

Usher Syndrome Type 2, in Male and Female Patients, via *GPR98* Gene Sequencing -- Test #698

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, 2010). To date, about 25 *GPR98* causative mutations have been reported, which include missense, nonsense, small deletions/insertions, and one large genomic deletion. Because the initial *GPR98* mutations were all identified in female patients, it was postulated that such mutations are lethal in males. However, recently *GPR98* mutations were reported in both female and male patients with typical USH2 (Hilgert et al. J Med Genet 46:272-276, 2009; Ebermann et al. J Med Genet 46:277-280, 2009). The *GPR98* gene encodes a G-protein-coupled receptor, which is expressed in the central nervous system.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all coding exons and splice sites of isoform b of the *GPR98* gene, which is the largest of three isoforms. 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_000005.9 mRNA: NM_032119.3 Protein: NP_115495.3 (CCDS 47246.1)

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 ~ 15% 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 *GPR98* Coding Exons** **\$ 3940**

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x104	83898 \$1360	Sequencing x104	83904 \$2060
Separation x1	83894 \$ 280	Interpretation/Report x1	83912 \$ 170

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

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