THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Genetic Testing for Hydrocephalus

Clinical Features:

L1 syndrome is the most common cause of congenital hydrocephalus and accounts for about 5-10% of males with congenital hydrocephalus[1]. The phenotypic spectrum of L1 syndrome, which can range from severe to mild, includes X-linked hydrocephalus [OMIM#307000], MASA syndrome [mental retardation, aphasia, shuffling gait and adducted thumbs, OMIM#303350] and X-linked corpus callosum agenesis [OMIM#304100][2]. In less severely affected males, hydrocephalus may be sub clinically present and only documented because of developmental delay. Intellectual disability ranges from mild to moderate. Intra- and interfamily phenotypic variations have been reported.

Autosomal recessive non-syndromic hydrocephalus [OMIM#236600] is characterized by onset in utero of enlarged ventricles due to a disturbance of cerebrospinal fluid accumulation. In general, the causes of hydrocephalus are heterogeneous and the majority of cases are secondary to neural tube defects, intracranial hemorrhages, trauma, tumors, teratogens or brain malformations. The remaining cases can be divided into the syndromic (two thirds of cases) and non-syndromic (one third of cases) [3,4].

Molecular Genetics:

Mutations in the *L1CAM* [OMIM#308840] gene are a cause L1 syndrome[1]. The majority of mutations in *L1CAM* are private (unique to each family) and all types of disease-causing mutations have been identified: nonsense, frameshift, splice-site and missense mutations. *L1CAM* codes for the neural L1 cell adhesion molecule and is involved in cell-to-cell adhesion at the cell surface.

In 2 unrelated families with autosomal recessive non-syndromic hydrocephalus, Drielsma *et al* identified 2 different homozygous truncating mutations in the *CCDC88C*[3]. *CCDC88C* gene encodes for the DVL1-binding protein DAPLE which has a role in the regulation of the WNT signaling pathway. More recently, Al-Dosari *et al* identified a homozygous truncating mutation in the *MPDZ*[4] gene in one large consanguineous Saudi family with non-syndromic hydrocephalus. MPDZ is localized to tight junctions and has been proposed to scaffold and attract other proteins for proper formation of tight junctions.

Hemizygous mutations in the *AP1S2* gene have been found to be associated with intellectual disability, and other variable features including choreoathetosis, congenital hydrocephalus, Dandy-Walker malformation, mild facial dysmorphism, delayed motor development, seizures, and brain iron/calcium deposition[5]. Highly variable expressivity has been reported and carrier females may be asymptomatic or may have some learning impairments[6]. Shaheen et al., 2017 identified a homozygous truncating mutation in *EML1* in a family with congenital hydrocephalus, global developmental delay and brain abnormalities[7]. Mutations in this gene have been reported in individuals with subcortical heterotopia and studies in mice have supported its role in neuronal migration defects[8]. Homozygous mutations in *WDR81* have been identified in individuals from two unrelated families with severe congenital hydrocephalus and cerebellar hypoplasia/absent cerebellum[7]. Biallelic mutations in this gene have also been associated with cerebellar ataxia, intellectual disability, quadrupedal locomotion (disequilibrium syndrome) (CMRQ-2)[9,10].

Inheritance:

In general, congenital hydrocephalus is a common condition affecting 0.6 per 100 live births. The prevalence of X-linked hydrocephalus with stenosis of the aqueduct of Sylvius, the most common genetic form of congenital hydrocephalus, is approximately 1 in 30,000. L1 syndrome is inherited in an X-linked manner. Recurrence risk for a carrier female is 50%. Carrier females may manifest clinical findings related to the syndrome.

Autosomal recessive non-syndromic hydrocephalus follows an autosomal recessive inheritance pattern. There have been no cases of germline mosaicism or *de novo* mutations reported. Therefore, parents of an affected

child are most likely obligate carriers. Recurrence risk for carrier parents is 25%. In general, congenital hydrocephalus is a common condition affecting 0.6 per 100 live births.

Test methods:

Comprehensive sequence coverage of the coding regions and splice junctions of the *L1CAM, CCDC88C, AP1S2, EML1, WDR81 and MPDZ* genes is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. The constructed genomic DNA library is sequenced using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20bp.

Deletion/duplication analysis is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Comprehensive Hydrocephalus Panel *(AP1S2, CCDC88C, EML1, L1CAM, MPDZ,* and *WDR81* sequence and deletion/duplication analysis)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$3500
CPT codes:	81406, 81407
Turn-around time:	6 weeks

L1CAM sequencing

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81407
Turn-around time:	4 weeks

L1CAM deletion/duplication analysis

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1000
CPT codes:	81406
Turn-around time:	4 weeks

Autosomal Recessive non-syndromic hydrocephalus sequencing panel (*CCDC88C* and *MPDZ* sequencing)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2000
CPT codes:	81407
Turn-around time:	4 weeks

Autosomal Recessive non-syndromic hydrocephalus del/dup panel (*CCDC88C* and *MPDZ* deletion/duplication)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$1545
CPT codes:	81407
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

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9. Gulsuner S, Tekinay AB, Doerschner K, et al. Homozygosity mapping and targeted genomic sequencing reveal the gene responsible for cerebellar hypoplasia and quadrupedal locomotion in a consanguineous kindred. *Genome Res.* 2011;21(12):1995-2003.
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