

X-Linked Mental Retardation with Cerebellar Hypoplasia and Distinctive Facial Appearance via *OPHN1* Gene Sequencing (Test #297)

Brief Description of Clinical Features: X-linked mental retardation with cerebellar hypoplasia and distinctive facial appearance (OMIM 300486) is a clinically heterogeneous disorder with intrafamilial and interfamilial phenotypic variability (Zanni et al. *Nuerology* 65:1364-1369, 2005). X-linked mental retardation with cerebellar hypoplasia and distinctive facial appearance is mainly characterized by moderate to severe mental retardation and cerebellar anomalies, particularly cerebellar vermis hypoplasia presented as isolated vermis hypoplasia, and common facial features such as prominent supraorbital ridges, hypotelorism, deep-set eyes, long tubular nose, short philtrum, thin upper lip and prominent chin (Billuart et al. *Nature* 392:923-926, 1998; Philip et al. *J Med Genet* 40:441-446, 2003; Zanni et al. 2005). Brain imaging (MRI) may also reveal cerebral atrophy, ventriculomegaly, and rarely hydrocephalus (Zanni et al. 2005). Other clinical findings such as tall stature, macrocephaly, hypotonia, developmental delay, seizures, oculomotor problems, language problems and neurological and behavioral problems such as dysmetria, adiadochokinesia, hyperactivity, and anxiety have been occasionally reported (Philip et al. 2003; Zanni et al. 2005).

Genetics: X-linked mental retardation with cerebellar hypoplasia is inherited as X-linked recessive disorder, where males are more severely affected than females. However heterozygous females may have mild cognitive impairments (Zanni et al. 2005). X-linked mental retardation with cerebellar hypoplasia is caused by mutations in the *oligophrenin-1 (OPHN1)* gene (Billuart et al. 1998). *OPHN1* gene encodes the oligophrenin-1 protein, which contains a domain common in Rho-GTPase-activating proteins suggesting a role in cell migration and outgrowth of axons and dendrites, neuronal morphogenesis and synapse maturation (Billuart et al. 1998; Zanni et al 2005). A mix of nonsense, splice site, frameshift and single and multiple exons deletion mutations have been reported in the *OPHN1* gene (Billuart et al. 1998; Philip et al. 2003; Bergmann et al. *Brain* 126:1537-1544, 2003; Chabrol et al. *Am J Med Genet* 138: 314-317, 2005).

Description of This Particular Test: This test involves bidirectional sequencing using genomic DNA of the 23 coding exon (exons 2-24) of the *OPHN1* gene. The full coding region of each exon plus ~50 bp of flanking non-coding DNA on each side are sequenced. As indicated, we will also perform sequencing of any single exon (Test #100) for family members of patients with known mutations and to confirm previous research results (\$190 charge).

Reference Sequences: Genomic: **NC_000023.10** mRNA: **NM_002547.2** Protein: **NP_002538.1 (CCDS 14388.1)**

Indications for Test: Candidates for this test are patients with symptoms consistent with X-linked mental retardation with cerebellar hypoplasia and family members of patients who have known *OPHN1* mutations.

Sensitivity of Test: *OPHN1* mutations were found in approximately 12% of patients with mental retardation with known cerebellar anomalies and in about 1% of X-linked mental retardation patients (Zanni et al. 2005).

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Prices: **Sequencing of *OPHN1* gene** **\$ 1320**

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x27	83898 \$ 420	Sequencing x27	83904 \$ 640
Separation x1	83894 \$ 80	Interpretation/Report x1	83912 \$ 110

Accreditation: CLIA ID #: **52D1027685** (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12).

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