Usher syndrome type 1 and nonsyndromic hearing loss secondary to *MYO7A* mutations

Disorder: Hearing loss affects about 1 in 500 newborns and a genetic etiology is suspected in two thirds of these patients. Hearing loss can be caused by mutations in many different genes which can be inherited in an autosomal dominant, autosomal recessive, X-linked or mitochondrial (maternal inheritance) manner.

Mutations in the *MYO7A* gene, which encodes myosin 7A protein, account for approximately 50% of Usher syndrome type 1. Usher syndrome type 1 is characterized by severe to profound congenital sensorineural hearing loss, balance disturbances with poor coordination, and retinitis pigmentosa with onset in childhood. Biallelic mutations in the *MYO7A* gene also account for approximately 3-6% of all early onset non-syndromic sensorineural hearing loss. Non-syndromic sensorineural hearing loss associated with the *MYO7A* gene may be inherited in an autosomal recessive manner, known as DFNB2, or in an autosomal dominant form, designated DFNA11.

Indications:

- Usher syndrome type 1
- Non-syndromic hearing loss of unknown etiology
- Carrier testing in a relative of a patient with proven *MYO7A* mutation

Specimen: At least 3 mLs whole blood in a lavender top (EDTA) tube. Label each tube with patient's name, birth date, and date of collection.

Testing Methodology: This test may be performed either by PCR and bidirectional sequence analysis of the coding regions and exon/intron boundaries of the *MYO7A* gene or by enrichment of the exons, flanking intronic and untranslated regions (5' and 3') of the genes specified above using microdroplet PCR technology followed by next-generation sequencing with > 40 fold coverage at every target base. All pathogenic and novel variants, as well as variants of unknown (indeterminate) significance, as determined bioinformatically, are confirmed by Sanger sequencing.

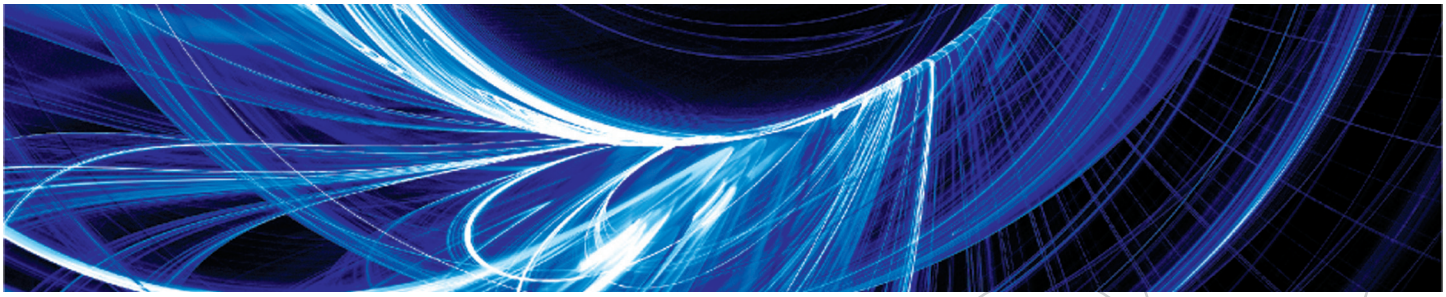
MYO7A sequencing is also available as part of our **Usher Syndrome** and **OtoSeq® Hearing Loss Panels** which detects mutations in *MYO7A*, as well as in other genes which cause Usher syndrome and/or nonsyndromic hearing loss. Please see our web site for details.

Test Sensitivity: This test detects 85% of the reported mutations in *MYO7A*. Mutations in *MYO7A* account for approximately 3-6% of congenital sensorineural hearing loss and 39-55% of Usher syndrome type 1.

The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed. Mutations in regulatory regions or other untranslated regions are not detected by this test. Large deletions involving entire single exons or multiple exons, large insertions and other complex genetic events have been reported in *MYO7A* and will not be identified using this test methodology. Rare primer site variants may lead to erroneous results.

Cincinnati Children's®
Human Genetics

Molecular Genetics Laboratory
CLIA#: 36D0656333
Phone: (513) 636-4474
Fax: (513) 636-4373
Email: moleculargenetics@cchmc.org
www.cchmc.org/hearing-loss



Turn-Around Time:

***MYO7A* full gene sequence analysis:** 42 days

Family specific mutation analysis: 28 days

Cost:

Please call 1-866-450-4198 for current pricing, insurance precertification, or with any billing questions.

CPT Codes:

***MYO7A* full gene sequence analysis**
81407

Family specific mutation analysis
81403

Results:

Each test report includes a detailed interpretation of the genetic findings, the clinical significance of the result, and specific recommendations for clinical management and additional testing, if warranted. Results will be reported to the referring physician or health care provider as specified on the test requisition form.

References:

Adato, A., D. Weil, et al. (1997). "Mutation profile of all 49 exons of the human myosin VIIA gene, and haplotype analysis, in Usher 1B families from diverse origins." Am J Hum Genet 61(4): 813-821

Astuto, L. M., M. D. Weston, et al. (2000). "Genetic heterogeneity of Usher syndrome: analysis of 151 families with Usher type I." Am J Hum Genet 67(6): 1569-1574.

Le Quesne Stabej, P., Z. Saihan, et al. (2012). "Comprehensive sequence analysis of nine Usher syndrome genes in the UK National Collaborative Usher Study." J Med Genet 49(1): 27-36.

Lim, L. H., J. K. Bradshaw, et al. (2003). "Genotypic and phenotypic correlations of DFNB1-related hearing impairment in the Midwestern United States." Arch Otolaryngol Head Neck Surg 129(8): 836-840.

Liu, X. Z., J. Walsh, et al. (1997). "Mutations in the myosin VIIA gene cause non-syndromic recessive deafness." Nat Genet 16(2): 188-190.

Millan, J. M., E. Aller, et al. (2011). "An update on the genetics of usher syndrome." J Ophthalmol 2011: 417217.

Ouyang, X. M., D. Yan, et al. (2005). "Characterization of Usher syndrome type I gene mutations in an Usher syndrome patient population." Hum Genet 116(4): 292-299.

Riazuddin, S., S. Nazli, et al. (2008). "Mutation spectrum of MYO7A and evaluation of a novel nonsyndromic deafness DFNB2 allele with residual function." Hum Mutat 29(4): 502-511.

Tamagawa, Y., K. Ishikawa, et al. (2002). "Phenotype of DFNA11: a nonsyndromic hearing loss caused by a myosin VIIA mutation." Laryngoscope 112(2): 292-297.

Weil, D., S. Blanchard, et al. (1995). "Defective myosin VIIA gene responsible for Usher syndrome type 1B." Nature 374(6517): 60-61.

Weil, D., P. Kussel, et al. (1997). "The autosomal recessive isolated deafness, DFNB2, and the Usher 1B syndrome are allelic defects of the myosin-VIIA gene." Nat Genet 16(2): 191-193.

Weston, M. D., P. M. Kelley, et al. (1996). "Myosin VIIA mutation screening in 189 Usher syndrome type 1 patients." Am J Hum Genet 59(5): 1074-1083.

Additional information and test requisitions are available at: **www.cchmc.org/hearing-loss**

Shipping Instructions

Please enclose a completed **test requisition, audiogram and MRI/CT report, if available** with the sample. **All information must be completed before the sample can be processed.** Place samples in Styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship to:

Cytogenetics and Molecular Genetics Laboratories
3333 Burnet Avenue NRB 1042
Cincinnati, OH 45229
513-636-4474