**Condition Description**

Mutations in the \( \text{NLGN3} \) (Xq13) and \( \text{NLGN4X} \) (Xq22.33 – also referred to as \( \text{NLGN4} \)) genes have been found in less than 1% of individuals with autism spectrum disorder (ASD). The clinical phenotype of affected individuals varies widely and can include autism of variable severity, X-linked intellectual disability without autism, Asperger syndrome, and pervasive developmental delay not otherwise specified (PDD-NOS). Onset may be gradual or abrupt and regression of milestones may occur. There are usually no dysmorphic features present. Carrier females are often unaffected, but neuropsychiatric disorders have been reported in a female carrying a deletion of exons 4-6 of \( \text{NLGN4X} \).

For patients with suspected \( \text{NLGN4X} \)-Related X-Linked Susceptibility to Autism Spectrum Disorder, sequence analysis is recommended as the first step in mutation identification. For patients in whom mutations are not identified by full gene sequencing, deletion/duplication analysis is appropriate.

This testing is for mutation in the \( \text{NLGN4X} \) gene only.

References:
- GeneReviews
- OMIM #300427: \( \text{NLGN4X} \) gene
- OMIM #300495: X-Linked Autism Disorder
- OMIM #300497: X-Linked Asperger Syndrome

**Genes**

\( \text{NLGN4X} \)

**Indications**

This test is indicated for:
- Confirmation of a clinical diagnosis of \( \text{NLGN4X} \)-Related X-Linked Susceptibility to Autism Spectrum Disorder.
- Carrier testing in adults with a family history of \( \text{NLGN4X} \)-Related X-Linked Susceptibility to Autism Spectrum Disorder.

**Methodology**

PCR amplification of 5 exons contained in the \( \text{NLGN4X} \) gene is performed on the patient’s genomic DNA. Direct sequencing of amplification products is performed in both forward and reverse directions, using automated fluorescence dideoxy sequencing methods. The patient's gene sequences are then compared to a normal reference sequence. Sequence variations are classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements, and does not detect large deletions.

**Detection**

Clinical Sensitivity: Mutations in the \( \text{NLGN3} \) and \( \text{NLGN4X} \) genes have been found in less than 1% of individuals with ASD. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient’s clinical and/or biochemical phenotype.

Analytical Sensitivity: ~99%

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml
Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

Related Tests

- Deletion/duplication analysis of the NLGN4X gene by CGH array is available for those individuals in whom sequence analysis is negative.
- Custom diagnostic mutation analysis (KM) is available to family members if mutations are identified by targeted mutation testing or sequencing analysis.
- Prenatal testing is available only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.
- X-Linked Intellectual Disability panels are available for 30, 60, and 90 genes.
- Sequencing and deletion/duplication analysis are also available for the NLGN3 gene.