XLMR 59: AP1S2 Gene Deletion/Duplication

Test Code: DA1S2  
Turnaround time: 2 weeks  
CPT Codes: 81228 x1  

Condition Description

In 1972, Fried reported a Scottish pedigree with X-linked mental retardation, in which some affected members had hydrocephalus. The family included six males with variable mental retardation. Two affected individuals had hydrocephalus, one of which was suspected to be the result of stenosis of the aqueduct of Sylvius. All had delayed motor development and difficulty walking as adults.

In 1999, Carpenter et al. described a four-generation family with nonspecific mental retardation, designated MRX59. The five affected males, ranging in age from 2 to 52 years, had a normal facial appearance and mild to severe mental retardation. Two of the affected males displayed aggressive behavior.

In 2003, Turner et al. described an X-linked recessive form of mental retardation in a family in which 10 males in four generations were affected. The main manifestations were severe to profound intellectual disability, muscular hypotonia in childhood, delayed walking, and in the adults, difficult and aggressive behavior. There was moderate reduction both in the occipitofrontal circumference and in height, and a similar facial appearance, triangular in shape with high forehead, prominent ears, and a small pointed chin.

In 2007, Saillour et al. reported a French family in which eight males spanning four generations had mental retardation. Four living patients were in specialized institutions. Other features included hypotonia, delayed motor development, and poor language skills. Among five patients who were examined, two had basal ganglia calcifications, and two had congenital hydrocephalus with stenosis of the aqueduct of Sylvius.

In a systematic sequencing screen of the coding exons of the X chromosome in 250 families with X-linked mental retardation (XLMR), Tarpey et al. (2006) identified two nonsense mutations and one consensus splice site mutation in the AP1S2 gene on Xp22 in three families, including the families reported by Carpenter et al. and Turner et al. Affected individuals in these families, designated MRX59, showed mild to profound mental retardation. Other features included hypotonia early in life and delay in walking. Saillour et al. (2007) later identified two pathogenic mutations in the AP1S2 gene in affected members of two unrelated families with X-linked mental retardation, including the family reported by Fried in 1972. In 2009, Tarpey et al. sequenced the coding exons of the X chromosome in 208 families with X-linked mental retardation. They identified three mutations in the AP1S2 gene in three families.

For patients with suspected XLMR 59, 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

AP1S2

Indications

This test is indicated for:
- Confirmation of a clinical diagnosis of XLMR 59 in individuals who have tested negative for sequence analysis
- Carrier testing in adults with a family history of XLMR 59 who have tested negative for sequence analysis

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**

- Sequence analysis of the AP1A2 gene is available and is required before deletion/duplication analysis.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.