

Usher Syndrome Type 1 via *MYO7A* Gene Sequencing -- Test #643

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. **Usher syndrome type 1** (USH1 OMIM 276900) is the most common type. It is distinguished by congenital onset of hearing loss, RP in the first decade of life, and abnormal vestibular function (Cohen et al. Int J Audiol 46:82-93, 2007). 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). The vestibular abnormality results in development delay in sitting and walking. See also the American Speech-Language-Hearing Association (www.asha.org) and Keats and Lentz (GeneReviews, 2010, www.genetests.org).

Genetics: USH1 is an autosomal recessive disease that is genetically heterogeneous. Mutations in four genes: *MYO7A*, *CDH23*, *PCDH15*, and *USH1C* account for ~ 75% of cases with detectable mutations (Weil et al. Nature 374:60-61, 1995; Bork et al. Am J Hum Genet 68:26-37, 2001; Ahmed et al. Am J Hum Genet 69:25-34, 2001; Bitner-Glindzicz et al. Nat Genet 26:56-60, 2000; Keats and Lentz, 2010). Mutations in the *MYO7A* gene account for up to 50% of the cases. Over 200 *MYO7A* mutations have been reported. The majority of mutations are missense, although chain termination mutations are also common. Large deletion/insertions or complex rearrangements are apparently rare. In addition to USH1, *MYO7A* mutations have been reported in patients with autosomal recessive (DFNB2 OMIM 600060) or autosomal dominant (DFNA11 OMIM 601317) nonsyndromic hearing loss (Liu et al. Nat Genet 16:188-190, 1997; Luijendijk et al. Hum Genet 115:149-156, 2004).

Description of This Particular Test: The *MYO7A* gene encodes myosin VIIa, a myosin motor protein. This test involves bidirectional DNA sequencing of all coding exons and splice sites of the *MYO7A* 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 (Test #100) or two (Test #200) exons in family members of patients with known mutations or to confirm previous results.

Reference Sequences: Genomic: NC_000011.8 mRNA: NM_000260.3 Protein: NP_000251.3

Indications for Test: All patients with symptoms suggestive of combined sensorineural hearing loss, RP and vestibular areflexia are candidates for testing. The *MYO7A* gene is also a candidate for patients presenting with familial nonsyndromic hearing loss (DFNB2 and DFNA11).

Sensitivity of Test: This test allows the detection of mutations in approximately 50% of patients with USH1 (Keats and Lentz, 2010). PreventionGenetics offers a sequencing panel of the four genes that are frequently mutated in patients with USH1 patients (Test #645).

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

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of all *MYO7A* Coding Exons \$ 2060

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x48	83898 \$ 700	Sequencing x48	83904 \$1050
Separation x1	83894 \$ 100	Interpretation/Report x1	83912 \$ 140

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

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