0.49356499	None	case
28	CNR1	dup:chr6:88858724-88861698	15	4602	8	4722	0.00325945	0.0016942	0.09389401	1.926831302	case
29	COPB2	del:chr3:139101777-139110135	1	4602	1	4722	0.0002173	0.000211777	0.7435504	1.026088129	case
30	DCN	del:chr12:91476569-91683308	2	4602	0	4722	0.00043459	0	0.24357959	None	case
31	DHCR7	dup:chr11:70876436-71281859	1	4602	0	4722	0.0002173	0	0.49356499	None	case
32	DISC1	del:chr1:231843962-231886652	1	4602	0	4722	0.0002173	0	0.49356499	None	case
33	DSTN	dup:chr20:17490410-17691406	1	4602	0	4722	0.0002173	0	0.49356499	None	case
34	ECHS1	dup:chr10:135174203-135183094	10	4602	0	4722	0.00217297	0	0.00085367	None	case

FIG. 15A

	A	B	C	D	E	F	G	H	I	J	K
44	EGFR	del:chr7:54727310-55442774	1	4602	0	4722	0.0002173	0	0.49356499	None	case
46	ERBB2	dup:chr17:37834542-37922259	1	4602	0	4722	0.0002173	0	0.49356499	None	case
47	ERP44	del:chr9:102723693-102744008	4	4602	2	4722	0.0008693	0.000942355	0.3317105	2.05306655	case
48	FZRL2	del:chr5:75875630-75913784	3	4602	2	4722	0.0006518	0.000942355	0.48793311	1.5394651	case
50	FKBP3	del:chr14:45578044-45619217	2	4602	0	4722	0.0004345	0	0.24357959	None	case
52	FURIN	dup:chr15:91237231-91697710	1	4602	0	4722	0.0002172	0	0.49356499	None	case
54	GLP1R	del:chr6:39022698-39055516	1	4602	0	4722	0.0002173	0	0.49356499	None	case
55	GLP2R	dup:chr17:9768956-9826778	1	4602	0	4722	0.0002173	0	0.49356499	None	case
56	GNA15	dup:chr19:3113854-3136845	3	4602	0	4722	0.0006518	0	0.12019589	None	case
57	GNAI1	dup:chr7:79464196-79822643	1	4602	0	4722	0.0002173	0	0.49356499	None	case
58	GNAI2	del:chr3:50291785-50324671	2	4602	0	4722	0.0004345	0	0.24357959	None	case
59	GNAI3	del:chr1:110136405-110140977	1	4602	0	4722	0.0002173	0	0.49356499	None	case
60	GNAO1	del:chr16:56340296-56362724	3	4602	0	4722	0.0006518	0	0.12019589	None	case
61	GNAQ	dup:chr9:80350949-80355315	1	4602	0	4722	0.0002173	0	0.49356499	None	case
62	GNB2L1	dup:chr5:180652242-180665489	1	4602	1	4722	0.0002173	0.000211772	0.7435504	1.026088129	case
64	GRB2	del:chr17:73358259-73374945	3	4602	0	4722	0.0006518	0	0.12019589	None	case
65	GRB7	dup:chr17:37834542-37922259	1	4602	0	4722	0.0002173	0	0.49356499	None	case
67	GRIK1	del:chr21:31213091-31226639	2	4602	0	4722	0.0004345	0	0.24357959	None	case
68	GRM1	del:chr6:146615383-146633818	2	4602	0	4722	0.0004345	0	0.24357959	None	case
69	GRM3	del:chr7:86410689-86455535	1	4602	0	4722	0.0002173	0	0.49356499	None	case
71	GRM5	del:chr11:88768276-88841459	4	4602	0	4722	0.0008693	0	0.05930499	None	case
73	GRM7	del:chr3:71694547197715	2	4602	0	4722	0.0004345	0	0.24357959	None	case
74	GRM8	del:chr7:126405246-126457778	1	4602	0	4722	0.0002173	0	0.49356499	None	case
75	GSN	dup:chr9:123997647-124057682	1	4602	0	4722	0.0002173	0	0.49356499	None	case
76	HNRNPA3	del:chr2:178029853-178087851	1	4602	1	4722	0.0002173	0.000211772	0.7435504	1.026088129	case
77	HOMER1	del:chr5:78666314-78673236	2	4602	0	4722	0.0004345	0	0.24357959	None	case
78	HOMER3	dup:chr19:19030957-19054720	9	4602	3	4722	0.0019557	0.000634532	0.06684957	3.082229815	case
81	HTT	dup:chr4:2906285-3080173	3	4602	0	4722	0.0006518	0	0.12019589	None	case
82	IMPDH2	del:chr3:49040462-49108428	1	4602	1	4722	0.0002173	0.000211772	0.7435504	1.026088129	case
83	IQGAP2	del:chr5:75795407-75805105	1	4602	0	4722	0.0002173	0	0.49356499	None	case
85	ITGB7	dup:chr12:53573903-53603737	3	4602	0	4722	0.0006518	0	0.12019589	None	case
86	ITPR1	del:chr3:4741821-4776094	1	4602	0	4722	0.0002173	0	0.49356499	None	case
88	LAMA4	dup:chr6:112573780-112614697	1	4602	0	4722	0.0002173	0	0.49356499	None	case
90	LRP2BP	del:chr4:186143007-186356464	2	4602	1	4722	0.0004345	0.000211772	0.49034699	2.05266087	case

FIG. 15B

	A	B	C	D	E	F	G	H	I	J	K
91	LYAR	dup:chr4:4082937-5142211	2	4602	0	4722	0.00043459	0	0.24357959	None	case
92	LYN	del:chr8:56803179-56814308	1	4602	0	4722	0.0002173	0	0.49356499	None	case
93	MAPK	dup:chr3:47936671-48029118	1	4602	0	4722	0.0002173	0	0.49356499	None	case
94	MAPK1	del:chr22:22205612-22260440	1	4602	0	4722	0.0002173	0	0.49356499	None	case
97	MTHFD1	del:chr14:64833333-64868203	1	4602	1	4722	0.0002173	0.000211 77	0.7435504	1.02608129	case
98	MTNR1A	dup:chr4:187437316-187505764	3	4602	0	4722	0.00065189	0	0.12019589	None	case
100	MX1	del:chr21:42685045-43399914	1	4602	0	4722	0.0002173	0	0.49356499	None	case
101	MYO6	del:chr6:76447205-76473071	1	4602	0	4722	0.0002173	0	0.49356499	None	case
102	NAA15	del:chr4:140264431-140264431	2	4602	0	4722	0.00043459	0	0.24357959	None	case
103	NCK1	dup:chr3:136487559-136606271	1	4602	0	4722	0.0002173	0	0.49356499	None	case
106	NPY2R	del:chr4:156087185-156160310	2	4602	0	4722	0.00043459	0	0.24357959	None	case
108	PCBP1	dup:chr2:70303218-70388870	1	4602	0	4722	0.0002173	0	0.49356499	None	case
109	PCBP3	dup:chr21:47323742-47342116	3	4602	1	4722	0.00065189	0.000211 77	0.30286889	3.07958252	case
110	PCDHA4	del:chr5:140227999-140246511	3	4602	1	4722	0.00065189	0.000211 77	0.30286889	3.07958252	case
111	PDE1C	del:chr7:32225283-32228302	3	4602	0	4722	0.00065189	0	0.12019589	None	case
113	PICK1	del:chr22:38462680-38518731	1	4602	0	4722	0.0002173	0	0.49356499	None	case
114	PIK3CA	del:chr3:178912662-178941323	1	4602	0	4722	0.0002173	0	0.49356499	None	case
115	PLA2G7	del:chr6:46629505-46679303	1	4602	0	4722	0.0002173	0	0.49356499	None	case
116	PLCB1	del:chr20:8400086-8412256	3	4602	0	4722	0.00065189	0	0.12019589	None	case
120	PRDX1	del:chr1:43936352-43955858	1	4602	1	4722	0.0002173	0.000211 77	0.7435504	1.02608129	case
121	PRKCA	del:chr17:64466865-64471675	3	4602	0	4722	0.00065189	0	0.12019589	None	case
122	PRPSAP1	del:chr17:74311348-74330638	3	4602	0	4722	0.00065189	0	0.12019589	None	case
124	PSMC1	dup:chr14:90621771-90729426	1	4602	0	4722	0.0002173	0	0.49356499	None	case
125	PSMD1	del:chr2:232025385-232035793	14	4602	2	4722	0.00304216	0.000423 55	0.00176964	7.20133494	case
127	PSMD13	del:chr11:2491322-2643380	5	4602	2	4722	0.00108648	0.000423 55	0.21605246	2.56689145	case
128	PSME1	dup:chr14:24587545-24687051	2	4602	0	4722	0.00043459	0	0.24357959	None	case
130	PXN	dup:chr12:120695141-120747913	3	4602	0	4722	0.00065189	0	0.12019589	None	case
131	RAB2A	del:chr8:61452046-61526953	1	4602	1	4722	0.0002173	0.000211 77	0.7435504	1.02608129	case
134	RANBP1	dup:chr22:20107729-20117344	13	4602	3	4722	0.00282486	0.000635 32	0.0092373	4.45609965	case
135	RAP2A	del:chr13:98076911-98096882	1	4602	0	4722	0.0002173	0	0.49356499	None	case
136	RCC1	del:chr1:28742323-28939138	3	4602	1	4722	0.00065189	0.000211 77	0.30286889	3.07958252	case
137	RGS12	dup:chr4:3434336-3436587	4	4602	1	4722	0.00086919	0.000211 77	0.17949275	4.10700304	case
139	RPA2	del:chr1:28107060-28267868	1	4602	0	4722	0.0002173	0	0.49356499	None	case
141	RPN2	del:chr20:35740795-35842923	1	4602	0	4722	0.0002173	0	0.49356499	None	case

FIG. 15C

	A	B	C	D	E	F	G	H	I	J	K
143	RUVBL2	dup:chr19:49485759-49517212	1	4602	0	4722	0.0002173	0	0.49356499	None	case
145	RYR2	del:chr1:237273380-237275393	4	4602	0	4722	0.00086919	0	0.05930489	None	case
146	S100A6	del:chr1:153460303-153509890	1	4602	0	4722	0.0002173	0	0.49356499	None	case
147	SACS	del:chr13:23903792-24224141	2	4602	0	4722	0.00043459	0	0.24357959	None	case
148	SDC3	dup:chr1:31375569-31387329	1	4602	0	4722	0.0002173	0	0.49356499	None	case
150	SERPINB9	del:chr6:2869032-3174946	1	4602	0	4722	0.0002173	0	0.49356499	None	case
154	SLC6A3	dup:chr5:1342714-1395077	2	4602	0	4722	0.00043459	0	0.24357959	None	case
156	SNRPB2	dup:chr20:16694602-16739851	3	4602	0	4722	0.00065189	0	0.12019589	None	case
159	SRC	del:chr20:35942718-36005274	1	4602	0	4722	0.0002173	0	0.49356499	None	case
160	STRAP	del:chr12:15992222-16094160	1	4602	0	4722	0.0002173	0	0.49356499	None	case
161	STX12	del:chr1:28086956-28107059	3	4602	0	4722	0.00065189	0	0.12019589	None	case
162	SYK	dup:chr9:93557698-93574650	1	4602	0	4722	0.0002173	0	0.49356499	None	case
165	TCP1	del:chr6:160152776-160207570	1	4602	0	4722	0.0002173	0	0.49356499	None	case
166	TEAD3	dup:chr6:35442397-35465785	3	4602	0	4722	0.00065189	0	0.12019589	None	case
167	TFAM	del:chr10:60134097-60150445	2	4602	0	4722	0.00043459	0	0.24357959	None	case
169	TJP1	del:chr15:29812778-30178613	4	4602	0	4722	0.00086919	0	0.05930489	None	case
173	TRAF2	dup:chr9:139776401-139821067	6	4602	1	4722	0.00130378	0.00021177	0.05831645	6.16318538	case
174	TUBA1A	del:chr12:49531458-49586489	7	4602	3	4722	0.00152108	0.00063532	0.16138949	2.39630033	case
175	TUBA3C	dup:chr13:19743860-19748709	17	4602	8	4722	0.00369405	0.0016942	0.04695909	2.18478735	case
177	TKN	dup:chr9:112796113-113112572	1	4602	0	4722	0.0002173	0	0.49356499	None	case
178	UBQLN4	del:chr1:155951602-156027550	1	4602	0	4722	0.0002173	0	0.49356499	None	case
180	VHL	dup:chr3:10186559-10211917	1	4602	1	4722	0.0002173	0.00021177	0.7435504	1.02608129	case
181	YWHAQ	del:chr2:9630231-9758621	1	4602	0	4722	0.0002173	0	0.49356499	None	case

FIG. 15D

FIG. 16A

Tier 1 Gene	GeneRange (hg19)	GeneRange +500kb(hg19)	GeneRange (hg18)	StartSNP (GeneRange +500kb)	EndSNP (GeneRange +500kb)
ACAT1	chr11:107992257-108018891	chr11:107492257-108518891	chr11:107497467-107523485	rs7925970	kgp3957860
ACCN1	chr17:31340105-32483825	chr17:30840105-32983825	chr17:28364218-29507938	rs2519865	kgp10854156
ACTR2	chr2:65454828-65498390	chr2:64954828-65998390	chr2:65308405-65351891	rs1477043	kgp4266233
ADCY1	chr7:45614124-45762714	chr7:45114124-46262714	chr7:45580649-45729239	rs2289367	kgp13398740
ADRBK1	chr11:67033904-67054029	chr11:66533904-67554029	chr11:66790480-66810605	kgp7862175	kgp2126040
ALDOA	chr16:30064410-30081741	chr16:29564410-30581741	chr16:29971972-29989236	kgp733881	kgp6386467,rs33997546
APP	chr21:27252860-27543446	chr21:26752860-28043446	chr21:26174731-26465003	rs7281883	kgp2004872
ARL15	chr5:53180613-53606403	chr5:52680613-54106403	chr5:53216370-53642160	kgp10474479	rs10058571
ATXN7L3	chr17:42269172-42275529	chr17:41769172-42775529	chr17:39624698-39631055	rs11650560	rs6503398
BDKRB2	chr14:96671134-96710666	chr14:96171134-97210666	chr14:95740887-95780419	kgp19731302	kgp1905230
CA8	chr8:61101422-61193954	chr8:60601422-61693954	chr8:61263976-61356508	kgp9568230	kgp1623935
CACNA1B	chr9:140772240-141019076	chr9:140272240-141519076	chr9:139892061-140136452	kgp18327422	kgp12374930
CACYBP	chr1:174968570-174981163	chr1:174468570-175481163	chr1:173235193-173247786	rs1013769	kgp15391194
CALM1	chr14:90863326-90874619	chr14:90363326-91374619	chr14:89933125-89944363	kgp828819	kgp22766175
CHRM3	chr1:239549864-240049896	chr1:238904964-240549896	chr1:237616487-238116519	kgp1999037	rs1537850
CIC	chr19:42788816-42799949	chr19:42288816-43299949	chr19:47480656-47491789	kgp21495548	kgp22794755
CNP	chr17:40118758-40129754	chr17:39618758-40629754	chr17:37372284-37383280	kgp4988562	kgp1573374

FIG. 16B

CNTN4	chr3:2140549-3099645	chr3:1640549-3599645	chr3:2117246-3074645	kgp7465125	kgp11488181,rs9811783
CRHR1	chr17:954314-1170453	chr17:454314-1670453	chr17:41217448-41268973	kgp12243700	kgp2967880
CTNNA2	chr2:79412356-80875988	chr2:78912356-81375988	chr2:79265864-80729416	kgp2692843	kgp6161954
DISC1	chr1:231664398-232177019	chr1:231164398-232677019	chr1:229829183-230243641	kgp15830047	kgp10247084
DPP6	chr7:153584418-154685995	chr7:153084418-155185995	chr7:153215351-154316928	rs1822707	rs7781545
DYNLL1	chr12:120907659-120936298	chr12:120407659-121436298	chr12:119392042-119420681	rs2393569	rs1169303
FPR1	chr19:52249022-52255150	chr19:51749022-52755150	chr19:56940837-56946962	rs11084062	kgp21351572
GAPDH	chr12:6643656-6647536	chr12:6143656-7147536	chr12:6513917-6517797	kgp12277967	kgp3951989
GNA15	chr19:3136190-3163766	chr19:2636190-3663766	chr19:3087190-3114766	kgp9441497	rs8109485
GNAI2	chr3:50263723-50296786	chr3:49763723-50796786	chr3:50238727-50271790	rs1049256	kgp1163947
GNAO1	chr16:56225250-56391356	chr16:55725250-56891356	chr16:54782751-54948857	rs36013	kgp16402238
GNAQ	chr9:80335190-80646219	chr9:79835190-81146219	chr9:79525010-79836012	rs3802497	kgp478959
GRIK1	chr21:30909253-31312282	chr21:30409253-31812282	chr21:29831124-30234153	kgp6759057	kgp13183414
GRIK3	chr1:37261127-37499844	chr1:36761127-37999844	chr1:37033714-37272431	kgp15160339	kgp6185747
GRM1	chr6:146348781-146758731	chr6:145848781-147258731	chr6:146390474-146800424	kgp17333275	rs17076442
GRM3	chr7:86273229-86494192	chr7:85773229-86994192	chr7:86111165-86332128	rs7809507	rs6950721
GRM5	chr11:88237743-88796816	chr11:87737743-89296816	chr11:87881005-88436464	kgp11022062	rs7123374
GRM7	chr3:6902801-7783218	chr3:6402801-8283218	chr3:6877926-7758217	rs17288121	kgp10770379
GRM8	chr7:126078651-126893147	chr7:125578651-127393147	chr7:125865887-126680383	rs11767202	kgp13721602
GSN	chr9:123963760-124095120	chr9:123463760-124595120	chr9:123003581-123134941	rs10984984	kgp10246924
HOMER1	chr5:78669785-78809700	chr5:78169785-79309700	chr5:78705541-78845456	kgp22480767	rs2438612
HTR2A	chr13:47407512-47471169	chr13:46907512-47971169	chr13:46305513-46368995	rs4942513	rs2185411
LARP7	chr4:113558119-113578742	chr4:113058119-114078742	chr4:113777568-113798191	kgp20778198	rs10516593
MAPK1	chr22:22113946-22221970	chr22:21613946-22721970	chr22:20443946-20551970	rs2019503	rs5758017

FIG. 16C

MTHFD1	chr14:64854758-64926725	chr14:64354758-65426725	chr14:63924845-63996474	kgp8236539	kgp19721535
MX1	chr21:42792519-42831141	chr21:42292519-43331141	chr21:41714311-41753008	rs7280789	kgp9356591
NARG1	chr4:140222675-140311935	chr4:139722675-140811935	chr4:140442125-140531385	kgp951257	kgp22761518
NEGR1	chr1:71868624--72748405	chr1:71368624-73248405	chr1:71641212-72520993	kgp15840593	kgp15187386
NLN	chr5:65018022--65125111	chr5:64518022-65625111	chr5:65053840-65155145	kgp8540617	kgp6780911
NMI	chr2:152126981-152146430	chr2:151626981-152646430	chr2:151835227-151854676	rs9789673	rs4303715
PCBP3	chr21:47063682-47355618	chr21:46563682-47855618	chr21:45888110-46180046	rs13047590	rs17371795
PDE1C	chr7:31792631--32338383	chr7:31292631-32838383	chr7:31759156-32305466	rs960434	rs10264489
PPP2R1A	chr19:526930554-52729678	chr19:521930554-53229678	chr19:573850455-57421483	kgp3827878	kgp21490256
PRPSAP1	chr17:74306867-74350279	chr17:73806867-74850279	chr17:71818609-71861526	kgp13936725	kgp5222426
PSMD11	chr17:30771501-30808042	chr17:30271501-31308042	chr17:27795614-27832155	kgp12010810	rs8065019
PSMD13	chr11:236807-252984	chr11:1-752984	chr11:226807-242984	kgp9815230	kgp7252222
PXN	chr12:120648241-120703574	chr12:120148241-121203574	chr12:119132632-119187946	kgp9790305	kgp10851563
QRICH2	chr17:74270129-74303761	chr17:73770129-74803761	chr17:71781724-71815356	kgp9494493	kgp13978344
RANBP1	chr22:20105023-20114706	chr22:19605023-20614706	chr22:18485023-18494704	kgp15081773	kgp240898
RAP2A	chr13:98086474-98120252	chr13:97586474-98620252	chr13:96884476-96918245	kgp1964422	kgp12456635
RCC1	chr1:28832454--28865708	chr1:28332454-29365708	chr1:28717331-28738194	kgp4972332	kgp10549261
RGS12	chr4:3315873-3441640	chr4:2815873-3941640	chr4:3285671-3411438	kgp6603457	kgp12100218
RIF1	chr2:152266396-152333860	chr2:151766396-152833860	chr2:151974645-152040665	rs13010870	kgp14366130
RUVBL2	chr19:49497155-49519182	chr19:48997155-50019182	chr19:54188967-54210994	kgp2866116	rs6509434
RYR1	chr19:38924339-39078204	chr19:38424339-39578204	chr19:43616179-43770044	kgp21463042	kgp10827233
RYR2	chr1:237205701-237997288	chr1:236705701-238497288	chr1:235272324-236063911	kgp15265824	kgp855991
SDC3	chr1:31342312--31381480	chr1:30842312-31881480	chr1:31114899-31154067	kgp3545961	rs1039630
SELE	chr1:169691780-169703220	chr1:169191780-170203220	chr1:167958404-167969844	kgp11738441	kgp5736867

FIG. 16D

SERPINB9	chr6:2887503-2903545	chr6:2387503-3403545	chr6:2832502-2848506	rs4959652	kgp9198993
SETD4	chr21:37415981-37451687	chr21:36915981-37951687	chr21:36337851-36373557	rs8131794	kgp10193814
SGTB	chr5:64961754-65017941	chr5:64461754-65517941	chr5:64997510-65053697	rs2367239	rs253229
SHANK1	chr19:51165083-51220195	chr19:50665083-51720195	chr19:55856895-55912007	kgp8880890	kgp5265049
SLC7A10	chr19:33699569-33716756	chr19:33199569-34216756	chr19:38391410-38408548	kgp3880561	kgp21532613
SORD	chr15:45315301-45367287	chr15:44815301-45867287	chr15:43102632-43154331	rs3752691	rs17627219
STRAP	chr12:16035287-16056410	chr12:15535287-16556410	chr12:15926554-15947677	kgp9763258	kgp18858589
TK1	chr17:76170159-76183285	chr17:75670159-76683285	chr17:73681754-73694880	kgp13960604	kgp4569268
TNIK	chr3:170780291-171178197	chr3:170280291-171678197	chr3:172264363-172660546	kgp17660929	kgp3100328
USP24	chr1:55532031-55681039	chr1:55032031-56181039	chr1:55304619-55453350	kgp3052862	kgp5594096
VHL	chr3:10183318-10195354	chr3:9683318-10695354	chr3:10158318-10168746	kgp6652387	rs9942062

FIG. 17A

Tier 2 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500kb)
ACAT2	chr6:160182988-160200087	chr6:159682988-160700087	chr12:51783540-51804590	kgp17016252	rs3119312
ACCN2	chr12:50451486-50477394	chr12:49951486-50977394	chr12:48737753-48763661	kgp6083801	kgp2326833
ACP1	chr2:264868-278282	chr2:1-778282	chr2:254871-268282	kgp14878812	kgp6217001
ACTB	chr7:5566778-5570232	chr7:5066778-6070232	chr7:5533304-5536758	kgp10503129	rs17136342
ADA	chr20:43248162-43280376	chr20:42748162-43780376	chr20:42681576-42713790	kgp505723	rs2207199
ADD1	chr4:2845583-2931802	chr4:2345583-3431802	chr4:2815381-2901587	kgp5601859	kgp5383382
ADD2	chr2:70834749-70995375	chr2:70334749-71495375	chr2:70688257-70848837	kgp14188216	kgp4077094
ADORA1	chr1:203096835-203136533	chr1:202596835-203636533	chr1:201363458-201403156	rs16850143	rs12568960
ADRA1B	chr5:159343739-159400017	chr5:158843739-159900017	chr5:159276317-159332595	rs17056747	kgp2774549
ADRA2A	chr10:112836789-112840662	chr10:112336789-113340662	chr10:112826910-112830560	kgp3219023	rs10787379
ADRA2C	chr4:3768295-3770253	chr4:3268295-4270253	chr4:3737872-3740016	kgp21189210	kgp21320659
ADRB2	chr5:148206155-148208197	chr5:147706155-148708197	chr5:148186348-148188381	kgp6738042	rs352336
ANXA2	chr15:60639349-60690185	chr15:60139349-61190185	chr15:58426641-58477477	kgp19904124	kgp1248561
APTX	chr9:32972603-33001639	chr9:32472603-33501639	chr9:32962607-33015110	kgp8123814	kgp22778750
AQP1	chr7:30893009-30965131	chr7:30393009-31465131	chr7:30917992-30931656	kgp13347683	rs11983505
ARHGAP24	chr4:86396283-86923823	chr4:85896283-87423823	chr4:86615307-87142847	kgp12192788	kgp20991115
ARRB1	chr11:74971165-75062875	chr11:74471165-75562875	chr11:74654129-74740521	kgp13077708	kgp12867051
ARRB2	chr17:4613788-4624795	chr17:4113788-5124795	chr17:4560537-4571544	kgp10630047	rs2304905

FIG. 17B

BDKRB1	chr14:96722546-96731100	chr14:96222546-97231100	chr14:95792311-95800853	rs10146784	kgp10194056
BTBD2	chr19:1985446-2015702	chr19:1485446-2515702	chr19:1936446-1966702	kgp9698924	rs12985186
BTG2	chr1:203274663-203278729	chr1:202774663-203778729	chr1:201541286-201545352	kgp11073362	kgp22834576
C17orf44	chr17:8123966-8127361	chr17:7623966-8627361	chr17:8064691-8068086	kgp14083005	kgp8066962
C1orf116	chr1:207191865-207206101	chr1:206691865-207706101	chr1:205258488-205272724	kgp15208593	rs12094477
C7orf25	chr7:42948871-42971805	chr7:42448871-43471805	chr7:42915396-42938330	kgp13766903	kgp8523923
CALB2	chr16:71392615-71424342	chr16:70892615-71924342	chr16:69950126-69981843	rs1774414	kgp16319275
CALM2	chr2:47387220-47403740	chr2:46887220-47903740	chr2:47146583-47257154	kgp12094177	kgp4237241
CALM3	chr14:90863326-90874619	chr14:90363326-91374619	chr19:51796351-51805879	kgp828819	kgp22766175
CAMK1	chr3:9799028-9811668	chr3:9299028-10311668	chr3:9774030-9786661	kgp4340327	kgp1318661
CAMK2B	chr7:44256748-44365230	chr7:43756748-44865230	chr7:44223273-44331749	rs10245456	kgp10338229
CAMK4	chr5:110559946-110820748	chr5:110059946-111320748	chr5:110587980-110848647	kgp11981357	kgp22673631
CCNB1	chr5:68462836-68474070	chr5:67962836-68974070	chr5:68498668-68509826	kgp5100830	rs28529133
CDC42	chr1:22379119-22419436	chr1:21879119-22919436	chr1:22251706-22292023	kgp15282552	rs209696
CENTG1	chr12:58118076-58135944	chr12:57618076-58635944	chr12:56404343-56422211	kgp22774357	rs12825103
CHGB	chr20:5891973-5906005	chr20:5391973-6406005	chr20:5840167-5854003	kgp19217529	kgp5406173
CHP	chr15:41523436-41574083	chr15:41023436-42074083	chr15:39310728-39361375	kgp9389002	kgp10815429
CHRM2	chr7:136553398-136701771	chr7:136053398-137201771	chr7:136203938-136352311	rs2882248	kgp11051162
CMPK	chr2:6988440-7005950	chr2:6488440-7505950	chr2:6905891-6923401	rs16865056	kgp6717309
CNR1	chr6:88849584-88875767	chr6:88349584-89375767	chr6:88910155-88932281	kgp11366911	kgp5424340
COPB2	chr3:139076432-139108522	chr3:138576432-139608522	chr3:140559122-140591212	kgp17652827	rs2554152
CYCS	chr7:25158269-25164980	chr7:24658269-25664980	chr7:25124799-25131480	kgp22782658	kgp9259047
DCN	chr12:91539034-91576806	chr12:91039034-92076806	chr12:90063165-90100937	rs11105720	rs1602946

FIG. 17C

DHCR7	chr11:71145456-71159477	chr11:70645456-71659477	chr11:70823104-70837125	rs2016495	kgp4157665
DLST	chr14:75348593-75370450	chr14:74848593-75870450	chr14:74418371-74440198	kgp6099186	rs11621369
DRD2	chr11:113280316-113346001	chr11:112780316-113846001	chr11:112785526-112851211	kgp12732525	rs1062613
DRD3	chr3:113847556-113918254	chr3:113347556-114418254	chr3:115330246-115400944	kgp18078164	kgp7361746
DSTN	chr20:17550598-17588652	chr20:17050598-18088652	chr20:17498598-17536652	kgp19350858	rs1581925
ECHS1	chr10:135175986-135186908	chr10:134675986-135686908	chr10:135025979-135036898	kgp21664075	kgp22837031
EGFR	chr7:55086724-55275031	chr7:54586724-55775031	chr7:55054218-55242525	kgp12053718	kgp3314724
EIF3S3	chr8:117657055-117768062	chr8:117157055-118268062	chr8:117726236-117837243	kgp10576753	rs1793723
ERBB2	chr17:37844392-37884915	chr17:37344392-38384915	chr17:35097918-35138441	kgp11528115	kgp670921
F2R	chr5:76011867-76031595	chr5:75511867-76531595	chr5:76047623-76067351	kgp22518836	kgp1549629
F2RL2	chr5:75911306-75919240	chr5:75411306-76419240	chr5:75947062-75954996	kgp10188048	kgp8041699
F2RL3	chr19:16999825-17002830	chr19:16499825-17502830	chr19:16860825-16863830	kgp9756004	kgp12567834
F3	chr1:94994731-95007413	chr1:94494731-95507413	chr1:94767460-94779903	kgp22732356	kgp5203715
FKBP3	chr14:45584801-45604009	chr14:45084801-46104009	chr14:44654858-44674272	kgp8973198	kgp19724486
FSCN1	chr7:5632435-5646287	chr7:5132435-6146287	chr7:5598979-5612812	kgp11535801	kgp22733484
FURIN	chr15:91411884-91426687	chr15:90911884-91926687	chr15:89212888-89227691	kgp19755110	kgp7570879
FYN	chr6:111981534-112194655	chr6:111481534-112694655	chr6:112089177-112301320	kgp9553033	kgp10843976
GLP1R	chr6:39016556-39055520	chr6:38516556-39555520	chr6:39124534-39163498	kgp11427391	kgp8067157
GLP2R	chr17:9729380-9793022	chr17:9229380-10293022	chr17:9670105-9733747	kgp13857921	kgp14095302
GNAI1	chr7:79764139-79848725	chr7:79264139-80348725	chr7:79602075-79686661	kgp3340161	kgp96572
GNAI3	chr1:110091185-110138452	chr1:109591185-110638452	chr1:109892708-109939975	rs28503409	kgp2138201
GNB2L1	chr5:180663927-180670906	chr5:180163927-181170906	chr5:180596533-180603512	kgp9825803	kgp22785368
GOT1	chr10:101156626-101190530	chr10:100656626-101690530	chr10:101146617-101180336	kgp21656902	kgp21815940

FIG. 17D

GP18A	chr17:4835591-4838325	chr17:4335591-5338325	chr17:4776371-4779067	kgp13949132	kgp11186643
GPR26	chr10:125425870-125456913	chr10:124925870-125956913	chr10:125415860-125444113	kgp7582662	kgp21578542
GRB2	chr17:73314156-73401790	chr17:72814156-73901790	chr17:70825751-70913385	kgp13841089	kgp14035219
GRB7	chr17:37894161-37903538	chr17:37394161-38403538	chr17:35147712-35157064	kgp14102913	kgp13833584
GRIA1	chr5:152870083-153193429	chr5:152370083-153693429	chr5:152850276-153173622	rs1438937	rs10057369
GRM2	chr3:51741080-51752625	chr3:51241080-52252625	chr3:51716127-51727665	rs4367100	rs13060808
GRM4	chr6:33989627-34113869	chr6:33489627-34613869	chr6:34097605-34231377	kgp17076142	rs6909637
GRM6	chr5:178405329-178422124	chr5:177905329-178922124	chr5:178337935-178354730	rs603852	rs11249632
HBXIP	chr1:110943876-110950546	chr1:110443876-111450546	chr1:110745399-110752069	kgp8686658	rs1936942
HD	chr6:125596496-125623282	chr6:125096496-126123282	chr6:125638195-125664981	rs11154263	rs11967627
HNRPA3	chr2:178077422-178088685	chr2:177577422-178588685	chr2:177785668-177796931	kgp14203861	rs1344924
HOMER3	chr19:19017768-19045219	chr19:18517768-19545219	chr19:18901011-18912983	rs13344313	rs4808199
HRPT2	chr1:193091088-193223942	chr1:192591088-193723942	chr1:191357711-191490565	kgp2473538	kgp12065536
HSP90AB1	chr6:44214848-44221614	chr6:43714848-44721614	chr6:44322826-44329592	kgp5836209	kgp8706663
IL8RB	chr2:218989997-219001975	chr2:218489997-219501975	chr2:218698242-218710220	kgp22730583	rs1055816
IMPDH2	chr3:49061761-49066875	chr3:48561761-49566875	chr3:49036765-49041879	kgp22731595	kgp5626213
IQGAP2	chr5:75699148-76003957	chr5:75199148-76503957	chr5:75734904-76039713	kgp22490664	rs11739698
ITGB1	chr10:33189245-33247293	chr10:32689245-33747293	chr10:33229251-33287299	kgp12034252	rs11009395
ITGB7	chr12:53585106-53601000	chr12:53085106-54101000	chr12:51871373-51887267	kgp19011413	kgp3313746
ITPR1	chr3:4535031-4889524	chr3:4035031-5389524	chr3:4510033-4864286	kgp17889944	kgp1749057
KIAA0090	chr1:19544583-19578046	chr1:19044583-20078046	chr1:19417170-19450633	rs624761	rs1009631
KIAA1683	chr19:18367905-18385319	chr19:17867905-18885319	chr19:18228907-18246235	kgp6435620	rs10412356
LAMA4	chr6:112429133-112575828	chr6:111929133-113075828	chr6:112535826-112682521	kgp16962466	kgp17024247

FIG. 17E

LRP2BP	chr4:186285031-186300172	chr4:185785031-186800172	chr4:186522026-186537166	kgp7238414	rs9994907
LRRC59	chr17:48458593-48474914	chr17:47958593-48974914	chr17:45813597-45829831	kgp1609816	kgp13856216
LTA	chr6:2825414-2827639	chr6:2825414-2827639	chr6:2787675-2789683	kgp11675228	rs6912537
LYAR	chr4:4269428-4291896	chr4:3769428-4791896	chr4:4320337-4342744	kgp22780996	kgp7317116
LYN	chr8:56792385-56925006	chr8:56292385-57425006	chr8:56954939-57086494	kgp8836202	rs2670027
MAP4	chr3:47892179-48130769	chr3:47392179-48630769	chr3:47867188-48105715	kgp17741397	rs35623035
MAPT	chr17:43971747-44105699	chr17:43471747-44605699	chr17:41327543-41461546	kgp22730329	kgp13941400
MARK4	chr19:45754515-45808541	chr19:45254515-46308541	chr19:50446681-50500381	kgp10230030	kgp21456098
MC4R	chr18:58038563-58040001	chr18:57538563-58540001	chr18:56189543-56190981	kgp7049183	kgp1258536
MGC11082	chr18:3602998-3604385	chr18:3102998-4104385	chr18:3592998-3594385	kgp15965827	kgp12318627
MRPL14	chr6:44081372-44095191	chr6:43581372-44595191	chr6:44189349-44203169	kgp17033193	rs527322
MRPS16	chr10:75006445-75012451	chr10:74506445-75512451	chr10:74678606-74682457	kgp21628722	rs12243089
MTNR1A	chr4:187454808-187476537	chr4:186954808-187976537	chr4:187691802-187713531	rs12648771	rs4476657
MTNR1B	chr11:92702788-92715948	chr11:92202788-93215948	chr11:92342436-92355596	kgp10063029	rs2658801
MYC	chr8:128748314-128753680	chr8:128248314-129253680	chr8:128817497-128822855	kgp3177285	kgp1944877
MYO6	chr6:76458908-76629254	chr6:75958908-77129254	chr6:76515628-76685974	kgp17262775	kgp17183304
NANS	chr9:100818958-100845365	chr9:100318958-101345365	chr9:99847709-99885178	rs10817759	rs2778908
NCK1	chr3:136581049-136667968	chr3:136081049-137167968	chr3:138063762-138150658	kgp117446	kgp10600232
NFKBIA	chr14:35870715-35873960	chr14:35370715-36373960	chr14:34940466-34943711	kgp19552677	kgp19707730
NPY2R	chr4:156129780-156138228	chr4:155629780-156638228	chr4:156349230-156357678	kgp3956236	kgp20850236
NUDC	chr1:27248223-27272887	chr1:26748223-27772887	chr1:27120810-27145474	rs11247955	kgp15594139
OPRD1	chr1:29138653-29190208	chr1:28638653-29690208	chr1:29011240-29062795	kgp9104521	kgp15855740
PAFAH1B3	chr19:42801184-42806952	chr19:42301184-43306952	chr19:47493024-47498563	kgp21540635	kgp22735078

FIG. 17F

PC8P1	chr2:70314584-70316334	chr2:69814584-70816334	chr2:70168204-70169836	kgp14596264	kgp6568959
PCDHA4	chr5:140186671-140391929	chr5:139686671-140891929	chr5:140166855-140372115	kgp6468526	kgp10727572
PCID1	chr11:32605313-32624037	chr11:32105313-33124037	chr11:32561889-32580613	kgp13035948	rs10836023
PCMT1	chr6:150070830-150132557	chr6:149570830-150632557	chr6:150112657-150174249	kgp17277449	kgp10169289
PDCD5	chr19:33072093-33078358	chr19:32572093-33578358	chr19:37763943-37770169	kgp21531284	rs7259333
PDE1B	chr12:54943176-54973023	chr12:54443176-55473023	chr12:53229670-53259290	kgp18962385	rs11171250
PDE6G	chr17:79617488-79623607	chr17:79117488-80123607	chr17:77227893-77234038	kgp317116	kgp13898509
PGM1	chr1:64058946-64125916	chr1:63558946-64625916	chr1:63831534-63898505	kgp175729	kgp15416792
PHKB	chr16:47495209-47735434	chr16:46995209-48235434	chr16:46052710-46292935	kgp8481371	rs16945930
PHKG2	chr16:30759619-30772497	chr16:30259619-31272497	chr16:30667237-30676183	kgp16316196	kgp22773724
PICK1	chr22:38453261-38471708	chr22:37953261-38971708	chr22:36783207-36801654	kgp5170623	kgp1759680
PIK3CA	chr3:178866310-178952497	chr3:178366310-179452497	chr3:180349004-180435191	rs7615444	rs1025864
PIK3R1	chr5:67511583-67597649	chr5:67011583-68097649	chr5:67547359-67633405	kgp7844449	rs7737296
PLA2G7	chr6:46672052-46703430	chr6:46172052-47203430	chr6:46780011-46811110	kgp4678268	kgp9155835
PLCB1	chr20:8113295-8865547	chr20:7613295-9365547	chr20:8061295-8813547	kgp19226483	rs2076234
PLCB3	chr11:64018994-64036924	chr11:63518994-64536924	chr11:63775697-63793195	kgp9427286	rs484886
PLCG2	chr16:81812898-81991899	chr16:81312898-82491899	chr16:80370430-80549400	kgp4622733	kgp3230988
PPIH	chr1:43124047-43142429	chr1:42624047-43642429	chr1:42896634-42915016	kgp1870818	rs11210802
PRDX1	chr1:45976706-45988562	chr1:45476706-46488562	chr1:45749293-45760196	rs3806405	kgp15560310
PRKCA	chr17:64298925-64806862	chr17:63798925-65306862	chr17:61729387-62237324	kgp13847618	kgp13994829
PRLHR	chr10:120352915-120355160	chr10:119852915-120855160	chr10:120342905-120345150	rs853584	kgp21690663
PRMT1	chr19:50180408-50191707	chr19:49680408-50691707	chr19:54872307-54883516	kgp1460116	kgp5315133
PSAT1	chr9:80912058-80945009	chr9:80412058-81445009	chr9:80101878-80134829	kgp2581728	kgp9769053

FIG. 17G

PSEN1	chr14:73603142-73690399	chr14:73103142-74190399	chr14:72672931-72756862	kgp8405661	kgp19611371
PSMA1	chr11:14526421-14665180	chr11:14026421-15165180	chr11:14482997-14621739	kgp12643195	kgp13010596
PSMC1	chr14:90722893-90738966	chr14:90222893-91238966	chr14:89792646-89808719	rs10140098	kgp19595798
PSMD1	chr2:231921577-232037540	chr2:231421577-232537540	chr2:231629852-231745717	rs1678155	kgp11602861
PSMD6	chr3:63996230-64009658	chr3:63496230-64509658	chr3:63971270-63984698	kgp9706776	kgp17718198
PSME1	chr14:24605377-24608176	chr14:24105377-25108176	chr14:23675217-23678016	kgp11494860	kgp2234181
PTHR2	chr2:209353736-209704818	chr2:208853736-210204818	chr2:209061981-209413063	kgp14652386	rs1020407
PYGL	chr14:51371934-51411248	chr14:50871934-51911248	chr14:50441686-50480984	kgp10991856	rs7146882
PYGM	chr11:64513860-64528187	chr11:64013860-65028187	chr11:64270436-64284763	kgp12876954	rs675671
RAB2	chr8:61429469-61536203	chr8:60929469-62036203	chr8:61592023-61698757	kgp7067636	rs3864667
RALA	chr7:39663151-39747723	chr7:39163151-40247723	chr7:39629686-39714242	kgp22733616	rs11768838
RCC2	chr1:17733250-17766250	chr1:17233250-18266250	chr1:17605865-17638807	kgp15535308	kgp7647703
RGS2	chr1:192778168-192781407	chr1:192278168-193281407	chr1:191044793-191048026	rs10921130	kgp11065785
RHOA	chr3:49396578-49449526	chr3:48896578-49949526	chr3:49371582-49424530	kgp11466037	rs868891
RPA2	chr1:28218048-28241236	chr1:27718048-28741236	chr1:28090635-28113823	rs12033326	kgp15705538
RPLP2	chr11:809935-812876	chr11:309935-1312876	chr11:799935-802876	kgp11473410	kgp7750669
RPN2	chr20:35807455-35870025	chr20:35307455-36370025	chr20:35240887-35303439	kgp9846122	kgp19260650
RPS14	chr5:149823791-149829319	chr5:149323791-150329319	chr5:149803984-149809512	kgp22444746	kgp22218062
RRM1	chr11:4137307-4223759	chr11:3637307-4723759	chr11:4072499-4116682	rs6578398	kgp4491491
S100A6	chr1:153507075-153508717	chr1:153007075-154008717	chr1:151773699-151775341	kgp15193014	rs10908627
SACS	chr13:23902964-24007841	chr13:23402964-24507841	chr13:22800964-22905841	kgp16818396	rs2765089
SARS	chr1:109756514-109780804	chr1:109256514-110280804	chr1:109558062-109582308	kgp5910329	rs1803687
SCTR	chr2:120197418-120282028	chr2:119697418-120782028	chr2:119913888-119998498	kgp12364473	kgp22762988

FIG. 17H

SET	chr9:131445933-131458675	chr9:130945933-131958675	chr9:130485754-130498496	kgp11282765	kgp18608937
SF3B14	chr2:24290453-24299314	chr2:23790453-24799314	chr2:24143957-24152818	kgp14521970	rs12474894
SHBG	chr17:7517381-7536700	chr17:7017381-8036700	chr17:7458106-7477395	kgp7760759	rs6503086
SIAH1	chr16:48390274-48482309	chr16:47890274-48982309	chr16:46947777-47039810	kgp4639784	kgp7644930
SLC2A1	chr1:43391045-43424847	chr1:42891045-43924847	chr1:43163632-43197434	kgp2036523	rs2782652
SLC6A3	chr5:1392904-1445543	chr5:892904-1945543	chr5:1445909-1498538	kgp22585075	kgp9690399
SNCA	chr4:90645249-90759447	chr4:90145249-91259447	chr4:90865727-90978470	kgp11552673	kgp8195783
SNRPB2	chr20:16710608-16722417	chr20:16210608-17222417	chr20:16658628-16670037	kgp19326624	kgp19208923
SOCS6	chr18:67956136-67997434	chr18:67456136-68497434	chr18:66107116-66148414	kgp10928836	rs4243325
SOCS7	chr17:36508006-36561846	chr17:36008006-37061846	chr17:33761530-33809545	rs12936144	rs4794796
SRC	chr20:35973087-36033821	chr20:35473087-36533821	chr20:35406501-35467235	kgp19359278	kgp9150551
STAU1	chr20:47729875-47805288	chr20:47229875-48305288	chr20:47163282-47238695	rs11905650	kgp19233876
STX12	chr1:28099693-28150963	chr1:27599693-28650963	chr1:27972280-28023550	kgp22731625	kgp15287949
SYK	chr9:93564011-93660842	chr9:93064011-94160842	chr9:92603890-92698304	kgp12394293	rs894962
TBCA	chr5:76986994-77072185	chr5:76486994-77572185	chr5:77022750-77107941	rs2928164	rs10059285
TBXA2R	chr19:3594503-3606831	chr19:3094503-4106831	chr19:3545503-3557658	kgp21472781	kgp1760692
TCP1	chr6:160199529-160210735	chr6:159699529-160710735	chr6:160119519-160130725	kgp16923201	kgp10518192
TEAD3	chr6:35441373-35464861	chr6:34941373-35964861	chr6:35549351-35572839	rs847861	kgp3339
TFAM	chr10:60145175-60155897	chr10:59645175-60655897	chr10:59815181-59825903	kgp9406331	kgp6514369
TGM2	chr20:36756863-36793700	chr20:36256863-37293700	chr20:36190277-36227114	rs6067098	kgp9992037
TJP1	chr15:29992356-30114706	chr15:29492356-30614706	chr15:27779648-27901998	kgp19895791	rs2604694
TLR10	chr4:38773859-38784611	chr4:38273859-39284611	chr4:38450646-38460984	kgp9612652	rs6531705
TMEM4	chr12:56704213-56710128	chr12:56204213-57210128	chr12:54990480-54996395	kgp6718939	kgp6565807

FIG. 17I

TPI1	chr12:6976583-6980110	chr12:6476583-7480110	chr12:6846966-6850253	kgp3883976	kgp18849054
TRAF2	chr9:139776384-139821067	chr9:139276384-140321067	chr9:138896205-138940888	rs3812570	kgp9465784
TRMT112	chr11:64084164-64085033	chr11:63584164-64585033	chr11:63840740-63841609	kgp1242205	rs2957154
TUBA1	chr12:49521565-49525304	chr12:49021565-50025304	chr12:47807832-47811571	kgp4948752	kgp18737983
TUBA1A	chr12:49578582-49582861	chr12:49078582-50082861	chr12:47864849-47869128	kgp5373125	kgp1407179
TUBA1B	chr12:49521566-49525304	chr12:49021566-50025304	chr12:47807832-47866883	kgp4948752	kgp18737983
TUBA2	chr12:49578793-49580616	chr12:49078793-50080616	chr12:47865060-47866883	kgp18983720	kgp75177
TUBB	chr6:1981087-1986127	chr6:1981087-1986127	chr6:1935034-1940074	kgp17000846	kgp16908954
TUBG1	chr17:40761357-40767256	chr17:40261357-41267256	chr17:38015219-38020777	rs12600570	kgp3534380
TXN	chr9:113006091-113018920	chr9:112506091-113518920	chr9:112046130-112058599	kgp18601393	kgp652846
TXNDC4	chr9:102741463-102861330	chr9:102241463-103361330	chr9:101781284-101901151	kgp22740558	rs10989168
TXNL2	chr10:131934639-131977932	chr10:131434639-132477932	chr10:131824629-131867922	kgp21587397	rs2921907
TYMS	chr18:657603-673499	chr18:157603-1173499	chr18:647603-663499	kgp1671520	kgp5560925
UBQLN4	chr1:156005091-156023516	chr1:155505091-156523516	chr1:154271715-154290140	rs12746592	kgp204451
UCHL1	chr4:41258897-41270446	chr4:40758897-41770446	chr4:40953685-40965203	rs10029833	kgp21157719
VIPR1	chr3:42530790-42579065	chr3:42030790-43079065	chr3:42519120-42554064	rs794894	kgp10771397
YWHAQ	chr2:9724105-9771106	chr2:9224105-10271106	chr2:9641556-9688557	kgp7327726	rs1138729
ZAP70	chr2:98330030-98356323	chr2:97830030-98856323	chr2:97696462-97722755	kgp10723114	kgp14308801

FIG. 18A

Tier 3 Gene	GeneRange(hg19)	GeneRange+500kb(hg19)	GeneRange(hg18)	StartSNP (GeneRange+500kb)	EndSNP (GeneRange+500 kb)
ABI3	chr17:47287588-47300587	chr17:46787588-47800587	chr17:44642587-44655586	rs7211412	kgp13987803
ACTA1	chr1:229566992-229569843	chr1:229066992-230069843	chr1:227633615-227636466	kgp706951	kgp9594907
ACTN2	chr1:236849769-236927558	chr1:236349769-237427558	chr1:234916392-234994181	kgp12139182	kgp9945691
ADCY5	chr3:123001142-123167392	chr3:122501142-123667392	chr3:124486088-124650082	kgp5729470	kgp18234294
ADCY8	chr8:131792546-132052835	chr8:131292546-132552835	chr8:131861728-132122017	rs11778881	kgp4563992
ADCYAP1R1	chr7:31092075-31151093	chr7:30592075-31651093	chr7:31058666-31112836	kgp6410265	kgp5976045
ADD3	chr10:111756107-111895323	chr10:111256107-112395323	chr10:111746097-111885313	kgp2922347	kgp21705322
AFAP1	chr4:7760439-7941653	chr4:7260439-8441653	chr4:7811339-7992553	kgp10066670	kgp2565038
AGTR1	chr3:148415657-148460790	chr3:147915657-148960790	chr3:149898347-149943480	kgp17969929	rs9827666
AHCYL1	chr1:110527386-110566364	chr1:110027386-111066364	chr1:110328830-110367887	kgp15280262	kgp8467474
AKAP12	chr6:151561133-151679694	chr6:151061133-152179694	chr6:151603201-151719602	kgp17415975	kgp17180004
AKAP13	chr15:85923870-86292586	chr15:85423870-86792586	chr15:83724874-84093590	rs11073778	kgp10945265
AKAP5	chr14:64932216-64941221	chr14:64432216-65441221	chr14:64001969-64010974	rs945029	rs4499147
AKAP9	chr7:91570188-91739987	chr7:91070188-92239987	chr7:91408127-91577925	kgp7513665	kgp8102448
AKR1C3	chr10:5005453-5149878	chr10:4505453-5649878	chr10:4995453-5139878	rs1679414	kgp8379007
AKT1	chr14:10S235686-105262080	chr14:104735686-105762080	chr14:104306731-104333125	kgp10896929	kgp7260890
ANK2	chr4:113739238-114304896	chr4:113239238-114804896	chr4:113958687-114524345	kgp8454825	kgp10144793
ANKRD24	chr19:4183350-4224811	chr19:3683350-4724811	chr19:4134350-4175811	kgp3226366	rs7255543

FIG. 18B

ANXA6	chr5:150480266-150537443	chr5:149980266-151037443	chr5:150460460-150517560	kgp22603058	rs11747938
ANXA7	chr10:75135188-75173841	chr10:74635188-75673841	chr10:74805194-74843847	kgp21588521	kgp5026768,rs2227568
APLP2	chr11:129939715-130014706	chr11:129439715-130514706	chr11:129445010-129519910	kgp22802171	rs7116475
AR	chrX:66763873-66950461	chrX:66263873-67450461	chrX:66680598-66860844	rs478505	kgp22776402
ARF1	chr1:228270360-228286913	chr1:227770360-228786913	chr1:226336983-226353536	kgp7035482	kgp5092378
ARF3	chr12:49329991-49351252	chr12:48829991-49851252	chr12:47616258-47637519	kgp9963537	kgp19162961
ARHGAP1	chr11:46698631-46722120	chr11:46198631-47222120	chr11:46655207-46678696	rs11038804	kgp12872953
ARHGEF1	chr19:42399421-42434296	chr19:41899421-42934296	chr19:47079106-47103444	kgp21546138	kgp9753873
ARL3	chr10:104433483-104474190	chr10:103933483-104974190	chr10:104423477-104464180	rs4919614	kgp2065500
ARL8B	chr3:5163929-5222601	chr3:4663929-5722601	chr3:5138929-5197601	kgp5083934	kgp17728482
ASCL2	chr11:2289727-2292182	chr11:1789727-2792182	chr11:2246303-2248758	kgp12845252	kgp7129584
ATF3	chr1:212738675-212794119	chr1:212238675-213294119	chr1:210805319-210860739	rs10863936	kgp12569686
ATN1	chr12:7033625-7053815	chr12:6533625-7553815	chr12:6903886-6924076	kgp18714644	kgp19128481
ATP1B1	chr1:169075946-169101960	chr1:168575946-169601960	chr1:167342570-167368584	rs10800363	kgp305361
ATP2B1	chr12:89981825-90049844	chr12:89481825-90549844	chr12:88505956-88573975	kgp4237218	kgp19117315
ATP2B2	chr3:10365706-10749716	chr3:9865706-11249716	chr3:10342743-10724716	kgp7774534	rs7625756
ATXN1	chr6:16299342-16761721	chr6:15799342-17261721	chr6:16407321-16869700	kgp2173519	rs6921352
ATXN3	chr14:92524895-92572965	chr14:92024895-93072965	chr14:91594648-91642718	kgp11986238	rs2146498
ATXN7	chr3:63850232-63989136	chr3:63350232-64489136	chr3:63825272-63964176	rs9311874	kgp797614
AVPR1A	chr12:63540215-63546590	chr12:63040215-64046590	chr12:61826482-61832857	rs952865	kgp3671976
B4GALT1	chr9:33110638-33167356	chr9:32610638-33667356	chr9:33100638-33157356	kgp18539535	kgp18370584
BANK1	chr4:102341117-102995969	chr4:101841117-103495969	chr4:102560140-103214992	rs6851921	kgp20796561
BCAP31	chrX:152965946-152990201	chrX:152465946-153490201	chrX:152619145-152643081	rs6627302	kgp22764947
BCAR1	chr16:75262927-75301951	chr16:74762927-75801951	chr16:73820428-73859452	kgp7158675	kgp16367309
BCL2	chr18:60790578-60986657	chr18:60290578-61486657	chr18:58941558-59137637	rs435439	rs1720898

FIG. 18C

BMI1	chr10:22610138-22620414	chr10:22110138-23120414	chr10:22645304-22660192	kgp3019331	rs12775513
BMPR2	chr2:203241049-203432474	chr2:202741049-203932474	chr2:202949294-203140719	rs2072504	kgp3183288
BOC	chr3:112930411-113006305	chr3:112430411-113506305	chr3:114413101-114488995	kgp12164746	kgp3299668
BPGM	chr7:134331530-134364567	chr7:133831530-134864567	chr7:133982094-134015107	kgp13720725	kgp8542611
BRCA1	chr17:41196311-41322420	chr17:40696311-41822420	chr17:38449839-38530994	kgp1014784	kgp13921789
BRCA2	chr13:32889616-32973809	chr13:32389616-33473809	chr13:31787616-31871809	rs2146284	rs9596502
BRD7	chr16:50352928-50402845	chr16:49852928-50902845	chr16:48910441-48960330	kgp3843480	kgp6018549
BRF2	chr8:37701397-37707431	chr8:37201397-38207431	chr8:37820560-37826569	rs7818467	kgp22772561
BRMS1	chr11:66104803-66112582	chr11:65604803-66612582	chr11:65861379-65869158	kgp22746103	kgp12809093
BTK	chrX:100604434-100645770	chrX:100104434-101145770	chrX:100491097-100532426	kgp22759057	kgp22747202
C1orf128	chr1:24104887-24114722	chr1:23604887-24614722	chr1:23977474-23987309	kgp283495	kgp2701674
C1orf42	chr1:152486978-152488481	chr1:151986978-152988481	chr1:150753602-150755105	kgp15694971	rs4363385
C1QBP	chr17:5336098-5342471	chr17:4836098-5842471	chr17:5276822-5283195	kgp14047547	rs17825455
C20orf20	chr20:61427804-61431945	chr20:60927804-61931945	chr20:60898282-60902390	kgp9228388	kgp19363625
C20orf24	chr20:35234136-35240960	chr20:34734136-35740960	chr20:34636369-34674374	rs6060820	rs1744760
C4orf14	chr4:57829515-57843826	chr4:57329515-58343826	chr4:57524272-57538583	kgp22756132	kgp1831456
C4orf17	chr4:100432160-100463460	chr4:99932160-100963460	chr4:100651222-100682483	kgp20878925	kgp21204347
C5orf25	chr5:175665369-175772990	chr5:175165369-176272990	chr5:175598008-175705596	kgp7679859	rs480782
C9orf25	chr9:34398181-34458568	chr9:33898181-34958568	chr9:34388181-34448568	kgp22772722	rs7031962
CABIN1	chr22:24407764-24574596	chr22:23907764-25074596	chr22:22737764-22904596	kgp5637302	kgp5793536
CABP1	chr12:121078421-121105127	chr12:120578421-121605127	chr12:119562804-119589510	kgp18737891	rs503720
CACNA1C	chr12:2162415-2807115	chr12:1662415-3307115	chr12:2032676-2677376	kgp9477564	kgp1276729
CALCR	chr7:93053798-93204042	chr7:92553798-93704042	chr7:92891734-93041978	kgp3815436	kgp10249142
CALD1	chr7:134464163-134655480	chr7:133964163-135155480	chr7:134114710-134306012	rs16874469	kgp22829820
CAMK2A	chr5:149599053-149669403	chr5:149099053-150169403	chr5:149579247-149649529	kgp9269229	kgp22536863

FIG. 18D

CAMK2G	chr10:75572258-75634349	chr10:75072258-76134349	chr10:75242264-75304349	kgp5617603	kgp4007437
CAMKK1	chr17:3763616-3796337	chr17:3263616-4296337	chr17:3710365-3743086	kgp4927794	kgp13998561
CAMKK2	chr12:121675494-121736111	chr12:121175494-122236111	chr12:120159877-120220494	kgp3636283,rs1800556	kgp3169612
CAPN2	chr1:223889294-223963720	chr1:223389294-224463720	chr1:221966741-222030343	rs2430408	kgp15138476
CASP3	chr4:185548849-185570629	chr4:185048849-186070629	chr4:185785843-185807623	kgp8529169	rs2046535
CASP6	chr4:110609784-110624629	chr4:110109784-111124629	chr4:110829233-110844078	kgp20840443	kgp20817413
CASP7	chr10:115438934-115490664	chr10:114938934-115990664	chr10:115428924-115480654	kgp12503193	rs12266538
CASP8	chr2:202098165-202152434	chr2:201598165-202652434	chr2:201806410-201860679	kgp6115041	rs12468196
CASR	chr3:121902529-122005344	chr3:121402529-122505344	chr3:123385219-123488034	kgp18115887	rs13095775
CAV1	chr7:115929905-116201239	chr7:115429905-116701239	chr7:115717141-115988466	kgp13705413	kgp1550529,rs13222576
CBL	chr11:119076989-119178859	chr11:118576989-119678859	chr11:118582199-118684069	kgp4184476	rs10892470
CBX1	chr17:46147413-46178883	chr17:45647413-46678883	chr17:43502412-43533882	kgp4510682	kgp14007862
CCDC106	chr19:56158953-56164526	chr19:55658953-56664526	chr19:60850765-60856338	kgp2072564	rs901476
CCND1	chr11:69455872-69469242	chr11:68955872-69969242	chr11:69165053-69178423	kgp12357966	rs1893085
CCNE1	chr19:30302900-30315215	chr19:29802900-30815215	chr19:34994740-35007059	kgp21358604	kgp21349680
CCR4	chr3:32993065-32996403	chr3:32493065-33496403	chr3:32968069-32971407	rs4955290	kgp3855989
CCR5	chr3:46411632-46417697	chr3:45911632-46917697	chr3:46386636-46392701	kgp17737690	rs936173
CD163	chr12:7623411-7656414	chr12:7123411-8156414	chr12:7514676-7547681	rs9668071	kgp3219786
CD5	chr11:60869929-60895323	chr11:60369929-61395323	chr11:60626505-60651899	rs7927817	kgp13056421
CD9	chr12:6309481-6347437	chr12:5809481-6847437	chr12:6179133-6217688	rs9669580	kgp1124940
CDC2	chr10:62538235-62553924	chr10:62038235-63053924	chr10:62208241-62223930	kgp21922934	rs3125326
CDKN2C	chr1:51433607-51440309	chr1:50933607-51940309	chr1:51206195-51212897	rs17106219	kgp15324656
CENTA1	chr7:937537-994306	chr7:437537-1494306	chr7:904063-960832	kgp4856315,rs3924019	kgp11391801
CETN3	chr5:89689528-89705603	chr5:89189528-90205603	chr5:89725284-89741359	rs277054	kgp22368793
CFTR	chr7:117120016-117308718	chr7:116620016-117808718	chr7:116907252-117095954	kgp13265715	kgp13590397

FIG. 18E

CHAT	chr10:50822349-50901939	chr10:50322349-51401939	chr10:50487146-50543156	kgp8189482	kgp8898453
CHD3	chr17:7788122-7816075	chr17:7288122-8316075	chr17:7728847-7756800	rs7208523	kgp11776706
CHUK	chr10:101948123-101989344	chr10:101448123-102489344	chr10:101938113-101979334	kgp6141810	kgp9150190
CISH	chr3:50643884-50649262	chr3:50143884-51149262	chr3:50618929-50624207	kgp5610191	rs6783700
CKAP1	chr19:36605888-36616849	chr19:36105888-37116849	chr19:41297728-41308689	rs7249516	rs3108171
CKMT2	chr5:80529138-80562217	chr5:80029138-81062217	chr5:80564894-80597973	kgp9822295	kgp7416171
CLTB	chr5:175819455-175843540	chr5:175319455-176343540	chr5:175752061-175776146	rs4867811	kgp1551194
CLU	chr8:27454433-27472328	chr8:26954433-27972328	chr8:27510367-27528244	kgp886026	rs4732823
CMIP	chr16:81478774-81745367	chr16:80978774-82245367	chr16:80036394-80302866	rs11150329	kgp16425289
CNGA2	chrX:150903217-150914036	chrX:150403217-151414036	chrX:150653873-150664692	rs1202896	kgp22766776
CNKSR2	chrX:21392535-21672813	chrX:20892535-22172813	chrX:21302900-21580700	kgp22768242	kgp22744096
CNN1	chr19:11649578-11661138	chr19:11149578-12161138	chr19:11510578-11522138	kgp11148982	rs8100428
CNR2	chr1:24200459-24239817	chr1:23700459-24739817	chr1:24073046-24112404	rs9887921	kgp7256331
COIL	chr17:55015560-55038411	chr17:54515560-55538411	chr17:52370559-52393410	rs7219528	kgp13879956
CORO1B	chr11:67205517-67211292	chr11:66705517-67711292	chr11:66962093-66967839	kgp8733070	kgp12910446
COX17	chr3:119388371-119396243	chr3:118888371-119896243	chr3:120871061-120878933	rs2903301	rs7634938
CPE	chr4:166300096-166419482	chr4:165800096-166919482	chr4:166519546-166638932	rs4541465	kgp20841166
CRADD	chr12:94071150-94288616	chr12:93571150-94788616	chr12:92595281-92768662	kgp18995270	rs10859694
CREM	chr10:35415768-35501886	chr10:34915768-36001886	chr10:35455806-35541892	kgp21684668	rs654221
CRIPT	chr2:46844324-46852881	chr2:46344324-47352881	chr2:46697811-46705687	kgp11216746	kgp5110136
CSNK2A1	chr20:463337-524482	chr20:1-1024482	chr20:411337-472482	kgp19358001	kgp2852236
CSNK2A2	chr16:58191811-58231782	chr16:57691811-58731782	chr16:56749312-56789283	kgp3607479	kgp9299300
CSNK2B	chr6:2919235-2923423	chr6:2919235-2923423	chr6:31741635-31748206	kgp7558035	kgp17052091
CTNNB1	chr3:41236400-41280845	chr3:40736400-41780845	chr3:41211404-41255849	kgp17791054	kgp17873276
DAPK3	chr19:3958451-3971038	chr19:3458451-4471038	chr19:3909451-3922038	kgp9392695	kgp6448823

FIG. 18F

DBN1	chr5:176883613-176900694	chr5:176383613-177400694	chr5:176816219-176833300	rs3733876	kgp6700800
DDIT4	chr10:74033676-74035797	chr10:73533676-74535797	chr10:73703682-73705803	kgp21593001	kgp10561095
DDX5	chr17:62494373-62502484	chr17:61994373-63002484	chr17:59926199-59932869	kgp14113893	rs4239089
DEFB1	chr8:6728096-6735529	chr8:6228096-7235529	chr8:6715508-6722939	kgp20078124	rs12680482
DGKD	chr2:234263152-234380743	chr2:233763152-234880743	chr2:233927891-234045482	rs12477794	rs28902188
DGKZ	chr11:46354454-46402104	chr11:45854454-46902104	chr11:46311314-46358680	rs2090602	kgp22737291
DIRAS2	chr9:93372113-93405108	chr9:92872113-93905108	chr9:92411933-92444928	rs7860989	kgp10944799
DLG1	chr3:196769430-197026143	chr3:196269430-197526143	chr3:198253827-198510540	kgp18074003	rs841672
DLG3	chrX:69664704-69725339	chrX:69164704-70225339	chrX:69581448-69642062	kgp22756738	kgp22752290
DLG4	chr17:7093209-7123369	chr17:6593209-7623369	chr17:7033933-7063781	kgp10999626	rs3744258
DNM1	chr9:130965662-131017527	chr9:130465662-131517527	chr9:130005483-130057348	kgp1183767	rs4836625
DNM3	chr1:171810620-172381857	chr1:171310620-172881857	chr1:170077260-170648480	kgp15671556	rs2213746
DNMT2	chr10:17184981-17243681	chr10:16684981-17743681	chr10:17224987-17283687	kgp1566842	kgp21855354
DPYSL2	chr8:26371708-26515693	chr8:25871708-27015693	chr8:26427707-26571610	rs11998023	rs12544814
DRD1	chr5:174867674-174871163	chr5:174367674-175371163	chr5:174800280-174803769	kgp4432341	kgp8293487
DRD1IP	chr5:174867675-174871163	chr5:174367675-175371163	chr5:174800281-174803769	kgp4432341	kgp8293487
DST	chr6:56479153-56716714	chr6:55979153-57216714	chr6:56430743-56816422	kgp1980963	rs12209200
DVL1	chr1:1270657-1284492	chr1:770657-1784492	chr1:1260520-1274355	kgp4076808	kgp15201879
DVL2	chr17:7128660-7137863	chr17:6628660-7637863	chr17:7069384-7078587	kgp1788685	kgp2456831,rs3744255
DVL3	chr3:183873283-183891314	chr3:183373283-184391314	chr3:185355977-185374008	kgp10156744	kgp4088221
EDF1	chr9:139756570-139760738	chr9:139256570-140260738	chr9:138876391-138880559	rs3829109	kgp4292076
EDG3	chr9:91606324-91620069	chr9:91106324-92120069	chr9:90796144-90809889	kgp18366537	kgp113389
EDG5	chr19:10332109-10341948	chr19:9832109-10841948	chr19:10193109-10202948	kgp21505357	kgp12277401
EDG8	chr19:10623418-10628668	chr19:10123418-11128668	chr19:10484418-10489668	rs4804478	kgp9055694
EEF1D	chr8:144661866-144679845	chr8:144161866-145179845	chr8:144733040-144750726	kgp20077380	kgp4311396

FIG. 18G

EEF2	chr19:3976053-3985461	chr19:3476053-4485461	chr19:3927053-3936461	kgp21334437	rs10406730
EFNB1	chrX:68048839-68066029	chrX:67548839-68566029	chrX:67965564-67982754	rs7879567	kgp22774708
EFNB2	chr13:107142078-107187388	chr13:106642078-107687388	chr13:105940096-105985338	rs9587049	kgp1472981
EIF1B	chr3:40351172-40353915	chr3:39851172-40853915	chr3:40326176-40328919	kgp17543799	kgp724180
ENO2	chr12:7023613-7032859	chr12:6523613-7532859	chr12:6893874-6903120	kgp6644683	kgp18788179
EPB41	chr1:29213602-29446558	chr1:28713602-29946558	chr1:29086214-29319545	kgp15837735	kgp8194212
EPB41L1	chr20:34679425-34820721	chr20:34179425-35320721	chr20:34142839-34284135	rs1886695	kgp10646202
EPB41L2	chr6:131160487-131384462	chr6:130660487-131884462	chr6:131202180-131426058	kgp3398782	kgp16921144
EPHB2	chr1:23037330-23241823	chr1:22537330-23741823	chr1:22909917-23114410	rs2473249	kgp22776625
ESR1	chr6:152011630-152424408	chr6:151511630-152924408	chr6:152053323-152466101	rs9478984	rs818451
ESR2	chr14:64693750-64805268	chr14:64193750-65305268	chr14:63763503-63875021	kgp3039416	kgp8515773
ESRRG	chr1:216676587-217311097	chr1:216176587-217811097	chr1:214743210-215377720	kgp2104463	kgp3054869
ETHE1	chr19:44010870-44031396	chr19:43510870-44531396	chr19:48702710-48723236	rs11668932	kgp561363
EWSR1	chr22:29663997-29696515	chr22:29163997-30196515	chr22:27994016-28026515	rs6005868	rs4823054
F11R	chr1:160965000-161008774	chr1:160465000-161508774	chr1:159231624-159275404	rs678456	kgp10744728
FADD	chr11:70049268-70053508	chr11:69549268-70553508	chr11:69726916-69731134	kgp12619639	kgp12640488
FAS	chr10:90729552-90775542	chr10:90229552-91275542	chr10:90740267-90765522	kgp6970830	kgp1640747
FBLIM1	chr1:16083153-16113084	chr1:15583153-16613084	chr1:15955740-15985671	rs16851480	kgp15648830
FER	chr5:108083522-108523373	chr5:107583522-109023373	chr5:108111421-108551272	rs11958626	rs845734
FEZ1	chr11:125315640-125366206	chr11:124815640-125866206	chr11:124820857-124871333	rs10160591	kgp12966369
FEZ2	chr2:36779403-36825332	chr2:36279403-37325332	chr2:36632904-36678836	kgp10246319	kgp9712350
FFAR1	chr19:35842444-35843367	chr19:35342444-36343367	chr19:40534294-40535197	rs8106116	kgp21511691
FFAR2	chr19:35939202-35941865	chr19:35439202-36441865	chr19:40631042-40633705	rs2112502	rs7247246
FKBP1A	chr20:1349620-1373816	chr20:849620-1873816	chr20:1297621-1321745	kgp4567229	kgp10348674
FLJ31945	chr13:50699952-50702599	chr13:50199952-51202599	chr13:49597953-49600600	kgp9786864	kgp16621897

FIG. 18H

FLJ41278	chr12:65277553-65371302	chr12:64777553-65871302	chr12:63563820-63657569	rs6581555	kgp1662303
FLNA	chrX:153576899-153603006	chrX:153076899-154103006	chrX:153230093-153256200	rs7049293	rs28412378
FLNB	chr3:57994126-58157982	chr3:57494126-58657982	chr3:57969166-58133017	rs7629743	rs11130670
FREQ	chr9:132934856-132999583	chr9:132434856-133499583	chr9:131974677-132039404	kgp12208188	kgp18380808
FRS2	chr12:69864128-69973562	chr12:69364128-70473562	chr12:68150395-68259829	kgp19095191	kgp12534834
FSHR	chr2:49189295-49381666	chr2:48689295-49881666	chr2:49043155-49235134	kgp297164	kgp11229604
FXN	chr9:71650478-71715094	chr9:71150478-72215094	chr9:70840163-70878772	rs265076	kgp213209
FXR1	chr3:180630233-180700539	chr3:180130233-181200539	chr3:182113145-182177647	kgp22773686	kgp3235523
G6PD	chrX:153759605-153775787	chrX:153259605-154275787	chrX:153412799-153428981	rs2239471	kgp22745531
GABRR1	chr6:89887222-89927496	chr6:89387222-90427496	chr6:89944690-89983779	kgp3728710	kgp17056993
GABRR2	chr6:89967238-90024967	chr6:89467238-90524967	chr6:90023957-90081686	kgp16994883	kgp9012178
GALR2	chr17:74070891-74073573	chr17:73570891-74573573	chr17:71582486-71585168	rs1042861	rs16967307
GAP43	chr3:115342150-115440334	chr3:114842150-115940334	chr3:116825141-116922842	rs10511341	kgp18168870
GC	chr4:72607410-72671237	chr4:72107410-73171237	chr4:72826274-72888622	rs10013437	kgp12025264
GFAP	chr17:42982993-42992920	chr17:42482993-43492920	chr17:40338518-40348394	rs8066197	rs12947718
GFI1	chr1:92940317-92952433	chr1:92440317-93452433	chr1:92712905-92725021	kgp80379	kgp15436210
GFI1B	chr9:135853893-135867084	chr9:135353893-136367084	chr9:134843714-134856903	kgp1227599	kgp22817803
GFPT1	chr2:69546900-69614386	chr2:69046900-70114386	chr2:69405910-69467829	kgp7360674	kgp14824626
GH1	chr17:61994562-61996198	chr17:61494562-62496198	chr17:59348294-59349930	kgp6455446	kgp10132757
GIT1	chr17:27900486-27916610	chr17:27400486-28416610	chr17:24924612-24940736	kgp14082001	rs8065059
GIT2	chr12:110367606-110434194	chr12:109867606-110934194	chr12:108851991-108918483	kgp8064273	kgp556710
GJA1	chr6:121756744-121770873	chr6:121256744-122270873	chr6:121798443-121812572	kgp5203283	kgp1494786
GJB1	chrX:70435061-70445065	chrX:69935061-70945065	chrX:70351786-70361777	kgp22820938	rs35542412
GMFB	chr14:54941208-54955744	chr14:54441208-55455744	chr14:54010958-54025494	kgp5212952	kgp7377769
GNA12	chr7:2767740-2883959	chr7:2267740-3383959	chr7:2734266-2850485	kgp9177535	kgp13694655

FIG. 18I

GNAS	chr20:57414794-57486250	chr20:56914794-57986250	chr20:56848189-56919645	rs471661	rs729997
GNAZ	chr22:23412668-23467221	chr22:22912668-23967221	chr22:21742668-21797221	kgp15075658	rs9680742
GPM6A	chr4:176554087-176923648	chr4:176054087-177423648	chr4:176791081-177160642	rs6849435	kgp8852764
GPSM2	chr1:109419602-109476957	chr1:108919602-109976957	chr1:109221125-109274567	kgp15175401	kgp15178378
GRB14	chr2:165349322-165478360	chr2:164849322-165978360	chr2:165057568-165186606	kgp8982508	kgp14153450
GRIA2	chr4:158141294-158287226	chr4:157641294-158787226	chr4:158361185-158506676	kgp22818527	rs6836401
GRIA3	chrX:122318095-122624766	chrX:121818095-123124766	chrX:122145776-122452447	rs7057244	rs12559968
GRIA4	chr11:105480799-105852819	chr11:104980799-106352819	chr11:104986009-105358029	kgp12888967	kgp2959570
GRIN1	chr9:140033608-140063214	chr9:139533608-140563214	chr9:139153429-139183029	kgp18425565	kgp18521447
GRIN2A	chr16:9847264-10276611	chr16:9347264-10776611	chr16:9762922-10184112	kgp16441783	rs9932893
GRIN2B	chr12:13714409-14133022	chr12:13214409-14633022	chr12:13605676-14024289	rs3741818	kgp7391296
GRK1	chr13:114321596-114438637	chr13:113821596-114938637	chr13:113369597-113373973	kgp16671784	rs11147317
GRK4	chr4:2965342-3042474	chr4:2465342-3542474	chr4:2935140-3012272	rs846252	rs6821202
GSK3A	chr19:42734337-42746736	chr19:42234337-43246736	chr19:47426177-47438576	kgp21481263	kgp10870487
GSK3B	chr3:119540801-119813264	chr3:119040801-120313264	chr3:121028235-121295203	kgp17616951	kgp4570827
GSTM4	chr1:110198697-110208123	chr1:109698697-110708123	chr1:110000225-110009648	rs595635	kgp15760598
HABP4	chr9:99212413-99253618	chr9:98712413-99753618	chr9:98252234-98293439	kgp18578220	kgp18630342
HAND1	chr5:153854531-153857824	chr5:153354531-154357824	chr5:153834724-153838017	kgp7530958	rs2431184
HAND2	chr4:174447651-174451378	chr4:173947651-174951378	chr4:174684226-174687953	kgp20847640	kgp20778226
HARS	chr5:140053489-140070971	chr5:139553489-140570971	chr5:140033673-140051155	rs6874491	rs12654953
HDAC6	chrX:48660286-48683380	chrX:48160286-49183380	chrX:48545430-48568324	kgp22835768	rs2015487
HES1	chr3:193853930-193856401	chr3:193353930-194356401	chr3:195336627-195339090	kgp11414670	rs7649259
HLA-A	chr6:1150035-1295564	chr6:1150035-1295564	chr6:30018304-30085130	rs9392258	rs9391920
HLA-C	chr6:2585738-2671188	chr6:2585738-2671188	chr6:2486041-2572197	rs9392400	kgp1905253
HLA-DQA2	chr6:4166320-4171833	chr6:4166320-4171833	chr6:3895192-3901275	kgp17451336	kgp17218419

FIG. 18J

HMGB1	chr13:31032878-31191510	chr13:30532878-31691510	chr13:29930878-30089510	rs1557088	kgp8054835
HMGN1	chr21:40714240-40721047	chr21:40214240-41221047	chr21:39636110-39643140	kgp4524272	kgp8317624
HMGN2	chr1:26798901-26803133	chr1:26298901-27303133	chr1:26671488-26675720	rs1429936	kgp8260087
HMMR	chr5:162887516-162918953	chr5:162387516-163418953	chr5:162820240-162851525	kgp9548441	rs1363073
HMOX2	chr16:4524718-4560348	chr16:4024718-5060348	chr16:4464719-4500349	kgp16414002	kgp7117794
HMP19	chr5:173472723-173536182	chr5:172972723-174036182	chr5:173405329-173468788	kgp22404239	rs12186684
HOMER2	chr15:83517728-83621476	chr15:83017728-84121476	chr15:81314789-81412477	rs1267659	kgp4123064
HRH4	chr18:22040592-22059921	chr18:21540592-22559921	chr18:20294590-20313919	rs7235445	kgp7887799
HSP90AA1	chr14:102547074-102606086	chr14:102047074-103106086	chr14:101616827-101675839	kgp3260354	kgp19714004
HSPA1A	chr6:31783290-31785719	chr6:31283290-32285719	chr6:31891315-31893698	kgp4709627	rs9296020
HSPA1B	chr6:3089162-3091686	chr6:3089162-3091686	chr6:3043109-3045633	kgp6503147	kgp5869121
HSPA4	chr5:132387661-132440709	chr5:131887661-132940709	chr5:132415560-132468608	kgp22352512	kgp7658141
HSPB1	chr7:75931874-75933614	chr7:75431874-76433614	chr7:75769858-75771546	kgp4195218	kgp10852432
HSPB3	chr5:53751430-53752214	chr5:53251430-54252214	chr5:53787201-53787964	rs16881895	rs3815916
HSPB8	chr12:119616594-119632551	chr12:119116594-120132551	chr12:118100977-118116934	kgp18981306	kgp18823622
HSPBP1	chr19:55773590-55791751	chr19:55273590-56291751	chr19:60465518-60483540	kgp3134010	kgp21533588
HSPE1	chr2:198364720-198368187	chr2:197864720-198868187	chr2:198073364-198076416	kgp9884304	kgp12004769
HSPH1	chr13:31710762-31736502	chr13:31210762-32236502	chr13:30608762-30634502	kgp16548529	kgp16811501
HTATIP	chr11:20385289-20405329	chr11:19885289-20905329	chr11:20341865-20361905	rs2707094	kgp309631
HTR2B	chr2:231972949-231989824	chr2:231472949-232489824	chr2:231681198-231698068	rs6761068	rs4973459
HTR2C	chrX:113818550-114144624	chrX:113318550-114644624	chrX:113724806-114050880	rs7055827	kgp22830072
HTR6	chr1:19991779-20006055	chr1:19491779-20506055	chr1:19864366-19878642	kgp15912015	kgp10523409
IGSF4	chr11:115044345-115375241	chr11:114544345-115875241	chr11:114549555-114880451	rs1607260	rs7928212
IKBKB	chr8:42128819-42190171	chr8:41628819-42690171	chr8:42247985-42309122	kgp9748756	kgp3164559
IKBKE	chr1:206643585-206670223	chr1:206143585-207170223	chr1:204710418-204736845	kgp15543770	kgp6359437

FIG. 18K

IKBKG	chrX:153770458-153793261	chrX:153270458-154293261	chrX:153423652-153446455	rs633	kgp22831959
IL4R	chr16:27325250-27376099	chr16:26825250-27876099	chr16:27232751-27283600	kgp11144142	kgp16489203
IL5RA	chr3:3108007-3152058	chr3:2608007-3652058	chr3:3086420-3127031	kgp10211459	kgp22835987
IL8RA	chr2:219027567-219031716	chr2:218527567-219531716	chr2:218735812-218739961	kgp14521358	rs16859170
INSR	chr19:7112265-7294011	chr19:6612265-7794011	chr19:7063265-7245011	kgp5914741	kgp21453659
IQCB1	chr3:121488609-121553926	chr3:120988609-122053926	chr3:122971299-123036616	rs11921531	rs6438722
IQGAP1	chr15:90931472-91045475	chr15:90431472-91545475	chr15:88732476-88846479	kgp1876985	kgp20028694
IRAK1	chrX:153275956-153285342	chrX:152775956-153785342	chrX:152929150-152938536	kgp22756383	rs6643680
IRS1	chr2:227596032-227663506	chr2:227096032-228163506	chr2:227304276-227371750	kgp12414080	kgp9391097
IRS4	chrX:107975726-107979607	chrX:107475726-108479607	chrX:107862367-107866295	kgp22794644	rs5985712
ITGB2	chr21:46305867-46348753	chr21:45805867-46848753	chr21:45130296-45173181	kgp13225366	rs11702782
ITGB3BP	chr1:63906440-63988944	chr1:63406440-64488944	chr1:63679049-63761423	rs1572109	kgp5171315
ITGB4	chr17:73717515-73753899	chr17:73217515-74253899	chr17:71229110-71265494	kgp2663142	kgp4575494
ITGB5	chr3:124481794-124606144	chr3:123981794-125106144	chr3:125964484-126088834	kgp5281659	kgp17765518
ITPKA	chr15:41786055-41795757	chr15:41286055-42295757	chr15:39573413-39583039	kgp22747722	kgp10507061
ITPKB	chr1:226819390-226926876	chr1:226319390-227426876	chr1:224886013-224991987	rs1219671	rs7519099
ITPR3	chr6:33589155-33664348	chr6:33089155-34164348	chr6:33697138-33772326	rs3117030	kgp4515850
IXL	chr19:39881963-39891203	chr19:39381963-40391203	chr19:44573803-44583043	kgp986483	kgp6117029
JAK1	chr1:65298905-65432619	chr1:64798905-65932619	chr1:65071493-65205207	kgp8976721	kgp9745392
KCNE1	chr21:35818987-35884573	chr21:35318987-36384573	chr21:34740857-34806443	kgp13187567	kgp5041106
KCNE4	chr2:223916861-223920355	chr2:223416861-224420355	chr2:223625105-223628599	kgp14948218	kgp14631899
KCNH2	chr7:150642043-150675402	chr7:150142043-151175402	chr7:150272981-150305947	kgp13542655	kgp7948285
KCNJ2	chr17:68164813-68176183	chr17:67664813-68676183	chr17:65676408-65687778	rs6501341	kgp2814913
KCNN2	chr5:113698015-113832197	chr5:113198015-114332197	chr5:113725914-113860096	kgp9619904	rs10056549
KCNN4	chr19:44270684-44285409	chr19:43770684-44785409	chr19:48962524-48977249	rs6509074	kgp21388839

FIG. 18L

KCNQ2	chr20:62037541-62103993	chr20:61537541-62603993	chr20:61507985-61574437	rs16983364	kgp19265466
KCNQ3	chr8:133133104-133493004	chr8:132633104-133993004	chr8:133210437-133562186	kgp20244043	rs4074676
KCNQ5	chr6:73331570-73908573	chr6:72831570-74408573	chr6:73388555-73962301	kgp7790415	rs9446983
KDR	chr4:55944425-55991762	chr4:55444425-56491762	chr4:55639405-55686519	kgp11624145	rs10022874
KIAA1377	chr11:101785745-101871793	chr11:101285745-102371793	chr11:101290955-101377003	kgp12804311	rs9667864
KIAA1549	chr7:138516126-138666064	chr7:138016126-139166064	chr7:138166666-138255110	rs11769851	kgp10209774
KIF3A	chr5:132028322-132073265	chr5:131528322-132573265	chr5:132056221-132101164	rs3805685	rs4958109
KIT	chr4:55524094-55606881	chr4:55024094-56106881	chr4:55218851-55301638	kgp4467115	kgp9403472
KLHL20	chr1:173684079-173755840	chr1:173184079-174255840	chr1:171950702-172022463	rs13374515	kgp5594942
KLHL3	chr5:136953188-137071779	chr5:136453188-137571779	chr5:136981087-137099678	rs2966736	rs10040989
KLK10	chr19:51515999-51523431	chr19:51015999-52023431	chr19:56207811-56215243	kgp9495392	kgp21503250
KRAS	chr12:25358179-25403854	chr12:24858179-25903854	chr12:25249446-25295121	kgp19038229	kgp1316534
KRT10	chr17:38974368-38978863	chr17:38474368-39478863	chr17:36227894-36232373	kgp7164026	kgp6621387
KRT18	chr12:53342654-53346685	chr12:52842654-53846685	chr12:51628921-51632952	rs406857	rs11834179
LCK	chr1:32716839-32751766	chr1:32216839-33251766	chr1:32489426-32524353	rs12037400	kgp6229337
LGALS2	chr22:37966252-37976024	chr22:37466252-38476024	chr22:36296198-36305970	kgp14999686	rs8135665
LMNA	chr1:156052368-156108548	chr1:155552368-156608548	chr1:154318992-154375172	kgp11675488	rs12408758
LMNB1	chr5:126112314-126172712	chr5:125612314-126672712	chr5:126140731-126200608	kgp5014465	kgp22418220
LOC100133669	chr8:144063447-144099807	chr8:143563447-144599807	chr8:144134822-144171182	rs10875483	kgp10850793
LOC154092	chr6:134758853-134825158	chr6:134258853-135325158	chr6:134800546-134866851	kgp11630779	kgp22793805
LOC339290	chr18:5238098-5246505	chr18:4738098-5746505	chr18:5222874-5228525	kgp5290787	kgp989326
LOC340357	chr8:12623570-12668910	chr8:12123570-13168910	chr8:12667941-12713281	kgp22754906	kgp20305069
LOC400604	chr17:48944039-48945732	chr17:48444039-49445732	chr17:46299038-46300731	kgp11815481	kgp10163248
LOC613126	chr7:91763906-91771854	chr7:91263906-92271854	chr7:91601842-91609790	kgp13774218	rs3731343
LTB4R	chr14:24780704-24787242	chr14:24280704-25287242	chr14:23850544-23855992	kgp19673807	rs8007336

FIG. 18M

LTF	chr3:46477495-46526724	chr3:45977495-47026724	chr3:46452499-46501728	kgp17788490	kgp1176589
LXN	chr3:158384202-158390482	chr3:157884202-158890482	chr3:159866899-159873176	rs6764092	kgp7955381
LYST	chr1:235824344-236030220	chr1:235324344-236530220	chr1:233890968-234096843	rs2295815	kgp9270301
MAD2L1BP	chr6:43597278-43608688	chr6:43097278-44108688	chr6:43705256-43716666	rs1537638	kgp1522302
MAGED1	chrX:51546154-51645450	chrX:51046154-52145450	chrX:51562894-51662190	kgp22779908	kgp22784919
MAP1A	chr15:43809805-43823818	chr15:43309805-44323818	chr15:41597097-41611110	kgp12180163	kgp10318377
MAP1LC3A	chr20:33134691-33148149	chr20:32634691-33648149	chr20:32598352-32611810	kgp19388199	kgp5639543
MAP2K1	chr15:66679210-66783882	chr15:66179210-67283882	chr15:64466264-64570936	kgp19795142	kgp382480
MAP2K4	chr17:11924134-12047051	chr17:11424134-12547051	chr17:11864859-11987776	rs16944942	rs9915536
MAP2K5	chr15:67835020-68099455	chr15:67335020-68599455	chr15:65622074-65886506	kgp19854650	kgp20006731
MAP3K10	chr19:40697650-40721482	chr19:40197650-41221482	chr19:45389490-45413314	kgp6290284	rs2561531
MAP3K3	chr17:61699774-61773670	chr17:61199774-62273670	chr17:59053506-59127402	kgp14048701	kgp5230870
MAP3K7	chr6:91225352-91296907	chr6:90725352-91796907	chr6:91282073-91353628	rs9451316	rs9451576
MAP3K7IP1	chr22:39745953-39827887	chr22:39245953-40327887	chr22:38075899-38157833	kgp10431646	rs137981
MAP3K7IP2	chr6:149639062-149732747	chr6:149139062-150232747	chr6:149680755-149774440	kgp9485571	kgp9110056
MAP3K8	chr10:30722949-30750762	chr10:30222949-31250762	chr10:30762871-30790767	kgp22034763	kgp11496819
MAP6	chr11:75297962-75379479	chr11:74797962-75879479	chr11:74975610-75057127	rs11236323	kgp695651
MAPK14	chr6:35995453-36079013	chr6:35495453-36579013	chr6:36103550-36186513	rs4711420	kgp10854130
MAPK3	chr16:30125425-30134630	chr16:29625425-30634630	chr16:30032926-30042131	kgp11463254	kgp2105557
MARCKS	chr6:114178526-114184652	chr6:113678526-114684652	chr6:114285219-114291345	kgp17187839	kgp1113238
MBP	chr18:74690788-74844774	chr18:74190788-75344774	chr18:72819776-72973762	kgp5208536	rs12960102
MCC	chr5:112357795-112824527	chr5:111857795-113324527	chr5:112385694-112852426	kgp22530369	kgp22589538
MGMT	chr10:131265453-131565783	chr10:130765453-132065783	chr10:131155455-131455358	kgp11264334	kgp1514587
MIP	chr12:56843285-56848435	chr12:56343285-57348435	chr12:55130150-55134696	kgp19052399,rs11834873	kgp18750923
MLF2	chr12:6857935-6876641	chr12:6357935-7376641	chr12:6728196-6746902	kgp18998724	rs1001653

FIG. 18N

MLLT3	chr9:20344967-20622514	chr9:19844967-21122514	chr9:20334967-20612514	kgp18504776	rs1016129
MNAT1	chr14:61201458-61435398	chr14:60701458-61935398	chr14:60271222-60505151	kgp5293246	rs7142051
MPHOSPH6	chr16:82181766-82203829	chr16:81681766-82703829	chr16:80739267-80761330	kgp406017	rs3852734
MRPS12	chr19:39421347-39423659	chr19:38921347-39923659	chr19:44113187-44115499	kgp21348524	kgp21366907
MRPS6	chr21:35445822-35515334	chr21:34945822-36015334	chr21:34367692-34437204	kgp11037760	rs2834555
MRVI1	chr11:10594637-10715535	chr11:10094637-11215535	chr11:10551213-10672111	rs7946995	kgp11739225
MSN	chrX:64887510-64961793	chrX:64387510-65461793	chrX:64804235-64878518	rs7887705	kgp22760405
MYF5	chr12:81110707-81113447	chr12:80610707-81613447	chr12:79634838-79637578	rs12313692	kgp5599463
MYF6	chr12:81101407-81103256	chr12:80601407-81603256	chr12:79625576-79627382	rs7954738	rs7972054
MYLK	chr3:123331142-123603149	chr3:122831142-124103149	chr3:124813832-125085839	kgp9270532	rs510324
MYO10	chr5:16662015-16936385	chr5:16162015-17436385	chr5:16715015-16989385	kgp22359577	kgp12241403
MYO7A	chr11:76839309-76926286	chr11:76339309-77426286	chr11:76516957-76603934	rs2186677	kgp304899
MYO9B	chr19:17186590-17324104	chr19:16686590-17824104	chr19:17047595-17185104	kgp21430919	kgp4164870
MYOC	chr1:171604556-171621823	chr1:171104556-172121823	chr1:169871179-169888396	rs1736563	kgp1482992
MYOD1	chr11:17741109-17743678	chr11:17241109-18243678	chr11:17697685-17700254	kgp10809253	rs12285714
MYOG	chr1:203052256-203055377	chr1:202552256-203555377	chr1:201318879-201322000	rs4950858	rs2798625
MYOT	chr5:137022409-137223540	chr5:136522409-137723540	chr5:137231472-137251440	kgp22294838	kgp5559791
MYT1L	chr2:1792884-2335045	chr2:1292884-2835045	chr2:1771891-2314052	kgp356515	kgp7720594
NACA	chr12:57106210-57119326	chr12:56606210-57619326	chr12:55392477-55405593	rs4759218	kgp11483848
NCALD	chr8:102698769-103137135	chr8:102198769-103637135	chr8:102767945-103206311	kgp11277997	rs16869664
NCF1C	chr7:74572383-74587816	chr7:74072383-75087816	chr7:74210380-74225695	kgp7635479	kgp954065
NCL	chr2:232319458-232329205	chr2:231819458-232829205	chr2:232027702-232037449	rs13415867	kgp12447433
NCOR2	chr12:124808956-125052010	chr12:124308956-125552010	chr12:123397062-123617963	rs11057368	kgp12274490
NEUROD1	chr2:182540832-182545392	chr2:182040832-183045392	chr2:182249438-182253626	kgp7038037	rs12612546
NF2	chr22:29999544-30094589	chr22:29499544-30594589	chr22:28329544-28424589	kgp15024372	kgp10478391

FIG. 18O

NFASC	chr1:204797781-204991950	chr1:204297781-205491950	chr1:203064445-203258572	rs12044614	kgp11817505
NFATC1	chr18:77155771-77289323	chr18:76655771-77789323	chr18:75256759-75390311	rs12150804	kgp11226294
NFATC2	chr20:50007764-50179168	chr20:49507764-50679168	chr20:49441171-49612777	rs761240	kgp19325060
NFKB2	chr10:104154228-104162281	chr10:103654228-104662281	chr10:104144218-104152271	kgp11777223	rs7897654
NFKBIB	chr19:39390339-39399534	chr19:38890339-39899534	chr19:44082454-44091374	kgp21403480	kgp4374047
NFKBIE	chr6:44225902-44233525	chr6:43725902-44733525	chr6:44333880-44341503	rs866236	kgp11221406
NGB	chr14:77731833-77737655	chr14:77231833-78237655	chr14:76801586-76807408	kgp4649405	rs11622713
NHP2L1	chr22:42069936-42084913	chr22:41569936-42584913	chr22:40399882-40414859	kgp22806642	kgp282841
NOS1	chr12:117645946-117799607	chr12:117145946-118299607	chr12:116135361-116283965	rs11068156	kgp763518
NP	chr14:20937541-20945248	chr14:20437541-21445248	chr14:20007381-20015088	kgp8768601	kgp19427360
NPHP1	chr2:110880913-110962639	chr2:110380913-111462639	chr2:110238202-110319928	rs10496434	kgp3845148
NRBP1	chr2:27650656-27665124	chr2:27150656-28165124	chr2:27504160-27518628	kgp14600002	kgp14258181
NRGN	chr11:124609828-124617102	chr11:124109828-125117102	chr11:124115038-124122312	kgp483624	kgp5783287
NUCB1	chr19:49403306-49426540	chr19:48903306-49926540	chr19:54095380-54118339	kgp282275	kgp9015400
OBSCN	chr1:228395860-228566575	chr1:227895860-229066575	chr1:226462483-226633198	kgp22809391	kgp706951
OGG1	chr3:9791627-9808353	chr3:9291627-10308353	chr3:9765704-9783342	rs17744749	rs1642974
OPRK1	chr8:54138275-54164194	chr8:53638275-54664194	chr8:54300828-54326747	kgp11808605	kgp7186378
OPRM1	chr6:154360442-154568001	chr6:153860442-155068001	chr6:154402135-154609693	kgp22790919	kgp7491549
P2RY1	chr3:152552735-152555843	chr3:152052735-153055843	chr3:154035425-154038533	rs4472028	kgp1812100
PA2G4	chr12:56498102-56507694	chr12:55998102-57007694	chr12:54784369-54793961	kgp18842835	rs12308290
PABPC4	chr1:40026484-40042521	chr1:39526484-40542521	chr1:39799074-39815003	rs6692557	rs6681804
PAEP	chr9:138453603-138458622	chr9:137953603-138958622	chr9:137593424-137598443	kgp4360258	rs11103302
PAFAH1B1	chr17:2496922-2588909	chr17:1996922-3088909	chr17:2443672-2535659	kgp13951566	kgp4861640
PAM	chr5:102201526-102366808	chr5:101701526-102866808	chr5:102229425-102393316	rs10075318	kgp4660412
PARD6A	chr16:67694850-67696681	chr16:67194850-68196681	chr16:66252351-66254182	kgp16268099,rs1106304	kgp16328412

FIG. 18P

PARD6B	chr20:49348080-49370278	chr20:48848080-49870278	chr20:48781487-48803685	kgp19335956	kgp19356310
PARD6G	chr18:77915116-78005397	chr18:77415116-78505397	chr18:76016105-76106388	kgp15973881	rs12960632
PAWR	chr12:79985744-80084790	chr12:79485744-80584790	chr12:78509875-78608921	rs2950386	kgp19124809
PCNT	chr21:47744035-47865682	chr21:47244035-48365682	chr21:46568463-46690110	kgp13165624	rs10483083
PCP4	chr21:41239346-41301322	chr21:40739346-41801322	chr21:40161216-40223192	kgp5198475	rs2837624
PDC	chr1:186412697-186430239	chr1:185912697-186930239	chr1:184679337-184696862	kgp15446019	kgp15206197
PDCD8	chrX:129263338-129299861	chrX:128763338-129799861	chrX:129091019-129127542	rs3131260	kgp22747824
PDCL	chr9:125580375-125590935	chr9:125080375-126090935	chr9:124620443-124630661	kgp11050939	rs7341862
PDE1A	chr2:183007182-183387507	chr2:182507182-183887507	chr2:182715427-183095498	kgp205462	kgp14271078
PDE4DIP	chr1:144676436-145076186	chr1:144176436-145576186	chr1:143388229-143787436	rs7548928	kgp15506281
PDE6D	chr2:232597146-232645974	chr2:232097146-233145974	chr2:232305390-232354218	kgp448503	rs11686328
PDIA2	chr16:330605-337209	chr16:1-837209	chr16:270606-277210	kgp4861413	rs3817833
PDLIM7	chr5:176910394-176924602	chr5:176410394-177424602	chr5:176843000-176857208	kgp10474318	kgp9286031
PDPK1	chr16:2587969-2653189	chr16:2087969-3153189	chr16:2527970-2593190	rs11876	rs2741932
PEA15	chr1:160175124-160185162	chr1:159675124-160685162	chr1:158441750-158451786	kgp15388960	kgp4800109
PELO	chr5:52083773-52098452	chr5:51583773-52598452	chr5:52119530-52134209	kgp7417119	kgp22419632
PFDN1	chr5:139624634-139682689	chr5:139124634-140182689	chr5:139604818-139662873	kgp2976589	rs3733707
PFDN4	chr20:52824501-52836492	chr20:52324501-53336492	chr20:52257908-52269899	kgp2671049	kgp19401284
PFDN5	chr12:53689234-53693234	chr12:53189234-54193234	chr12:51975501-51979501	kgp9320945	kgp18934893
PFKFB2	chr1:207207760-207254368	chr1:206707760-207754368	chr1:205293242-205320991	rs6666087	kgp15524399
PFN1	chr17:4848946-4851825	chr17:4348946-5351825	chr17:4789691-4792570	kgp459103	rs11869909
PGK1	chrX:77359665-77382324	chrX:76859665-77882324	chrX:77246321-77268980	kgp22784498	kgp22747606
PHKA1	chrX:71798663-71934029	chrX:71298663-72434029	chrX:71715388-71850754	kgp22784635	kgp22830838,rs5982097
PHKA2	chrX:18910415-19002480	chrX:18410415-19502480	chrX:18820336-18912401	kgp22820040	kgp22735291
PHKG1	chr7:56148674-56160689	chr7:55648674-56660689	chr7:56116168-56128183	rs4947514	kgp13251786

FIG. 18Q

PIAS4	chr19:4007748-4038067	chr19:3507748-4538067	chr19:3958748-3989067	kgp21496330	rs966384
PIK3C3	chr18:39535198-39661446	chr18:39035198-40161446	chr18:37789196-37915444	kgp16093917	kgp16001617
PIK3CG	chr7:106505722-106547592	chr7:106005722-107047592	chr7:106292958-106334828	kgp13830163	kgp58259
PLCB2	chr15:40580097-40600174	chr15:40080097-41100174	chr15:38367389-38387466	rs594863	kgp19835274
PLCD1	chr3:38048986-38071154	chr3:37548986-38571154	chr3:38023990-38046137	rs155528	kgp8999289
PLD1	chr3:171318194-171528504	chr3:170818194-172028504	chr3:172801338-173011198	kgp17613784	kgp17918658
PLD2	chr17:4710395-4726727	chr17:4210395-5226727	chr17:4657377-4673694	rs9915202	kgp10024037
PLEKHA4	chr19:49340353-49371884	chr19:48840353-49871884	chr19:54032166-54063670	kgp21466232	kgp7036888
PLK1	chr16:23690200-23701688	chr16:23190200-24201688	chr16:23597701-23609189	kgp6012631	kgp22747639
POLA2	chr11:65029431-65065088	chr11:64529431-65565088	chr11:64786007-64821664	rs637332	rs12800057
POLB	chr8:42195972-42229331	chr8:41695972-42729331	chr8:42315186-42348470	kgp20057794	kgp20541648
POLR2C	chr16:57496550-57505921	chr16:56996550-58005921	chr16:56054051-56063422	kgp12245826	rs3888264
POLR3F	chr20:18448032-18465286	chr20:17948032-18965286	chr20:18396032-18413286	kgp4834782	kgp4034265
PPARA	chr22:46546498-46639653	chr22:46046498-47139653	chr22:44925162-45018317	kgp1216941	kgp15069036
PPEF1	chrX:18709044-18846034	chrX:18209044-19346034	chrX:18618965-18755955	kgp22764965	kgp22802655
PPEF2	chr4:76781025-76823681	chr4:76281025-77323681	chr4:77000049-77042705	kgp3982074	kgp4693685
PPM1A	chr14:60712469-60765805	chr14:60212469-61265805	chr14:59782222-59835559	kgp19716116	kgp5849461
PPP1R13B	chr14:104200087-104313927	chr14:103700087-104813927	chr14:103269840-103383680	kgp19713395	kgp19494408
PPP1R14A	chr19:38741876-38747231	chr19:38241876-39247231	chr19:43433716-43439012	kgp7541975	kgp4659188
PPP3CA	chr4:101944586-102268628	chr4:101444586-102768628	chr4:102163609-102487376	kgp4575683	kgp7268908
PPYR1	chr10:47083533-47088320	chr10:46583533-47588320	chr10:46503539-46508326	kgp507194	rs11259820
PQBP1	chrX:48755194-48760422	chrX:48255194-49260422	chrX:48640138-48645364	rs28833838	rs2015487
PREI3	chr2:198364721-198418423	chr2:197864721-198918423	chr2:198072966-198126668	kgp9884304	kgp9480848
PRG2	chr11:57154833-57191532	chr11:56654833-57691532	chr19:763517-772952	kgp13043879	kgp12981403
PRKACA	chr19:14202506-14228559	chr19:13702506-14728559	chr19:14063506-14089559	kgp6577295	kgp559477

FIG. 18R

PRKCB1	chr16:23847300-24231932	chr16:23347300-24731932	chr16:23754801-24139433	rs7190829	rs2343354
PRKCD	chr3:53195222-53226733	chr3:52695222-53726733	chr3:53170262-53201773	rs11715796	kgp8788109
PRKCG	chr19:54385466-54410901	chr19:53885466-54910901	chr19:59077278-59102713	kgp1393848	kgp11043930
PRKCI	chr3:169940219-170023770	chr3:169440219-170523770	chr3:171422913-171506464	kgp17942550	rs12485248
PRKCZ	chr1:1981908-2116834	chr1:1481908-2616834	chr1:1971768-2106694	kgp15756715	kgp907107
PRKG1	chr10:52750910-54058110	chr10:52250910-54558110	chr10:52420950-53725280	kgp22035660	rs7923443
PSCD2	chr19:48972465-48985571	chr19:48472465-49485571	chr19:53664277-53677383	rs16981057	rs5464
PSEN2	chr1:227058272-227083804	chr1:226558272-227583804	chr1:225124895-225150427	rs3219110	kgp1301981,rs3014274
PSG9	chr19:43757434-43773682	chr19:43257434-44273682	chr19:48449274-48465522	kgp21418993	kgp7929858
PSMA2	chr7:42956461-42971805	chr7:42456461-43471805	chr7:42922986-42938330	kgp13636285	kgp8523923
PSMD2	chr3:184017021-184026840	chr3:183517021-184526840	chr3:185499715-185509534	kgp4284536	rs11711955
PSPC1	chr13:20277008-20357159	chr13:19777008-20857159	chr13:19146895-19255083	kgp249471	kgp2992302
PTGIR	chr19:47123724-47128354	chr19:46623724-47628354	chr19:51815564-51820194	kgp21532737	rs184290
PTMAP7	chr2:232573235-232578250	chr2:232073235-233078250	chr2:232281479-232286494	kgp6878597	kgp14464906
PTP4A1	chr6:64231650-64293489	chr6:63731650-64793489	chr6:64289609-64351448	rs4710239	kgp357802
PTP4A3	chr8:142432006-142441620	chr8:141932006-142941620	chr8:142501188-142510802	rs12678285	kgp3296894
PTPN11	chr12:112856535-112947717	chr12:112356535-113447717	chr12:111340918-111432100	kgp22816522	rs1293743
PTPN12	chr7:77166772-77269388	chr7:76666772-77769388	chr7:77004770-77107322	kgp4690058	rs3807707
PTPN6	chr12:7055739-7070479	chr12:6555739-7570479	chr12:6926000-6940740	kgp18831609	kgp18845056
PTPRA	chr20:2844824-3019315	chr20:2344824-3519315	chr20:2792824-2967315	kgp725112	rs2853218
PTPRJ	chr11:48002109-48192394	chr11:47502109-48692394	chr11:47958685-48148970	kgp11833163	kgp12755942
PTPRS	chr19:5158505-5340814	chr19:4658505-5840814	chr19:5109505-5291814	kgp6271833	kgp4407357
PTPRU	chr1:29563027-29653325	chr1:29063027-30153325	chr1:29435633-29525903	rs12068075	kgp9719744
RAB27A	chr15:55495163-55582013	chr15:54995163-56082013	chr15:53283091-53369293	kgp19829554	rs11631355
RAB3B	chr1:52373627-52456436	chr1:51873627-52956436	chr1:52157422-52228936	kgp22830492	rs10493168

FIG. 18S

RAB5A	chr3:19988571-20026667	chr3:19488571-20526667	chr3:19963762-20001647	rs1348231	kgp8738867
RAB8B	chr15:63481727-63559973	chr15:62981727-64059973	chr15:61268780-61347026	kgp20037308	rs17773778
RABAC1	chr19:42460832-42463528	chr19:41960832-42963528	chr19:47152675-47155311	kgp22776019	kgp2186225
RAC1	chr7:6414125-6443598	chr7:5914125-6943598	chr7:6380650-6410123	kgp13594313	kgp2338008
RACGAP1	chr12:50382944-50419307	chr12:49882944-50919307	chr12:48669211-48705574	rs12317050	kgp2525417
RAF1	chr3:12625099-12705700	chr3:12125099-13205700	chr3:12600099-12680700	kgp17997932	kgp3531880
RALB	chr2:120997639-121052286	chr2:120497639-121552286	chr2:120726883-120768756	rs17661862	kgp5177758
RASSF1	chr3:50367216-50378367	chr3:49867216-50878367	chr3:50342220-50353371	kgp8151957	kgp7341826
RBM23	chr14:23369853-23388396	chr14:22869853-23888396	chr14:22439693-22458236	rs3811239	kgp128686
RBMS	chr3:50126340-50156397	chr3:49626340-50656397	chr3:49952595-50112488	kgp22823256	rs375544
RCVRN	chr17:9801026-9808684	chr17:9301026-10308684	chr17:9741751-9749409	rs8082538	kgp2141837
REL	chr2:61108751-61150178	chr2:60608751-61650178	chr2:60962255-61003682	kgp8245960	kgp14294452
RELA	chr11:65421066-65430443	chr11:64921066-65930443	chr11:65177647-65186951	kgp6667058	kgp4478491
RELB	chr19:45504706-45541456	chr19:45004706-46041456	chr19:50196551-50233292	kgp9280266	kgp9663255
RFC5	chr12:118454505-118470042	chr12:117954505-118970042	chr12:116938892-116954422	rs11068526	kgp19024344
RGS10	chr10:121259338-121302222	chr10:120759338-121802222	chr10:121249328-121292212	kgp21619652	kgp5105745
RGS13	chr1:192605267-192629440	chr1:192105267-193129440	chr1:190871904-190896012	rs11806786	kgp1816960
RGS14	chr5:176784843-176799599	chr5:176284843-177299599	chr5:176717449-176732205	rs1000144	kgp11311419
RGS16	chr1:182567757-182573548	chr1:182067757-183073548	chr1:180834380-180840171	kgp15787070	kgp4798391
RGS18	chr1:192127591-192154945	chr1:191627591-192654945	chr1:190394214-190421568	rs1338034	kgp6525246
RGS19	chr20:62704534-62711324	chr20:62204534-63211324	chr20:62174978-62181768	rs1630157	kgp19264714
RGS4	chr1:163038395-163046592	chr1:162538395-163546592	chr1:161305019-161313216	kgp15623644	kgp15384575
RGS5	chr1:163112088-163291581	chr1:162612088-163791581	chr1:161378720-161439496	kgp15331781	kgp2554099
RGS7	chr1:240938816-241520478	chr1:240438816-242020478	chr1:239005439-239587101	rs16839692	kgp15345284
RHO	chr3:129247481-129254187	chr3:128747481-129754187	chr3:130730171-130736877	kgp12236862	kgp11280524

FIG. 18T

RHOH	chr4:40198526-40246281	chr4:39698526-40746281	chr4:39874921-39922676	rs3912392	rs17513557
RIC8A	chr11:208529-215110	chr11:1-715110	chr11:198529-205110	kgp9815230	rs11246286
RIC8B	chr12:107168398-107283094	chr12:106668398-107783094	chr12:105692528-105807224	kgp7665070	kgp2084662
RIOK3	chr18:21032786-21063099	chr18:20532786-21563099	chr18:19286784-19317097	kgp4053645	kgp16177785
RIPK1	chr6:3064121-3115421	chr6:2564121-3615421	chr6:3009120-3060420	rs17208835	kgp17120238
RIPK2	chr8:90769974-90803292	chr8:90269974-91303292	chr8:90839109-90872433	rs7813237	rs2214416
RIT1	chr1:155867600-155881177	chr1:155367600-156381177	chr1:154134224-154147801	kgp10974682	rs12022607
RIT2	chr18:40323191-40695657	chr18:39823191-41195657	chr18:38577189-38949655	rs6507465	kgp3440940
RNF10	chr12:120972131-121015397	chr12:120472131-121515397	chr12:119456514-119499780	kgp19140786	kgp19017203
RNF11	chr1:51701944-51739119	chr1:51201944-52239119	chr1:51474532-51511707	kgp4558813	kgp7772065
RPL10	chrX:153627678-153632038	chrX:153127678-154132038	chrX:153279911-153283874	rs2071127	rs4074307
RPL12	chr9:130209952-130213711	chr9:129709952-130713711	chr9:129249775-129253505	kgp11622632	rs3802355
RPL37A	chr2:217363519-217366188	chr2:216863519-217866188	chr2:217071764-217074433	kgp2247391	kgp7636371
RRAD	chr16:66955581-66959439	chr16:66455581-67459439	chr16:65513082-65516940	kgp16522328	kgp16305055
RTN4	chr2:55199326-55277734	chr2:54699326-55777734	chr2:55052830-55131238	kgp3749465	rs3748945
S100A8	chr1:153362507-153363664	chr1:152862507-153863664	chr1:151629131-151630173	rs6587709	kgp4686042
SAT1	chrX:23801274-23804327	chrX:23301274-24304327	chrX:23711224-23714248	kgp22758306	kgp22759648
SCN8A	chr12:51985019-52202299	chr12:51485019-52702299	chr12:50271286-50488566	rs7979705	kgp7295633
SDC1	chr2:20400557-20425194	chr2:19900557-20925194	chr2:20264038-20288675	kgp14253812	kgp8380770
SDC2	chr8:97505881-97624037	chr8:97005881-98124037	chr8:97575057-97693213	rs1421221	kgp1305908
SDC4	chr20:43953928-43977064	chr20:43453928-44477064	chr20:43387342-43410478	rs8116486	kgp19276986
SDCBP	chr8:59465727-59495419	chr8:58965727-59995419	chr8:59628281-59657973	rs954172	kgp20217944
SDCBP2	chr20:1290554-1373816	chr20:790554-1873816	chr20:1238620-1257838	kgp9852208	kgp10348674
SDPR	chr2:192699031-192712006	chr2:192199031-193212006	chr2:192407280-192420226	kgp6263901	kgp14266860
SELENBP1	chr1:151336779-151345164	chr1:150836779-151845164	chr1:149603403-149611788	rs12406660	rs6684312

FIG. 18U

SEMG1	chr20:43835637-43838414	chr20:43335637-44338414	chr20:43269087-43271823	rs6094023	rs6094202
SEMG2	chr20:43835637-43853099	chr20:43335637-44353099	chr20:43269087-43286513	rs6094023	rs6017667
SEPT4	chr17:56597610-56618179	chr17:56097610-57118179	chr17:53952614-53964410	kgp1250021	rs34058624
SETDB1	chr1:150898814-150937220	chr1:150398814-151437220	chr1:149165511-149203837	rs12759551	kgp1978717
SGOL1	chr3:20202084-20227724	chr3:19702084-20727724	chr3:20177088-20202687	kgp9539943	kgp18040639
SGOL2	chr2:201390864-201448818	chr2:200890864-201948818	chr2:201099186-201156750	kgp9074393	kgp14634946
SH2B3	chr12:111843751-111889427	chr12:111343751-112389427	chr12:110328134-110373810	kgp7682395	kgp10017505
SHC1	chr1:154934773-154946959	chr1:154434773-155446959	chr1:153201397-153213464	kgp11196367	kgp15752431
SIRT2	chr19:39369194-39390502	chr19:38869194-39890502	chr19:44061039-44082201	kgp21526327	kgp9511717
SLC1A1	chr9:4490426-4587469	chr9:3990426-5087469	chr9:4480443-4577469	kgp7074545	kgp9946842
SLC6A9	chr1:44457171-44497134	chr1:43957171-44997134	chr1:44234741-44269721	rs6687571	rs6672462
SLC9A3R1	chr17:72744762-72765499	chr17:72244762-73265499	chr17:70256378-70277089	kgp14032523	kgp14006779
SMAD3	chr15:67358194-67487533	chr15:66858194-67987533	chr15:65145248-65274587	kgp1676807	kgp19813377
SMAD5	chr5:135468535-135518422	chr5:134968535-136018422	chr5:135496434-135546321	kgp5717445	kgp8569495
SMN2	chr5:70220767-70248842	chr5:69720767-70748842	chr5:70256523-70284594	rs28591114	kgp22633148
SMPD3	chr16:68392229-68482409	chr16:67892229-68982409	chr16:66949730-67039905	kgp2756941	kgp16310484
SNAP23	chr15:42787503-42825259	chr15:42287503-43325259	chr15:40575126-40612548	rs1668586	kgp19741111
SNAP25	chr20:10199476-10288066	chr20:9699476-10788066	chr20:10147476-10236065	kgp4923784	kgp19370207
SNAP91	chr6:84262604-84419127	chr6:83762604-84919127	chr6:84319331-84475831	kgp17413387	kgp16958869
SNTA1	chr20:31995762-32031698	chr20:31495762-32531698	chr20:31459423-31495359	kgp994844	kgp22753335
SNURF	chr15:25200069-25244225	chr15:24700069-25744225	chr15:22751162-22795318	kgp20028287	kgp5644000
SOX4	chr6:21593971-21598849	chr6:21093971-22098849	chr6:21701950-21706828	kgp3609791	rs9466264
SPAG1	chr8:101170262-101254132	chr8:100670262-101754132	chr8:101239438-101323306	kgp5198147	kgp20550876
SPG7	chr16:89574804-89624174	chr16:89074804-90124174	chr16:88102305-88151675	kgp3688149	rs3809643
SPP1	chr4:88896801-88904563	chr4:88396801-89404563	chr4:89115825-89123587	kgp20744622	kgp20764098

FIG. 18V

SPTBN1	chr2:54683453-54898583	chr2:54183453-55398583	chr2:54536957-54752087	kgp14832324	kgp12300457
SQSTM1	chr5:179233387-179265077	chr5:178733387-179765077	chr5:179170503-179197683	kgp10101186	kgp2553327
SRGAP3	chr3:9022277-9291311	chr3:8522277-9791311	chr3:8997277-9266311	kgp5324812	kgp18088153
STARD13	chr13:33677271-34250932	chr13:33177271-34750932	chr13:32575306-33148932	kgp1217969	kgp9105015
STC2	chr5:172741725-172756506	chr5:172241725-173256506	chr5:172674331-172689112	kgp22378380	kgp10706002
STRN	chr2:37064840-37193615	chr2:36564840-37693615	chr2:36928975-37047119	kgp3533593	kgp9369923
STRN4	chr19:47222767-47250251	chr19:46722767-47750251	chr19:51914607-51941560	kgp21470253	rs4804031
STX4	chr16:31044415-31051485	chr16:30544415-31551485	chr16:30951916-30958986	kgp16259387	kgp7678241
STX5	chr11:62574331-62599563	chr11:62074331-63099563	chr11:62330944-62356136	kgp10937693	kgp568990
STXBP1	chr9:130374485-130454995	chr9:129874485-130954995	chr9:129414388-129494816	rs1768374	kgp4399986
STXBP3	chr1:109289284-109352148	chr1:108789284-109852148	chr1:109090807-109153671	rs6583070	rs17036360
SULT1E1	chr4:70706929-70725870	chr4:70206929-71225870	chr4:70741518-70760459	kgp22798798	kgp5241292
SUMO4	chr6:149721494-149722182	chr6:149221494-150222182	chr6:149763187-149763875	rs1871921	kgp17155476
SYT1	chr12:79257772-79845788	chr12:78757772-80345788	chr12:77781903-78367834	kgp11848377	kgp18913198
SYT9	chr11:7273180-7490276	chr11:6773180-7990276	chr11:7229756-7446846	rs7928685	kgp8567849
TANC1	chr2:159825145-160089170	chr2:159325145-160589170	chr2:159533391-159797416	rs4664962	kgp22743229
TANK	chr2:161993465-162092683	chr2:161493465-162592683	chr2:161701711-161800928	kgp7233899	rs1006427
TAOK2	chr16:29985187-30003582	chr16:29485187-30503582	chr16:29892722-29911082	rs257868	kgp2310172
TBCD	chr17:80709939-80901062	chr17:80209939-81401062	chr17:78303228-78494351	rs11653735	kgp10867492
TBCE	chr1:235530727-235612280	chr1:235030727-236112280	chr1:233597350-233678903	rs2673969	kgp15284682
TBK1	chr12:64845839-64895899	chr12:64345839-65395899	chr12:63132203-63182158	kgp18934034	kgp19122002
TCF1	chr5:134240810-134298336	chr5:133740810-134798336	chr5:134268709-134326235	kgp22161149	kgp4823163
TCF3	chr19:1609288-1652328	chr19:1109288-2152328	chr19:1560294-1603328	rs2302109	kgp2427498
TCF4	chr18:52889561-53303188	chr18:52389561-53803188	chr18:51040559-51454183	kgp10409423	rs1792746
TDGF1	chr3:46616044-46623952	chr3:46116044-47123952	chr3:46594216-46598956	kgp980076	kgp18003873

FIG. 18W

TEP1	chr14:20833825-20881579	chr14:20333825-21381579	chr14:19905765-19951420	rs1780944	rs12435821
TERT	chr5:1253286-1295162	chr5:753286-1795162	chr5:1306286-1348162	kgp22831882	rs4975846
TGFA	chr2:70674411-70781147	chr2:70174411-71281147	chr2:70527924-70634613	kgp14279885	kgp4236793
TIAM1	chr21:32490735-32931290	chr21:31990735-33431290	chr21:31412606-31853161	rs1702403	rs1892577
TM4SF1	chr3:149086804-149095568	chr3:148586804-149595568	chr3:150569494-150578258	kgp18120845	kgp17746361
TMSB4X	chrX:12993225-12995346	chrX:12493225-13495346	chrX:12903145-12905267	kgp22760889	kgp22772999
TNFRSF14	chr1:2487804-2495267	chr1:1987804-2995267	chr1:2479150-2486613	rs2803309	kgp11439882
TNFRSF1A	chr12:6437922-6451283	chr12:5937922-6951283	chr12:6308183-6321522	kgp6731378,rs4764519	kgp19158534
TNFRSF1B	chr1:12227059-12269277	chr1:11727059-12769277	chr1:12149646-12191864	kgp15495881	rs3010872
TNIP2	chr4:2743386-2758103	chr4:2243386-3258103	chr4:2713184-2727859	kgp20948263	kgp5432833
TNNI2	chr11:1860232-1862910	chr11:1360232-2362910	chr11:1817480-1819484	kgp11231095	rs800123
TNNI3	chr19:55663135-55669100	chr19:55163135-56169100	chr19:60354947-60360912	rs13382124	kgp21397937
TNNT2	chr1:201328141-201346805	chr1:200828141-201846805	chr1:199594764-199613428	rs12733378	rs10920269
TOMM20	chr1:235272657-235292256	chr1:234772657-235792256	chr1:233339282-233358754	kgp8358331	kgp15139309
TOP2A	chr17:38544772-38574202	chr17:38044772-39074202	chr17:35798321-35827695	kgp7375263	kgp10420460
TP53	chr17:7571719-7590863	chr17:7071719-8090863	chr17:7512444-7531588	kgp12029669	kgp11286494
TRADD	chr16:67188088-67193812	chr16:66688088-67693812	chr16:65745589-65751313	kgp16482196	kgp16510307,rs28521023
TRAF1	chr9:123664670-123691451	chr9:123164670-124191451	chr9:122704492-122731300	kgp6551598	rs306777
TRAF6	chr11:36505316-36531863	chr11:36005316-37031863	chr11:36467298-36488398	kgp12764289	rs333778
TRBV21-1	chr7:142344427-142344887	chr7:141844427-142844887	chr7:142025416-142025876	kgp2155197	kgp9570297
TRIM2	chr4:154074269-154260474	chr4:153574269-154760474	chr4:154293719-154479918	rs6849505	rs6843172
TRIM29	chr11:119981993-120008863	chr11:119481993-120508863	chr11:119487203-119514073	kgp12998914	rs7122702
TRIO	chr5:14143828-14509458	chr5:13643828-15009458	chr5:14196828-14562458	rs1445678	kgp8041369
TRPC1	chr3:142443265-142526729	chr3:141943265-143026729	chr3:143925955-144009419	rs9842771	rs7641069
TRPC3	chr4:122800182-122872909	chr4:122300182-123372909	chr4:123019881-123092359	kgp21231448	kgp5789583

FIG. 18X

TRPC4	chr13:38210772-38443939	chr13:37710772-38943939	chr13:37108794-37341935	kgp22792521	rs7338958
TRPV1	chr17:3468739-3512705	chr17:2968739-4012705	chr17:3415489-3459454	kgp8654960	rs9890881
TRPV4	chr12:110220891-110271212	chr12:109720891-110771212	chr12:108705276-108755595	kgp11365980	kgp19139284
TRPV6	chr7:142568959-142583490	chr7:142068959-143083490	chr7:142279081-142293599	kgp9647465	kgp2837315
TSC22D4	chr7:100064141-100076902	chr7:99564141-100576902	chr7:99902077-99914838	kgp5759639	kgp10599319
TSHR	chr14:81421868-81612646	chr14:80921868-82112646	chr14:80491621-80682399	kgp19546597	rs10134565
TSPAN6	chrX:99883794-99891794	chrX:99383794-100391794	chrX:99770450-99778450	kgp22794008	rs7059563
TTBK1	chr6:43211221-43255997	chr6:42711221-43755997	chr6:43319199-43363975	kgp17369454	kgp17498760
TTC1	chr5:159436179-159492550	chr5:158936179-159992550	chr5:159368757-159425128	kgp5018309	kgp22489460
TTK	chr6:80714321-80752244	chr6:80214321-81252244	chr6:80771077-80808958	kgp949561	kgp12311980
TTN	chr2:179390717-179672150	chr2:178890717-180172150	chr2:179098963-179380395	rs959775	rs6433773
TUB	chr11:8040790-8127654	chr11:7540790-8627654	chr11:8016755-8084228	kgp12365126	kgp1066384
TUBA8	chr22:18593452-18614498	chr22:18093452-19114498	chr22:16940685-16994498	rs1034470	kgp9877961
UBE2V2	chr8:48920994-48974454	chr8:48420994-49474454	chr8:49083547-49137007	kgp3293751	kgp20374954
ULK1	chr12:132379278-132407707	chr12:131879278-132907707	chr12:130945231-130973649	kgp7696078	kgp11815104
USP7	chr16:8985950-9057341	chr16:8485950-9557341	chr16:8893451-8964842	kgp79060	rs1035944
VAV1	chr19:6772721-6857371	chr19:6272721-7357371	chr19:6723721-6808371	kgp21410647	kgp21471951
VCL	chr10:75754950-75879914	chr10:75254950-76379914	chr10:75424956-75549920	rs7099640	kgp21840278
VDAC1	chr5:133307565-133340824	chr5:132807565-133840824	chr5:133335505-133368723	kgp22321002	kgp9499928
VIL2	chr6:159186773-159239340	chr6:158686773-159739340	chr6:159106761-159159328	rs9366083	kgp10633571
VIM	chr10:17270257-17279592	chr10:16770257-17779592	chr10:17310475-17319598	kgp1974218	kgp8572563
VTN	chr17:26694298-26697373	chr17:26194298-27197373	chr17:23718425-23721500	rs12602762	kgp2208161
WDR62	chr19:36545782-36596012	chr19:36045782-37096012	chr19:41237622-41287852	kgp5818871	kgp7464156
WDR91	chr7:134868589-134896316	chr7:134368589-135396316	chr7:134520524-134546811	kgp7394785	kgp4752834
WWC1	chr5:167719064-167899308	chr5:167219064-168399308	chr5:167651669-167829342	rs10454965	rs7724207

FIG. 18Y

XK	chrX:37545132-37591383	chrX:37045132-38091383	chrX:37430051-37476322	kgp22781551	kgp22821350
YWHAB	chr20:43514343-43537161	chr20:43014343-44037161	chr20:42947757-42970575	rs4364072	rs2247619
YWHAE	chr17:1247833-1303556	chr17:747833-1803556	chr17:1194592-1250267	rs4968122	kgp1552188
YWHAG	chr7:75956107-75988342	chr7:75456107-76488342	chr7:75794051-75826252	kgp13357645	kgp7952605
YWHAZ	chr8:101930803-101965623	chr8:101430803-102465623	chr8:102000089-102034745	rs4075553	kgp4135753
ZNF24	chr18:32912177-32924426	chr18:32412177-33424426	chr18:31166175-31178424	kgp5227729	kgp15931312

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/037596

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68; G01N 33/68 (2016.01)
CPC - C12Q 1/6883; C12Q 2600/106; C12Q 2600/156; G01N 33/5008; G01N 33/6803 (2016.08)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC - C12Q 1/68; G01N 33/68
CPC - C12Q 1/6883; C12Q 2600/106; C12Q 2600/156; G01N 33/5008; G01N 33/6803; G01N 2500/04; G01N 2500/10; G01N 2800/30; G01N 2800/302; G01N 2800/304

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 435/7.8; 436/501; 514/220 (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Patents, Google Scholar
Search terms used: autism copy number variants 22q11.2 deletion duplication (ACAT1 OR ACAT2 OR ACCN1 OR ACCN2 OR ACP1) fasoracetam (NS-105 OR NFC-1)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2014/0303243 A1 (THE CHILDREN'S HOSPITAL OF PHILADELPHIA) 09 October 2014 (09.10.2014) entire document	7-10, 29-34 --- 1-6, 11, 12
Y	US 2010/0216734 A1 (BARLOW et al) 26 August 2010 (26.08.2010) entire document	1-6, 11, 12
Y	GHELARDINI et al. "DM235 (Sunifiram): a Novel Nootropic with Potential as a Cognitive Enhancer," Naunyn-Schmiedeberg's Archives of Pharmacology, 01 June 2002 (01.06.2002), Vol. 365, Pgs. 419-26. entire document	12
P, X	US 2016/0032390 A1 (PHILADELPHIA CHILDREN HOSPITAL) 04 February 2016 (04.02.2016) entire document	1-12, 29-34

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 2016	16 SEP 2016
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/037596

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 13-28, 35-48
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.