

X-linked Hydrocephalus with Aqueductal Stenosis: *L1CAM* Gene Sequencing

Test Code: SL1CA

Turnaround time: 6 weeks

CPT Codes: 81407 x1

Condition Description

Mutation of the *L1CAM* gene (Xq28) is characterized by hydrocephalus, mental retardation, spasticity of the legs, and adducted thumbs. The phenotypic spectrum of *L1CAM* mutations includes X-linked hydrocephalus with stenosis of the aqueduct of Sylvius (HSAS), MASA syndrome (mental retardation, aphasia (delayed speech), spastic paraplegia (shuffling gait), adducted thumbs), SPG1 (X-linked complicated hereditary spastic paraplegia type 1), and X-linked complicated corpus callosum agenesis. The group of conditions as a whole can be referred to as L1 syndrome.

Hydrocephalus in L1 syndrome may be present prenatally and result in stillbirth or death in early infancy. Males with HSAS are born with severe hydrocephalus and adducted thumbs. Seizures may occur. In less severely affected males, hydrocephalus may be subclinically present and documented only because of developmental delay. Mild-to-moderate ventricular enlargement is compatible with long survival. Mental retardation is usually severe and is independent of shunting procedures in individuals with severe hydrocephalus. In MASA syndrome, mental retardation ranges from mild (IQ of 50-70) to moderate (IQ of 30-50). The degree of intellectual impairment does not necessarily correlate with head size or severity of hydrocephalus; males with severe mental retardation and a normal head circumference have been reported. All phenotypes can be observed in affected individuals in the same family. Females may manifest minor features such as adducted thumbs and/or subnormal intelligence. Rarely do females manifest the complete L1 syndrome phenotype.

X-linked hydrocephalus with stenosis of the aqueduct of Sylvius is the most common genetic form of congenital hydrocephalus, with a prevalence of approximately one in 30,000. This accounts for approximately 5%-10% of males with nonsyndromic congenital hydrocephalus.

While mutation detection rates are unknown, point mutations, partial gene deletions, and partial gene duplications have all been reported. Although uncommon, *de novo* disease-causing mutations have been reported.

For patients with a suspected *L1CAM*-related disorder, 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.

[Click here](#) for the GeneTests summary on this condition.

Genes

[L1CAM](#)

Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of L1 syndrome
- Carrier testing in adult females with a family history of L1 syndrome

Methodology

Next Generation Sequencing: In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

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

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.

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: 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.

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 *L1CAM* 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 109 different X-linked intellectual disability genes is available.
- [Custom diagnostic mutation analysis](#) 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.