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 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:
Comprehensive sequence coverage of the coding regions and splice junctions of the *OPHN1* gene 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.

Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes
and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

**OPHN1 mutation analysis**

Sample specifications: 3 to 10cc of blood in a purple top (EDTA) tube  
Cost: $1000  
CPT codes: 81405, 81406  
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:**


*Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS’ NEEDS*