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Deafness and Hereditary Hearing Loss Overview

Authors: **Richard JH Smith, MD**
Guy Van Camp, PhD

About the Authors / Author History

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Summary

Disease characteristics. Several hundred genes are known to cause hereditary hearing loss and deafness. The hearing loss may be conductive, sensorineural, or a combination of both; syndromic or nonsyndromic; and prelingual (before language develops) or postlingual (after language develops).

Diagnosis/testing. Genetic forms of hearing loss must be 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 molecular genetic testing. Molecular genetic tests are available for many types of syndromic and nonsyndromic deafness, often only on a research basis. On a clinical basis, molecular genetic testing is available for the diagnosis of branchiootorenal (BOR) syndrome *(EYA1* gene), Mohr-Tranebjaerg syndrome (deafness-dystonia-optic atrophy syndrome; *TIMM8A* gene), Pendred syndrome *(SLC26A4* gene), Usher syndrome type 2A *(USH2A* gene), Usher syndrome type 3 (one mutation in *USH3A*), DFNA3 and DFNB1 *(GJB2* and *GJB6* genes), DFN3 *(POU3F4* gene), DFNB4 *(SLC26A4* gene), DFNA6/14 *(WFS1* gene), DFNA8/12, DFNB9 *(OTOF* gene), and DFNB21 *(TECTA* 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.

Management. Hereditary hearing loss is managed by a team including an otolaryngologist, an audiologist, a clinical geneticist, and a pediatrician, and sometimes an educator of the Deaf, a neurologist, and a pediatric ophthalmologist. Treatment includes hearing aids and vibrotactile devices; cochlear implantation is considered in children over

12 months of age with severe-to-profound hearing loss. Early auditory intervention through amplification, otologic surgery, or cochlear implantation is essential for optimal cognitive development in children with prelingual deafness; children at risk for hereditary hearing los should receive screening audiometry.

Genetic counseling. Hereditary hearing loss can be inherited in an autosomal dominant, autosomal recessive, or X-linked recessive manner, as well as by mitochondrial inheritance. 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.

Definition

Clinical Manifestations

Hearing loss is described by:

- **Type**
  - **Conductive hearing loss** results from abnormalities of the external ear and/or the ossicles of the middle ear.
  - **Sensorineural hearing loss** results from malfunction of inner ear structures (i.e., cochlea).
  - **Mixed hearing loss** is a combination of conductive and sensorineural hearing loss.
  - **Central auditory dysfunction** results from damage or dysfunction at the level of the eighth cranial nerve, auditory brain stem, or cerebral cortex.
- **Onset**
  - **Prelingual hearing loss** is present before speech develops. All congenital (present at birth) hearing loss is prelingual, but not all prelingual hearing loss is congenital.
  - **Postlingual hearing loss** occurs after the development of normal speech.

Severity of hearing loss. Hearing is measured in **decibels** (dB). The threshold or 0 dB mark for each frequency refers to the level at which normal young adults perceive a tone burst 50% of the time. Hearing is considered normal if an individual's thresholds are within 15 dB of normal thresholds. Severity of hearing loss is graded as:

- Mild (26-40 dB)
- Moderate (41-55 dB)
- Moderately severe (56-70 dB)
- Severe (71-90 dB)
- Profound (90 dB)

Percent hearing impairment. To calculate the percent hearing impairment, 25 dB is subtracted from the pure tone average of 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz. The result is multiplied by 1.5 to obtain an ear-specific level. Impairment is determined by weighting the better ear five times the poorer ear [JAMA 1979] (see Table 1).

Note: 1) Because conversational speech is at approximately 50-60 dB HL (hearing level), calculating **functional** impairment based on pure tone averages can be misleading. For example, a 45-dB hearing loss is functionally much more significant than 30% implies. (2) A different rating scale is appropriate for young children, for whom even limited hearing loss can have a great impact on language development [Northern & Downs 2002].

Table 1. Percent Hearing Impairment

% Impairment	Pure Tone Average (dB) [1]	% Residual Hearing
100%	91 dB	0%
80%	78 dB	20%
60%	65 dB	40%
30%	45 dB	70%

1. Pure tone average of 500 Hz, 1000 Hz, 2000 Hz, 3000 Hz

Frequency of hearing loss. The frequency of hearing loss is designated as:

- Low (<500 Hz)
- Middle (501-2000 Hz)
- High (>2000 Hz)

"Hearing impairment" and "hearing loss" are often used interchangeably by healthcare professionals to refer to hearing determined by audiometry to be below threshold levels for normal hearing.

Deaf (small "d"). A colloquial term that implies hearing thresholds in the severe-to-profound range by audiometry.

Deaf culture (always a capital "D"). Members of the Deaf community in the US are deaf and use American Sign Language. As in other cultures, members are characterized by unique social and societal attributes. Members of the Deaf community (i.e., the Deaf) do NOT consider themselves to be hearing "impaired," nor do they feel that they have a hearing "loss." Rather, they consider themselves deaf. Their deafness is not considered to be a pathology or disease to be treated or cured.

Hard of hearing. This term is more functional than audiologic. It is used by the Deaf to signify that a person has some usable hearing — anything from mild to severe hearing loss. In the Deaf community persons who are deaf do not use oral language, while those who are hard of hearing usually have some oral language.

Establishing the Diagnosis

Physiologic tests objectively determine the functional status of the auditory system and can be performed at any age.

Physiologic tests include:

- **Auditory brainstem response testing (ABR, also known as BAER, BSER).** ABR uses a stimulus (clicks) to evoke electrophysiologic responses, which originate in the eighth cranial nerve and auditory brainstem and are recorded with surface electrodes. ABR "wave V detection threshold" correlates best with hearing sensitivity in the 1500- to 4000-Hz region in neurologically normal individuals; ABR does not assess low frequency (<1500 Hz) sensitivity.
- **Auditory steady-state response testing (ASSR).** ASSR is an electrophysiologic measure of hearing acuity used extensively in Australia, Asia, and Canada, and now more frequently in the United States and Europe. Skin electrodes measure whether the auditory response is phase locking to changes in a continuous tonal stimulus. Since the stimulus is a continuous signal, the average sound pressure level that can be delivered is higher than is possible with ABR, which uses click stimuli. This difference means that ASSR can often provide an estimate of hearing sensitivity in children who demonstrate no response to ABR testing.
- **Evoked otoacoustic emissions (EOAEs).** EOAEs are sounds originating within the cochlea that are measured in the external auditory canal using a probe with a microphone and transducer. EOAEs reflect primarily the activity of the outer hair cells of the cochlea across a broad frequency range and are present in ears with hearing sensitivity better than 40-50 dB HL.
- **Immittance testing (tympanometry, acoustic reflex thresholds, acoustic reflex decay).** Immittance audiometry assesses the peripheral auditory system, including middle ear pressure, tympanic membrane mobility, eustachian tube function, and mobility of the middle ear ossicles.

Audiometry subjectively determines how the individual processes auditory information, i.e., hears. Audiometry consists of behavioral testing and pure tone audiometry.

- **Behavorial testing** includes behavioral observation audiometry (BOA) and visual reinforcement audiometry (VRA). BOA is used in infants from birth to age six months, is highly dependent on the skill of the tester, and is subject to error. VRA is used in children from age six months to 2.5 years and can provide a reliable, complete audiogram, but is dependent on the child's maturational age and the skill of the tester.
- **Pure-tone audiometry** (air and bone conduction) involves determination of the lowest intensity at which an individual "hears" a pure tone, as a function of frequency (or pitch). Octave frequencies from 250 (close to middle C) to 8000 Hz are tested using earphones. Intensity or loudness is measured in decibels (dB), defined as the ratio between two sound pressures. 0 dB HL is the average threshold

for a normal hearing adult; 120 dB HL is so loud as to cause pain. Speech reception thresholds (SRTs) and speech discrimination are assessed.

- **Air conduction audiometry** presents sounds through earphones; thresholds depend on the condition of the external ear canal, middle ear, and inner ear.
- **Bone conduction audiometry** presents sounds through a vibrator placed on the mastoid bone or forehead, thus bypassing the external and middle ears; thresholds depend on the condition of the inner ear.
- **Conditioned play audiometry** (CPA) is used to test children from age 2.5 to five years. A complete frequency-specific audiogram for each ear can be obtained from a cooperative child.
- **Conventional audiometry** is used to test individuals age five years and older; the individual indicates when the sound is heard.
- **Audioprofile** refers to the recording of several audiograms on a single graph (Figure 1). These audiograms may be from one individual at different times, but more frequently they are from different members of the same family segregating deafness usually in an autosomal dominant fashion. By plotting numerous audiograms with age on the same graph, the age-related progression of hearing loss can be appreciated within these families. Often the composite picture is characteristic of specific genetic causes of autosomal dominant nonsyndromic hearing loss. One of the most characteristic audioprofiles is associated with DFNA6/14/38 hearing loss caused by mutations in *WFS1*.

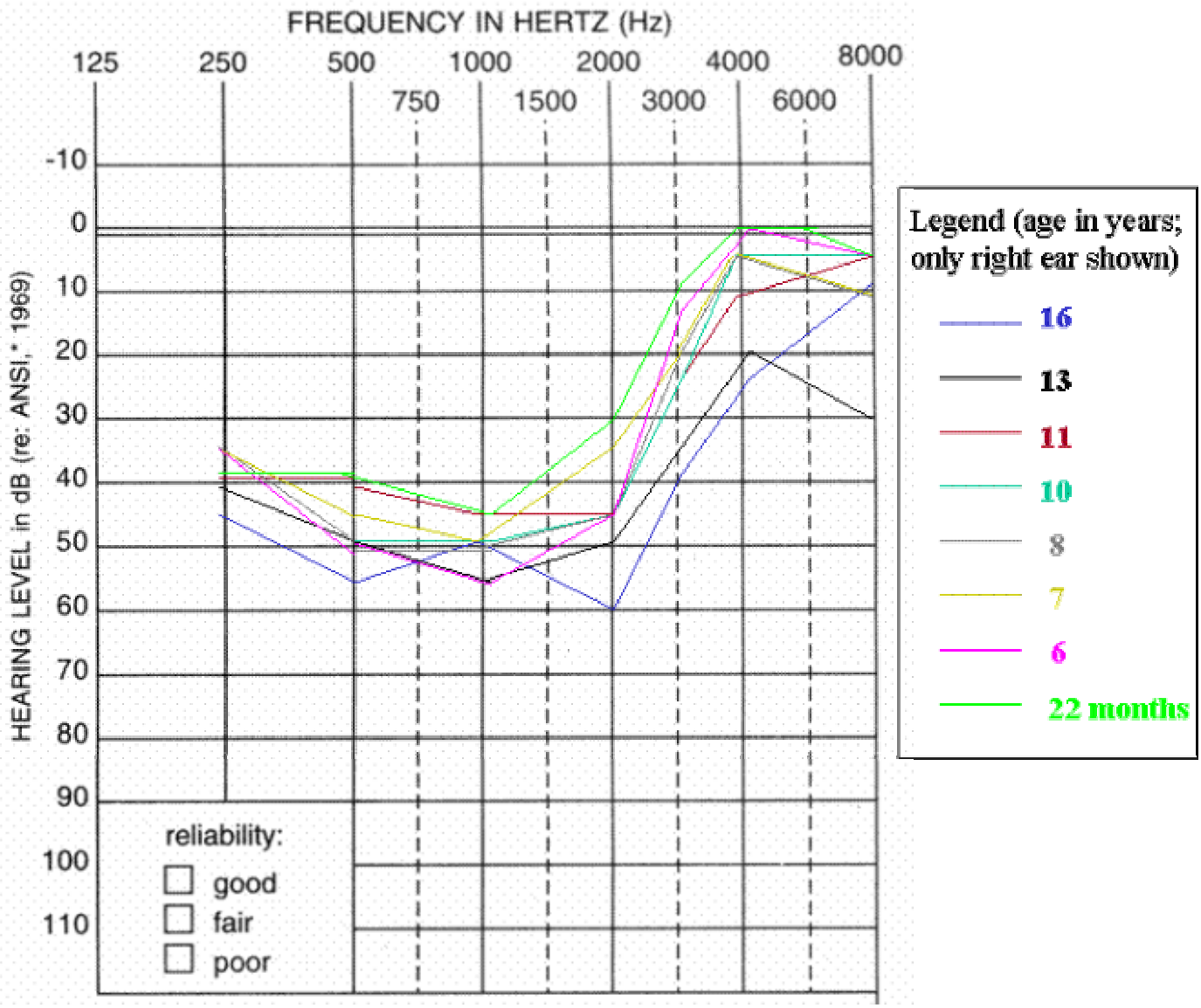

Figure 1

Other

- Congenital hearing loss can be identified through universal screening of newborns, which has been advocated by the National Institutes of Health and is available in most states although requirements and implementation strategies vary (see status of newborn screening by state).
- Parental concerns about possible hearing loss or observed delays in speech development require auditory screening in any child.

Differential Diagnosis

In children with delayed speech development, the auditory system should be assessed. In the presence of normal audiometry associated with progressive loss of speech and temporal lobe seizures, the diagnosis of Landau-Kleffner syndrome should be considered.

Delayed speech suggesting possible hearing loss can also be seen in young children with autism (see Autism Overview).

Prevalence

Between 1/2000 (0.05%) and 1/1000 (0.1%) children are born with profound hearing loss [Marazita et al 1993 , Cohen & Gorlin 1995]. More than 50% of prelingual deafness is genetic, most often autosomal recessive and nonsyndromic. The disorder DFNB1, caused by mutations in the *GJB2* gene (which encodes the protein connexin 26) and the *GJB6* gene (which encodes the protein connexin 30), accounts for 50% of autosomal recessive nonsyndromic hearing loss. The carrier rate in the general population for a recessive deafness-causing *GJB2* mutation is about one in 33. A small percentage of prelingual deafness is syndromic or autosomal dominant nonsyndromic.

In the general population, the prevalence of hearing loss increases with age. This change reflects the impact of genetics and environment, and also interactions between environmental triggers and an individual's genetic predisposition, as illustrated by aminoglycoside-induced ototoxicity (see Nonsyndromic Hearing Loss and Deafness, Mitochondrial), middle ear effusion, and possibly otosclerosis.

Causes

The causes of prelingual deafness in children are outlined in Figure 2 .

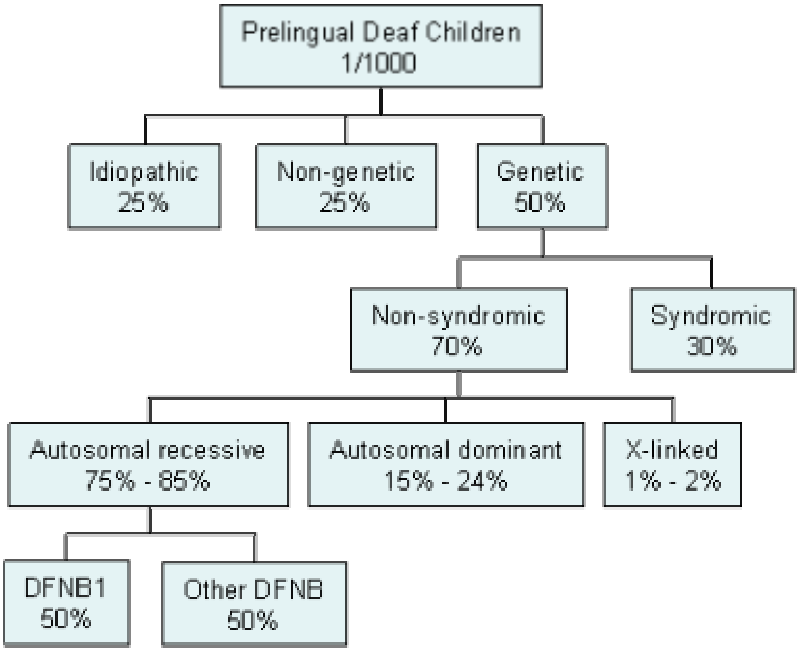

Figure 2. Causes of Prelingual Deafness in Children

The following text provides an overview of all hereditary hearing loss and deafness.

Environmental Causes

Acquired hearing loss in children commonly results from prenatal infections from "TORCH" organisms (i.e., **to**xoplasmosis, **r**ubella, **c**ytomegalic virus, and **h**erpes), or postnatal infections, particularly bacterial meningitis caused by *Neisseria meningitidis, Haemophilus influenzae,* or *Streptococcus pneumoniae*. Meningitis from many other organisms, including *Escherichia coli, Listeria monocytogenes, Streptococcus agalactiae,* and *Enterobacter cloacae,* can also cause hearing loss. Asymptomatic congenital cytomegalovirus (CMV) infection is often unrecognized and can be associated with variable, fluctuating, sensorineural hearing loss [Harris et al 1984 , Hicks et al 1993 , Schildroth 1994]. **Acquired hearing loss in adults** is most often attributed to environmental factors, especially noise exposure, but susceptibility probably reflects an environmental-genetic interaction. For example, aminoglycoside-induced hearing loss is more likely in persons with an A-to-G transition at nucleotide position 1555 in the mitochondrial genome (mtDNA). (See Nonsyndromic Hearing Loss and Deafness, Mitochondrial .)

Heritable Causes

Single-Gene Disorders

Syndromic hearing impairment is associated with malformations of the external ear or other organs or with medical problems involving other organ systems. **Nonsyndromic**

hearing impairment has no associated visible abnormalities of the external ear, nor are there any related medical problems; however, it can be associated with abnormalities of the middle ear and/or inner ear.

This overview focuses on the clinical features and molecular genetics of common syndromic and nonsyndromic types of hereditary hearing loss. Links are provided to the disorders profiled in *GeneReviews*.

Syndromic Hearing Impairment

Over 400 genetic syndromes that include hearing loss have been described [Gorlin et al 1995]. Syndromic hearing impairment may account for up to 30% of prelingual deafness, but its relative contribution to all deafness is much smaller, reflecting the occurrence and diagnosis of postlingual hearing loss. Syndromic hearing loss discussed here is categorized by mode of inheritance.

Autosomal Dominant Syndromic Hearing Impairment

Waardenburg syndrome (WS) is the most common type of autosomal dominant syndromic hearing loss. It consists of variable degrees of sensorineural hearing loss and pigmentary abnormalities of the skin, hair (white forelock), and eyes (heterochromia iridis). Since affected persons may dye their hair, the presence of a white forelock should be specifically sought in the history and physical examination. Four types are recognized — WS I, WS II, WS III, and WS IV — based on the presence of other abnormalities. WS I and WS II share many features but have an important phenotypic difference: WS I is characterized by the presence of dystopia canthorum (i.e., lateral displacement of the inner canthus of the eye) while WS II is characterized by its absence. In WS III, upper-limb abnormalities are present, and in WS IV, Hirschsprung disease is present. Mutations in *PAX3* cause WS I and WS III. Mutations in *MITF* cause some cases of WS II. Mutations in *EDNRB*, *EDN3*, and *SOX10* cause WS IV.

Branchiootorenal syndrome is the second most common type of autosomal dominant syndromic hearing loss. It consists of conductive, sensorineural, or mixed hearing loss in association with branchial cleft cysts or fistulae, malformations of the external ear including preauricular pits, and renal anomalies. Penetrance is high, but expressivity is extremely variable. In approximately 40% of families segregating a BOR phenotype, mutations in the *EYA1* gene can be identified; in a few other families mutations have been found in *SIX1* [Ruf et al 2004], consistent with the known interaction of EYA1 and SIX1 proteins in transcription regulation. The BOR phenotype is also caused by mutations in other as-yet-unidentified genes.

Stickler syndrome consists of progressive sensorineural hearing loss, cleft palate, and spondyloepiphyseal dysplasia resulting in osteoarthritis. The syndrome is quite common, and three types are recognized, based on the molecular genetic defect: STL1 *(COL2A1)*, STL2 *(COL11A1)*, and STL3 *(COL11A2)*. STL1 and STL2 are characterized by severe myopia, which predisposes to retinal detachment; this aspect of the phenotype is absent in

STL3 because the *COL11A2* gene is not expressed in the eye. Causative mutations have been found in the genes causing STL1, STL2, and STL3.

Neurofibromatosis 2 (NF2) is associated with a rare, potentially treatable type of deafness. The hallmark of NF2 is hearing loss secondary to bilateral vestibular schwannomas. The hearing loss usually begins in the third decade, concomitant with the growth of a vestibular schwannoma, and is generally unilateral and gradual, but can be bilateral and sudden. A retrocochlear lesion can often be diagnosed by audiologic evaluation, although the definitive diagnosis requires magnetic resonance imaging (MRI) with gadolinium contrast. Affected persons are at risk for a variety of other tumors including meningiomas, astrocytomas, ependymomas, and meningioangiomatosis. Mutations in NF2 are causative. Molecular genetic testing of the *NF2* gene is available for presymptomatic at-risk family members to facilitate early diagnosis and treatment.

Autosomal Recessive Syndromic Hearing Impairment

Usher syndrome is the most common type of autosomal recessive syndromic hearing loss. It consists of dual sensory impairments: affected individuals are born with sensorineural hearing loss and then develop retinitis pigmentosa (RP). Usher syndrome affects over 50% of the deaf-blind in the United States. The vision impairment from retinitis pigmentosa (RP) is usually not apparent in the first decade, making funduscopic examination before ten years of age of limited utility. However, electroretinography (ERG) can identify abnormalities in photoreceptor function in children as young as two to four years of age. During the second decade, night blindness and loss of peripheral vision become evident and inexorably progress.

Three types of Usher syndrome are recognized based on the degree of hearing impairment and result of vestibular function testing.

- Usher syndrome type I is characterized by congenital severe-to-profound sensorineural hearing loss and abnormal vestibular dysfunction. Affected persons find traditional amplification ineffective and usually communicate manually. Because of the vestibular deficit, developmental motor milestones for sitting and walking are always reached at later-than-normal ages.
- Usher syndrome type II is characterized by congenital mild-to-severe sensorineural hearing loss and normal vestibular function. Hearing aids provide effective amplification for these persons and their communication is usually oral.
- Usher syndrome type III is characterized by progressive hearing loss and progressive deterioration of vestibular function.

Pendred syndrome is the second most common type of autosomal recessive syndromic hearing loss. The syndrome is characterized by congenital severe-to-profound sensorineural hearing impairment and euthyroid goiter. Goiter is not present at birth and develops in early puberty (40%) or adulthood (60%). Delayed organification of iodine by the thyroid can be documented by a perchlorate discharge test. The deafness is associated with an abnormality of the bony labyrinth (Mondini dysplasia or dilated vestibular aqueduct) that can be

diagnosed by CT examination of the temporal bones. Vestibular function is abnormal in the majority of affected persons. Mutations in *SLC26A4* are identified in about 50% of multiplex families. Such genetic testing is appropriate for persons with Mondini dysplasia or an enlarged vestibular aqueduct and progressive hearing loss.

Early studies reported that Pendred syndrome accounted for up to 7.5% of congenital deafness, but contemporary studies suggest that the prevalence of Pendred syndrome is lower; mutations of the *SLC26A4* gene are also a cause of nonsyndromic hearing loss (DFNB4).

Jervell and Lange-Nielsen syndrome is the third most common type of autosomal syndromic hearing loss. The syndrome consists of congenital deafness and prolongation of the QT interval as detected by electrocardiography [the abnormal QTc (c=corrected) is greater than 440 msec]. Affected individuals have syncopal episodes and may have sudden death. Although a screening EKG is not highly sensitive, it may be suitable for screening deaf children. High-risk children (i.e., those with a family history that is positive for sudden death, SIDS, syncopal episodes, or long QT syndrome) should have a thorough cardiac evaluation. Mutations in two genes have been described in affected persons.

Biotinidase deficiency is caused by a deficiency in biotin, a water-soluble B-complex vitamin that covalently attaches to four carboxylases essential for gluconeogenesis (pyruvate carboxylase), fatty acid synthesis (acetyl CoA carboxylase), and catabolism of several branched-chain amino acids (propionyl-CoA carboxylase and beta methylcrotonoyl-CoA carboxylase). If biotinidase deficiency is not recognized and corrected by daily addition of biotin to the diet, affected persons develop neurologic features such as seizures, hypertonia, developmental delay, and ataxia, as well as visual problems and some degree of sensorineural hearing loss in at least 75% of children who become symptomatic. Cutaneous features are also present and include a skin rash, alopecia, and conjunctivitis. With biotin treatment, neurologic and cutaneous manifestations resolve; however, the hearing loss and optic atrophy are usually irreversible. Therefore, whenever a child presents with episodic or progressive ataxia and progressive sensorineural deafness, with or without neurologic or cutaneous symptoms, biotinidase deficiency should be considered. To prevent metabolic coma, diet and treatment should be initiated as soon as possible [Heller et al 2002 , Wolf et al 2002].

Refsum disease consists of severe progressive sensorineural hearing loss and retinitis pigmentosa caused by faulty phytanic acid metabolism. Although extremely rare, it is important that Refsum disease be considered in the evaluation of a deaf person because it can be treated with dietary modification and plasmapharesis. The diagnosis is established by determining the serum concentration of phytanic acid. (See also Peroxisome Biogenesis Disorders, Zellweger Syndrome Spectrum .)

X-Linked Syndromic Hearing Impairment

Alport syndrome is characterized by progressive sensorineural hearing loss of varying severity, progressive glomerulonephritis leading to end-stage renal disease, and variable

ophthalmologic findings (i.e., anterior lenticonus). Hearing loss usually does not manifest before age ten years. Autosomal dominant, autosomal recessive, and X-linked forms are described. X-linked inheritance accounts for about 85% of cases, and autosomal recessive inheritance accounts for about 15% of cases. Autosomal dominant inheritance has been reported on occasion.

Mohr-Tranebjaerg syndrome (deafness-dystonia-optic atrophy syndrome) was first described in a large Norwegian family with progressive, postlingual, nonsyndromic hearing impairment. Re-evaluation of this family has revealed additional findings, including visual disability, dystonia, fractures, and mental retardation, indicating that this form of hearing impairment is syndromic rather than nonsyndromic. The gene for this syndrome, *TIMM8A*, is involved in the translocation of proteins from the cytosol across the inner mitochondrial membrane (TIM system) and into the mitochondrial matrix.

Mitochondrial Syndromic Hearing Impairment

Mitochondrial DNA mutations have been implicated in a variety of diseases ranging from rare neuromuscular syndromes such as Kearns-Sayre syndrome (see Mitochondrial DNA Deletion Syndromes), MELAS , MERRF , and NARP , to common conditions like diabetes mellitus, Parkinson disease, and Alzheimer disease (see Mitochondrial Disorders Overview). One mutation, the 3243 A-to-G transition in the gene *MTTL1*, has been found in 2% to 6% of individuals with diabetes mellitus in Japan. Sixty-one percent of persons with diabetes mellitus and this mutation have hearing loss. The hearing loss is sensorineural and develops only after the onset of the diabetes mellitus. The same mutation is associated with MELAS , raising questions of penetrance and tissue specificity, issues further confounded by heteroplasmy.

Nonsyndromic Hearing Impairment

More than 70% of hereditary hearing loss is nonsyndromic [Cremers et al 1991 , van Camp et al 1997]. Disorders discussed in this section are organized by mode of inheritance. The different gene loci for nonsyndromic deafness are designated DFN (for DeaFNess). Loci for genes inherited in an autosomal dominant manner are referred to as DFNA, those for genes inherited in an autosomal recessive manner as DFNB, and those for genes inherited in an X-linked manner as DFN. The number following these designations reflects the order of gene mapping and/or discovery.

- Several recessive and dominant loci have been mapped to the same chromosomal region, and, in these cases, allelic variants of a single gene have been found. Examples include: DFNB1 and DFNA3, both of which map to 13q12 and are caused by mutations in the genes *GJB2* and *GJB6*; DFNB2 and DFNA11, both of which map to 11q13.5 and are caused by mutations in *MYO7A*, the gene that also causes Usher syndrome 1B ; and DFNB21 and DFNA8/12, both of which are caused by mutations in *TECTA*.
- Nonsyndromic and syndromic co-localizations include DFNB18 and Usher syndrome type 1C (caused by mutations in *USH1C)*; DFNB12 and Usher syndrome

type 1D (caused by mutations in *CDH23*); DFNB4 and Pendred syndrome (caused by mutations in the gene *SLC26A4*); DFNA6/14 and Wolfram syndrome (caused by mutations in *WFS1*).

- Most autosomal recessive loci cause prelingual severe-to-profound hearing loss. An exception is DFNB8, in which the hearing impairment is postlingual and rapidly progressive. Of the autosomal dominant loci, most cause postlingual hearing impairment. Some exceptions are DFNA3, DFNA8, DFNA12, and DFNA19. DFNA6/14 also is noteworthy as the hearing loss primarily affects the low frequencies.
- Several genotype-phenotype relationships have been defined. For example, α-tectorin, the protein encoded by *TECTA*, has three distinct domains: an entactin G1 (ENTG1) domain, a zonadhesin (ZA) domain with von Willebrand factor type D repeats 0-4 (VWFD 0-4), and a zona pellucida (ZP) domain. In families segregating DFNA8/12, the mutations in *TECTA* are missense mutations, with the audioprofile dependent on the location of the mutation. Missense mutations in the ZP domain cause stable or progressive hearing loss involving the mid frequencies, while missense mutations in the ZA domain result in progressive hearing loss in the high frequencies. In families segregating DFNB21, the mutations result in premature protein truncation and act like null alleles. Examples include frameshift mutations, nonsense mutations, and deletions. In all cases, the hearing loss is prelingual, symmetric, and moderate to severe in degree.
- X-linked nonsyndromic hearing loss can be either pre- or postlingual; one disorder, DFN3, has mixed hearing loss.
- Within the prelingual nonsyndromic hearing loss group, inheritance is 75-80% autosomal recessive, 20-25% autosomal dominant, and 1-1.5% X-linked. Similar data are not available for postlingual nonsyndromic hearing impairment, but most described families demonstrate autosomal dominant inheritance.
- Seven loci for familial otosclerosis have been mapped; no disease genes have been identified.

Autosomal Dominant Nonsyndromic Hearing Impairment

Family studies of autosomal dominant nonsyndromic hearing loss have shown that heterogeneity is high. Unlike autosomal recessive nonsyndromic hearing loss, which is also extremely heterogeneous but in which the majority of cases are caused by mutations in a single gene in many world populations, a single gene responsible for the majority of cases of autosomal dominant nonsyndromic hearing loss has not been identified. In spite of this limitation, the audioprofile can be distinctive and useful in predicting candidate genes for mutation screening. For example, mutations in *WFS1* are found in 75% of families segregating autosomal dominant nonsyndromic hearing impairment that initially affects the low frequencies while sparing the high frequencies. Characteristic audioprofiles are noted in Table 2 , which lists the genes known to be associated with autosomal dominant nonsyndromic hearing impairment.

Table 2. Clinical Manifestations and Molecular Genetics of Known Genes Causing

Autosomal Dominant Nonsyndromic Hearing Impairment				
Locus Name	**Chromosomal Locus**	**Gene Symbol**	**Onset/Decade**	**Audioprofile**
DFNA1	5q31	*DIAPH1*	Postlingual/1st	Low frequency progressive
DFNA2	1p35.1	*GJB3*	Postlingual/2nd	High frequency progressive
	1p34	*KCNQ4*		
DFNA3	13q11-q12	*GJB2*	Prelingual	
	13q12	*GJB6*		
DFNA4	19q13	*MYH14*	Postlingual	Flat/gently downsloping
DFNA5	7p15	*DFNA5*	Postlingual/1st	High frequency progressive
DFNA6/14/38	4p16.1	*WFS1*	Prelingual	Low frequency progressive
DFNA8/12	11q22-q24	*TECTA*		Mid-frequency loss
DFNA9	14q12-q13	*COCH*	Postlingual/2nd	High frequency progressive
DFNA10	6q23	*EYA4*	Postlingual/3rd, 4th	Flat/gently downsloping
DFNA11	11q13.5	*MYO7A*	Postlingual/1st	
DFNA13	6p21.3	*COL11A2*	Postlingual/2nd	Mid-frequency loss
DFNA15	5q31	*POU4F3*	Postlingual	High frequency progressive
DFNA17	22q11.2	*MYH9*		
DFNA20/26	17q25	*ACTG1*		
DFNA22	6q13	*MYO6*		
DFNA28	8q22	*TFCP2L3*		Flat/gently downsloping
DFNA36	9q13-q21	*TMC1*		
DFNA39	4q21.3	*DSPP*		High frequency progressive
DFNA48	12q13-q14	*MYO1A*		Progressive

Adapted from Van Camp & Smith (2003)

Autosomal Recessive Nonsyndromic Hearing Impairment

In many world populations, 50% of persons with autosomal recessive nonsyndromic hearing loss have mutations in *GJB2* [Zelante et al 1997 , Estivill et al 1998 , Kelley et al 1998]. The other 50% of cases are attributed to mutations in numerous other genes, many of which have been found to cause deafness in only one or two families [Scott et al 1998]. (See DFNB1 .) Extensive genotype-phenotype studies have shown that it is possible to predict the hearing loss associated with *GJB2* mutations based on the specific genotype [Snoeckx et al 2005].

The other 50% of cases are attributed to mutations in numerous other genes, many of which have been found to cause deafness in only one or two families [Zbar et al 1998].

Clinical manifestations and molecular genetics of known genes causing autosomal recessive nonsyndromic hearing impairment are summarized in Table 3 .

Table 3. Clinical Manifestations and Molecular Genetics of Known Genes Causing Autosomal Recessive Nonsyndromic Hearing Impairment

Locus Name	Chromosomal Locus	Gene Symbol	Onset	Type
DFNB1	13q11-112	*GJB2*	Prelingual [1]	Usually stable
	13q12	*GJB6*		
DFNB2	11q13.5	*MYO7A*	Prelingual, postlingual	Unspecified
DFNB3	17p11.2	*MYO15*	Prelingual	Stable
DFNB4	7q31	*SLC26A4*	Prelingual, postlingual	Stable, progressive
DFNB6	3p21	*TMIE*	Prelinqual	Stable
DFNB7/11	9q13-q21	*TMC1*		
DFNB8/10	21q22.3	*TMPRSS3*	Postlingual [2] /Prelingual	Progressive, stable
DFNB9	2p22-p23	*OTOF*	Prelingual	Stable
DFNB12	10q21-q22	*CDH23*		
DFNB16	15q15	*STRC*		
DFNB18	11p15.1	*USH1C*		

DFNB21	11q22-q24	*TECTA*		
DFNB22	16p12.2	*OTOA*		
DFNB29	21q22.3	*CLDN14*		
DFNB30	10p11.1	*MYO3A*		
DFNB31	9q32-q34	*DFN31*		—
DFNB36	1p36.31	*ESPN*		—
DFNB37	6q13	*MYO6*		—

Adapted from Van Camp et al (2003)
1. Prelingual deafness also includes congenital deafness.
2. The onset of DFNB8 hearing loss is postlingual (10-12 years of age), while the onset of DFNB10 hearing loss is prelingual (congenital). This phenotypic difference reflects a genotypic difference - the DFNB8-causing mutation is a splice site mutation, suggesting that inefficient splicing is associated with a reduced amount of normal protein, which is sufficient to prevent prelingual deafness but not sufficient to prevent eventual hearing loss.

X-Linked Nonsyndromic Hearing Impairment

DFN3 (Xq21.1) is characterized by a mixed conductive-sensorineural hearing loss, the conductive component of which is caused by stapedial fixation. In contrast to other types of conductive hearing loss, surgical correction is precluded because an abnormal communication between the cerebrospinal fluid and perilymph results in leakage ("perilymphatic gusher") and complete loss of hearing when the oval window is fenestrated or removed. The causative gene is *POU3F4*. Molecular genetic testing is available on a clinical basis [Vore et al 2005].

Other X-linked nonsyndromic hearing loss phenotypes include profound prelingual hearing loss characteristic of both DFN2 and DFN4, as well as bilateral high-frequency impairment beginning at five to seven years of age and progressing, by adulthood, to severe-to-profound hearing impairment, over all frequencies, characteristic of DFN6. For the DFN5, DFN7, and DFN8 loci, results are not yet published.

Clinical manifestations and molecular genetics of known genes causing X-linked nonsyndromic hearing impairment are summarized in Table 4 .

Table 4. Clinical Manifestations and Molecular Genetics of X-Linked Nonsyndromic Hearing Impairment

Locus Name	Chromosomal Locus	Gene Symbol	Onset	Type and Degree	Frequencies
DFN2	Xq22	—	Prelingual	Stable	All

				sensorineural; profound	
DFN3	Xq21.1	*POU3F4*		Progressive, mixed; variable, but progresses to profound	
DFN4	Xp21	—		Stable sensorineural; profound	
DFN5	Withdrawn	—	—	—	—
DFN6	Xp22	—	Postlingual (1st decade)	Progressive sensorineural; severe to profound	High frequencies evolving to include all frequencies by adulthood
DFN7	Withdrawn	—	—	—	—
DFN8	Reserved	—	—	—	—

Adapted from Van Camp et al (2003)

Mitochondrial Nonsyndromic Hearing Impairment

Some mitochondrial DNA mutations cause nonsyndromic hearing loss [Fischel-Ghodsian 1998] (see Table 5). In two families, a homoplasmic mutation at nt1555 (A-to-G) in the mitochondrial *MTRNR1* gene has been reported. This mutation also occurs in persons with aminoglycoside-induced ototoxic hearing loss. Two other families with maternally inherited nonsyndromic hearing loss have been identified with heteroplasmy for an A-to-G transition at nt7445 of the *MTTS1* gene. The penetrance of the hearing impairment caused by these mitochondrial mutations is quite low, suggesting that unidentified genetic or environmental factors play a role in the progression of the hearing impairment (see Mitochondrial Nonsyndromic Hearing Loss).

Table 5. Mitochondrial Nonsyndromic Hearing Impairment

Gene Symbol	Mutation	Severity	Penetrance
MTRNR1	961 (different mutations)	Variable	Highly variable, aminoglycoside induced

	1555 A>G		
MTTS1	7445 A>G		Highly Variable
	7472 ins C		
	7510 T>C		

Adapted from Van Camp et al (2003)

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 craniofacial 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, dilation of the internal auditory canal), which should be considered in persons with progressive hearing loss. Because inner-ear defects are associated with mutations in *SLC26A4* (see Pendred syndrome), and *POU3F4* [Vore et al 2005], 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.

Other genes known to cause nonsyndromic deafness are listed in Tables 2-5 . 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)* make 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, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory. —ED.

Mode of Inheritance

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

Risk to Family Members — Autosomal Dominant Hereditary Hearing Loss

Parents of a proband

- Most individuals diagnosed as having autosomal dominant hereditary hearing loss have a deaf 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 molecular genetic testing.

Note: Although most individuals diagnosed with autosomal dominant hereditary hearing loss have a deaf parent, the family history may appear to be negative because of 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.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the deafness-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

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 deafness-causing mutation.
- Heterozygotes are asymptomatic.

Sibs of a proband

- At conception, each sib has a 25% chance of being deaf, a 50% chance of having normal hearing and being a carrier, and a 25% chance of having normal hearing and not being a carrier.
- Once an at-risk sib is known to have normal hearing, the risk of his/her being a carrier is 2/3.
- Heterozygotes are asymptomatic.
- 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.

Offspring of a proband. All of the offspring are obligate carriers.

Other family members of a proband. The sibs of obligate heterozygotes have a 50% chance of being heterozygotes.

Risk to Family Members — X-Linked Hereditary Hearing Loss

Parents of a proband

- The father of a male with X-linked hearing loss will not have the disease nor will he be a carrier of the mutation.
- Women who have a son and another male relative with X-linked hearing loss are obligate heterozygotes.
- If pedigree analysis reveals that the deaf male is the only individual in the family with hearing loss, several possibilities regarding his mother's carrier status need to be considered:
    - He has a *de novo* deafness-causing mutation and his mother is not a carrier;
    - His mother has a *de novo* deafness-causing mutation, as either:
        - a "germline mutation" (i.e., occurring at the time of her conception and thus present in every cell of her body); or
        - "germline mosaicism" (i.e., present in some of her germ cells only);
    - His maternal grandmother has a *de novo* deafness-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 deafness-causing mutation with each pregnancy.
    - Sons who inherit the mutation will be deaf; daughters who inherit the mutation are carriers and are likely to have normal hearing.
- 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 deafness-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 deaf.

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 of inheriting it.

Offspring of a proband

- All offspring of females with a mtDNA mutation are at risk of inheriting the mutation.
- Offspring of males with a 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.

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 or comes from a highly inbred community, the subsequent offspring have close to a 25% probability of deafness because of the high likelihood of autosomal recessive inheritance.

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 lower than 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 his/her reproductive partner has 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 about the cause of their own deafness, including information on medical, educational, 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 , Arnos 2003].

- The use of certain terms is preferred: probability or chance versus risk; deaf and hard of hearing versus 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 deaf individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for some forms of hereditary hearing loss is technically possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The deafness-causing allele(s) of a deaf family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Requests for prenatal testing for conditions such as hearing loss are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the deafness-causing mutation(s) has/have been identified in a deaf family member. For laboratories offering PGD, see Testing.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Involvement

If an individual or the parents of a child raise concern about the possibility of hearing loss (if the child is young, the concern may be delayed speech development or poor social interaction), the initial evaluation should include a detailed history to explore possible acquired forms of hearing loss, a family history with pedigree construction, and a thorough otolaryngologic examination with particular attention to otoscopy and features that might suggest a syndromic type of deafness.

An accurate test to quantitate hearing acuity is paramount and if one is not obtained, a return appointment should be scheduled as soon as possible to complete this part of the evaluation.

Based on the above data, more specific tests can be requested (for example, mutation screening of genes implicated in deafness).

Treatment of Manifestations

Ideally, the team evaluating and treating the deaf individual should consist of an otolaryngologist with expertise in the management of early childhood otologic disorders, an audiologist experienced in the assessment of hearing loss in children, a clinical geneticist, and a pediatrician. The expertise of an educator of the Deaf, a neurologist, and a pediatric ophthalmologist may also be required.

An important part of the evaluation is determining the appropriate habilitation option. Possibilities include hearing aids, vibrotactile devices, and cochlear implantation. Cochlear implantation can be considered in children over 12 months of age with severe-to-profound hearing loss.

Prevention of Primary Manifestations

Whenever a child presents with progressive sensorineural hearing loss and progressive ataxia, with or without neurologic or cutaneous symptoms, biotinidase deficiency should be considered, with initiation of treatment as early as possible to prevent irreversible sequelae.

Prevention of Secondary Complications

Regardless of its etiology, uncorrected hearing loss has consistent sequelae. Auditory deprivation through the age of two years is associated with poor reading performance, poor communication skills, and poor speech production. Educational intervention is insufficient to completely remediate these deficiencies. In contrast, early auditory intervention, whether through amplification, otologic surgery, or cochlear implantation, is effective.

Although decreased cognitive skills and performance in mathematics and reading are associated with deafness, examination of persons with hereditary hearing loss has shown that these deficiencies are not intrinsically linked to the cause of the deafness. For example, assessment of cognitive skills in individuals with connexin 26-related deafness reveals a normal Hiskey IQ and normal reading performance after cochlear implantation. Thus, early identification and timely intervention is essential for optimal cognitive development in children with prelingual deafness.

Surveillance

Sequential audiologic examinations are essential to document the stability or progression of the hearing loss and to identify and treat superimposed hearing losses, such as middle ear effusion.

Agents/Circumstances to Avoid

Noise exposure is a well-recognized environmental cause of hearing loss. Since this risk can be minimized by avoidance, persons with documented hearing loss should be counseled appropriately.

Testing of Relatives at Risk

At a minimum, all children with a risk for hereditary hearing loss should receive screening audiometry.

Therapies Under Investigation

Current habilitation options for persons with hearing loss are focused on amplification with hearing aids and/or cochlear implants. Therapies under investigation include the use of short cochlear implant electrodes in combination with hearing aids to combine electric and acoustic speech processing and the use of binaural implants [Gantz et al 2005].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. -ED.

- **American Society for Deaf Children**
  3820 Hartzdale Drive
  Camp Hill PA 17011
  Phone: 800-942-2732 (parent hotline); 717-703-0073 (business V/TTY)
  Fax: 717-909-5599
  Email: asdc@deafchildren.org
  www.deafchildren.org

- **The Morton Hearing Research Group**
  www.brighamandwomens.org/bwh_hearing

- **National Association of the Deaf**
  8630 Fenton Street Suite 820
  Silver Spring MD 20910
  Phone: 301-587-1788 (voice); 301-587-1789 (TTY)

Fax: 301-587-1791
Email: NADinfo@nad.org
www.nad.org

- **National Library of Medicine Genetics Home Reference**
  Nonsyndromic deafness

- **NCBI Genes and Disease**
  Deafness

- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**
  3417 Volta Place NW
  Washington DC 20007
  Phone: 866-337-5220; 202-337-5220; 202-337-5221 (TTY)
  Fax: 202-337-8314
  Email: info@agbell.org
  www.agbell.org

- **my baby's hearing**
  This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.
  www.babyhearing.org

- **Teaching Case-Genetic Tools**
  Cases designed for teaching genetics in the primary care setting.
  Case 10. A Newborn Boy with a Failed Newborn Hearing Screen
  Case 11. Parents Seek Reproductive Counseling Following the Diagnosis of DFNB1-Related Hearing Loss in Their Son

Resources Printable Copy

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Author Information

Richard JH Smith, MD
Department of Otolaryngology
University of Iowa Hospitals and Clinics
Iowa City

Guy Van Camp, PhD
Department of Genetics
University of Antwerp
Antwerp

Author History

Glenn Edward Green, MD; University of Arizona (1999-2005)
Richard JH Smith, MD (1999-present)
Guy Van Camp, PhD (1999-present)

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- 4 December 2006 (rjs) Revision: clinical testing available for DFNB21 and DFNA8/12
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- 30 December 2005 (me) Comprehensive update posted to live Web site
- 18 February 2005 (rjs) Revision: clinical availability of testing, *KCNQ4*-related DFNA2
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