

SUMMARY

The present inventors have performed genome wide association study on several large patient cohorts and have successfully identified a number of target genes harboring copy number variations associated with autism and ASD. Thus, in accordance with the present disclosure, kits are provided for performance of a method for detecting a propensity for developing autism or autistic spectrum disorder is provided. An exemplary kit comprises means for obtaining a sample from a patient and testing the sample for the presence or absence of at least one deletion containing CNV in a target polynucleotide, wherein if the CNV is present, the patient has an increased risk for developing autism and/or autistic spectrum disorder. In a preferred example, the deletion containing CNV is selected from the group of CNVs provided in Table II. In another example, the kit includes reagents for performing the step of detecting the presence of said CNV and further comprises specific reagents for performing a process selected from the group consisting of detection of specific hybridization, measurement of allele size, restriction fragment length polymorphism analysis, allele-specific hybridization analysis, single base primer extension reaction, and sequencing of an amplified polynucleotide.

In one aspect, the present disclosure refers to a method for diagnosing a propensity for the development of autism or autistic spectrum disorder (ASD) in a subject suffering from a 22q11.2 deletion syndrome, comprising: detecting in a nucleic acid in a biological sample obtained from said subject, at least one CNV in a group of target genes, wherein the target genes are mGluR network genes, wherein, if a CNV is present in at least one other mGluR network gene outside of the 22q 11.2 region, said subject has an increased risk for developing ASD.

In another aspect, the present disclosure refers to a kit, comprising:

- a) means for obtaining a sample from a subject;
- b) reagents suitable for identifying the presence or absence of at least one CNV in a group of target genes and a deletion in chromosome 22q11.2, wherein the target genes are mGluR network genes; and
- c) instructions for use; as a combined preparation for use in diagnosing autism or an autistic spectrum disorder (ASD) as disclosed herein.

In another example, the present disclosure provides a method for identifying agents which alter neuronal signaling and/or morphology. An exemplary method entails providing cells expressing at least one CNV listed in Table 2 and cells which express the cognate wild type sequences corresponding to the CNV containing

5 sequence, contacting both cell types with a test agent and analyzing whether the agent alters neuronal signaling and/or morphology of cells comprising the CNV relative to those which lack the genetic alteration, thereby identifying agents which alter neuronal signaling and morphology in CNV containing cells. In cases where the CNV is a deletion, vectors encoding such CNVs contain nucleic acids flanking the
10 affected region of deletion of a suitable length, such that cloning and transformation of cells with the CNV containing nucleic acid is possible.

Also provided is a method of treating autism or ASD in a human subject determined to have at least copy number variation (CNV) associated with an autistic or ASD phenotype, said at least one CNV being selected from the group consisting of
15 CNVs set out in Table 2, the method comprising administering to said human subject a therapeutically effective amount of at least one agent which is known to be

efficacious in the signaling pathway adversely affected by the presence of said CNV. In a preferred example, patients are tested for the presence or absence of at least one CNV containing gene is selected from the group consisting of ATP10A, GABRA5, GABRB3, GABRG3, GGTL2, HBII-52-45, HBII-52-46, IPW, LOC648691, LOC96610, MAGEL2, MIR650, MKRN3, NCRNA00221, NDN, OCA2, OR4S2, PAR-SN, PAR1, PAR5, POM121L1P, PRAME, SNORD107, SNORD108, SNORD109A, SNORD109B, SNORD115-11, SNORD115-29, SNORD115-36, SNORD115-43, SNORD115-44, SNORD115-48, SNORD64, SNRPN, SNURF, UBE3A, ZNF280A, ZNF280B. In yet another example, the CNV is determined to reside in a gene important for GABA signaling and the agent is listed in Table 3 or Table 4. In a particularly preferred example, the CNV alters GABA signaling and the agent is topiramide.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: The design of the present study is shown. 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.)

Figure 2: A graph showing the 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.

Figure 3: A schematic of a first-degree interactome of the GABAR-A family highlighting copy number defects enriched in cases (red) vs controls (blue).

Figure 4: 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

What is claimed is:

1. A method for diagnosing a propensity for the development of autism or autistic spectrum disorder (ASD) in a subject suffering from a 22q11.2 deletion syndrome, comprising:

detecting in a nucleic acid in a biological sample obtained from said subject, at least one CNV in a group of target genes, wherein the target genes are mGluR network genes, wherein, if a CNV is present in at least one other mGluR network gene outside of the 22q 11.2 region, said subject has an increased risk for developing ASD.

2. The method of claim 1, wherein the mGluR network genes belong to the GRM family of genes.

3. The method of any one of the preceding claims, wherein the at least one CNV is detected in a target gene selected from GRM1, GRM3, GRM5, GRM7 and GRM8.

4. The method of any of the preceding claims, wherein the ASD is syndromic ASD.

5. The method of any one of the preceding claims, further comprising a step of isolating said nucleic acids prior to detection.

6. The method of any one of the preceding claims, further comprising amplifying said group of target genes prior to detection.

7. The method of any one of the preceding claims, wherein said target genes are analyzed by performing a process selected from the group consisting of detection of specific hybridization, measurement of allele size, restriction fragment length polymorphism analysis, allele-specific hybridization analysis, single base primer extension reaction, and sequencing.

8. The method of any one of the preceding claims, wherein said target genes are

analyzed by performing a process selected from the group consisting of Southern and Northern blotting, direct sequencing and PCR amplification followed by hybridization of amplified products to a microarray comprising reference nucleic acid sequences.

9. The method of any one of the preceding claims, wherein the biological sample is a body fluid sample such as a blood sample, a urine sample, a serum sample or a gastric lavage sample, or a cell sample such as a sample of brain cells, of white cells or of mononuclear cells.

10. A kit, comprising:

a) means for obtaining a sample from a subject;

b) reagents suitable for identifying the presence or absence of at least one CNV in a group of target genes and a deletion in chromosome 22q11.2, wherein the target genes are mGluR network genes; and

c) instructions for use;

as a combined preparation for use in diagnosing autism or an autistic spectrum disorder (ASD) as claimed in claim 1.

11. The kit of claim 10, wherein the ASD is syndromic ASD.

12. The kit of claim 10, wherein the mGluR network genes are selected from GRM1, GRM3, GRM5, GRM7 and GRM8.