

Usher Syndrome Type 3 via *CLRN1* Gene Sequencing -- Test #647

Brief Description of Clinical Features: Usher syndrome is a clinically heterogeneous disorder characterized by progressive retinitis pigmentosa (RP) and sensorineural hearing impairment, with or without vestibular abnormalities. Three types are recognized based on the age of onset, severity of symptoms, and the vestibular involvement (Smith et al. Am J Med Genet 50:32-38, 1994). Patients with **Usher syndrome type 3** (USH3 OMIM 276902) are born with normal hearing and vision. Hearing loss usually begins during childhood or early teens, and RP begins in the teens. Vestibular involvement may occur later in life. Features of RP include night blindness progressing to constriction of the peripheral visual field with eventually loss of central vision, abnormal fundus with bone-spicule deposits/attenuated retinal vessels, and abnormal electroretinographic (ERG) findings (Daiger et al. Arch Ophthalmol 125:151-158, 2007). See also the Hereditary Hearing Loss Homepage (<http://hereditaryhearingloss.org>).

Genetics: USH3 is an autosomal recessive disease that is caused by mutations in the *CLRN1* gene (Joensuu et al. Am J Hum Genet 69:673-684, 2001). *CLRN1* encodes clarin-1, which is presumed to be involved in sensory synapses (Adato et al. Eur J Hum Genet 10:339-350, 2002). To date, about 20 *CLRN1* causative mutations have been reported. Mutations include missense, nonsense, splicing, and small insertions or deletions. Although most *CLRN1* mutations are private, a nonsense mutation (c.528T>G, p.Tyr176Stop) appears to be common in Finnish USH3 families, and a missense mutation (c.144T>G, p.Asn48Lys) was found in several USH3 families in the Ashkenazi Jewish population (Fields et al. Am J Hum Genet 71:607-617, 2002).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all coding exons and splice sites of the *CLRN1* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. As indicated, we will sequence one exon (Test #100, \$190) or two exons (Test #200, \$340) in family members of patients with known mutations or to confirm previous results.

Reference Sequences: Genomic: NC_000003.10 mRNA: NM_052995.2 Protein: NP_443721.1 (CCDS 35492.1)

Indications for Test: Patients with combined, progressive postlingual sensorineural hearing loss and RP, with or without vestibular abnormality.

Sensitivity of Test: Unknown at this time.

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

Specimen Requirements: See page 4 of Requisition Form.

Price: Sequencing of all *CLRN1* Coding Exons \$ 440

CPT Codes:

Sample Ascertainment x1	83890	\$ 30	DNA Isolation x1	83891	\$ 40
Amplification x4	83898	\$ 100	Sequencing x4	83904	\$ 150
Separation x1	83894	\$ 30	Interpretation/Report x1	83912	\$ 90

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

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