Prenatal Testing for L1CAM Gene Mutations:
X-Linked Hydrocephalus and L1CAM-Related Disorders

Also known as: L1 Syndrome, L1 Cell Adhesion Molecule; MASA Syndrome, CRASH Syndrome

Mendelian Inheritance in Man Number: 307000 (X-linked Hydrocephalus / Congenital stenosis of the aqueduct of Sylvius); 303350 (MASA syndrome)

Clinical Features in Newborns and Children:
The L1CAM-related disorders are X-linked neurologic diseases caused by mutations in the L1CAM gene. Congenital hydrocephalus causing macrocephaly due to stenosis of the aqueduct of Sylvius may occur as an isolated finding, but it is frequently associated with other features, including hypoplastic or flexed, adducted thumbs, varying degrees of mental retardation, and spastic paraplegia, particularly of the lower extremities. MASA syndrome is the diagnosis typically given to individuals who exhibit Mental retardation, Aphasia, Shuffling gait, and Adducted thumbs. CRASH syndrome includes Corpus callosum agenesis/hypoplasia, Retardation, Adducted thumbs, Spastic paraplegia, and Hydrocephalus. There can be significant phenotypic variability within families, with some males severely affected and diagnosed prenatally, while others may have no macrocephaly and long survival. Approximately 5% of female harboring a L1CAM mutation exhibit clinical symptoms.

Prenatal Ultrasound Findings:
L1CAM genetic testing should be considered in male fetuses with hydrocephalus, particularly in the presence of hypoplastic or adducted thumbs and/or an X-linked family history. L1CAM genetic testing could also be considered in female fetuses with hydrocephalus due to aqueductal stenosis (Wilson et al., 2009). Ultrasound examination may be normal in affected fetuses; therefore, pregnancies at risk to inherit a specific known familial mutation can be offered targeted molecular testing regardless of ultrasound findings, if desired.

Inheritance Pattern: X-linked recessive

Indications for Fetal Testing:
- Full sequencing for fetuses with prenatal ultrasound findings suggestive of X-linked hydrocephalus/L1CAM-related disorder.
- Mutation-specific testing for fetuses with a family history of a known L1CAM mutation

Test Method:
Using genomic DNA, analysis is performed by bi-directional sequencing of the coding region (exons 1-28) and the flanking splice sites of the L1CAM gene. Because sequencing cannot detect large deletions in females, concurrent targeted array CGH analysis with exon-level resolution (ExonArrayDx) also is performed on female fetuses to evaluate for a deletion of one or more exons of L1CAM gene. For known familial mutations, the relevant portion of the L1CAM gene will be analyzed in duplicate.

Additionally, genotype analysis of maternal and fetal DNA for several polymorphic markers to test for maternal cell contamination will be performed. Therefore, in all prenatal cases a maternal sample should accompany the fetal sample.

Test Sensitivity:
Approximately 74-90% of male patients with hydrocephalus, a positive family history and more than one typical associated finding of an L1CAM-related disorder have an identifiable mutation in the L1CAM gene by sequencing. L1CAM mutations are identified in 15%-25% of males with hydrocephalus, a negative family history, and no other L1CAM associated findings. Large deletions of an exon or more are not detectable by sequence analysis in females; however, the addition of ExonArrayDx deletion/duplication testing is expected to make the sensitivity in females comparable to the sensitivity in males. The sensitivity of L1CAM analysis in prenatal cases ascertained based on fetal ultrasound abnormalities is currently unknown.

Mutation Spectrum:
Mutations occur throughout the coding sequence of the L1CAM gene. All types of mutations have been observed, including nonsense, missense, splice site, deletions and insertions. There is some evidence of genotype/phenotype correlation in this group of disorders, as mutations resulting in premature protein truncation are typically associated with a severe phenotype, while missense mutations affecting the cytoplasmic domain are associated with a milder phenotype. Missense mutations in the extracellular L1 protein domains cause either a severe or milder phenotype. However, there can be striking phenotypic variability even within members of the same family.

**Specimen Requirements and Shipping/Handling:**

- **Prenatal Specimen:** 20 mg villi preferred (minimum 15 mg) or 20 mL amniotic fluid or 2 T25 flasks of cultured CV or cultured amniocytes. Ship overnight at ambient temperature, using a cool pack in hot weather.
- **Prenatal Specimen: Based on Specific Known Mutation (test #902):** 20mg villi preferred (minimum 15mg) or 20 mL amniotic fluid or 2 T25 flasks of cultured CV or cultured amniocytes. Ship overnight at ambient temperature, using a cool pack in hot weather.
- **Maternal cell contamination studies (required for all prenatal testing):** 1-4 ml maternal blood in a lavender-top EDTA tube. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping. Alternatively, buccal brushes (GeneDx kit only) or DNA can be used. *The maternal sample should accompany the prenatal specimen or be shipped to arrive prior to or concurrently with the prenatal sample*

*If more than one prenatal test is ordered, 30 mL amniotic fluid, 30mg villi or 3 T-25 flasks of cultured cells are requested*

**Required Forms:**

- Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions (last page of submission form)

**Prices and Turn-Around Time – Fees subject to change without notice:**

- Test #2553: Prenatal diagnosis (full gene sequencing) for male fetus based on ultrasound findings: $3,000 Approx. 2wks
- Test #2553E: Prenatal diagnosis (full gene sequencing + deletion/duplication) for female fetus based on ultrasound findings: $3,500 Approx. 2 wks
- Test #902: Prenatal diagnosis for a specific known mutation: $2,000 Approx. 2 wks

All codes and units apply:

**Test #2553 Prenatal L1CAM Testing in male fetus:**

- 83891 x 20 units = $ 230
- 83898 x 20 units = $ 700
- 83894 x 20 units = $ 230
- 83904 x 40 units = $1640
- 83892 x 4 units = $ 80
- 83912 x 4 units = $ 120

**Test #2553E Prenatal L1CAM Testing in female fetus:**

- 83891 x 22 units = $ 242
- 83898 x 20 units = $ 700
- 83894 x 20 units = $ 230
- 83904 x 40 units = $1640
- 83892 x 4 units = $ 80
- 83912 x 4 units = $ 120
- 88386 x 1 unit = $ 488

**TOTAL**

- $3,000
- $3,500

**CPT codes for Test #902 Prenatal Testing for Specific Known L1CAM mutation:**

- 83891 x 5 units = $ 160
- 83898 x 10 units = $ 710
- 83894 x 5 units = $ 160
- 83904 x 10 units = $ 750
- 83892 x 2 units = $ 60
- 83912 x 5 units = $ 160

**TOTAL**

- $ 2000

**Possible ICD9 Codes:** 655.83 – abnormal ultrasound findings; 655.23 – family history possibly affecting fetus