



The University of Chicago Genetic Services Laboratories

5841 S. Maryland Ave., Rm. G701, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES ☐ (888) 824 3637
Local: (773) 834 0555 ☐ FAX: (773) 702 9130
ucgslabs@genetics.uchicago.edu ☐ dnatesting.uchicago.edu
CLIA #: 14D0917593 CAP #: 18827-49

OPHN1 Sequencing for X-linked Mental Retardation with Cerebellar Hypoplasia

Clinical Features:

The hallmark features seen in patients with *OPHN1* mutations include moderate to severe mental retardation and cerebellar hypoplasia [OMIM #300486], particularly cerebellar vermis hypoplasia (CVH). CVH may also be called "Dandy-Walker variant" due to the phenotypic overlap with Dandy-Walker malformation (DWM). Specifically, CVH consists of isolated vermis hypoplasia while DWM includes vermis hypoplasia and several other features such as enlarged posterior fossa. In patients with *OPHN1* mutations, magnetic resonance imaging (MRI) may also reveal cerebral atrophy, ventriculomegaly, and rarely hydrocephalus. Physical findings may include tall stature, macrocephaly, and common facial features such as prominent supraorbital ridges, hypotelorism, deep-set eyes, long tubular nose, short philtrum, thin upper lip and prominent chin. Hypotonia and developmental delay are noticed in most patients in early childhood, who then develop moderate to severe mental retardation. About half of all patients experience seizures. Oculomotor problems include nystagmus, strabismus, and occasionally external ophthalmoplegia. Other neurological and behavioral findings may include dysmetria, adiadochokinesia, hyperactivity, and anxiety. Most heterozygous females have mild cognitive handicaps (1, 2).

Dr. William Dobyns at the Seattle Children's Research Institute is available to review MRI scans and give recommendations regarding genetic testing. Please contact Dr. Dobyns (wbd@uw.edu) or his coordinators, Carissa Adams (carissa.adams@seattlechildrens.org) and Brandi Bratrude (brandi.bratrude@seattlechildrens.org) to arrange this, if desired.

Molecular and Biochemical Genetics:

Mutations of the *OPHN1* [OMIM #300127] gene, or *oligophrenin-1*, have been identified in patients with X-linked mental retardation with cerebellar hypoplasia (1, 2). *OPHN1* has 23 coding exons and is highly expressed in fetal brain tissue (3). The oligophrenin-1 protein contains a domain common in Rho-GTPase-activating proteins and is postulated to affect cell migration and outgrowth of axons and dendrites (3). Philip N, et al [2003] reported that 2/6 (33%) males with moderate mental retardation and CVH had mutations in *OPHN1* (1). Zanni G, et al [2005] found that 2/17 (12%) males with mental retardation and cerebellar anomalies had *OPHN1* mutations (2).

Inheritance:

Mutations in *OPHN1* are inherited in an X-linked pattern and result in clinical features in affected males and females. Males are more severely affected than females. A woman who has more than one affected son is an obligate carrier. Recurrence risk for carrier mothers is 50%.

Additional Resources:

Dandy-Walker Alliance, Inc.

DC Office: 301-919-2653
FL Office: 321-446-0349
submission@dandy-walker.org

Developmental Disorders Research Center Chicago

William B. Dobyns, Principal Investigator
Contact Hailly Butler (hailly.butler@seattlechildrens.org)

Test Methods:

We offer mutation analysis of all 23 coding exons and intron/exon boundaries of *OPHN1* by direct sequencing of amplification products in both the forward and reverse directions. We also offer deletion/duplication analysis of the *OPHN1* gene by oligonucleotide array-CGH to identify copy number changes involving one or more exons. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. 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.

OPHN1 sequencing may be ordered alone, or as part of our cerebellar hypoplasia panel which includes sequencing of a total of 7 genes. Please see our information sheet on our Cerebellar Hypoplasia Next Generation Sequencing Panel for more details.

OPHN1 sequencing analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	\$1800
CPT codes:	81406
Turn-around time:	4 weeks

OPHN1 deletion/duplication analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	\$1000
CPT codes:	81405
Turn-around time:	4 weeks

Deletion/duplication analysis for two or more genes (by array-CGH)

Sample specifications:	3 to 10 cc of blood in a purple top (EDTA) tube
Cost:	\$1545
CPT codes:	81479
Turn-around time:	4-6 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. Philip N, Chabrol B, Lossi AM et al. Mutations in the oligophrenin-1 gene (OPHN1) cause X linked congenital cerebellar hypoplasia. J Med Genet 2003; 40: 441-446.
2. Zanni G, Saillour Y, Nagara M et al. Oligophrenin 1 mutations frequently cause X-linked mental retardation with cerebellar hypoplasia. Neurology 2005; 65: 1364-1369.
3. Billuart P, Bienvenu T, Ronce N et al. Oligophrenin-1 encodes a rhoGAP protein involved in X-linked mental retardation. Nature 1998; 392: 923-926.

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