



## The University of Chicago Genetic Services Laboratories

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### Genetic Testing for Autosomal Recessive Non-syndromic Hydrocephalus

#### Clinical Features:

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) (1, 2).

#### Molecular Genetics:

In 2 unrelated families with autosomal recessive non-syndromic hydrocephalus, Drielsma *et al* identified 2 different homozygous truncating mutations in the *CCDC88C* [OMIM#611204]. *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* [OMIM#603785] 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.

#### Inheritance:

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:

This panel includes full gene sequencing for the *CCDC88C* and *MPDZ* genes. We offer mutation analysis of all 30 coding exons and intron/exon boundaries of *CCDC88C* and all 46 coding exons and intron/exon boundaries of *MPDZ* by direct sequencing of amplification products in both the forward and reverse directions. 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.

We also offer testing for X-linked hydrocephalus. This testing includes analysis for the *L1CAM* gene. Please see our information sheet on *L1CAM* testing.

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

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$2,900
CPT codes:	81407
Turn-around time:	4 weeks

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

Sample specifications:	3 to 10 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.

**References:**

1. Drielsma A, Jalas C, Simonis N et al. Two novel CCDC88C mutations confirm the role of DAPLE in autosomal recessive congenital hydrocephalus. J Med Genet 2012: 49: 708-712.
2. Al-Dosari MS, Al-Owain M, Tulbah M et al. Mutation in MPDZ causes severe congenital hydrocephalus. J Med Genet 2013: 50: 54-58.

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