HEARING LOSS PANEL TIER I

Genes Tested

GJB2 (connexin 26)	*GJB6 (connexin 30)*
Hearing Loss mtDNA Panel: *MTRNR1* (961, 1555,1494), *MTTS1* (7445, 7511), *MTTL1* (3243, 3271), *MTTK* (8344)	

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.

Rationale for Testing: Identification of the specific cause of a child's hearing loss is an important part of a comprehensive hearing loss evaluation. Identification of a specific genetic mutation provides important information about long-term prognosis and medical management. It also provides very specific information on which to base genetic counseling for parents and other at-risk family members. Finally, identification of a genetic mutation, early in the evaluation process, may eliminate the need for further, more invasive and costly medical procedures and tests.

Hearing Loss Panel Tier I testing is indicated for patients with sensorineural hearing loss (SNHL) of unknown etiology who have had no previous molecular genetic studies. Tier I testing identifies the most common genetic causes of childhood hearing loss.

Mutations in *GJB2*, which encodes the protein, connexin 26, are the most frequent cause of autosomal recessive nonsyndromic hearing loss. Mutations in the *GJB2* gene are found in various populations, with carrier rates of approximately 1 in 30 in the United States Caucasian population, and 1 in 20 in the Ashkenazi Jewish population. Large deletions involving *GJB6* are identified in approximately 1% of North American patients with hearing loss, typically in association with a single *GJB2* mutation (digenic inheritance). Nonsyndromic hearing loss secondary to mutations in the *MTTS1* and *MTRNR1* genes accounts for about 1% of childhood hearing loss in the United States. Mutations in *MTTL1* and *MTTK* are associated with MELAS and MERRF which usually present with neurological symptoms. The 3243 mutation in *MTTL1* has also been associated with Maternally inherited diabetes mellitus and deafness (MIDD).

Indications:

- Patient with hearing loss of unknown etiology and no previous molecular genetic studies.

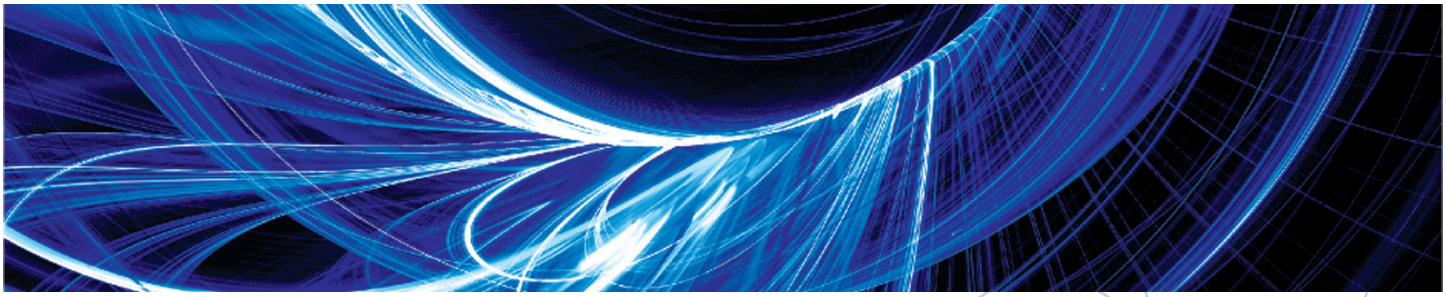
Specimen: At least 2 mLs whole blood in a lavender top (EDTA) tube. Alternately, six cytobrushes (cheek swabs) may be collected. (Please call 1-513-636-4474 for a free cytobrush collection kit). Label each tube or brush with patient's name, birth date, and date of collection.

Testing Methodology: PCR-based sequencing of exon 2 and the exon1/intron1 boundary of the *GJB2* gene; PCR and gel electrophoresis of the 342kb deletion in the *GJB6* gene; PCR based sequence analysis for the specific mutations in in mtDNA *MTRNR1* (961, 1555,1494), *MTTS1* (7445, 7511), *MTTL1* (3242, 3271), and *MTTK* (8344).

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



Note: *GJB2* sequencing, *GJB6* deletion analysis and hearing loss mtDNA panel are also orderable as individual tests.

Test Sensitivity:

Overall, approximately 40% of the genetic causes of hearing loss can be identified through the **Hearing Loss Panel Tier I**. Mutations in the *GJB2* gene account for approximately 18% of congenital sensorineural hearing loss in our Midwestern U.S. population. PCR-based sequencing detects > 99% of mutations (nucleotide substitutions, and small base pair insertions and deletions) in *GJB2*. Deletions in the *GJB6* gene are identified in approximately 1-2% of individuals with hearing loss and heterozygous mutations in *GJB2*. The 342kb deletion in *GJB6* is the most commonly identified deletion in this gene; this test methodology does not detect other very rare deletions in *GJB6*. Approximately 1% of individuals with hearing loss carry a mutation in one of the mitochondrial genes associated with non-syndromic hearing loss, specifically *MTTS1* and *MTRNR1*. Patients with mutations in *MTTL1* and *MTTK* very rarely have isolated sensorineural hearing loss before developing other symptoms of MERRF or MELAS. 70% of the mitochondrial mutations related to non-syndromic hearing loss are detected by our targeted mutation screening protocol.

Turn-Around Time: 28 days

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

CPT Codes: 81252, 81254, 81401

Results: Each **Hearing Loss Panel Tier I** test report include 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.

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References:

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Jacobs, H. T., T. P. Hutchin, et al. (2005). "Mitochondrial DNA mutations in patients with postlingual, nonsyndromic hearing impairment." Eur J Hum Genet 13(1): 26-33.

Kokotas, H., M. B. Petersen, et al. (2007). "Mitochondrial deafness." Clin Genet 71(5): 379-391.

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Preciado, D. A., L. H. Lim, et al. (2004). "A diagnostic paradigm for childhood idiopathic sensorineural hearing loss." Otolaryngol Head Neck Surg 131(6): 804-809.

Scott, D. A., M. L. Kraft, et al. (1998). "Identification of mutations in the connexin 26 gene that cause autosomal recessive nonsyndromic hearing loss." Hum Mutat 11(5): 387-394.

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