# L1CAM Gene Analysis in X-linked Hydrocephalus and Related Syndromes

**Disorder also known as**: L1 Syndrome, L1 Cell Adhesion Molecule, MASA Syndrome, CRASH Syndrome

**Clinical Features:**
These related neurological syndromes with X-linked inheritance are allelic disorders due to variant in the L1CAM gene. Congenital hydrocephalus and resultant macrocephaly due to stenosis of the aqueduct of Sylvius may occur as an isolated finding, but is frequently associated with other features, including hypoplastic or flexed, adducted thumbs. Patients exhibit varying degrees of mentally retardation and spastic paraplegia, particularly of the lower extremities. MASA syndrome includes Mental retardation, Aphasia, Shuffling gait, and Adducted thumbs. In addition, 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 females harboring a L1CAM variant exhibit clinical disease symptoms.

**Genetics:**
X-linked Hydrocephalus and Related Syndromes have an x-linked recessive pattern of inheritance.

**Test Methods:**
In males, analysis is performed by bi-directional sequencing of all 28 coding exons and their exon/intron splice junctions of the L1CAM gene. Large deletions of one or more exons are detectable by sequencing in males; however, partial gene duplications would not be identified by sequencing. Targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available as a reflex test to evaluate for a partial gene duplication. In females, sequencing cannot detect large deletions or duplications, so ExonArrayDx is performed concurrently to evaluate for a deletion or duplication of one or more exons of the L1CAM gene. Any variant identified is confirmed by repeat analysis using sequencing, restriction fragment analysis, or other methods, as appropriate. Prenatal analysis of the entire L1CAM gene is also available for fetal specimens when fetal ultrasound abnormalities are suggestive of an L1CAM-related disorder.

**Test Sensitivity:**

| Clinical Characteristics* and Family History | Detection Rate[4] |
|---|---|
| Family history and 3 or more clinical characteristics | 74-90% |
| Patient with 3 or more clinical characteristics of L1 Syndrome | 58-66% |
| Patient with fewer than 3 characteristics | 16-18% |
| Family history with more than 1 affected relative | 51% |
| Family history with 1 affected male | 18% |
| Male with hydrocephalus, negative family history and no other findings | 15-25% |

*Include hydrocephalus, aqueductal stenosis, adducted thumbs, and agenesis/dysgenesis of corpus callosum.

Because large deletions are not detectable by sequence analysis in a female, L1CAM sequencing is less efficient for a female than for a male individual. Therefore, concurrent sequencing and deletion/duplication analysis (ExonArrayDx) are performed for females. The sensitivity of L1CAM analysis in prenatal cases ascertained based on fetal ultrasound abnormalities is currently unknown.

**Variant Spectrum:**

Variants occur throughout the coding sequence of the gene and are of all types, including nonsense, missense, splice-site, deletions and insertions. Deletions of an exon or larger account for ~3% of the published variants. Rarely, large duplications have also been described.4 There is some evidence of genotype/ phenotype correlation in this group of disorders, as variants resulting in premature protein truncation are associated with a severe phenotype, while missense variants affecting the cytoplasmic domain are associated with a milder phenotype. Missense variants 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.

**References:**

1. Jouet, M. (1994) Nature Genet. 7: 402-407, 1994.
2. Finckh, U. (2000) Am. J. Med. Genet. 92: 40-46.
3. Jackson, SR. (2009) Pediatr Surg Int. 25(9):823-5.
4. Vos, J. (2010) J Med Genet. 47(3):169-75.