

SUMMARY OF THE INVENTION

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 invention, 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 embodiment, the deletion containing CNV is selected from the group of CNVs provided in Table II. In another embodiment, 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, there is provided a method for diagnosing a propensity for the development of autism or autistic spectrum disorder (ASD), comprising:

- a) obtaining a biological sample comprising nucleic acids from a subject; and
- b) detecting in said nucleic acid, at least one CNV in a group of target genes, wherein the target genes are mGluR network genes, wherein if said CNV is present, said subject has an increased risk for developing autism and/or ASD.

In one aspect, there is provided a kit for diagnosing autism or an autistic spectrum disorder (ASD), 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, wherein the target genes are mGluR network genes; and
- c) instructions for use.

In one aspect, there is provided an agent for use in a method of treating ASD in a human subject determined to have at least copy number variation (CNV) associated with an ASD phenotype, said at least one CNV being in a group of target genes, wherein the target genes are mGluR network genes, wherein said agent is known to be efficacious in the signaling pathway adversely affected by the presence of said CNV, wherein said signaling pathway is the glutaminergic signaling pathway, the method comprising administering to said human subject a therapeutically effective amount of said agent.

In one aspect, there is provided a kit for use in a method for detecting a propensity for developing autism or autistic spectrum disorder, the kit comprising:

a) providing a plurality of nucleic acids comprising CNVs present in autistic or ASD patients identified using genome wide association studies of large patient cohorts, said CNVs being listed in Table II;

a) means for obtaining a sample from a patient and isolating nucleic acid therefrom;

b) reagents suitable for identifying the presence or absence of at least one deletion containing CNV in a target polynucleotide and means for creating a report from said identifying.

In one aspect, there is provided a method for identifying agents which alter neuronal signaling and/or morphology, comprising:

a) providing cells expressing a nucleic acid sequence comprising at least one CNV as described herein;

b) providing cells which express the cognate wild type sequences corresponding to the CNV of step a);

c) contacting the cells of steps a) and b) with a test agent and

d) analyzing whether said agent alters neuronal signaling and/or morphology of cells of step a) relative to those of step b), thereby identifying agents which alter neuronal signaling and morphology.

In one aspect, there is provided the use of 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 the manufacture of a medicament for 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 CNVs set out in Table 2.

In one aspect, there is provided a kit for detecting a propensity for developing autism or autistic spectrum disorder, the kit comprising:

a) reagents suitable for obtaining a sample from a patient and isolating nucleic acid therefrom;

5 b) reagents suitable for amplifying the nucleic acid of step a);

 c) a microarray comprising nucleic acids of known sequence with the amplified nucleic acids of step b), thereby identifying the presence or absence of at least one deletion containing CNV in a target polynucleotide, said CNV being listed in Table II; and means for creating a report indicating that if said CNV is present,
10 said patient has an increased risk for developing autism and/or autistic spectrum disorder.

In another aspect, the present invention 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
15 express the cognate wild type sequences corresponding to the CNV containing 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
20 CNV is a deletion, vectors encoding such CNVs contain nucleic acids flanking the 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
25 or ASD phenotype, said at least one CNV being selected from the group consisting of 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

What is claimed is:

1. A method for diagnosing a propensity for the development of autism or autistic spectrum disorder (ASD), comprising:
 - a) obtaining a biological sample comprising nucleic acids from a subject; and
 - b) detecting in said nucleic acid, at least one CNV in a group of target genes, wherein the target genes are mGluR network genes,wherein if said CNV is present, said subject has an increased risk for developing autism and/or 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.
2. The method of any of the preceding claims, wherein the ASD is syndromic ASD.
3. The method of any of the preceding claims, wherein the subject suffers from a 22q11.2 deletion syndrome and wherein, if a CNV is present in at least one other mGluR network gene outside of the 22q11.2 region, said subject has an increased risk for developing ASD.
6. The method of any one of the preceding claims, further comprising a step of isolating said nucleic acids prior to detection.
7. The method of any one of the preceding claims, further comprising amplifying said group of target genes prior to detection.
8. The method of any one of the preceding claims, wherein step b) comprises analyzing said target genes 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.
9. The method of any one of the preceding claims, wherein step b) comprises analyzing said target genes 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.

10. 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.

11. A kit for diagnosing autism or an autistic spectrum disorder (ASD), 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, wherein the target genes are mGluR network genes; and
- c) instructions for use.

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

13. The kit of claim 11, wherein the mGluR network genes are selected from GRM1, GRM3, GRM5, GRM7 and GRM8.

14. An agent for use in a method of treating ASD in a human subject determined to have at least copy number variation (CNV) associated with an ASD phenotype, said at least one CNV being in a group of target genes, wherein the target genes are mGluR network genes, wherein said agent is known to be efficacious in the signaling pathway adversely affected by the presence of said CNV, wherein said signaling pathway is the glutaminergic signaling pathway, the method comprising administering to said human subject a therapeutically effective amount of said agent.

15. The agent for the use of claim 14, wherein the group of target genes is as defined in any one of claims 1 to 10.