

Usher Syndrome Type 2 and Nonsyndromic Hearing Loss via *DFNB31* Gene Sequencing -- Test #697

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, 2011, 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, 2004; Mburu et al. Nat Genet 34:421-428, 2003; Keats and Lentz, 2011). Several *DFNB31* causative mutations have been reported and include missense, nonsense, splicing and small deletions/insertions. In addition to USH2, *DFNB31* mutations have been reported in patients affected with Nonsyndromic Hearing Loss (NSHL, OMIM 607084) (Mburu et al. 2003; Tlili et al. Hum Mutat 25:503, 2005). The *DFNB31* gene encodes whirlin, which is expressed in the inner ear, retina, and developing brain. Whirlin interacts with several proteins from the Usher protein network, including usherin and GPR98 (Maerker et al. Hum Mol Genet 17: 71-86, 2008).

Description of This Particular Test: This test involves bidirectional DNA sequencing of all coding exons and splice sites of the long isoform (isoform 1) of the *DFNB31* 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_000009.11 mRNA: NM_015404.3 Protein: NP_056219.3 (CCDS 6806.1)

Indications for Test: Patients with combined congenital sensorineural hearing loss and RP and normal vestibular function, without *USH2A* or *GPR98* mutations; and patients with NSHL.

Sensitivity of Test: This test allows the detection of mutations in ~ 5% of patients with USH2 (Keats and Lentz, 2011).

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 *DFNB31* Coding Exons \$ 890

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x16	83898 \$ 270	Sequencing x16	83904 \$ 380
Separation x1	83894 \$ 60	Interpretation/Report x1	83912 \$ 110

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

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