ZDHHC9-related XLMR: ZDHHC9 Gene Deletion/Duplication

Test Code: DZDH9  
Turnaround time: 2 weeks  
CPT Codes: 81228 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 concentrate and cellular distribution of its target proteins and thereby cause disease.

For patients with suspected ZDHHC9-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:

Genes

ZDHHC9

Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of ZDHHC9-related XLMR in an individual in whom sequence analysis is negative
- Carrier testing in adult females with a family history of ZDHHC9-related XLMR in whom sequence analysis is 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 ZDHHC9 gene is available and is required before deletion/duplication analysis.
- X-Linked Intellectual Disability panels are available for 30, 60, and 90+ genes.
- 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.