Condition Description

Mutations in the CASK gene (Xp11.4) have been reported to cause X-linked intellectual disability and brain malformation. The original patients characterized had severe intellectual disability, brainstem and cerebellar hypoplasia, and microcephaly. Some of these patients were female, indicating that females may be as severely affected as males. Other symptoms included hearing loss, optic atrophy, and dysmorphic features.

Later studies identified individuals with CASK mutations who had various combinations of milder intellectual disability, microcephaly, congenital nystagmus, and dysmorphic facial features. Some individuals had nonsyndromic intellectual disability. Carrier females were variably affected, with some phenotypically normal.

An Italian family was identified in which a CASK mutation caused a form of FG syndrome (FG syndrome-4). Affected males displayed severe intellectual disability, aggressive and hyperactive behavior, macrocephaly, dysmorphic features, deafness, and severe constipation. Carrier females had mild intellectual disability and mild dysmorphic features.

In a study of 358 probable XLID families, four male probands were found to have CASK mutations. In a study of 45 probands with intellectual disability and either nystagmus or microcephaly, two individuals were found to have CASK mutation; both had nystagmus and intellectual disability.

The CASK gene codes for the calcium/calmodulin-dependent serine protein kinase. The CASK protein interacts with multiple other proteins and is thought to be involved in synaptic interaction, protein trafficking, and regulation of neural development.

For patients with suspected CASK-Related XLID, 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 #300749: Mental Retardation and Microcephaly with Pontine and Cerebellar Hypoplasia.

Genes

CASK

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of CASK-related XLID in individuals who have tested negative for sequence analysis
- Carrier testing in adult females with a family history of CASK-related XLID in whom sequence analysis was negative.

Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

Please note that a "backbone" of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

Detection

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

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.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample, if appropriate. Contact the laboratory if further information is needed.

Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Sequencing analysis of the CASK gene is available and is required before deletion/duplication analysis.
- A next-generation sequence analysis panel of 90+ XLID genes is available.
- A CGH array-based test for deletion/duplication analysis of 90+ XLID genes is available.
- Prenatal testing is available to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.