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
- Carrier testing in adult females with a family history of XLMR 59

**Methodology**

PCR amplification of 4 exons contained in the AP1S2 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. 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 EGL Genetics, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Deletion/duplication analysis of the \textit{AP1S2} gene by CGH array is available for those individuals in whom sequence analysis is negative.
- A CGH array-based test for deletion/duplication analysis of 64 different X-linked intellectual disability 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 adult females who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.