

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

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

### **Clinical Features:**

#### *Clinical Features in Newborns and Children:*

The L1CAM-related disorders are X-linked neurologic diseases caused by variants 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 variant 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.<sup>3</sup> Ultrasound examination may be normal in affected fetuses; therefore, pregnancies at risk to inherit a specific known familial variant can be offered targeted molecular testing regardless of ultrasound findings, if desired.

### **Genetics:**

Genetic variants in L1CAM tied to hydrocephalus and L1CAM-related disorders have an x-linked recessive pattern of inheritance.

### **Test Methods:**

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 variants, 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 variant in the L1CAM gene by sequencing. L1CAM variants 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.

### **Variant Spectrum:**

Variants occur throughout the coding sequence of the L1CAM gene. All types of variants 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 variants resulting in premature protein truncation are typically 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. Finckh, U. Am. J. Med. Genet. 92: 40-46, 2000.
2. Jouet, M. Nature Genet. 7: 402-407, 1994;
3. Wilson et al., Genet Test and Mol Biomark 13(4): 515-519 (2009).