The University of Chicago Genetic Services Laboratories

5841 S. Maryland Ave., Rm. L035, MC 0077, Chicago, Illinois 60637
Toll Free: (888) UC GENES (888) 824 3637
Local: (773) 834 0555 FAX: (773) 834 0556
ucgslabs@genetics.uchicago.edu www.genes.uchicago.edu
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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 University of Chicago is available to review MRI scans and give recommendations regarding genetic testing. Please contact Mary King at 773-702-8247 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 Mary King at 773-702-8247

Test Methods:

The University of Chicago Laboratory offers 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.

OPHN1 sequencing:

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$2025
CPT codes:	83891, 83898 x 4, 83904 x 9, 83912
Turn-around time:	4 - 6 weeks

Testing for a known mutation in additional family members

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$390
CPT codes:	83891, 83898 x 2, 83894, 83912
Turn-around time:	3 – 4 weeks

Prenatal testing for a known mutation

Sample specifications:	2 T25 flasks of cultured cells from amnio or CVS or 10ml of amniotic fluid
Cost:	$590
CPT codes:	83891, 83898 x 2, 83894, 83912, 99051
Turn-around time:	1-2 weeks

Results:

You will be informed of the results of your case as soon as it has been completed. Results, along with an interpretive report, will be faxed and mailed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

Laboratory Faculty and Staff:

Soma Das, Ph.D.
Director, Molecular Genetics Laboratory
ABMG Certified Molecular Geneticist

Stuart Schwartz, Ph.D.
Director, Cytogenetics Laboratory
ABMG Certified Cytogeneticist

Eden Haverfield, Ph.D.
Assistant Director, Molecular Genetics Laboratory

Melissa Dempsey, M.S.
Certified Genetic Counselor

Darrel J. Waggoner, M.D.
Clinical Advisor
ABMG Certified Clinical Geneticist

William B. Dobyns, M.D.
Clinical Advisor
ABMG Certified Clinical Geneticist

References:

1. Philip N, et al. Mutations in the oligophrenin-1 gene (*OPHN1*) cause X-linked congenital cerebellar hypoplasia (2003) J Med Genet 40:441-446.
2. Zanni G, et al. Oligophrenin 1 mutations frequently cause X-linked mental retardation with cerebellar hypoplasia (2005) Neurology 65: 1364-69.
3. Billuart P, et al. Oligophrenin-1 encodes a rhoGAP protein involved in X-linked mental retardation (1998) Nature 392: 923-6.

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