ZDHHC9-related XLMR: ZDHHC9 Gene Sequencing

Test Code: SZDH9
Turnaround time: 4 weeks
CPT Codes: 81479 x1

Condition Description

In a study of 250 families with at least two males with X-linked mental retardation and no known molecular diagnosis, Raymond et al. found four families with four different mutations in highly conserved residues of the zinc finger DHHC-type containing 9 gene (ZDHHC9 - Xq26.1). The presenting phenotype in the families was moderate mental retardation (MR) in two or more males. In three of the families, the MR phenotype was associated with a Marfanoid habitus, although the affected individuals did not meet the Ghent criteria for Marfan syndrome.

In one family, a mutation was found in two male siblings and their mother. The siblings were referred at ages 6 and 4 years for developmental delay and moderate learning disability. In the older boy, developmental delay was noted at age 8 months because he was floppy and not sitting. He was not walking at age 18 months and speech and language were delayed. The younger boy had similar clinical features but developmental progression was slower.

In the second family, a mutation was again found in two male siblings and their mother. The mutation was not found in an unaffected male sibling. The affected males presented with developmental delay. The older boy walked at 3.5 years and developed limited speech at 4.5 years. A diagnosis of Marfan syndrome was considered at age 13 years. The younger boy had similar features as the older boy, and developed schizophrenia as an adult. The unaffected male sibling is intellectually normal and does not have Marfanoid features.

In the third family, a mutation was found in two male siblings and their mother. The boys presented with developmental delay, mental retardation, and Marfanoid features. The older brother sat at age 13 months, walked at age 3 years, and talked at age 4 years. He attended a school for children with special needs and lives in a supervised home. The younger brother has similar features.

In the fourth family, a mutation was found in the male proband, his mother, the mother's brother, and two of the mother's maternal male cousins. The proband presented with Marfanoid features and delayed sitting at 12 months of age. The mother reported that her affected brother had a similar appearance and significant learning difficulties.

The ZDHHC9 gene is a palmitoyltransferase that catalyzes posttranslational modification of the HRAS and NRAS proteins. The degree of palmitoylation determines the temporal and spatial locations of the proteins in the plasma membrane and Golgi complex. Mutations in this gene are believed to later the concentrations and cellular distribution of its target proteins and thereby cause disease.

References:

Genes

ZDHHC9

Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of ZDHHC9-related XLMR
- Carrier testing in adult females with a family history of ZDHHC9-related XLMR

Methodology

PCR amplification of 9 exons contained in the ZDHHC9 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: Unknown. In a study of 250 families with at least two males with X-linked mental retardation and no known molecular diagnosis, Raymond et al. found four families with four different mutations in the ZDHHC9 gene. 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 ZDHHC9 gene by CGH array is available for those individuals in whom sequence analysis is negative.
- X-Linked Intellectual Disability panels are available for 30, 60, and 90+ genes.
- Custom diagnostic mutation analysis (KIM) 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.