

Hearing Loss Panel, Nonsyndromic (*GJB2*) Sequencing, (*GJB6*) 2 Deletions and Mitochondrial 2 Mutations

TO DETERMINE CARRIER STATUS OR ETIOLOGY FOR NONSYNDROMIC HEARING LOSS

Disease Overview

- Nonsyndromic hearing loss (NSHL) is characterized by sensorineural hearing loss with no other associated medical findings.
- Hearing loss associated with *GJB2* (Connexin 26) or *GJB6* (Connexin 30) mutations is usually bilateral and stable with prelingual onset.
- Hearing loss associated with mitochondrial (mtDNA) mutations varies in severity and age of onset.
- m.1555A>G is associated with stable, severe to profound hearing loss with variable age of onset.
- m.7445A>G is associated with palmoplantar keratoderma and progressive, mild to severe hearing loss of childhood onset.

Epidemiology

- One in 1,000 newborns has profound deafness.
- One in 2,600 newborns has NSHL.
- Approximately one in 6,500 individuals has NSHL due to *GJB2* mutations.
- Approximately one in 30 individuals with NSHL has a *GJB6* deletion.
- Approximately one in 50 individuals with NSHL has a mitochondrial mutation.

Genetics

- 77 percent of nonsyndromic congenital hearing loss is autosomal recessive.
- Half of all autosomal recessive NSHL (DFNB1) occurs due to mutations in the *GJB2* gene. The most common *GJB2* mutation in persons of Northern European ancestry is c.35delG.
- Compound heterozygosity for a *GJB2* mutation and a *GJB6* deletion accounts for 2–4 percent of autosomal recessive NSHL.
- Approximately 20 percent of *GJB2* heterozygotes with NSHL have a deletion in the *GJB6* gene.
- Homozygosity or compound heterozygosity for *GJB6* deletions is rare.
- 1–2 percent of NSHL occurs due to mtDNA mutations, with dominant maternal inheritance.

Indications for Ordering

- Diagnostic testing for individuals with NSHL.
- Carrier testing for relatives of an affected individual with a known *GJB2*, *GJB6*, or mtDNA mutation.

Interpretation

- Lack of detectable mutations does not exclude a diagnosis of NSHL.
- Heterozygosity for a *GJB2* or *GJB6* mutation connotes carrier status for NSHL but is not responsible for symptoms. Rarely, *GJB2* mutations can cause autosomal dominant hearing loss.
- Compound heterozygosity for a *GJB6* deletion and a *GJB2* mutation causes autosomal recessive NSHL.
- The presence of an mtDNA mutation is consistent with NSHL.
- Homozygosity for a *GJB2* or *GJB6* mutation results in NSHL.

Limitations

- *GJB2* regulatory region mutations, deep intronic mutations, and large deletions/duplications will not be detected.
- Only the targeted *GJB6* and mtDNA mutations will be identified.
- The etiology of hearing loss caused by other genetic or environmental causes will not be determined.
- Rare diagnostic errors can occur due to primer-site mutations.

Methodology

- *GJB2* Sequencing: Invader[®] DNA assay targets the c.35delG mutation in the *GJB2* gene; additionally, the entire coding region, exon/intron boundaries, and 5'-UTR of the *GJB2* gene is bidirectionally sequenced.
- *GJB6* 2 Deletions: Multiplex PCR using deletion-specific primers followed by capillary gel electrophoresis.
- mtDNA 2 Mutations: Targeted bidirectional sequencing of mitochondrial DNA 1555 and 7445 regions.

Indications for Ordering

- Connexin 26 (*GJB2*) Sequencing (ARUP test #0051374)—for patients with NSHL.
- Hearing Loss, Nonsyndromic, Connexin 30 (*GJB6*) 2 Deletions (ARUP test #2001956)—for patients with NSHL and only one identifiable *GJB2* mutation.
- Hearing Loss, Nonsyndromic Mitochondrial DNA 2 Mutations (ARUP test #2002044)—for patients with NSHL without deleterious mutations in *GJB2* or *GJB6*.
- Connexin 26 (*GJB2*), 35delG Mutation (ARUP test #0051383)—for patients with a family history of the *GJB2* 35delG mutation.
- Hearing Loss, Nonsyndromic Panel (*GJB2*) Sequencing, (*GJB6*) 2 Deletions and Mitochondrial DNA 2 Mutations (ARUP test #2001992)—for patients who have not had prior testing to determine the etiology for NSHL.

References

1. ACMG statement. Genetics Evaluation Guidelines for the Etiologic Diagnosis of Congenital Hearing Loss. *Genet Med* 2002;4(3):162–71.
2. Putcha GV, et al. A multicenter study of the frequency and distribution of *GJB2* and *GJB6* mutations in a large North American cohort. *Genet Med* 2007; 9(7):413–26.
3. del Castillo FJ, et al. A novel deletion involving the connexin-30 gene, del(*GJB6*-D13S1854), found in trans with mutations in the *GJB2* gene (connexin-26) in subjects with DFNB1 non-syndromic hearing impairment. *J Med Genet* 2005;42:588–94.
4. Bravo O, et al. Cochlear 6talterations in deaf and unaffected subjects carrying the deafness-associated 1555G mutation in the mitochondrial 12S rRNA gene. *Biochem Biophys Res Commun* 2006;344(2):511–6.

Test Information

0051374	Connexin 26 (<i>GJB2</i>) Sequencing
0051383	Connexin 26 (<i>GJB2</i>), 35delG Mutation
2001956	Hearing Loss, Nonsyndromic, Connexin 30 (<i>GJB6</i>) 2 Deletions
2001992	Hearing Loss, Nonsyndromic Panel (<i>GJB2</i>) Sequencing, (<i>GJB6</i>) 2 Deletions and Mitochondrial DNA 2 Mutations
2002044	Hearing Loss, Nonsyndromic Mitochondrial DNA 2 Mutations

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.