

Auditory neuropathy and non-syndromic hearing loss secondary to *OTOF* (Otoferlin) 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.

Biallelic mutations in the *OTOF* gene, which encodes for the otoferlin protein, are a common cause of auditory neuropathy and early onset nonsyndromic hearing loss. Auditory neuropathy is characterized by varying levels of hearing loss on standard hearing tests, very abnormal auditory brainstem testing and signs of normal hair cell function (i.e. the presence of otoacoustic emission and cochlear microphonics). Children with auditory neuropathy typically have poor speech discrimination and do not respond well with hearing aids. Cochlear implants are often beneficial in this group of patients. Non-syndromic hearing loss, designated as DFNB9, as well as auditory neuropathy associated with *OTOF* mutations are inherited as autosomal recessive disorders.

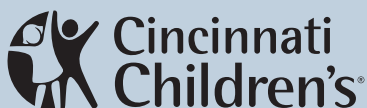
Indications:

- Auditory neuropathy
- Non-syndromic hearing loss of unknown etiology
- Carrier testing in a relative of a patient with proven *OTOF* mutation

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

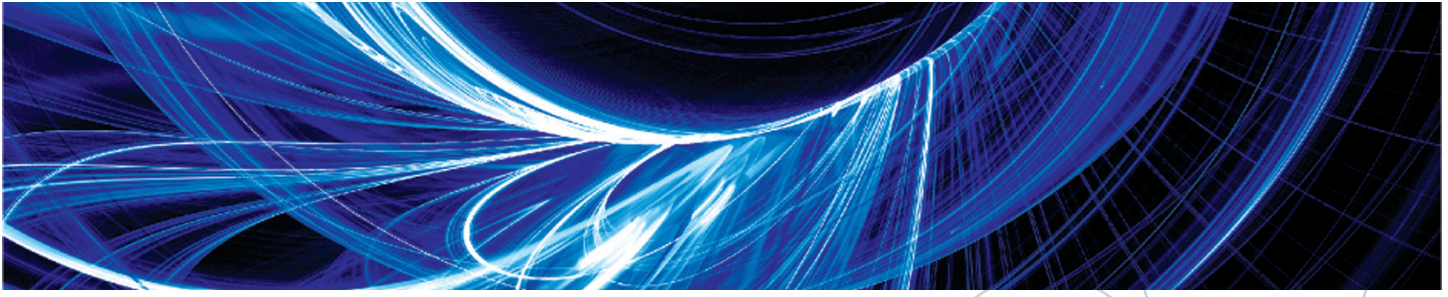
Testing Methodology: This test may be performed either by PCR and bidirectional sequence analysis of the coding regions and exon/intron boundaries of the *OTOF* gene or by enrichment of the exons, flanking intronic and untranslated regions (5' and 3') of the genes specified above using microdroplet PCR 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.

OTOF sequencing is also available as part of our **OtoSeq® Hearing Loss Panel** which detects mutations in *OTOF*, as well as in 22 other genes which cause hearing loss. Please see our web site for details.



Human Genetics

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Test Sensitivity: This test detects an estimated 99% of the reported mutations in *OTOF*. Mutations in *OTOF* account for approximately 3-6% of nonsyndromic sensorineural hearing loss and approximately 30-35% of auditory neuropathy. 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 *OTOF* and will not be identified using this test methodology. Rare primer site variants may lead to erroneous results.

Turn-Around Time:

***OTOF* 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:

***OTOF* full gene sequence analysis:**
81479

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:

Rodriguez-Ballesteros, M., F. J. del Castillo, et al. (2003). "Auditory neuropathy in patients carrying mutations in the otoferlin gene (*OTOF*)." *Hum Mutat* 22(6): 451-456.

Varga, R., P. M. Kelley, et al. (2003). "Non-syndromic recessive auditory neuropathy is the result of mutations in the otoferlin (*OTOF*) gene." *J Med Genet* 40(1): 45-50.

Yasunaga, S., M. Grati, et al. (1999). "A mutation in *OTOF*, encoding otoferlin, a *FER-1*-like protein, causes *DFNB9*, a nonsyndromic form of deafness." *Nat Genet* 21(4): 363-369.

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
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Cincinnati, OH 45229
513-636-4474