Prenatal L1CAM Analysis in X-Linked Hydrocephalus and Related Syndromes

Clinical Features:
Clinical Features in Newborns and Children:
Variants in the L1CAM gene result in a spectrum of allelic disorders with X-linked inheritance; L1 syndrome, MASA syndrome, and CRASH syndrome have been used to describe disorders on this spectrum. 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.1-2 Approximately 5% of female harboring a L1CAM variant exhibit clinical symptoms.3

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.4 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:
X-linked

Test Methods:
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate
sequence or copy number data. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

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.**

**Clinical Sensitivity:**
The sensitivity of L1CAM testing for fetuses with ultrasound features of hydrocephalus and/or other L1-related features is unknown. According to GeneReviews, “apparently normal ultrasound findings in a pregnancy with a priori increased risk are not reliable in ruling out L1 syndrome in the fetus.”

<table>
<thead>
<tr>
<th>Clinical Characteristics* and Family History</th>
<th>Detection Rate(^4)</th>
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</thead>
<tbody>
<tr>
<td>Family history and 3 or more clinical characteristics</td>
<td>79-85%</td>
</tr>
<tr>
<td>Patient with 3 or more clinical characteristics of L1 Syndrome</td>
<td>58-66%</td>
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<tr>
<td>Patient with fewer than 3 characteristics</td>
<td>16-18%</td>
</tr>
<tr>
<td>Family history with more than 1 affected relative</td>
<td>51%</td>
</tr>
<tr>
<td>Family history with 1 affected male</td>
<td>18%</td>
</tr>
<tr>
<td>Male with hydrocephalus, negative family history and no other findings</td>
<td>15-25%</td>
</tr>
</tbody>
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*Include hydrocephalus, aqueductal stenosis, adducted thumbs, and agenesis/dysgenesis of corpus callosum.
References: