

Genetic Consultation and Evaluation Related to Hearing Loss

Genetic information provided below, as well as other information on other genetic conditions, may be found at <http://www.genetests.org> and the American College of Medical Genetics Policy Statement (2002) Genetic Evaluation Guidelines for Etiologic Diagnosis of Congenital Hearing Loss. *Genet Med* 4(3):162-171 (<http://www.geneticsinmedicine.org>).

Diagnosis/testing: Genetic forms of hearing loss must be carefully distinguished from acquired (non-genetic) causes of hearing loss. The genetic forms of hearing loss are diagnosed by otologic, audiologic, and physical examination, family history, ancillary testing (such as CT examination of the temporal bone), and DNA-based testing. DNA-based genetic tests are available for many types of syndromic and nonsyndromic deafness, although usually only on a research basis. On a clinical basis, DNA-based testing is available for the diagnosis of branchio-oto-renal (BOR) syndrome (EYA1 gene), Mohr-Tranebjaerg syndrome (deafness-dystonia-optic atrophy syndrome; TIMM8A gene), Pendred syndrome (SLC26A4 gene), Usher syndrome type IIA (USH2A gene), one mutation in USH3A, DFNB1 (GJB2 gene), DFNB3 (POU3F4 gene), DFNB4 (SLC26A4 gene), and DFNA6/14 (WFS1 gene). Testing for deafness-causing mutations in the GJB2 gene (which encodes the protein connexin 26) and GJB6 (which encodes the protein connexin 30) plays a prominent role in diagnosis and genetic counseling.

Evaluation Strategy: Correctly diagnosing the specific cause of hearing loss in an individual can provide information on prognosis and is essential for accurate genetic counseling. The following is usually required:

- **Family history:** A three-generation family history with attention to other relatives with hearing loss and associated findings should be obtained. Documentation of relevant findings in relatives can be accomplished either through direct examination of those individuals or through review of their medical records, including audiograms, otologic examinations, and DNA-based testing.
- **Clinical examination:** All persons with hearing loss of unknown cause should be evaluated for features associated with syndromic deafness. Important features include branchial cleft pits, cysts or fistulae; pre-auricular pits; telecanthus; heterochromia iridis; white forelock; pigmentary anomalies; high myopia; pigmentary retinopathy; goiter; and cranio-facial anomalies. Because the autosomal dominant forms of syndromic deafness tend to have variable expressivity, correct diagnosis may depend on careful physical examination of the proband as well as other family members.
- **Audiologic findings:** Hearing status can be determined at any age (see Definition). Individuals with progressive hearing loss should be evaluated for Alport syndrome, Pendred syndrome, and Stickler syndrome and have temporal bone-computed tomography. Sudden or rapidly progressive hearing loss can be seen with temporal bone anomalies (as in Pendred syndrome and BOR syndrome), neoplasms (associated with NF2), and immunologic-related deafness, as well as trauma, infections (syphilis, Lyme disease), and metabolic, neurologic, or circulatory disturbances.

- Temporal bone CT: Computed tomography of the temporal bones is useful for detecting malformations of the inner ear (i.e., Mondini deformity, Michel aplasia, enlarged/dilated vestibular aqueduct), which should be considered in persons with progressive hearing loss. Because inner ear defects (enlarged/dilated vestibular aqueduct and Mondini dysplasia) are associated with mutations in SLC26A4 (see Pendred syndrome), detection of temporal bone anomalies by CT examination can help direct molecular genetic testing (see below).
- Testing: Cytomegalovirus (CMV) testing needs to be considered in infants with sensorineural hearing loss. The diagnosis of in utero CMV exposure requires detection of elevated CMV antibody titers or a positive urine culture in the neonatal period. Although these tests can be obtained at a later time, their interpretation is confounded by the possibility of postnatally acquired CMV infection, which is common and is not associated with hearing loss.
- Molecular genetic testing: Molecular genetic testing of the GJB2 gene (which encodes the protein connexin 26) and the GJB6 gene (which encodes the protein connexin 30) (see DFNB1), molecular genetic testing should be considered in the evaluation of individuals with congenital nonsyndromic sensorineural hearing loss. Strong consideration also should be given to "pseudo-dominant" inheritance of DFNB1. Pseudo-dominant inheritance refers to occurrence of an autosomal recessive disorder in two or more generations of a family; such inheritance tends to occur when the carrier rate in the general population is high. GJB2 and GJB6 molecular genetic testing should be performed in families with nonsyndromic hearing loss in which two generations are involved.
- Inner ear defects: (enlarged/dilated vestibular aqueduct and Mondini dysplasia) are associated with mutations in SLC26A4 (see Pendred syndrome), and the detection of these temporal bone anomalies by CT examination should prompt consideration of molecular genetic testing.
- Although molecular genetic testing is available for a number of these genes, the large size of many (MYO7A, MYO15) and their low relative contribution to deafness (DFNB9, HDIA1, TECTA, COCH, POU4F3) makes it impractical to offer such testing on a clinical basis at this time.

Genetic Counseling: Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal or cultural issues that individuals may face or to substitute for consultation with a genetic professional.

Genetic counseling and risk assessment depend on accurate determination of the specific genetic diagnosis. In the absence of a specific diagnosis, empiric recurrence risk figures, coupled with GJB2 and GJB6 molecular genetic testing results, can be used for genetic counseling.

Mode of Inheritance: Hereditary hearing loss may be inherited in an autosomal dominant manner, an autosomal recessive manner, or an X-linked recessive manner. Mitochondrial disorders with hearing loss also occur.

1. Risk to Family Members - Autosomal **Dominant** Hereditary Hearing Loss

- Parents of a Proband
 - Most individuals diagnosed as having autosomal dominant hereditary hearing loss have an affected parent; the family history is rarely negative.

- A proband with autosomal dominant hereditary hearing loss may have the disorder as the result of a de novo gene mutation. The proportion of cases caused by de novo mutations is unknown but thought to be small. Recommendations for the evaluation of parents of a proband with an apparent de novo mutation include audiometry and genetic testing. Although most individuals diagnosed with autosomal dominant hereditary hearing loss have an affected parent, the family history may appear to be negative because of alternate paternity, adoption, early death of a parent, failure to recognize hereditary hearing loss in family members, late onset in a parent, reduced penetrance of the mutant allele in an asymptomatic parent, or a de novo mutation for hereditary hearing loss.
- Sibs of a proband
 - The risk to sibs depends upon the genetic status of a proband's parents. If one of the proband's parents has a mutant allele, the risk to the sibs of inheriting the mutant allele is 50%. Depending upon the specific syndrome, clinical severity and disease phenotype may differ between individuals with the same mutation; thus, age of onset and/or disease progression may not be predictable.
- Offspring of a proband
 - Individuals with autosomal dominant hereditary hearing loss have a 50% chance of transmitting the mutant allele to each child.
 - Depending upon the specific syndrome, clinical severity and disease phenotype may differ between individuals with the same mutation; thus, age of onset and/or disease progression may not be predictable.

2. Risk to Family Members - Autosomal **Recessive** Hereditary Hearing Loss

- Parents of a proband
 - The parents are obligate heterozygotes and, therefore, carry a single copy of a disease-causing mutation.
 - Heterozygotes are asymptomatic.
- Sibs of a proband
 - At conception, the sibs have a 25% chance of being affected, a 50% chance of being unaffected and carriers, and a 25% chance of being unaffected and not carriers. Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3. Heterozygotes are asymptomatic. .
- Offspring of a proband.
 - All of the offspring are obligate carriers.
 - Depending upon the specific syndrome, clinical severity and disease phenotype may differ between individuals with the same mutations; thus, age of onset and/or disease progression may not be predictable. For probands with GJB2-related deafness and severe-to-profound deafness, siblings with the identical GJB2 genotype have a 91% chance of having severe-to-profound deafness and a 9% chance of having mild-to-moderate deafness. For probands with GJB2-related deafness and mild-to-moderate deafness, siblings with the identical GJB2 genotype have a 66% chance of having mild-to-moderate deafness and a 34% chance of having severe-to-profound deafness.
- Other family members of a proband.
 - The sibs of obligate heterozygotes have a 50% chance of being heterozygotes.

3. Risk to Family Members - **X-Linked Recessive** Hereditary Hearing Loss

- Parents of a proband:

- Women who have an affected son and another affected male relative are obligate heterozygotes. If pedigree analysis reveals that an affected male is the only affected individual in the family, several possibilities regarding his mother's carrier status need to be considered:
 - He has a de novo disease-causing mutation and his mother is not a carrier;
 - His mother has a de novo disease-causing mutation, as either: a “germline mutation” (i.e., at the time of her conception and thus present in every cell of her body); or “germline mosaicism” (i.e., in her germ cells only);
 - His maternal grandmother has a de novo disease-causing mutation.
 - No data are available, however, on the frequency of de novo gene mutations nor on the possibility or frequency of germline mosaicism in the mother.
- Sibs of a proband:
 - The risk to sibs depends upon the genetic status of the proband's mother. A female who is a carrier has a 50% chance of transmitting the disease-causing mutation with each pregnancy. Sons who inherit the mutation will be affected; daughters who inherit the mutation are carriers and are likely to be unaffected.
 - If the mother is not a carrier, the risk to sibs is low but greater than that of the general population because the possibility of germline mosaicism exists. Depending upon the specific syndrome, clinical severity and disease phenotype may differ between individuals with the same mutation; thus, age of onset and/or disease progression may not be predictable.
- Offspring of a proband.
 - Males with X-linked hereditary hearing loss will pass the disease-causing mutation to all of their daughters and none of their sons.
- Other family members of a proband.
 - The proband's maternal aunts may be at risk of being carriers and the aunt's offspring, depending upon their gender, may be at risk of being carriers or of being affected.

4. Risk to Family Members - **Mitochondrial** Disorders with Hearing Loss as a Possible Feature

- Parents of a proband
 - The mother of a proband (usually) has the mitochondrial mutation and may or may not have symptoms. The father of a proband is not at risk of having the disease-causing mtDNA mutation. Alternatively, the proband may have a de novo mitochondrial mutation.
- Sibs of a proband
 - The risk to the sibs depends upon the genetic status of the mother. If the mother has the mitochondrial mutation, all sibs are at risk for inheriting it.
- Offspring of a proband
 - All offspring of females with an mtDNA mutation are at risk of inheriting the mutation. Offspring of males with an mtDNA mutation are not at risk.
- Other family members of a proband.
 - The risk to other family members depends upon the genetic status of the proband's mother. If she has a mitochondrial mutation, her siblings and mother are also at risk.

5. Risk to Family Members - **Empiric Risks**

If a specific diagnosis cannot be established (and/or the mode of inheritance cannot be established), the following empiric figures can be used:

- The subsequent offspring of a hearing couple with one deaf child and an otherwise negative family history of deafness have an 18% empiric probability of deafness in future children. If the deaf child does not have DFNB1 based on molecular genetic testing of GJB2 (which codes for the protein connexin 26), the recurrence risk is 14% for deafness unrelated to connexin 26. If the hearing couple is consanguineous, the subsequent offspring have close to a 25% probability of deafness due to the high likelihood of an autosomal recessive disorder.
- The offspring of a deaf person and a hearing person have a 10% empiric risk of deafness. Most of the risk is attributed to autosomal dominant syndromic deafness. If both syndromic deafness and a family history of autosomal recessive inheritance can be excluded, the risk of deafness is chiefly related to pseudo-dominant occurrence of recessive deafness. GJB2 (which codes for the protein connexin 26) testing can identify much of this risk.
- The child of a non-consanguineous deaf couple in whom autosomal dominant deafness has been excluded has an approximately 15% empiric risk for deafness. However, if both parents have connexin 26-related deafness, the risk to their offspring is 100%. Conversely, if the couple has autosomal recessive deafness known to be caused by mutations at two different loci, the chance of deafness in their offspring is below that of the general population.
- The child of a hearing sib of a deaf proband (presumed to have autosomal recessive nonsyndromic deafness) and a deaf person has a 1/200 (0.5%) empiric risk for deafness, or five times the general population risk. GJB2 and GJB6 molecular genetic testing can clarify if the risks are higher. If the hearing sib is a carrier of a GJB2 mutation or a GJB6 mutation and marries a person with DFNB1 deafness, the chance of having a deaf child is 50%.

Related Genetic Counseling Issues:

- Communication with individuals who are deaf requires the services of a skilled interpreter.
- Deaf persons may view deafness as a distinguishing characteristic and not as a handicap, impairment, or medical condition requiring a “treatment” or “cure”, or to be “prevented”. In fact, having a child with deafness may be preferred over having a child with normal hearing [Arnos et al 1992].
- Many deaf people are interested in obtaining information and social services rather than information about prevention, reproduction, or family planning. As in all genetic counseling, it is important for the counselor to identify, acknowledge, and respect the individual's/family's questions, concerns, and fears [Middleton et al 1998].
- The use of certain terms is preferred: probability or chance vs. risk; deaf and hard of hearing vs. hearing impaired. Terms such as “affected”, “abnormal”, and “disease-causing” should be avoided.

DNA Banking:

- DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only.