

XLMR with Epilepsy: *ATP6AP2* Gene Sequencing

Test Code: SATP2

Turnaround time: 6 weeks

CPT Codes: 81479 x1

Condition Description

Intellectual disability (ID) is a non-progressive cognitive impairment affecting 1-3% of the Western population. It is estimated that up to 50% of moderate-severe cases have genetic causes and approximately 10% are due to X-linked intellectual disability disorders (XLID). XLID can be syndromic or nonsyndromic and is observed in all ethnic groups. More than 100 XLID syndromes have been described in the literature to date. Fragile X is the most common XLID syndrome (~1 in 4000 males) while others can be quite rare with only a few patients reported in the literature. Males can have moderate to severe intellectual disability depending on the syndrome, and carrier females can also be affected, but typically have milder clinical symptoms.

Hedera et al. evaluated a family with intellectual disability and epilepsy that was inherited as an X-linked trait. Affected individuals had mild to moderate intellectual disability and tonic-clonic seizures. The age of onset for seizures varied from four to 14 months of age and the frequency ranged from 20 seizures per day to several seizures per month. There was no history of psychomotor regression once the seizures began. In addition to intellectual disability and seizures, the affected family members had developmental delay, speech delay, normal hearing, and no dysmorphic features.

A silent mutation (p.D107) in the *ATP6AP2* (Xp11.4) gene was found to segregate in this family. This change was not identified in 1200 X-chromosomes of healthy controls.

For patients with suspected XLMR with epilepsy, 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:

- Hedera et al. (2002) *Ann Neurol* 51:45-50.
- Ramser et al. (2005) *Hum Mol Gen* 14:1019-1027.
- [OMIM #300556](#): *ATP6AP2* gene
- [OMIM #300423](#): XLMR with Epilepsy

Genes

[ATP6AP2](#)

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of XLMR with epilepsy.
- Carrier testing in adults with a family history of XLMR with epilepsy.

Methodology

PCR amplification of 9 exons contained in the *ATP6AP2* 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 clinical and/or biochemical phenotype.

Analytical Sensitivity: ~99%

Specimen Requirements

Submit only 1 of the following specimen types

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection Kit

Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:

Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: DNA, Isolated**Specimen Requirements:**

Microtainer

8µg

Isolation using the Perkin Elmer™ Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:

Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Whole Blood (EDTA)**Specimen Requirements:**

EDTA (Purple Top)

Infants and Young Children (2 years of age to 10 years old: 3-5 ml

Older Children & Adults: 5-10 ml

Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:

Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Related Tests

- Deletion/duplication analysis of the *ATP6AP2* gene by CGH array is available for those individuals in whom sequence analysis is negative.
- 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 only for known familial mutations to individuals who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.
- X-Linked Intellectual Disability panels are available for 30, 60, and 90 genes.