L1CAM Gene Analysis in X-linked Hydrocephalus and Related Syndromes

CLINICAL FEATURES

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 and resultant macrocephaly due to stenosis of the aqueduct of Sylvius may occur as an isolated finding, but are frequently associated with other features, including hypoplastic or flexed, adducted thumbs. Patients exhibit varying degrees of intellectual disability 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[1-2]. Approximately 5% of females harboring an *L1CAM* variant may exhibit clinical disease symptoms[3].

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.

CLINICAL SENSITIVITY

Clinical Characteristics* and Family History	Detection Rate[4]
Family history and 3 or more clinical characteristics	79-85%
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.

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