XLMR 94: GRIA3 Gene Sequencing

Condition Description

Mutations in the GRIA3 gene (Xq25-q26) (OMIM #305915) have been associated with syndromic X-linked intellectual disability (XLID) (OMIM #300699). In a study of 400 males with XLID who had normal karyotype and negative fragile X testing, missense GRIA3 mutations were found in four males and a 0.4 Mb deletion of the GRIA3 gene was found in 3 males. Phenotypic features common in the males with GRIA3 mutations included moderate intellectual disability, poor muscle bulk, muscle weakness, asthenic body habitus, and hyporeflexia. Other features included seizures, macrocephaly, myoclonic jerks, and autistic behavior.

A partial duplication of the GRIA3 gene was also reported in a family with X-linked intellectual disability. Two affected brothers had delayed psychomotor development with severely delayed and poor language acquisition. One of the brothers also had dysmorphic features and fits of anger. The mother of the affected individuals displayed facial hypotonia, language and learning disabilities and moderately short upper lip. An apparently balanced t(X;12)(q24;q15) translocation that disrupted the GRIA3 gene was identified in a woman with intellectual disability, bipolar disorder, seizures, and cyclic vomiting. A partial tandem duplication of exons 1-6 of the GRIA3 gene was found in a boy with nonsyndromic intellectual disability. His carrier mother was unaffected.

For patients with suspected GRIA3-Related- XLMR, 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.

References:
- OMIM# 305915: GRIA3 gene
- OMIM# 300699: XLMR 94

Genes

GRIA3

Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of XLMR 94.
- Carrier testing in adults with a family history of XLMR 94.

Methodology

PCR amplification of 15 exons contained in the GRIA3 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: In a study of 400 males with XLID who had normal karyotype and negative fragile X testing, missense GRIA3 mutations were found in four males and a 0.4 Mb deletion of the GRIA3 gene was found in 3 males.

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) or ACD (yellow 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 GRIA3 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.