NONSYNDROMIC SENSORINEURAL HEARING LOSS, DFNB1

GJB2 & GJB6 SEQUENCING and GJB6 DELETION ANALYSIS

Hearing loss is the most common sensory disorder, present in 1 of every 500 newborns. The majority of prelingual hearing loss is genetic, and most cases are nonsyndromic. The different loci for nonsyndromic deafness are designated DFN and are named based on mode of inheritance.

**DFNA:** Autosomal dominant
**DFNB:** Autosomal recessive
**DFNX:** X-linked

The number following the above designations reflects the order of gene mapping and/or discovery.

An estimated 75% to 80% of nonsyndromic genetic hearing loss is autosomal recessive. In many populations, approximately 50% of this hearing loss can be attributed to DFNB1, which is variable in presentation but typically characterized by congenital, non-progressive, mild to profound sensorineural hearing loss. DFNB1 (OMIM 220290 and 612645) is caused by mutations in *GJB2* and/or *GJB6* (OMIM 121001 and 604418). The majority of individuals with DFNB1 have two identifiable mutations in *GJB2* (connexin 26). However, about 2% of individuals with DFNB1 have a single heterozygous mutation in *GJB2* and one of two large deletions that include part of *GJB6* (connexin 30).

DFNA3 (OMIM 601544 and 612643), an autosomal dominant form of hearing loss, is also caused by mutations in *GJB2* and *GJB6*. DFNA3 is typically characterized by childhood-onset, progressive, moderate-to-severe high-frequency sensorineural hearing loss. Ten missense mutations in *GJB2* and one missense mutation in *GJB6* are associated with DFNA3.

Several autosomal dominant dermatologic conditions have also been associated with mutations in *GJB2* and *GJB6*.

**GJB2**

- **Palmoplantar keratoderma with deafness (OMIM 148350)**
  - High-frequency progressive hearing loss
  - Progressive hyperkeratosis of palms and soles
- **Keratitis-ichthyosis-deafness (KID) syndrome (OMIM 148210) and Hystrix-like ichthyosis-deafness (HID) syndrome (OMIM 602540)**
  - Profound hearing loss
  - Vascularizing keratitis
  - Progressive erythrokeratoderma
  - Scarring alopecia
  - Predisposition to squamous cell carcinoma
  - KID and HID syndromes are caused by the same *GJB2* mutation and likely represent a single clinical entity
- **Vohwinkel syndrome (OMIM 124500)**
  - Often associated with mild to moderate hearing loss
  - Diffuse keratoderma
  - Pseudoainhum (circumferential hyperkeratosis of the digits) which can lead to autoamputation
**Bart-Pumphrey syndrome (OMIM 149200)**
- Congenital profound hearing loss
- Knuckle pads
- Leukonychia (white discoloration on nails)
- Palmoplantar keratoderma

**GJB6**

**Hidrotic ectodermal dysplasia 2 (Clouston syndrome) (OMIM 129500)**
- Normal function of sweat and sebaceous glands; normal teeth
- Alopecia or hypotrichosis
- Nail dystrophy
- Skin hyperpigmentation
- Clubbing of the fingers

**Testing:**
Testing is performed by sequencing untranslated exon 1, coding exon 2, and the surrounding intronic regions of *GJB2*. This will detect point mutations, small deletions, and small insertions. It will not detect a partial or whole gene deletion or duplication. *GJB6* is analyzed for the common 309 kb deletion, and coding exon 3 is sequenced.

A negative test result does not rule out a genetic cause of sensorineural hearing loss as there are many other genes associated with this trait.

**Turn-around time:** 10 - 14 business days

**CPT codes and cost:**
- GJB2 Proband (Sequencing): 81252 $300
- GJB2 Known Mutation testing: 81253 $200
- GJB6 Proband (Deletion and Sequencing): 81254 $300

**BILLING:** We do not bill third party payers (insurance companies) for samples received from external sources. The person or institution (Clinical Lab; Send-out Lab; Physician Office) sending the sample is responsible for full payment of the invoices within 30 days of receipt of the invoice. If the patient is on Medical assistance, please contact the lab prior to sample submission. Direct patient billing will only be accepted when a valid credit card form is received with the patient sample.

**Online resources:**
GeneReviews:

Facsimile Verification Form

Name of Facility receiving Fax: __________________________________________________
Name of Physician/Lab receiving Fax: ____________________________________________
Street Address: __________________________________________________________________
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Fax Number: ______________________________________________
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By signing this Facsimile Verification Form, I validate the accuracy of the above information and assume responsibility for assuring that the Fax machine is in a location which will maintain confidentiality of all reports transmitted by the Molecular Diagnostics Laboratory of the Alfred I. duPont Hospital for Children, to the above fax number.

Authorized Contact Person: ______________________________________________

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Please complete this Facsimile Verification Form and fax back to 302.651.6795.
If you have any questions regarding this form please contact Susan Kirwin, Assistant Director of The Molecular Diagnostics Laboratory, at 302.651.6777.

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For Direct Patient Billing

Prepayment for the testing services is required prior to beginning our testing. Please complete this form and include this paperwork with the shipment of the patient sample.

Billing questions can be addressed to: Denise Axsmith
Senior Budget/Financial Analyst
Nemours/A.I. duPont Hospital for Children
daxsmith@nemours.org
Phone: 302.651.6802
Fax: 302.651.6881

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