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Deafness and Hereditary Hearing Loss Overview

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Summary

Disease characteristics. Hereditary hearing loss and deafness may be conductive, sensorineural, or a combination of both; syndromic (associated with malformations of the external ear or other organs or with medical problems involving other organ systems) or nonsyndromic (no associated visible abnormalities of the external ear or any related medical problems); 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 (e.g., CT examination of the temporal bone), and molecular genetic testing. Molecular genetic testing, available in clinical laboratories for many types of syndromic and nonsyndromic deafness, plays a prominent role in diagnosis and genetic counseling.

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.

Management. *Treatment of manifestations:* Hereditary hearing loss is managed by a team that includes 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 determining the appropriate habilitation option such as hearing aids and vibrotactile devices; cochlear implantation is considered in children over age 12 months 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.

Surveillance: Sequential audiologic examinations to document 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.

Evaluation of relatives at risk: Children at risk for hereditary hearing loss should undergo molecular genetic testing (if the family-specific mutation[s] are known) and screening audiometry.

Definition

Clinical Manifestations

Hearing loss is described by **type** and **onset**:

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 shown in Table 1.

Table 1. Severity of Hearing Loss in Decibels (dB)

Severity	Hearing Threshold in Decibels
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 [Journal of the American Medical Association 1979] (see Table 2).

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 2. 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") is 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. They include the following:

- **Auditory brain stem response testing (ABR, also known as BAER, BSER)** uses a stimulus (clicks) to evoke electrophysiologic responses, which originate in the eighth cranial nerve and auditory brain stem 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)** is like ABR in that both are auditory evoked potentials and they are measured in similar ways. ASSR uses an objective, statistics-based mathematical detection algorithm to detect and define hearing thresholds. ASSR can be obtained using broadband or frequency-specific stimuli and can offer hearing threshold differentiation in the severe to profound range. It is frequently used to give frequency-specific information which ABR does not give. Test frequencies of 500, 1000, 2000, and 4000 Hz are commonly used.
- **Evoked otoacoustic emissions (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)** 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.

- **Behavioral 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*.

Other

- Congenital hearing loss can be identified by newborn hearing screening (NBHS), which has been advocated by the National Institutes of Health. NBHS is universally required by law or rule in 33 states plus the District of Columbia. In most of the remaining states, NBHS is universally offered but not yet required. California and Texas remain exceptions and offer NBHS to select populations or by request [National Newborn Screening and Genetics Resource Center, National Newborn Screening Status Report (pdf)].
- 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

Hearing loss is the most common birth defect and the most prevalent sensorineural disorder in developed countries [Hilgert et al 2009]. One of every 500 newborns has bilateral permanent sensorineural hearing loss ≥40 dB; by adolescence, prevalence increases to 3.5 per 1000 [Morton & Nance 2006].

A small percentage of prelingual deafness is syndromic or autosomal dominant nonsyndromic. More than 50% of prelingual deafness is genetic, most often autosomal recessive and nonsyndromic. Approximately 50% of autosomal recessive nonsyndromic hearing loss can be attributed to the disorder DFNB1, caused by mutations in *GJB2* (which encodes the protein connexin 26) and *GJB6* (which encodes the protein connexin 30). The carrier rate in the general population for a recessive deafness-causing *GJB2* mutation is approximately one in 33.

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.

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.

In developed countries, however, the most common environmental, non-genetic cause of congenital hearing loss is congenital cytomegalovirus (CMV) infection. Its overall birth prevalence is approximately 0.64%; 10% of this number have symptomatic CMV. Of asymptomatic cases, up to 4.4% develop unilateral or bilateral hearing loss before primary school, although there is marked ethnic variation. The diagnosis of CMV hearing loss can be difficult to make, often can go unrecognized, and can be associated with variable, fluctuating, sensorineural hearing loss [Kenneson & Cannon 2007].

Acquired hearing loss in adults is most often attributed to environmental factors but susceptibility most likely reflects environmental-genetic interactions. Age-related and noise-induced hearing losses are the most frequent examples of complex 'environmental-genetic' hearing loss; however, to date only a few genes have been associated with these complex traits [Huyghe et al 2008, Konings et al 2009].

An environmental interaction pertinent to medical care has been the finding that 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 or 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 [Toriello et al 2004]. 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). Because 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 (BOR) 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

EYA1 can be identified; in a few other families mutations have been found in *SIX1* [Ruf et al 2004] and *SIX5* [Hoskins et al 2007]. 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. 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 *COL11A2* is not expressed in the eye.

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 presymptomatic at-risk family members facilitates 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 RP is usually not apparent in the first decade, making fundoscopic examination before age ten years of limited utility. However, electroretinography (ERG) can identify abnormalities in photoreceptor function in children as young as age two to four years. 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 sensorineural hearing loss that is usually (though not invariably) severe-to-profound 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 approximately 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 *SLC26A4* 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 (abnormal QTc [c=corrected] >440 msec). Affected individuals have syncopal episodes and may have sudden death. Although a screening ECG 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. Some degree of sensorineural hearing loss is present 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 (e.g., 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 approximately 85% of cases, and autosomal recessive inheritance accounts for approximately 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. Reevaluation of this family has revealed additional findings, including visual disability, dystonia, fractures, and intellectual disability, indicating that this form of hearing impairment is syndromic rather than nonsyndromic. *TIMM8A*, the gene in which mutations occur to cause this syndrome, 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 *MTTL1,* has been found in 2%-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 [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 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.

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 reported families demonstrate autosomal dominant inheritance.

Autosomal recessive and autosomal dominant colocalizations include the following:

- DFNB1 and DFNA3; both map to 13q12 and are caused by mutations in the genes *GJB2* and *GJB6.*
- DFNB2 and DFNA11; both map to 11q13.5 and are caused by mutations in *MYO7A*, the gene that also causes Usher syndrome 1B.
- DFNB21 and DFNA8/12; both are caused by mutations in *TECTA*.

Nonsyndromic and syndromic colocalizations include the following:

- 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 *SLC26A4*
- DFNA6/14/38 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.

Most autosomal dominant loci cause postlingual hearing impairment.

- Some exceptions are DFNA3, DFNA8, DFNA12, and DFNA19.
- DFNA6/14/38 is also noteworthy as the hearing loss primarily affects the low frequencies.

X-linked nonsyndromic hearing loss can be either pre- or postlingual; one disorder, DFNX3, has mixed hearing loss.

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 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 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.

Autosomal Dominant Nonsyndromic Hearing Impairment

Family studies of autosomal dominant nonsyndromic hearing loss have shown that as in autosomal recessive nonsyndromic hearing loss, heterogeneity is high. However, unlike autosomal recessive nonsyndromic hearing loss, in which the majority of cases are caused by mutations in a single gene *(GJB2)* in many world populations, autosomal dominant nonsyndromic hearing loss does not have an identifiable single gene responsible for the majority of cases.

Audioprofiling can be used to prognosticate the rate of hearing loss per year in an individual with autosomal dominant nonsyndromic hearing loss of known cause [Hildebrand et al 2008].

Furthermore, the audioprofile in autosomal dominant nonsyndromic hearing loss can be distinctive (see Table 3), and thus useful in developing an evaluation strategy for molecular genetic testing [Hildebrand et al 2008]. (See Evaluation Strategy.) Note: Multi-gene testing for NSHL is available and is described in Evaluation Strategy, **Molecular genetic testing**.

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

Locus Name	Gene Symbol	Onset/Decade	Audioprofile	Molecular Genetic Test Availability

DFNA1	*DIAPH1*	Postlingual/1st	Low frequency progressive	Clinical Testing
DFNA2	*KCNQ4*	Postlingual/2nd	High frequency progressive	Clinical Testing
DFNA2B	*GJB3*	Postlingual/4th	High frequency progressive	Clinical Testing
DFNA3	*GJB2*	Prelingual	High frequency progressive	Clinical Testing
	GJB6			Clinical Testing
DFNA4	*MYH14*	Postlingual	Flat/gently downsloping	Clinical Testing
DFNA5	*DFNA5*	Postlingual/1st	High frequency progressive	Clinical Testing
DFNA6/14/38	*WFS1*	Prelingual	Low frequency progressive	Clinical Testing
DFNA8/12	*TECTA*		Mid-frequency loss	Clinical Testing
DFNA9	*COCH*	Postlingual/2nd	High frequency progressive	Clinical Testing
DFNA10	*EYA4*	Postlingual/3rd, 4th	Flat/gently downsloping	Clinical Testing
DFNA11	*MYO7A*	Postlingual/1st		Clinical Testing
DFNA13	*COL11A2*	Postlingual/2nd	Mid-frequency loss	Clinical Testing
DFNA15	*POU4F3*	Postlingual	High frequency progressive	Clinical Testing
DFNA17	*MYH9*	Postlingual	High frequency progressive	Clinical Testing
DFNA20/26	*ACTG1*	Postlingual	High frequency progressive	Clinical Testing
DFNA22	*MYO6*	Postlingual	High frequency progressive	Clinical Testing
DFNA23	*SIX1*	Prelingual	Downsloping	Clinical Testing
DFNA25	*SLC17AB*	Postlingual/2nd-6th decades	High frequency progressive	Clinical Testing
DFNA28	*TFCP2L3*	Postlingual	Flat/gently downsloping	Clinical Testing
DFNA36	*TMC1*	Postlingual	Flat/gently downsloping	Clinical Testing
DFNA39	*DSPP*	Postlingual	High frequency progressive	Research only
DFNA44	*CCDC50*	Postlingual	Low to mild frequencies progressive	Clinical Testing
DFNA48	*MYO1A*	Postlingual	Progressive	Clinical Testing
				Clinical

DFNA50	*MIR96*	Postlingual/2nd	Flat progressive	Testing
DFNA51	*TJP2 & FAM189A2*	Postlingual/4th	High frequency progressive	Research only

Adapted from Van Camp & Smith [2010]

Test Availability refers to availability in the GeneTests™ Laboratory Directory. *GeneReviews* designates a molecular genetic test as clinically available only if the test is listed in the GeneTests™ Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.

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] (see DFNB1). 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 [Hilgert et al 2009] (see Evaluation Strategy).

Clinical manifestations and molecular genetics of genes implicated in autosomal recessive nonsyndromic hearing impairment are summarized in Table 4. Note: Multi-gene testing for NSHL is available and is described in Evaluation Strategy, **Molecular genetic testing**.

Table 4. Clinical Manifestations and Molecular Genetics of Known Genes Causing Autosomal Recessive Nonsyndromic Hearing Impairment

Locus Name	Gene Symbol	Onset	Type	Molecular Genetic Test Availability
DFNB1	*GJB2*	Prelingual [1]	Usually stable	Clinical Testing
	GJB6			Clinical Testing
DFNB2	*MYO7A*	Prelingual, postlingual	Unspecified	Clinical Testing
DFNB3	*MYO15*	Prelingual	Severe to profound; stable	Clinical Testing
DFNB4	*SLC26A4*	Prelingual, postlingual	Stable, progressive	Clinical Testing
DFNB6	*TMIE*	Prelinqual	Severe to profound; stable	Clinical Testing
DFNB7/11	*TMC1*			Clinical Testing
DFNB8/10	*TMPRSS3*	Postlingual [2], Prelingual	Progressive, stable	Clinical Testing
DFNB9	*OTOF*	Prelingual	Usually severe to profound; stable	Clinical Testing
DFNB12	*CDH23*	Prelingual	Severe to profound; stable	Clinical Testing
DFNB16	*STRC*	Prelingual	Severe to profound; stable	Clinical Testing
DFNB18	*USH1C*	Prelingual	Severe to profound; stable	Clinical Testing
DFNB21	*TECTA*	Prelingual	Severe to profound; stable	Clinical Testing
DFNB22	*OTOA*	Prelingual	Severe to profound; stable	Clinical

				Testing
DFNB23	*PCDH15*	Prelingual	Severe to profound; stable	Clinical Testing
DFNB24	*RDX*	Prelingual	Severe to profound; stable	Clinical Testing
DFNB25	*GRXCR1*	Prelingual	Moderate to profound; progressive	Research only
DFNB28	*TRIOBP*	Prelingual	Severe to profound; stable	Clinical Testing
DFNB29	*CLDN14*	Prelingual	Severe to profound; stable	Clinical Testing
DFNB30	*MYO3A*	Prelingual	Severe to profound; stable	Clinical Testing
DFNB31	*DFN31*	Prelingual	—	Clinical Testing
DFNB32/82	*GPSM2*	Prelingual	Severe to profound; stable	Research only
DFNB35	*ESRRB*	Unknown	Severe to profound	Clinical Testing
DFNB36	*ESPN*	Prelingual	—	Clinical Testing
DFNB37	*MYO6*	Prelingual	—	Clinical Testing
DFNB39	*HGF*	Prelingual	Severe to profound; downsloping	Clinical Testing
DFNB49	*MARVELD2*	Prelingual	Moderate to profound; stable	Clinical Testing
DFNB53	*COL11A2*	Prelingual	Severe to profound; stable	Research only
DFNB59	*PJVK*	Prelingual	Severe to profound; stable	Clinical Testing
DFNB61	*SLC26A5*	Prelingual	Severe to profound; stable	Clinical Testing
DFNB63	*LRTOMT*	Prelingual	Severe to profound; stable	Clinical Testing
DFNB67	*LHFPL5*	Prelingual	Severe to profound; stable	Clinical Testing
DFNB73	*BSND*	Prelingual	Severe to profound; stable	Research only
DFNB77	*LOXHD1*	Postlingual	Moderate to profound; progressive	Clinical Testing
DFNB79	*TPRN*	Prelingual	Severe to Profound; stable	Research only
DFNB84	*PTPRQ*	Prelingual	Moderate to profound; progressive	Research only

Adapted from Van Camp & Smith [2010]

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1. Prelingual deafness also includes congenital deafness.
2. The onset of DFNB8 hearing loss is postlingual (age 10-12 years), 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 that is sufficient to prevent prelingual deafness but not sufficient to prevent eventual hearing loss.

X-Linked Nonsyndromic Hearing Impairment

DFNX3 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.

Other X-linked nonsyndromic hearing loss phenotypes include profound prelingual hearing loss characteristic of both DFNX2 and DFNX4, as well as bilateral high-frequency impairment beginning between age five and seven years and progressing by adulthood to severe-to-profound hearing impairment over all frequencies, characteristic of DFNX6. For the DFNX5, DFNX7, and DFNX8 loci, results are not yet published.

Clinical manifestations and molecular genetics of known genes causing X-linked nonsyndromic hearing impairment are summarized in Table 5. Note: Multi-gene testing for NSHL is available and is described in Evaluation Strategy, **Molecular genetic testing**.

Table 5. Clinical Manifestations and Molecular Genetics of X-Linked Nonsyndromic Hearing Impairment

Locus Name	Gene Symbol	Onset	Type and Degree	Frequencies	Molecular Genetic Test Availability
DFNX1 (DFN2)	*PRPS1*	Postlingual	Progressive sensorineural; severe to profound	All	Clinical Testing
DFNX2 (DFN3)	*POU3F4*	Prelingual	Progressive, mixed; variable, but progresses to profound	All	Clinical Testing

Adapted from Van Camp & Smith [2010]

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Nonsyndromic Hearing Loss and Deafness, Mitochondrial

The majority of mutations in mitochondrial genes cause of a broad spectrum of maternally inherited multisystem disorders; however, mutations in a subset of genes, mainly *MT-RNR1* and *MT-TS1*, cause nonsyndromic hearing loss by a currently unknown mechanism [Fischel-Ghodsian 1998] (see Table 6 and Nonsyndromic Hearing Loss and Deafness, Mitochondrial).

MT-RNR1 encodes for the 12S ribosomal RNA. One mutation in this gene, 1555G>A, is a frequent cause of maternally inherited nonsyndromic hearing loss. In some individuals with the 1555G>A mutation, the hearing loss is induced by the administration of appropriate doses of aminoglycosides; however, phenotypic variation is great, consistent with the effect of modifier genes [Kokotas et al 2007].

MT-TS1 encodes for the transfer $RNA^{Ser(UCN)}$. Two families with heteroplasmy for an A-to-G transition at nt7445 of this gene have been identified; however, penetrance of hearing loss was low, and it has been suggested that *MT-TS1* mutations on their own play an insignificant role in hearing loss.

MT-CO1 encodes cytochrome c oxidase subunit 1. Six individuals with severe-to-profound deafness showed cosegregation of a homoplasmic G-to-A transition at nt7444 of *MT-CO1* and the 1555A>G mutation in *MT-RNR1* [Pandya et al 1999]. Five of the six individuals showed maternal inheritance and two had a previous history of aminoglycoside use. As opposed to the variable hearing loss associated with *MT-RNR1* 1555A>G, all individuals with this double mutation showed severe-to-profound impairment and penetrance was complete.

Table 6. Mitochondrial Nonsyndromic Hearing Impairment

Gene Symbol	Mutation	Severity	Penetrance	Molecular Genetic Test Availability
	961 different			

MT-RNR1	mutations 1494C>T 1555A>G	Variable	Highly variable, aminoglycoside induced	Clinical Testing
MT-TS1	7445A>G 7472insC 7510T>C 7511T	Variable	Highly variable	Clinical Testing
MT-CO1	7444G>A	Severe to profound	Complete, aminoglycoside associated; associated with *MT-RNR1* 1555A>G	Clinical Testing

Adapted from Van Camp & Smith [2010]

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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 molecular genetic 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; preauricular 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.
- Mutations in *WFS1* are found in 75% of families with dominantly inherited hearing loss that initially affects the low frequencies while sparing the high frequencies [Cryns et al 2003].

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.

Detection of temporal bone anomalies by CT examination can help direct molecular genetic testing because inner-ear defects are associated with mutations in:

- *SLC26A4* (see Pendred syndrome)
- *POU3F4* [Vore et al 2005]

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. Currently available molecular genetic testing is summarized in Table 3, Table 4, Table 5, and Table 6.

The extreme genetic heterogeneity and the frequent lack of phenotypic variability make genetic diagnosis of NSHL difficult using single-gene screening techniques. For this reason, several groups have developed multi-gene screening panels for NSHL (see Testing). It is important to note that these screening panels vary by laboratory both in the techniques used and the number of genes sequenced. Some laboratories target only reported mutations in several genes, while other laboratories sequence all genes implicated in NSHL. It is likely that as such tests become more widespread, the management of genetic hearing loss will change to a single comprehensive genetic test for all types of hearing loss.

When single-gene testing is performed, prioritization of genes for testing can be based on epidemiologic and/or phenotypic data. For example, molecular genetic testing of *GJB2* (which encodes the protein connexin 26) and *GJB6* (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 consistent with autosomal recessive inheritance or in families with apparent "pseudodominant" inheritance of DFNB1. Pseudodominant 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.

In children with congenital severe-to-profound presumed autosomal recessive nonsyndromic hearing loss in whom *GJB2* and *GJB6* at the DFNB1 locus are not identified, Usher syndrome type 1 should be considered if developmental motor milestones for sitting and walking independently are delayed.

When CT examination of the temporal bones discloses an enlarged/dilated vestibular aqueduct or Mondini dysplasia, mutation screening of *SLC26A4* should be completed (see Pendred Syndrome).

In families segregating autosomal dominant nonsyndromic deafness, screening of candidate genes selected by audioprofiling is valuable (see Table 3); computer algorithms are being developed to facilitate this approach [Hildebrand et al 2008].

In cases where these initial approaches do not yield a diagnosis, screening of all genes associated with NSHL using a multi-gene panel (see Testing) may yield a diagnosis [Shearer et al 2010].

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.

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 on 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 on 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 on 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 maternity (e.g., with assisted reproduction) 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 on 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) a "germline mutation" (i.e., occurring at the time of her conception and thus present in every cell of her body); or (b) "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 on 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 of the possibility of germline mosaicism.
- Depending on 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 on 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 on 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 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 on 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 [Green et al 1999].

- If the deaf child does not have DFNB1 based on molecular genetic testing of *GJB2* and *GJB6*, the recurrence risk is 14% for deafness unrelated to connexin 26 [Green et al 1999].
- 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 [Green et al 1999].

- 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 pseudodominant occurrence of recessive deafness. *GJB2* 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 [Green et al 1999].

- If both parents have *GJB2*-related deafness, the risk to their offspring is 100%.
- 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."

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.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are deaf.

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. See Testing for a list of laboratories offering DNA banking.

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 approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately 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, discussion of these issues is appropriate.

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

Note: It is the policy of *GeneReviews* to include in *GeneReviews*™ chapters any clinical uses of testing available from laboratories listed in the GeneTests™ Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Management

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 age 12 months with severe-to-profound hearing loss.

In children with congenital severe-to-profound autosomal recessive nonsyndromic hearing loss who are positive for mutations in *GJB2* and *GJB6* at the DFNB1 locus and who elect to receive cochlear implants, performance outcome is outstanding [Bauer et al 2003].

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 age 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 [Smith et al 2005].

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 *GJB2*-related hearing loss reveals a normal Hiskey IQ and normal reading performance after cochlear implantation [Bauer et al 2003]. 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

- Identify and treat superimposed hearing losses, such as middle ear effusion.

In a person with autosomal recessive nonsyndromic hearing loss caused by mutations in *SLC26A4*, the hearing loss can progress and annual audiometric testing may be warranted. Additionally, thyroid function should be followed if the diagnosis is consistent with Pendred syndrome.

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.

Evaluation of Relatives at Risk

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

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

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.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

Resources

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.—ED.

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page PubMed

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Chapter Notes

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Revision History

- 5 January 2012 (cd) Revision: clinical testing for mutations in *MT-CO1* associated with hearing loss and multi-gene hearing loss/deafness panels now listed in the GeneTests™ Laboratory Directory
- 14 October 2010 (me) Comprehensive update posted live
- 2 December 2008 (rjs) Revision: DFNB23 added
- 28 October 2008 (me) Comprehensive update posted live
- 30 January 2007 (rjs) Revision: clinical testing and prenatal diagnosis available for DFNB9
- 4 December 2006 (rjs) Revision: clinical testing available for DFNB21 and DFNA8/12
- 22 August 2006 (rjs) Revision: to incorporate concerns of reader regarding hearing impairment scales
- 30 December 2005 (me) Comprehensive update posted to live Web site
- 18 February 2005 (rjs) Revision: clinical availability of testing, *KCNQ4*-related DFNA2
- 15 July 2004 (rjs) Revision: use of an interpreter
- 18 December 2003 (cd,rjs) Revision: change in test availability
- 3 November 2003 (me) Comprehensive update posted to live Web site
- 13 January 2003 (cd) Revision: test availability
- 24 April 2001 (me) Comprehensive update posted to live Web site

- 14 February 1999 (pb) Overview posted to live Web site
- 30 October 1998 (rjs) Original overview submission [Supported in part by grants 1RO1DC02842 and 1RO1DC03544 (RJHS) and Belgian National Fonds voor Wetenschappelijk Onderzoek (GVC).]

Figures

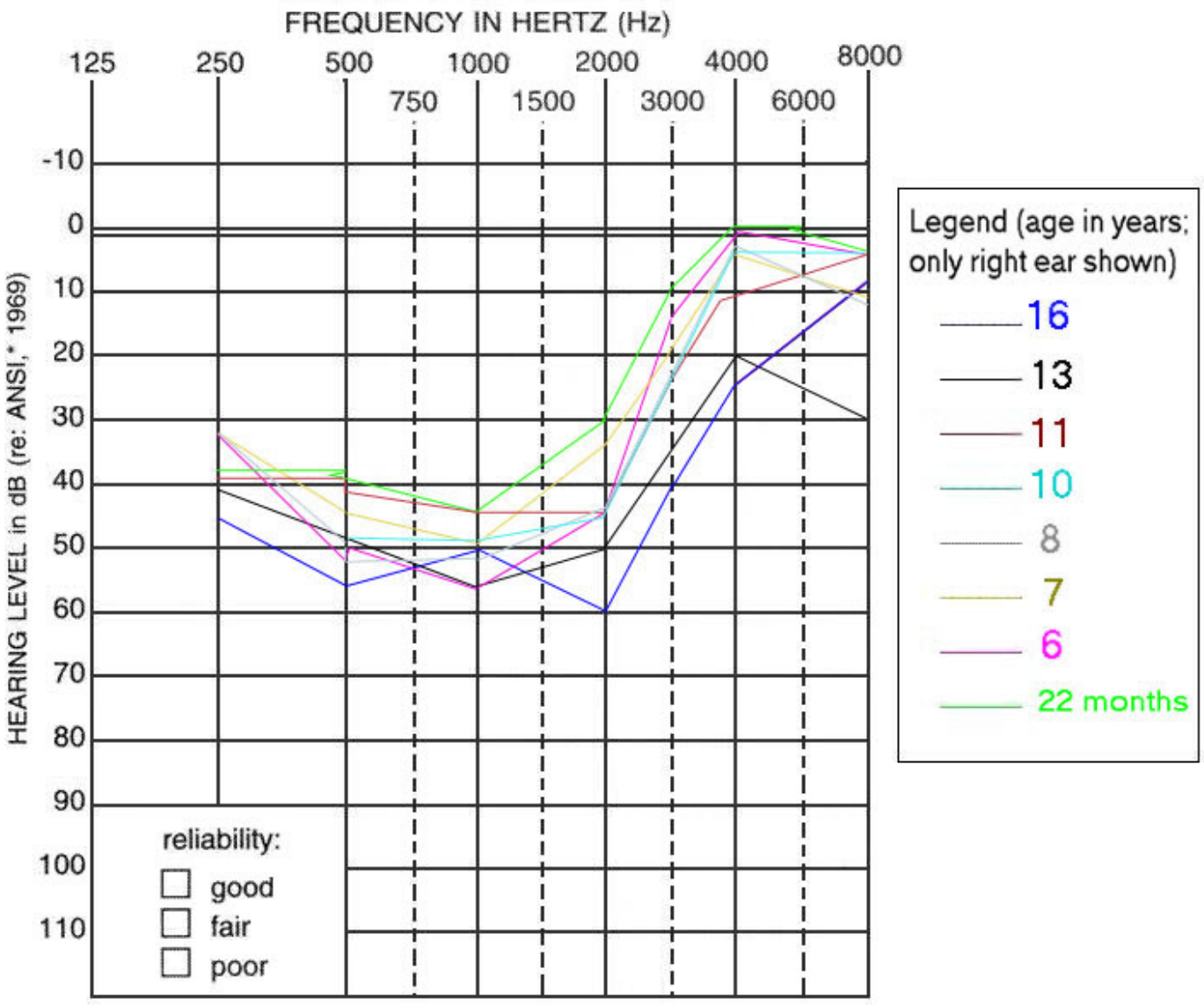

Figure 1. Audioprofile

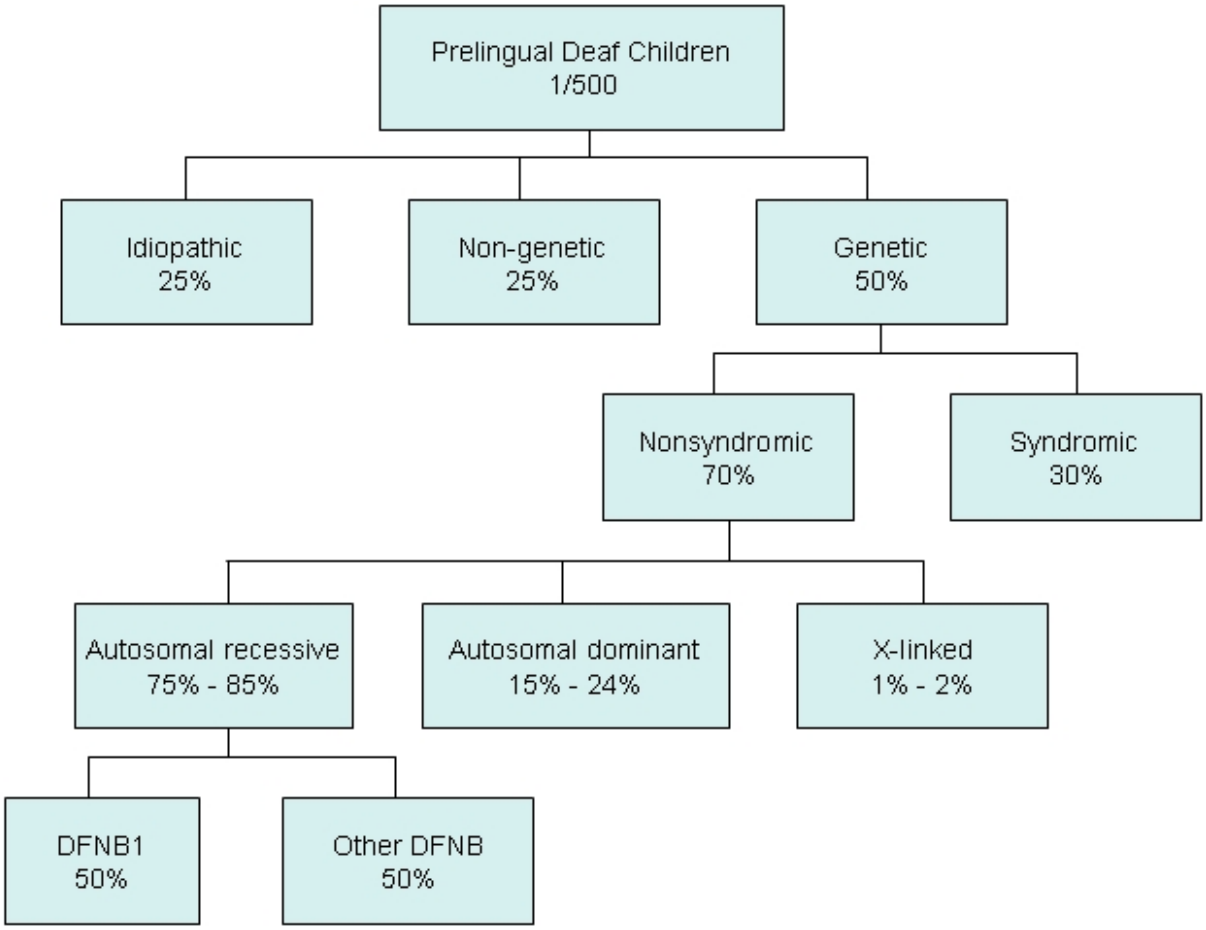

Figure 2. Causes of prelingual hearing loss ≥40dB in children