

Usher Syndrome Type 2 via *USH2A* Gene Sequencing -- Test #648

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). **Usher syndrome type 2** (USH2 OMIM 276901) is characterized by mild to severe congenital hearing loss, RP with onset in the teens and normal vestibular function. 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 Keats and Lentz (GeneReviews, 2009, www.genetests.org) and the Hereditary Hearing Loss Homepage (<http://hereditaryhearingloss.org>).

Genetics: USH2 is a genetically heterogeneous autosomal recessive disease. Mutations in three genes: *USH2A*, *GPR98*, and *DFNB31* account for nearly all cases with detectable mutations (Eudy et al. Science 280:1753-1757, 1998; Weston et al. Am J Hum Genet 74:357-366; Mburu et al. Nat Genet 34:421-428, 2003; Keats and Lentz, 2009). Over 120 *USH2A* causative mutations have been reported to date. The majority of mutations are missense. Other mutations include nonsense, splicing, and small insertions or deletions. Although most *USH2A* mutations are private, a single nucleotide deletion, c.2299delG, predicted to result in a frameshift with premature termination codon, has been identified in several populations (Dreyer et al. Am J Hum Genet 69: 228–234, 2001). In addition to USH2, *USH2A* mutations have been reported in patients with non-syndromic autosomal recessive RP (AR-RP OMIM 608400) (Rivolta et al. Am J Hum Genet 66:1975-1978, 2000).

Description of This Particular Test: The *USH2A* gene encodes usherin, which is involved in the development of the inner ear and eye. This test involves bidirectional DNA sequencing of all coding exons and splice sites of the *USH2A* 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_000001.9 mRNA: NM_206933.2 Protein: NP_996816.2 (CCDS 31025.1)

Indications for Test: Patients with combined congenital sensorineural hearing loss and RP, with normal vestibular function.

Sensitivity of Test: This test allows the detection of mutations in ~ 80% of patients with USH2 (Keats and Lentz, 2009).

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 *USH2A* Coding Exons \$ 3350

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x86	83898 \$1150	Sequencing x86	83904 \$1720
Separation x1	83894 \$ 230	Interpretation/Report x1	83912 \$ 180

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

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