Hereditary Hearing Loss - GJB2 and GJB6 Testing

Last Literature Review: March 2022 Last Update: November 2022

Hearing loss can be syndromic or nonsyndromic and may be a result of genetic, physiologic, or disease factors. Depending on the cause, hearing loss may have a variable age of onset from birth to early childhood and range in severity from mild to profound. A genetic cause is found in 50% of individuals born with hearing loss. Genetic testing to determine the etiology of hearing loss can identify previously unrecognized syndromic forms of hearing loss and may be used for genetic counseling to assess the chance of recurrence.[1]

Disease Overview

Symptoms

Hearing loss may be:

- Prelingual or postlingual in onset
- Syndromic (associated with other findings) or nonsyndromic
- Sensorineural, conductive, or mixed etiology
- Variable in presentation based on genetic and environmental cause(s) of the hearing loss

Prevalence and/or Incidence

- 1/500 born with hearing loss[2]
  - 50% of individuals with hearing loss have a genetic cause.[2]
- Up to 50% of individuals with severe-to-profound autosomal recessive hearing loss have one or two pathogenic variants in the *GJB2* gene. However, the prevalence varies by ethnicity.[2]
  - Approximately 99% of these individuals are homozygous or compound heterozygous for pathogenic variants in *GJB2*.
  - Approximately 1% of these individuals have one *GJB2* pathogenic variant and a *GJB6* deletion.
    - Large *GJB6* gene deletions involving *GJB2* cis-regulatory elements result in loss of *GJB2* expression.

Genotype-Phenotype Correlation

- *GJB2* (connexin 26) or *GJB6* (connexin 30) biallelic variants: sensorineural NSHL that is commonly stable and bilateral with prelingual onset
  - Truncating *GJB2* variants are associated with a higher chance for severe hearing loss than nontruncating variants
- *GJB2* autosomal dominant sequence variants: causative of autosomal dominant deafness type 3A (DFNA3A) as well as syndromic forms of hearing loss including keratosis and ichthyosis

Test Interpretation

Connexin 26 (*GJB2*) Sequencing and Deletion/Duplication

Gene(s) Tested

GJB2 (NM_004004)

Featured ARUP Testing

Connexin 26 (GJB2) Sequencing and Deletion/Duplication 3004720

Method: Massively Parallel Sequencing

- Diagnostic test or carrier screening for *GJB2*-related nonsyndromic hearing loss (NSHL)
- May be used as first-tier genetic test for individuals with suspected autosomal recessive NSHL

Hearing Loss, Nonsyndromic, Connexin 30 (GJB6) 2 Deletions 2001956

Method: Polymerase Chain Reaction (PCR)/Capillary Electrophoresis

- Diagnostic test for individuals with NSHL and one identified *GJB2* variant
- Carrier screening if family history of *GJB6* deletion or for reproductive partner of individual with *GJB6* or *GJB2* pathogenic variants

Familial Targeted Sequencing 3005867

Method: Massively Parallel Sequencing

- Testing for a known familial sequence variant by sequencing gene of interest. A copy of the family member's test result documenting the familial gene variant is REQUIRED.
- To determine if the variant(s) of interest are detectable by this assay, contact an ARUP genetic counselor at 800-242-2787.

Testing Procedure

This test is performed using the following sequence of steps:

- Selected genomic regions, primarily coding exons and exon-intron boundaries, from the targeted genes are isolated from extracted genomic DNA using a probe-based hybrid capture enrichment workflow.
- Enriched DNA is sequenced by massively parallel sequencing (MPS; also known as next generation sequencing [NGS]) followed by paired-end read alignment and variant calling using a custom bioinformatics pipeline. The pipeline includes an algorithm for detection of large (single exon-level or larger) deletions and duplications.
- Sanger sequencing is performed as necessary to fill in regions of low coverage and in certain situations, to confirm variant calls.
- Large deletion/duplication calls made using MPS are confirmed by an orthogonal exon-level microarray when sample quality and technical conditions allow.

Clinical Sensitivity

Greater than 99% for GJB2-associated hearing loss (DFNB1A)[3]

Analytic Sensitivity/Specificity

Variant Class	Analytic Sensitivity (PPA) Estimate[a] (%) and 95% Credibility Region (%)	Analytic Specificity (NPA) (%)
SNVs	>99 (96.9-99.4)	>99.9
Deletions 1-10 bp[b]	93.8 (84.3-98.2)	>99.9
Insertions 1-10 bp[b]	94.8 (86.8-98.5)	>99.9
Exon-level[c] Deletions	97.8 (90.3-99.8) (single coding GJB2 exon)	>99.9
Exon-level[c] Duplications	83.3 (56.4-96.4) (single coding GJB2 exon)	>99.9

[a]Genes included on this test are a subset of a larger methods-based validation from which the PPA values are derived. These values do not apply to testing performed by multiplex ligation-dependent probe amplification (MLPA).

[b]Variants greater than 10 bp may be detected, but the analytic sensitivity may be reduced.

[c]In most cases, a single exon deletion or duplication is less than 450 bp and 3 exons span a genomic region larger than 700 bp.

bp, base pairs; NPA, negative percent agreement; PPA, positive percent agreement; SNVs, single nucleotide variants

Limitations

- A negative result does not exclude a heritable form of hearing loss.
- Diagnostic errors can occur due to rare sequence variations.
- Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplant.
- The following will not be evaluated:
  - Variants outside the coding regions, intron-exon boundaries and selected noncoding variants of *GJB2*
  - Regulatory region variants and deep intronic variants
  - Breakpoints of large deletions/duplications
  - Noncoding transcripts
- The following may not be detected:
  - Deletions/duplications/insertions of any size by massively parallel sequencing
  - Some variants due to technical limitations in the presence of pseudogenes, repetitive, or homologous regions
  - Low-level somatic variants

Hearing Loss, Nonsyndromic, Connexin 30 (*GJB6*) 2 Deletions

Gene(s) Tested

GJB6

Clinical Sensitivity

Dependent on ethnicity[2]

Analytical Sensitivity

99%

Limitations

- Diagnostic errors can occur due to rare sequence variations.
- *GJB6* variants other than 309kb del(GJB6-D13S1830) and 232kb del(GJB6-D13S1854) will not be identified.
- Interpretation of this test result may be impacted if the individual has had an allogeneic stem cell transplant.

References

1. Alford RL, Arnos KS, Fox M, et al. American College of Medical Genetics and Genomics guideline for the clinical evaluation and etiologic diagnosis of hearing loss. *Genet Med*. 2014;16(4):347-355.

2. Shearer AE, Hildebrand MS, Smith RJH. Hereditary hearing loss and deafness overview. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews*. University of Washington, Seattle. Last update Jul 2017; accessed Dec 2021.

3. Smith RJH, Jones MKN. Nonsyndromic hearing loss and deafness, DFNB1. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews.* University of Washington, Seattle. Last update Aug 2016; accessed Dec 2021.

Additional Resources

Usami S, Nishio S. Nonsyndromic hearing loss and deafness, mitochondrial. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews.* University of Washington, Seattle. Last update Jun 2018; accessed Dec 2021.

Related Information

Hereditary Nonsyndromic Hearing Loss - Connexin 26 or 30

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