CASK-related XLID: CASK Gene Sequencing

**Test Code:** SCASK  
**Turnaround time:** 4 weeks  
**CPT Codes:** 81479 x1

## 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
- Carrier testing in adult females with a family history of CASK-related XLID

## Methodology

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

## Detection

Clinical Sensitivity: Unknown. 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 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.

**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 EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Deletion/duplication analysis of the CASK gene by CGH array is available for those individuals in whom sequence analysis is negative (VK).
- 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.
- 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 to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.