Hereditary Hearing Loss - GJB2 Testing

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In the United States, up to 3 in every 1,000 infants are born with hearing loss, with the majority of cases being hereditary. Hereditary hearing loss can be syndromic or nonsyndromic. Age of onset varies, and severity can range from mild to profound. The American College of Medical Genetics and Genomics (ACMG) recommends genetic testing to determine the etiology of confirmed hearing loss in individuals with a clinical picture compatible with a hereditary cause. An estimated 50% of autosomal recessive nonsyndromic hearing loss is caused by variants in the DFNB1 locus (*GJB2* and *GJB6* genes).[1]

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)

Disease Overview

Prevalence and/or Incidence

- 2-3/1,000 born with hearing loss[1]
  - 70% of hereditary hearing loss is nonsyndromic.[1]
    - 50% of autosomal recessive (AR) nonsyndromic hearing loss results from variants in the *GJB2* and *GJB6* genes.[1]
      - Approximately 1% of these individuals are compound heterozygous for a *GJB2* variant and a large deletion involving *GJB2* cis-regulatory elements (eg, *GJB6*) resulting in loss of *GJB2* expression.[2]

Genotype-Phenotype Correlation

- *GJB2* (connexin 26) or *GJB6* (connexin 30) biallelic variants: sensorineural nonsyndromic hearing loss (NSHL) that is commonly stable and bilateral with prelingual onset[2]
  - Truncating *GJB2* variants are associated with a higher chance for severe hearing loss than nontruncating variants.[2]
- *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[2]

Test Interpretation

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

Gene(s) Tested

GJB2 (NM_004004)

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)[2]

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:
  - Connexin 30 (*GJB6*) variants
  - 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

References

1. Li MM, Tayoun AA, DiStefano M, et al. Clinical evaluation and etiologic diagnosis of hearing loss: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2022;24(7):1392-1406.

2. Smith RJH, Azaiez H, Booth K. *GJB2*-related autosomal recessive nonsyndromic hearing loss. In: Adam MP, Feldman J, Mirzaa GM, et al, eds. *GeneReviews*. University of Washington, Seattle; 1993-2024. Updated Jul 2023; accessed Sep 2024.