

Hereditary Hearing Loss Screen

Background & Method

Mutations in the *GJB2* and *GJB6* genes at the DFNB1 locus at chromosome 13q12-13 account for about 50% of individuals with severe to profound congenital autosomal recessive nonsyndromic hearing loss (1-3). About 98% of such cases are caused by two mutations (one in each allele) in the gap junction beta 2 gene (*GJB2*, which encodes the connexin 26 protein). The remaining 2% of cases are double heterozygotes with one mutation in the *GJB2* gene and a second large 309 kb deletion involving the nearby *GJB6* gene (gap junction beta 6, which encodes the connexin 30 protein)(5,6).

This test involves DNA sequencing of the coding region of *GJB2* (exon2) and associated intronic regions are sequenced since this should identify ~98% of mutations (test code HHL). Reflex testing, which increases the sensitivity is performed for individuals referred for diagnostic testing in whom only one connexin 26 mutation is detected. In such cases, it is important to determine if there is a second rare mutation or if the individual is a coincidental carrier their deafness has another etiology. Reflex testing will also be performed for cases referred for carrier testing where a specific mutation has not been identified in an affected family member.

The reflex test consists of (1) direct sequencing of PCR-amplified genomic DNA detects mutations in the *GJB2* noncoding exon 1 and flanking intronic junctions and (2) deletion-specific PCR is employed to detect the large 309 kb deletion involving a portion of the *GJB6* gene (*GJB6_D13S1830del309kb*)(ref 5,6). The deletion, previously reported as 342 kb, is more precisely reported as 309 kb (ref 6). Rare deletions with breakpoints outside of this region will not be detected by this test.

Please inquire about information on testing

- a relative with a known *GJB2* mutation (testcode HHLREL)
- only for the *GJB6_D13S1830del309kb* deletion (test code HHL30)

Indications for Testing

- Clarify etiology of childhood onset neurosensory hearing loss or deafness
- Help predict recurrence risk for families with a child with hearing loss or deafness
- Evaluation of a relative with a known connexin 26 mutation (testcode HHLREL)
- Mutation typing for the connexin 30 deletion (test code HHL30) in a symptomatic individual whose previous *GJB2* sequencing test results identified only one mutation.

Genetic Counseling

Genetic counseling can be useful to patients and families considering genetic testing. The laboratory can provide referrals to genetics clinics in the patient's locale or a listing can be found at www.genetests.org

Ordering

1. Obtain blood sample.
2. Fill out a Clinical Lab Request - Genetics for each patient.
(available at <http://depts.washington.edu/labweb/Divisions/MolDiag/MolDiagGen/index.htm>).
- Request "Deafness/Hearing Loss"

3. Provide items needed for test interpretation:
Clinical history: Indicate
Ethnic background
Pedigree
4. Call Laboratory Medicine Community Services at (206)598-6066 to arrange the best method of shipment.

Sample Requirements and Specimen Handling

Whole blood - EDTA (purple top) - adults - 5 mL, minimum - 1 mL.
Samples should be received within 72 hours of collection.
Samples may be refrigerated until shipped.
For prenatal diagnosis specimens, consult laboratory.
Heparin (green top) tubes are not acceptable.

Test Frequency and Reporting

Test results usually within 1-2 weeks of specimen receipt.
A written interpretative report is issued.

References

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2. Hone SW, Smith RJH. Genetic screening for hearing loss. *Clin Otolaryngol* 28:285-290, 2003.
3. Smith RJH, Scott DA, Sheffield VJ, Van Camp G. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2003. Available at <http://www.genetests.org>
4. American College of Medical Genetics, Genetic Evaluation of Congenital Hearing Loss Expert Panel. Genetics evaluation of guidelines for the etiologic diagnosis of congenital hearing loss. *Genetics in Medicine* 4:162-171, 2002. Also available at <http://www.acmg.net/resources/policy-list.asp>.
5. Wu B-L et al., Use of a multiplex PCR/Sequencing strategy to detect both connexin 30 (GJB6) 342 kb deletion and connexin 26 (GJB2) mutations in cases of childhood deafness. *AJMG* 121A:102-108, 2003.
6. del Castillo FJ, Rodriguez-Ballesteros M, Alvarez A, 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. *Am J Med Genet* 42:588-594, 2005..