Condition Description

Mutations in the *OPHN1* gene (Xq12) are associated with X-linked mental retardation with subtle facial dysmorphism and cerebellar anomalies, including hypoplasia of the vermis, expansion of the cisterna magna, and retrocerebellar cysts. Phenotypic features can include neonatal hypotonia with motor delay but no obvious ataxia, marked strabismus, early-onset complex partial seizures, and moderate to severe intellectual disability. Other affected individuals with *OPHN1* mutations are reported to have moderate to severe intellectual disability associated with enlargement of the lateral ventricles and cerebellar hypoplasia, seizures, ataxia, strabismus, and hypogenitalism with cryptorchidism, hypoplastic scrotum, and microphallus.

Facial features associated with *OPHN1* mutations include mild facial dysmorphism with long face, prominent forehead, deep-set eyes, marked infraorbital creases, strabismus, short or upturned philtrum, and large ears. Obligate female carriers have been reported to show subtle facial changes and/or reduced cerebellar size in some cases.

In one study, four different novel mutations were identified in the *OPHN1* gene: two mutations were found in a group of 17 unrelated males with mental retardation and known cerebellar anomalies (12%) and two mutations were found in a group of 196 unrelated males with X-linked intellectual disability without previous brain imaging studies (1%). Retrospective imaging studies, when possible, detected cerebellar hypoplasia in the latter patients.

Both point mutations and deletions have been reported in the *OPHN1* gene.

For patients with suspected XLMR with cerebellar hypoplasia and distinctive facial appearance, 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.

Click here for the OMIM summary on this condition.

Genes

*OPHN1*

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of XLMR with cerebellar hypoplasia and distinctive facial appearance
- Carrier testing in adult females with a family history of XLMR with cerebellar hypoplasia and distinctive facial appearance

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) 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**

- Deletion/duplication analysis of the *OPHN1* gene by CGH array is available for those individuals in whom sequence analysis is negative (YS).
- A CGH array-based test for deletion/duplication analysis of 64 different X-linked intellectual disability genes is available (OL).
- 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 adult females who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.