Clinical aspects of hereditary hearing loss

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Hearing loss is an etiologically diverse condition with many disease-related complications and major clinical, social, and quality of life implications. As the rate of acquired hearing loss secondary to environmental causes decreases and improvements in the diagnosis of abnormalities occur, the significance of genetic factors that lead to deafness increases. Advancements in molecular biology have led to improved detection and earlier intervention in patients with hearing loss. Subsequently, earlier implementation of educational services and cochlear implant technology in patients with profound hearing loss now results in superior communication skills and enhanced language development. The aim of this review is to provide a comprehensive framework underlying the causes of hearing impairment and to detail the clinical management for patients with hereditary hearing loss. **Genet Med 2007;9(7):393–408.**

Key Words: hereditary hearing loss, deafness, genetics, mutation, newborn hearing screening, congenital hearing loss, acquired hearing loss, syndromic hearing loss, nonsyndromic hearing loss

Table of Contents

Overview	393	X-linked	399
Important terminology	394	Alport	399
Classification of hearing loss	394	Mohr-Tranebjaerg	399
Type	394	Mitochondrial	399
Onset	394	Nonsyndromic hearing impairment	399
Severity	395	Autosomal dominant	399
Frequency	395	Autosomal recessive	399
Epidemiology of hearing loss	395	X-linked	400
Prevalence and cause	395	Mitochondrial	400
Environmental causes of hearing loss	395	Clinical evaluation & diagnosis of hearing loss	400
Early newborn hearing screening	395	Family history	400
Hereditary causes of hearing loss	396	Physical examination	401
Syndromic hearing impairment	396	Audiologic findings	401
Autosomal dominant	396	Laboratory and radiologic assessment	403
Waardenburg	396	Molecular genetic testing	404
Branchio-oto-renal	396	Prenatal testing	404
Stickler	397	Related genetic counseling issues	405
Neurofibromatosis 2	397	Management	405
Autosomal recessive	398	Intervention	405
Pendred	398	Agents and circumstances to avoid	405
Usher	398	Prevention of hearing impairment	406
Jervell	398	Resources	406
Biotinidase	398	Suggested reading	406
Refsum	399		

Hearing loss is the most common sensory disorder. It can be classified as conductive, sensorineural, or mixed (a combination of both); syndromic or nonsyndromic; and prelingual or postlingual. Estimates of the different types of genetic deafness exceed 400, and to date, 60 genes for syndromic and nonsyn-

dromic hearing loss have been identified.¹ The expression patterns of these genes in the inner ear can be visualized on the Hereditary Hearing Loss Homepage (<http://webh01.ua.ac.be/hhh/>) (Fig. 1).²

In the investigation of hearing loss, genetic forms must be distinguished from acquired (nongenetic) causes. The diagnosis of hereditary hearing loss requires otologic, audiologic, and physical examinations; a family history; ancillary testing (e.g., computed tomography examination of the temporal bone); and molecular genetic analysis. Molecular genetic tests are available for many types of syndromic and nonsyndromic deafness, although often only on a research basis. Clinically, testing of *GJB2* and *GJB6* plays a prominent role in diagnosis and genetic counseling because mutations in these genes account for more than 50% of severe-to-profound autosomal

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Fig. 1. Cochlear expression patterns of *GJB2* BM, basilar membrane; BSL, bony spiral lamina; CC, Claudius cell; DC, Deiters cell; ESC, external sulcus cell; HC, Hensen cell; IDC, interdental cell; IHC, inner hair cell; IPC, inner pillar cell; ISC, inner sulcus cell; Li, limbus; OHC, outer hair cell; OPC, outer pillar cell; RM, Reissner membrane; SG, spiral ganglion; SL, spiral ligament; SM, scala media; SP, spiral prominence; ST, scala tympani; StV, stria vascularis; SV, scala vestibuli; TM, tectorial membrane. With permission from Van Camp G, Smith RJH. Hereditary Hearing Loss Homepage, 2003. <http://webh01.ua.ac.be/hhh/>. Accessed 24 January 2007.

recessive nonsyndromic deafness in many world populations. Table 1 indicates the other forms of deafness for which molecular genetic testing is currently available.

A genetic hearing loss may be inherited in an autosomal dominant, autosomal recessive, or X-linked Mendelian manner, or through the maternal lineage by mitochondrial inheritance. Genetic counseling and risk assessment are dependent on the 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, may be used for genetic counseling.

IMPORTANT TERMINOLOGY

“Hearing impairment” and “hearing loss” are often used interchangeably by health care professionals when referring to hearing below threshold levels for normal hearing determined by audiometry.

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”) refers to members of the Deaf community in the United States who are deaf and use American Sign Language. As in other cultures, the Deaf are characterized by unique social and societal attributes. They 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 is a term that is more functional than audiologic. It is used by the Deaf to signify that a person has some

Table 1

Molecular genetic testing available for clinical diagnosis of hereditary deafness

Syndromic deafness	Gene clinically tested
Branchio-Oto-Renal syndrome	<i>EYA1</i>
Mohr-Tranebjaerg syndrome (deafness-dystonia-optic atrophy syndrome)	<i>TIMM8A</i>
Pendred syndrome	<i>SLC26A4</i>
Usher syndrome type 1B	<i>USH1B</i>
Usher syndrome type 2A	<i>USH2A</i>
Usher syndrome type 3	<i>USH3A</i> (one mutation)
Wolfram syndrome	<i>WFS1</i>
Nonsyndromic deafness	Gene clinically tested
DFNA3 and DFNB1	<i>GJB2</i> and <i>GJB6</i>
DFN3	<i>POU3F4</i>
DFNB4	<i>SLC26A4</i>
DFNA 6/14	<i>WFS1</i>
DFNA 8/12	<i>TECTA</i>
DFNA9	<i>COCH</i>
DFNB9	<i>OTOF</i>
DFNB21	<i>TECTA</i>
Mitochondrial hearing loss	Gene clinically tested <i>MTRNR1</i> , <i>MTTS1</i> , <i>MTTL1</i>

usable hearing; anything from mild to severe hearing loss. In the Deaf community, persons who are deaf do not use oral language, whereas those who are hard of hearing usually have some oral language.

CLASSIFICATION OF HEARING LOSS

Hearing loss is classified by type, onset, severity, and frequency.

Type

Conductive hearing loss results from abnormalities of the external ear and/or the ossicles of the middle ear. In contrast, sensorineural hearing loss results from the malfunction of inner ear structures such as the cochlea. Mixed hearing loss is a combination of both conductive and sensorineural hearing loss, and central auditory dysfunction results from damage or dysfunction at the level of the eighth cranial nerve, auditory brainstem, or cerebral cortex.

Onset

Prelingual hearing loss is present before speech develops. All congenital hearing loss is prelingual, but not all prelingual hearing loss is congenital. Postlingual hearing loss occurs after the development of normal speech.

Severity

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 follows:

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

To calculate the percent hearing impairment, 25 dB is subtracted from the pure tone average of 500 Hz, 1000 Hz, 2000 Hz, and 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 (Table 2).³

Note:

1. Because conversational speech is at approximately 50 to 60 dB hearing level (HL), calculating functional impairment on the basis of pure tone averages can be misleading. For example, a 45 dB hearing loss is functionally much more significant than 30% implies.⁴

2. A different rating scale is appropriate for young children, for whom even limited hearing loss can have a great impact on language development (Table 2).⁴

Frequency

The frequency of hearing loss is designated as follows:

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

EPIDEMIOLOGY OF HEARING LOSS

Prevalence and cause

Profound hearing loss is present in 1 of every 1000 to 2000 newborn infants. However, milder but still clinically significant degrees of unilateral or bilateral hearing loss occur in an additional one to two infants.^{5,6} More than 50% of all prelingual deafness cases are hereditary in nature, with the remaining 40% to 50% of cases secondary to environmental factors such as infectious or iatrogenic causes (Fig. 2).^{7,8} The majority of genetic hearing loss diagnosed in infancy and early childhood is autosomal recessive in inheritance and nonsyndromic. Deaf-

ness at the DFNB1 locus is secondary to mutations in *GJB2* and/or *GJB6*, which encode the proteins connexin 26 and connexin 30, respectively, and accounts for 50% of autosomal recessive nonsyndromic hearing loss. The carrier rate for the general U.S. population of northern European descent for a recessive deafness-causing *GJB2* mutation is approximately 1 in 33.⁹

Generally, the prevalence of hearing loss increases with age, reflecting the important impact of both genetics and the environment in its development. Indeed, interactions between environmental triggers and an individual's genotype can contribute to the development of hearing loss. For example, aminoglycoside-induced toxicity is potentiated on a genetic background that includes the mitochondrial DNA 1555 A-to-G mutation.¹⁰

Environmental causes of hearing loss

Acquired hearing loss in children commonly results from prenatal infections from the "TORCH" organisms (**t**oxoplasmosis, **r**ubella, **c**ytomegalovirus, and **h**erpes), or postnatally secondary to bacterial meningitis caused by *Neisseria meningitidis*, *Haemophilus influenzae*, or *Streptococcus pneumoniae*, although meningitis-related hearing loss can be the sequelae of infections from *Escherichia coli*, *Listeria monocytogenes*, *Streptococcus agalactiae*, and *Enterobacter cloacae* (Fig. 2). Perhaps most noteworthy is hearing loss from asymptomatic congenital cytomegalovirus infection. This type of sensorineural hearing loss is highly variable, can fluctuate, and can be difficult to diagnose definitively, although a recently developed polymerase chain reaction-based assay can retrospectively diagnose patients by using preserved umbilical cord blood.^{11–14}

Acquired hearing loss in adults is most often attributed to environmental factors, the most common being noise exposure. However, an individual's susceptibility to hearing loss most likely reflects an environmental–genetic interaction.

Age-related hearing loss (presbycusis) is acquired and characterized by diminished hearing sensitivity and speech comprehension in noisy environments, slowed central processing of acoustic information, and impaired localization of sound. Affected persons may have difficulty in conversation, music appreciation, orientation to alarms, and participation in social activities.¹⁵ The aging population in the Western world and the high prevalence of presbycusis combine to make age-related hearing loss a common social and health challenge. Ten percent of the Western population have a hearing loss severe enough to impair communication, and this rate increases to 40% in individuals aged more than 65 years.

Early newborn hearing screening

For the detection of congenital hearing loss, the U.S. federal government facilitated the creation of Early Hearing Detection and Intervention (EHDI) programs for early newborn hearing screening (<http://www.infanthearing.org>). EHDI programs aim to screen neonates for hearing loss immediately after birth or before hospital discharge. The programs include a follow-up arm to confirm hearing loss in neonates who do not pass their initial screening test so that intervention can be initiated to prevent delayed language acquisition.¹⁶

Table 2

Percent hearing impairment

Impairment (%)	Pure tone average (dB) ^a	Residual hearing (%)
100%	91 dB	0%
80%	78 dB	20%
60%	65 dB	40%
30%	45 dB	70%

^a Pure tone average of 500 Hz, 1000 Hz, 2000 Hz, and 3000 Hz.

Fig. 2. Hereditary and environmental causes of congenital hearing loss.

EHDI program guidelines include three phases: screening, audiologic evaluation, and intervention (Fig. 3). In the first phase, newborns are screened with evoked otoacoustic emissions (EOAE) or auditory brainstem response (ABR) to detect permanent bilateral or unilateral sensory or conductive hearing loss averaging 30 to 40 dB HL or more in the frequency region important for speech recognition. In the second phase, all infants who do not pass the initial screen are evaluated with a series of diagnostic audiologic tests, preferably before the age of 3 months. In the third phase, early intervention services are implemented before the age of 6 months for all infants with confirmed hearing loss.¹⁶

Fig. 3. EHDI screening protocols. EOAE, evoked otoacoustic emissions; ABR, auditory brainstem response; dB, decibel; OAE, otoacoustic emissions; ASSR, auditory steady-state response. Adapted with permission from www.infanthearing.org.

HEREDITARY CAUSES OF HEARING LOSS

Syndromic hearing impairment

Syndromic hearing impairment accounts for up to 30% of prelingual deafness, but its relative contribution to *all* deafness is smaller because of the impact of postlingual hearing loss. Some of the more prevalent forms of syndromic hearing loss are listed in Table 3.

Autosomal dominant syndromic hearing impairment

Waardenburg syndrome

Waardenburg syndrome (WS) is the most common type of autosomal dominant syndromic hearing loss. It consists of variable degrees of prelingual nonprogressive sensorineural hearing loss accompanied by 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 or absence 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 a lateral displacement of the inner canthus of the eye, which is known as dystopia canthorum, whereas in WS II this feature is absent. In WS III upper-limb abnormalities are present, and in WS IV, Hirschsprung disease is present. Mutations in *PAX3* cause both WS I and WS III, and mutations in *MITF* and *SNA12* are responsible for some cases of WS II.^{17–21} Mutations in *EDNRB*, *EDN3*, and *SOX10* have been confirmed to cause WS IV.^{22–24}

Branchio-oto-renal syndrome

Branchio-Oto-Renal (BOR) syndrome is the second most common type of autosomal dominant syndromic hearing loss. The BOR phenotype includes conductive, sensorineural, or

Table 3

The molecular genetics associated with syndromic hearing loss

Syndrome	Chromosomal locus	Gene symbol
<i>Autosomal dominant</i>		
Branchio-oto-renal (BOR)		
BOR1	8q13.3	<i>EYA1</i>
BOR2	1q31	Unknown
BOS3	14q	<i>SIX1</i>
Waardenburg		
WS1	2q35	<i>MITF</i>
WS2	3p14.1-p12.3	<i>SNAI2</i>
WS3 (Klein-Waardenburg syndrome)	2q35	<i>PAX3</i>
WS4 (Shah-Waardenburg or Waardenburg-Hirschsprung)	13q22	<i>EDNRB</i>
	20q13.2-q13.3	<i>EDN3</i>
	22q13	<i>SOX10</i>
Stickler		
STL1	12q13.11-13.2	<i>COL2A1</i>
STL2	6p1.3	<i>COL11A2</i>
STL3	1p21	<i>COL11A</i>
STL4	6q13	<i>COL9A1</i>
Neurofibromatosis		
NF2	22q12	<i>NF2</i>
<i>Autosomal recessive</i>		
Pendred	7q21-34	<i>SLC26A4/PDS</i>
Usher		
USH1A	14q32	Unknown
USH1B	11q13.5	<i>MYO7A</i>
USH1C	11p15.1	<i>USH1C</i>
USH1D	10q22.1	<i>CDH23</i>
USH1E	21q21	Unknown
USH1F	10Q21-22	<i>PCDH15</i>
USH1G	17Q24-25	<i>SANS</i>
USH2A	1q41	<i>USH2A</i>
USH2B	3p23-24.2	Unknown
USH2C	5q14.3-q21.3	<i>VLGR1</i>
USH3	3q21-q25	<i>USH3A</i>
Jervell and Lange-Nielsen		
JLNS1	11p15.5	<i>KCNQ1</i>
JLNS2	21q22.1-q22.2	<i>KCNE1</i>
Biotinidase deficiency	3p25	<i>BTBD</i>
Refsum	10pter-p11.2	<i>PHYH</i>
	6q22-q24	<i>PEX7</i>

(Continued)

Table 3

Continued

Syndrome	Chromosomal locus	Gene symbol
<i>X-linked</i>		
Alport	Xq22	<i>COL4A5</i>
	2q36-2q37	<i>COL4A3</i>
	2q36-2q37	<i>COL4A4</i>
Mohr-Tranebjaerg syndrome	Xq22	<i>TMM8A</i>

Adapted with permission from Van Camp G, Smith RJH. Hereditary Hearing Loss Homepage, 2003. <http://webh01.ua.ac.be/hhh/>. Accessed 24 January 2007.

mixed hearing loss; branchial cleft cysts or fistulae; malformations of the external ear; preauricular pits; and renal anomalies.^{25,26} Penetrance is high, and expressivity is extremely variable.²⁷⁻²⁹ In approximately 40% of families segregating a BOR phenotype, mutations in the *EYA1* gene have been identified. Mutations in *SIX1* were recently discovered in a few BOR families without *EYA1* mutations,³⁰ which is consistent with the known interaction of *EYA1* and *SIX1* proteins in transcriptional regulation and their involvement in the development of the mammalian ear and kidney.³¹⁻³³ There are a large number of BOR cases that appear to be genetic but for which no mutation has been identified.

Stickler syndrome

Stickler syndrome is an autosomal dominant disorder of type 2 collagen resulting in sensorineural hearing loss, cleft palate, congenital myopia, and spondyloepiphyseal dysplasia that eventually leads to osteoarthritis. The syndrome is common, and three forms are recognized based on the precise molecular genetic defect involved. STL1 is caused by mutations in *COL2A1*, STL2 is caused by mutations in *COL11A1*, and STL3 occurs secondary to mutations in *COL11A2*.³⁴⁻³⁷ STL1 and STL2 are characterized by severe myopia, which predisposes individuals to retinal detachment. Myopia is absent in STL3 because the *COL11A2* gene is not expressed in the eye. Because of the substantial risk for retinal detachment, ophthalmologic assessment is mandatory in all persons diagnosed with STL1 and STL2.

Neurofibromatosis 2

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. Impairment primarily begins in the third decade, concomitant with the growth of a vestibular schwannoma, and is generally unilateral and gradual but may be bilateral and sudden.³⁸ A retrocochlear lesion can often be diagnosed by audiologic evaluation, although the definitive diagnosis requires magnetic resonance imaging with gadolinium contrast. Affected persons are at risk for a variety of other tumors including meningiomas, astrocytomas, ependymomas, and meningioangiomas.³⁹ Mutations in *NF2*, which encodes the protein Merlin, are causative, and molecular genetic testing of *NF2* is available for presymptomatic, at-risk family members to facilitate early diagnosis and treatment.

Autosomal recessive syndromic hearing impairment

Pendred syndrome

Pendred syndrome is the most common form of syndromic hearing loss and is characterized by congenital severe-to-profound sensorineural hearing impairment, structural defects of the temporal bone and inner ear, 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 hearing loss is associated with an abnormality of the bony labyrinth (Mondini dysplasia or dilated vestibular aqueduct) that can be diagnosed by computed tomography of the temporal bones (Fig. 4).^{40,41} Vestibular function is abnormal in the majority of affected persons.

Mutations in *SLC26A4* (*PDS*) can be identified in approximately 50% of multiplex families with a Pendred syndrome phenotype, and genetic testing of this gene 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.^{42,43} Mutations in *SLC26A4* also cause autosomal recessive nonsyndromic hearing loss at the *DFNB4* locus.

Usher syndrome

Usher syndrome is one of the most common types of autosomal recessive syndromic hearing loss and is characterized by dual sensory impairments. Affected individuals are born with sensorineural hearing loss and early in life develop retinitis pigmentosa, a progressive degeneration of the retina that leads to loss of night vision, restriction of visual fields, and blindness by adolescence. Usher syndrome affects more than 50% of the deaf-blind in the United States.⁴⁴ It is of significance to note that the visual impairment from retinitis pigmentosa is usually not apparent in the first decade, thus making funduscopic examination before 10 years of age of limited utility. However, electroretinography can identify abnormalities in photoreceptor function in children as young as 2 to 4 years of age. During the second decade, night blindness and loss of peripheral vision become evident and inexorably progress.

Usher syndrome is both phenotypically and genotypically heterogeneous. Three types are recognized on the basis of the degree of hearing impairment and vestibular function. Usher syndrome type I is characterized by congenital severe-to-profound sensori-

neural hearing loss and vestibular dysfunction. Affected persons find traditional sound amplification ineffective and usually communicate manually. Because of the vestibular deficit, developmental motor milestones for sitting and walking are generally achieved later than normal. Usher syndrome type II is characterized by congenital mild-to-severe sensorineural hearing loss and normal vestibular function. Hearing aids provide effective sound amplification for these persons, and their communication is usually oral. Usher syndrome type III is the rarest form and is characterized by progressive hearing loss and progressive deterioration of vestibular function.⁴⁵

Jervell and Lange-Nielsen syndrome

Jervell and Lange-Nielsen syndrome is the third most common type of autosomal syndromic hearing loss. The syndrome consists of congenital sensorineural hearing loss and prolongation of the QT interval as detected by electrocardiography (the abnormal QTc [c = corrected] is > 440 ms). Affected individuals have syncope episodes and may have sudden death. Although a screening electrocardiogram 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, sudden infant death syndrome, syncope episodes, or long QT syndrome) should have a thorough cardiac evaluation. Mutations in two genes, *KCNQ1* and *KCNE1*, have been identified in affected persons.^{46,47}

Biotinidase deficiency

Biotinidase deficiency is secondary to absence of the water-soluble B-complex vitamin biotin. Biotin covalently binds to four carboxylases that are essential for gluconeogenesis, fatty acid synthesis, and catabolism of several branched-chain amino acids. If biotinidase deficiency is not recognized and corrected by daily addition of biotin to the diet, affected persons develop neurologic features such as seizures, hypertonias, developmental delay, ataxia, and visual problems. Furthermore, in at least 75% of children who become symptomatic, sensorineural hearing loss develops and can be both profound and persistent even after treatment is initiated.⁴⁸ Cutaneous features are also present and include a skin rash, alopecia, and conjunctivitis. With treatment that consists of biotin replacement, the neurologic and cutaneous manifestations resolve; however, the hearing loss and optic atrophy are usually irreversible. Therefore, if a child presents with episodic or progressive ataxia and progressive sensorineural deafness,

Fig. 4. Dilated vestibular aqueduct (arrows) as shown by computed tomography scan of the temporal bone in a person with Pendred syndrome.

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.^{48,49}

Refsum disease

Refsum disease is a postlingual severe progressive sensorineural hearing loss associated with retinitis pigmentosa, peripheral neuropathy, cerebellar ataxia, and elevated protein levels in the cerebrospinal fluid without an increase in the number of cells.⁵⁰ It is caused by defective phytanic acid metabolism, and as such, the diagnosis is established by determining the serum concentration of phytanic acid. Two genes, *PHYH* and *PEX7*, have been implicated in the majority of Refsum cases, although a small number of patients exist in whom mutations have not been found.⁵¹ Although Refsum disease is rare, it is important that it be considered in the evaluation of a deaf person because it can be easily treated with dietary modification and plasmapheresis.

X-linked syndromic hearing impairment

Alport syndrome

Alport syndrome is characterized by progressive postlingual sensorineural hearing loss of varying severity, progressive glomerulonephritis leading to end-stage renal disease, and variable ophthalmologic findings such as anterior lenticonus. Hearing loss usually does not manifest before the first decade of life, and the progressive myopia secondary to anterior lenticonus is considered by some authors to be sufficient to diagnose Alport syndrome.⁵² Autosomal dominant, autosomal recessive, and X-linked inheritance are described. X-linked forms account for approximately 85% of cases and are attributable to mutations in *COL4A5*, a member of the type IV collagen gene family.⁵³ Autosomal recessive inheritance accounts for the majority of the remaining 15% of cases, with only a few autosomal dominant cases documented.

Mohr-Tranebjaerg syndrome (deafness-dystonia-optic atrophy syndrome)

Mohr-Tranebjaerg syndrome was first described in a large Norwegian family with apparent progressive postlingual nonsyndromic hearing impairment and classified as DFN1.⁵⁴ Reevaluation of this family, however, revealed additional findings, including visual disability, dystonia, fractures, and mental retardation, indicating that this form of hearing impairment is syndromic rather than nonsyndromic.⁵⁵ 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.^{56,57}

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; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; myoclonic epilepsy and ragged red fibers; and neuropathy, ataxia, and retinitis pigmentosa syndrome; to common conditions,

such as diabetes mellitus, Parkinson disease, and Alzheimer disease. 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.⁵⁸ Sixty-one percent of patients with diabetes mellitus carrying this mutation also have hearing loss.^{58–60} The hearing loss is sensorineural and develops only after the onset of the diabetes mellitus. The same mutation is associated with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes, raising questions of penetrance and tissue specificity, issues further confounded by heteroplasmy associated with mitochondrial conditions.

Nonsyndromic hearing impairment

More than 70% of hereditary hearing loss is nonsyndromic.^{61,62} 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, loci for genes inherited in an autosomal recessive manner are referred to as DFNB, and loci for genes inherited in an X-linked manner are referred to as DFN. The number following these designations reflects the order of gene mapping and/or discovery.

It is important to realize that several recessive and dominant loci have been mapped to the same chromosomal region, and in many of these cases, allelic variants of a single gene have been found. Examples include 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*.

Autosomal dominant nonsyndromic hearing impairment

The characteristic phenotype of a person with autosomal dominant nonsyndromic hearing impairment is a progressive postlingual hearing loss that begins in the second to third decades of life. The condition is extremely heterogeneous, with multiple genes implicated in its pathogenesis. Audioprofiles may be distinct and therefore 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 (Fig. 5). Characteristic phenotypes are noted in Table 4, which also lists the genes known to be associated with autosomal dominant nonsyndromic hearing impairment.

Autosomal recessive nonsyndromic hearing impairment

In many world populations, mutations in *GJB2* account for 50% of persons with autosomal recessive nonsyndromic hearing loss.^{63–65} The remaining 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.^{66,67} Extensive genotype–phenotype studies have shown that it is possible to predict the hearing loss associated with *GJB2* mutations based on the specific genotype (Fig. 6).⁶⁸ The largest study to date involved a cross-sectional analysis of *GJB2* genotype and audiometric data from

Fig. 5. Audiogram for a family with DFNA6/14/38 hearing loss. An audiogram is a recording of several audiograms on a single graph. These audiograms may be from one individual at different times, but frequently they are from different members of the same family segregating deafness usually in an autosomal dominant fashion. This represents a high-frequency hearing loss. dB, decibel; ANSI, American National Standards Institute. Adapted from Smith RJH, Van Camp G. Deafness and hereditary hearing loss review. (Last revised January 30, 2007.) Available at: <http://www.genetests.org>. Reprinted with permission from the University of Washington, Seattle.

1531 persons from 16 different countries with autosomal recessive, mild-to-profound, nonsyndromic deafness.⁶⁸

The clinical manifestations, molecular genetics, and phenotypes of genes known to cause autosomal recessive nonsyndromic hearing impairment are summarized in Table 5.

X-linked nonsyndromic hearing impairment

DFN3 (mapped to Xq21.1) is characterized by a mixed conductive-sensorineural hearing loss, the conductive component of which is caused by stapedial fixation. In contrast with other types of conductive hearing loss, surgical correction is not accepted because an abnormal communication between the cerebrospinal fluid and perilymph results in leakage known as “perilymphatic gusher.” Thus, a complete loss of hearing occurs when the oval window is fenestrated or removed. Radiology with computed tomography is helpful and demonstrates a dilation of the internal auditory meatus with an abnormal communication between the subarachnoid space and the cochlear endolymph. The causative gene for DFN3 is *POU3F4*.⁶⁹

Additional X-linked nonsyndromic hearing loss phenotypes include profound prelingual hearing loss characteristic of both DFN2 and DFN4. DFN6 is characterized by a bilateral high-frequency impairment beginning at 5 to 7 years of age and progressing, by adulthood, to severe-to-profound hearing impairment, covering all frequencies.

Clinical manifestations and molecular genetics of genes known to cause X-linked nonsyndromic hearing impairment are summarized in Table 6.

Mitochondrial nonsyndromic hearing impairment

Some mitochondrial DNA mutations cause nonsyndromic hearing loss (Table 7). In two families, a homoplasmic mutation at nt1555 (A-to-G) in the mitochondrial *MTRNR1* gene has been reported. This mutation is also present 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 low, suggesting that unidentified genetic or environmental factors play an important role in the progression of the hearing impairment.⁷⁰

CLINICAL EVALUATION AND DIAGNOSIS OF HEARING LOSS

Correctly diagnosing the specific cause of hearing loss can provide important prognostic information and is essential for accurate genetic counseling. The following clinical assessments are recommended.

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 through direct examination of those individuals or through review of their medical records, including au-

Table 4

Clinical manifestations, molecular genetics, and phenotypes associated with autosomal dominant nonsyndromic hearing impairment

Locus name	Chromosomal locus	Gene symbol	Phenotype
DFNA1	5q31	<i>DIAPH1</i>	Postlingual low-frequency hearing loss (first decade)
DFNA2	1p35.1	<i>GJB3</i>	Postlingual high-frequency hearing loss (second)
	1p34	<i>KCNQ4</i>	
DFNA3 ^a	13q11-q12	<i>GJB2</i>	Prelingual high-frequency hearing loss
	13q12	<i>GJB6</i>	
DFNA4	19q13	<i>MYH14</i>	Postlingual hearing loss with flat/gently downsloping audioprofile
DFNA5	7p15	<i>DFNA5</i>	Postlingual high-frequency hearing loss (first)
DFNA6/14/38 ^b	4p16.1	<i>WFS1</i>	Prelingual low-frequency hearing loss
DFNA8/12 ^a	11q22-q24	<i>TECTA</i>	Prelingual mid-frequency hearing loss
DFNA9	14q12-q13	<i>COCH</i>	Postlingual high-frequency hearing loss (second)
DFNA10	6q23	<i>EYA4</i>	Postlingual hearing loss with flat/gently downsloping audioprofile (third/fourth)
DFNA11	11q13.5	<i>MYO7A</i>	Postlingual hearing loss (first)
DFNA13	6p21.3	<i>COL11A2</i>	Postlingual mid-frequency hearing loss (second)
DFNA15	5q31	<i>POU4F3</i>	Postlingual high-frequency hearing loss
DFNA17	22q11.2	<i>MYH9</i>	Postlingual high-frequency hearing loss
DFNA20/26	17q25	<i>ACTG1</i>	Postlingual high-frequency hearing loss
DFNA22	6q13	<i>MYO6</i>	Postlingual high-frequency hearing loss
DFNA28	8q22	<i>TFCP2L3</i>	Postlingual hearing loss with flat/gently downsloping audioprofile
DFNA36	9q13-q21	<i>TMCI</i>	
DFNA39	4q21.3	<i>DSPP</i>	Postlingual high-frequency hearing loss
DFNA48	12q13-q14	<i>MYO1A</i>	Postlingual hearing loss

^a Most autosomal dominant disorders cause postlingual hearing impairment. Some exceptions are DFNA3, DFNA8, and DFNA12.^b DFNA6/1438 is noteworthy because the hearing loss primarily affects the low frequencies.Adapted with permission from Van Camp G, Smith RJH. Hereditary Hearing Loss Homepage, 2003. <http://webh01.ua.ac.be/hhh/>. Accessed 24 January 2007.

diagrams, otologic examinations, and DNA-based testing with appropriate consent.

Physical 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 and skeletal anomalies. Neurologic examination of vestibular function with an ophthalmologic examination should be completed. The variable expressivity associated with syndromic deafness requires careful physical examination of the proband and other family members to make a correct diagnosis.

Audiologic findings

Establishing the diagnosis of a child or adult with presumed hereditary hearing loss can be difficult. One must both objectively assess auditory function and subjectively determine how a person processes auditory information,

that is, hears. Physiologic tests, such as the ABR and the EOA, are important objective determinants of the functional status of the auditory system and can be performed at any age. Audiometry refers to subjective testing that consists of both behavioral testing and pure tone measurement of air and bone sound conduction.

ABR uses sound stimuli in the form of clicks to evoke electrophysiologic responses that originate in the eighth cranial nerve and auditory brainstem. Surface electrodes record these responses and create a "wave V detection threshold." The ABR detection threshold correlates best with hearing sensitivity in the 1500- to 4000-Hz region in neurologically normal individuals. However, ABR does not reliably assess responses at low frequency (<1500 Hz).

Auditory steady-state response testing is an electrophysiologic measure of hearing acuity. Skin electrodes measure if the auditory response is phase locking to alterations in a continuous tonal stimulus. The continuous signal denotes that the average sound pressure level delivered is higher than that achieved with ABR, which uses repetitive click stimuli. This difference allows for auditory steady-state response testing to

Fig. 6. Relative frequencies of the degree of hearing impairment in the three classes of genotypes: biallelic truncating (T/T), compound heterozygous truncating/nontruncating (T/NT), and biallelic nontruncating (NT/NT). (With permission from Snoeckx RL, Huygen PL, Feldmann D, Marlin S, et al. *GJB2* mutations and degree of hearing loss: a multicenter study. *Am J Hum Genet* 2005;77:945–957.)

T/T mutations comprised 35% of all genotypes, and the degree of hearing impairment in these persons was profound in 59% to 64% of persons, severe in 25% to 28% of persons, moderate in 10% to 12% of persons, and mild in 0% to 3% of persons. NT/NT mutations comprised 24% of all genotypes, and the degree of hearing impairment was mild in 53% of persons and severe to profound in 20% of persons. T/NT mutations comprised 40% of all genotypes, and the degree of hearing impairment was profound in 24% to 30% of persons and severe in 10% to 17% of persons.

provide a measure of hearing sensitivity in children who demonstrate no response to ABR testing.

EOAEs are sounds that originate within the cochlea and are measured in the external auditory canal using a probe with a microphone and transducer. EOAEs principally reflect the activity of the outer hair cells of the cochlea across a broad frequency range. EOAEs are only present in ears with hearing sensitivity better than 40 to 50 dB HL.

Immittance testing includes tympanometry, testing of acoustic reflex thresholds, and acoustic reflex decay. Immittance audiometry evaluates the peripheral auditory system, including middle ear pressure, tympanic membrane mobility, eustachian tube function, and mobility of the middle ear ossicles.

Behavioral testing includes behavioral observation audiometry and visual reinforcement audiometry. Behavioral observation audiometry is used in infants from birth to age 6 months and is highly dependent on the skill of the tester. Thus, behavioral observation audiometry is subject to error. Visual reinforcement audiometry is used in children from age 6 months to 2.5 years and may provide a reliable, complete audiogram. However, the skill of the tester is also essential to visual reinforcement audiometry, as is the child's maturational age.

Pure-tone audiometry (air and bone conduction) seeks to determine 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, defined as the ratio between two sound pressures. The average threshold for a normal hearing adult is between 0 and 20 dB HL, whereas sound at 120 dB HL is so loud that it can cause pain. Speech reception thresholds and speech discrimination are both assessed during pure-tone audiometric testing.

Air conduction audiometry presents sounds through earphones with thresholds dependent on the condition of the external ear canal, middle, and inner ear. Bone conduction audiometry presents sounds through a vibrator placed on the mastoid bone or forehead, bypassing the external and middle ears. Thus, thresholds are dependent on the condition of the inner ear. Conditioned play audiometry is used to test children from age 2.5 to 5 years. If a child is cooperative, a complete frequency-specific audiogram for each ear can be obtained. In conventional audiometry, the individual indicates when the sound is heard and is used to test individuals age 5 years and older.

An audioprofile refers to the recording of several audiograms on a single graph (Fig. 5). The audiograms may be from one individual at different times, but more frequently they are from different members of the same family that segregate for

Table 5

Clinical manifestations, molecular genetics, and phenotypes associated with autosomal recessive nonsyndromic hearing impairment

Locus name	Chromosomal locus	Gene symbol	Phenotype
DFNB1	13q11-112	<i>GJB2</i>	Prelingual ^a hearing loss that remains relatively stable
	13q12	<i>GJB6</i>	
DFNB2	11q13.5	<i>MYO7A</i>	Prelingual or postlingual hearing loss of unspecified type
DFNB3	17p11.2	<i>MYO15</i>	Prelingual hearing loss that remains relatively stable
DFNB4	7q31	<i>SLC26A4</i>	Prelingual or postlingual hearing loss that may be stable or progressive. May also be associated with dilation of the vestibular aqueduct.
DFNB6	3p21	<i>TMIE</i>	Prelingual hearing loss that remains relatively stable
DFNB7/11	9q13-q21	<i>TMC1</i>	Prelingual hearing loss that remains relatively stable
DFNB8/10	21q22.3	<i>TMPRSS3</i>	Postlingual (DFNB8) ^b or prelingual (DFNB10) hearing loss that may be progressive or stable
DFNB9	2p22-p23	<i>OTOF</i>	Prelingual hearing loss that remains relatively stable
DFNB12	10q21-q22	<i>CDH23</i>	Prelingual hearing loss that remains relatively stable
DFNB16	15q15	<i>STRC</i>	Prelingual hearing loss that remains relatively stable and is more pronounced in the higher frequencies
DFNB18	11p15.1	<i>USH1C</i>	Prelingual hearing loss that remains relatively stable
DFNB21	11q22-q24	<i>TECTA</i>	Prelingual severe-to-profound isolated SNHL
DFNB22	16p12.2	<i>OTOA</i>	Prelingual moderate-to-severe SNHL
DFNB23	10q21.1	<i>PCDH15</i>	Prelingual severe-to-profound SNHL
DFNB28	22q13.1	<i>TRIOBP</i>	Prelingual severe-to-profound SNHL
DFNB29	21q22.3	<i>CLDN14</i>	Prelingual profound SNHL
DFNB30	10p11.1	<i>MYO3A</i>	Progressive hearing loss that first affects the high frequencies and begins in the second decade is severe in high and middle frequencies and moderate at low frequencies by age 50 y
DFNB31	9q32-q34	<i>DFN31</i>	Prelingual profound SNHL
DFNB36	1p36.31	<i>ESPN</i>	Prelingual hearing loss of unspecified or unknown type
DFNB37	6q13	<i>MYO6</i>	Prelingual hearing loss of unspecified or unknown type
DFNB67	6p21.1-p22.3	<i>TMHS</i>	Prelingual profound SNHL

SNHL, sensorineural hearing loss.

^a Prelingual deafness also includes congenital deafness.^b The onset of DFNB8 hearing loss is postlingual (10–12 years of age), whereas 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.Adapted with permission from Van Camp G, Smith RJH. Hereditary Hearing Loss Homepage, 2003. <http://webh01.ua.ac.be/hhh/>. Accessed 24 January 2007.

deafness in an autosomal dominant trend. Plotting several audiograms with respective ages on the same graph allows for an age-related progression of hearing loss to be appreciated within a particular family. The composite picture is often characteristic of a specific genetic cause of autosomal dominant nonsyndromic hearing loss. One of the more characteristic audioprofiles is associated with DFNA6/14/38 hearing loss caused by mutations in *WFS1* (Fig. 5).

In older children or adults, a standard audiogram can be obtained. The presence or absence of hearing loss in other family members should be documented by formal audiometric testing. Individuals with progressive hearing loss should be evaluated for Alport syndrome, Pendred syndrome, and Stickler syndrome. Testing should also include temporal bone computed tomography.

Sudden or rapidly progressive hearing loss can present with temporal bone anomalies or be secondary to a neoplasm. Furthermore, immunologic diseases, trauma, infections such as syphilis and Lyme disease, and metabolic, neurologic, or circulatory disturbances may also lead to sudden hearing loss.

Laboratory and radiologic assessment

A thorough history and physical examination will support specific laboratory evaluations that are directed toward the suspected diagnosis. This includes an immunoglobulin-M antibody assay in the first few years of life to assess for intrauterine infections such as cytomegalovirus and hemoglobinopathy testing that may be associated with sensorineural hearing loss. Urinalysis and renal function tests may also be performed if Alport syndrome is suspected, and thyroid function tests

Table 6

Clinical manifestations, molecular genetics, and phenotypes associated with X-linked nonsyndromic hearing impairment

Locus name	Chromosomal locus	Gene symbol	Phenotype
DFN2	Xq22	—	Prelingual profound SNHL in all frequencies
DFN3	Xq21.1	<i>POU3F4</i>	Mixed variable prelingual hearing loss that progresses to profound in all frequencies
DFN4	Xp21	—	Stable prelingual profound SNHL in all frequencies
DFN5	Withdrawn	—	—
DFN6	Xp22	—	Progressive severe-to-profound postlingual (first decade) SNHL that begins with high-frequency hearing loss that evolves to include all frequencies by adulthood.
DFN7	Withdrawn	—	—
DFN8	Reserved	—	—

SNHL, sensorineural hearing loss.

Adapted with permission from Van Camp G, Smith RJH. Hereditary Hearing Loss Homepage, 2003. <http://webh01.ua.ac.be/hhh/>. Accessed 24 January 2007.**Table 7**

Clinical manifestations, molecular genetics, and phenotypes associated with mitochondrial nonsyndromic hearing impairment

Gene symbol	Mutation	Phenotype
<i>MTRNR1</i>	961 different mutations inc.1494 C>Tc.1555 A>G	Commonly secondary to aminoglycoside use with variably severity and highly variable penetrance
<i>MTTS1</i>	c.7445 A>Gc.7472 ins Cc.7510 T>Cc.7511 T	Variably severe hearing loss with highly variable penetrance

Adapted with permission from Van Camp G, Smith RJH. Hereditary Hearing Loss Homepage, 2003. <http://webh01.ua.ac.be/hhh/>. Accessed 24 January 2007.

should be ordered for patients with presumed Pendred syndrome.⁷¹

Computed tomography is the best radiologic test for the evaluation of hearing impairment for anatomic abnormalities such as Mondini malformation or dilated vestibular aqueduct.^{72,73} Patients with hearing loss should also receive renal ultrasound to assess for abnormalities that may be associated with syndromic hearing loss such as BOR.

Molecular genetic testing

GJB2 and *GJB6* molecular testing should be considered in the evaluation of individuals with congenital nonsyndromic sensorineural hearing loss and in families with nonsyndromic hearing loss in which two generations are involved. Strong consideration should also be given to “pseudodominant” inheritance of DFNB1. Pseudodominant inheritance refers to occurrence of an autosomal recessive disorder in two or more generations of a family and tends to occur when the carrier rate in the general population is high, as can be seen with assortative mating in the Deaf community.

Inner-ear defects (enlarged/dilated vestibular aqueduct and Mondini dysplasia) are associated with mutations in both *SLC26A4* and *POU3F4*, and the detection of these temporal bone anomalies by computed tomography examination should prompt consideration of molecular genetic testing.⁷⁴

Other genes known to cause nonsyndromic deafness are listed in Tables 3 to 7. Although molecular genetic testing is

available for a number of these genes, the large size of many of these genes and their relatively small contribution to deafness make it impractical to offer such testing on a clinical basis at this time.

Prenatal testing

Prenatal diagnosis for some forms of hereditary hearing loss is technically possible by analysis of DNA extracted from fetal cells. Fetal material can be obtained by amniocentesis at 15 to 18 weeks' gestation or chorionic villus sampling at 10 to 12 weeks' gestation. Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements. It is important to note that for optimal evaluation, the deafness-causing allele(s) of a deaf family member should be identified before prenatal testing is performed.

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 may be available for families in whom the deafness-causing mutation(s) has/have been identified in a deaf family member.

Related genetic counseling issues

Communication with individuals who are deaf requires the services of a skilled interpreter. 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.^{75,76} Furthermore, members of the Deaf community may view hearing loss 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 by Deaf parents over having a child with normal hearing.⁷⁷ 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.

Management

Management of hereditary hearing loss is performed by a team that includes 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. It may also be necessary to incorporate the expertise of an educator of the Deaf, a neurologist, and a pediatric ophthalmologist. 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.

If an individual or the parents of a child raise concern about the possibility of hearing loss or, if the child is young, and there is concern regarding 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 physical examination focusing on features that might suggest a syndromic type of deafness should also be performed.

An accurate test to quantify 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. On the basis of the data recorded from the initial evaluation, more specific tests can be requested that may include mutation screening of genes implicated in deafness.

In contrast with many other medical conditions, the management and treatment of hearing loss largely involves the social welfare system and incurs a growing cost to society. For a child with prelingual severe to profound sensorineural hearing loss, the total lifetime cost of hearing loss includes special education services, medical expenses, and the purchase of assisted devices, altogether exceeding U.S. \$1,000,000.⁷⁸ Thus, early screening is only the first step in a successful and cost-effective program whose main goals are early diagnosis and management, language development, and long-term success after intervention.

Intervention

Auditory deprivation through the age of 2 years is associated with poor reading performance, poor communication skills, and poor speech production. Thus, an important component of the evaluation is to determine which avenue of habilitation best suits the individual. Interventional services should begin before the age of 6 months for all infants, and possible treatments include hearing aids, vibrotactile devices, or cochlear implantation, which are now considered in children aged more than 12 months with severe-to-profound hearing loss.

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 intelligence quotient and normal reading performance after cochlear implantation. Yet, it must be noted that educational intervention alone is insufficient to completely remediate these deficiencies, and evidence suggests that early auditory intervention, whether through amplification, otologic surgery, or cochlear implantation, is effective.⁷⁹

EHDI programs have reduced the average age at which hearing loss is confirmed (from 20–30 months to 2–3 months) and now provide screening for approximately 93% of all newborn infants before hospital discharge.⁸⁰ Infants in whom appropriate intervention is begun within 6 months of life are able to maintain language, social, and emotional development that is commensurate with their physical development, in contrast with those in whom hearing loss is not detected until after 6 months of age. This observation is not dependent on the mode of communication, rather, improved language is found in early identified children who speak, sign, or use both modes of communication.⁸¹

Although EHDI programs have dramatically improved the average age at which hearing loss is first recognized, early newborn hearing screens may fail to identify children with progressive hearing loss, which accounts for approximately 15% of preschool children with sensorineural hearing loss.⁸² Furthermore, recent studies suggest that some children with *GJB2* mutations may fail to express the phenotype of hearing loss at birth but then have a later onset of hearing loss. Whether this phenomena is attributable to the current EHDI criteria used to identify hearing loss or a true delay in the onset is unknown.⁸³ Thus, it is essential for primary care providers to have a low threshold for reevaluating an infant's hearing if parents show concern about possible hearing loss or observe delays in speech development, even if their children have passed a newborn hearing screen.

Agents and circumstances to avoid

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

PREVENTION OF HEARING IMPAIRMENT

An ideal therapy has not yet arrived to correct hearing loss through replacement or regeneration of inner and outer hair cells. Although practices to one day repair inner-ear damage are currently under way, existing measures for the prevention of hearing loss must attempt to decrease the frequency of acquired and genetic hearing loss.^{84–87} Improved implementation of vaccination programs in developing nations, avoidance of exacerbating factors such as noise, and focused genetic counseling and health education in populations with a high prevalence of consanguinity are several methods that may assist in decreasing the prevalence of acquired and hereditary hearing loss.

RESOURCES

- 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
[http://ghr.nlm.nih.gov/condition = nonsyndromicdeafness](http://ghr.nlm.nih.gov/condition=nonsyndromicdeafness)
- 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

Suggested reading

- Holden-Pitt L, Albertorio J. Thirty years of the Annual Survey of Deaf and Hard-of-Hearing Children & Youth: a glance over the decades. *Am Ann Deaf* 1998;143:72–76.
- Kittrell AP, Arjmand EM. The age of diagnosis of sensorineural hearing impairment in children. *Int J Pediatr Otorhinolaryngol* 1997;40:97–106.

Meyerhoff WL, Cass S, Schwaber MK, Sculerati N, et al. Progressive sensorineural hearing loss in children. *Otolaryngol Head Neck Surg* 1994;110:569–579.

Reardon W. Genetic deafness. *J Med Genet* 1992;29:521–526.

Rose SP. Genetic studies of profound prelingual deafness. PhD Thesis. Indianapolis: Indiana University, 1975.

Wander RJA, Jacobs C, Skjeldal OH. Refsum disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular basis of inherited disease. New York: McGraw Hill, 1995:3301–3321.

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References

1. Toriello HV, Reardon W, Gorlin RF, editors. Hereditary hearing loss and its syndromes, 2nd ed. New York: Oxford University Press, 2004.
2. Van Camp G, Smith RJH. Hereditary Hearing Loss Homepage, 2003. <http://webh01.ua.ac.be/hhh/>. Accessed 24 January 2007.
3. Guide for the evaluation of hearing handicap. *JAMA* 1979;241:2055–2059.
4. Northern JL, Downs M. Hearing in children. Baltimore: Lippincott, Williams, and Wilkins, 2002.
5. Morton NE. Genetic epidemiology of hearing impairment. *Ann N Y Acad Sci* 1991; 630:16–31.
6. White KR. The current status of EHDI programs in the United States. *Ment Retard Dev Disabil Res Rev* 2003;9:79–88.
7. Marazita ML, Ploughman LM, Rawlings B, Remington E, et al. Genetic epidemiological studies of early-onset deafness in the U.S. school-age population. *Am J Med Genet* 1993;46:486–491.
8. Cohen MM, Gorlin RJ. Epidemiology, etiology, and genetic patterns. In: Gorlin RJ, Toriello HV, Cohen MM, editors. Hereditary hearing loss and its syndromes. New York: Oxford Press, 1995:9–21.
9. Green GE, Scott DA, McDonald JM, Woodworth GG, et al. Carrier rates in the midwestern United States for GJB2 mutations causing inherited deafness. *JAMA* 1999;281:2211–2216.
10. Fischel-Ghodsian N. Genetic factors in aminoglycoside toxicity. *Ann N Y Acad Sci* 1999;884:99–109.
11. Harris S, Ahlfors K, Ivarsson S, Lernmark B, et al. Congenital cytomegalovirus infection and sensorineural hearing loss. *Ear Hear* 1984;5:352–355.
12. Hicks T, Fowler K, Richardson M, Dahle A, et al. Congenital cytomegalovirus infection and neonatal auditory screening. *J Pediatr* 1993;123:779–782.
13. Schildroth AN. Congenital cytomegalovirus and deafness. *Am J Audiol* 1994;3:27–38.
14. Ogawa H, Baba Y, Suzutani T, Inoue N, et al. Congenital cytomegalovirus infection diagnosed by polymerase chain reaction with the use of preserved umbilical cord in sensorineural hearing loss children. *Laryngoscope* 2006;116:1991–1994.
15. Gates G, Mills J. Presbycusis. *Lancet* 2005;366:1111–1120.
16. Guilford P, Ben Arab S, Blanchard S, Levilliers J, et al. Joint Committee on Infant Hearing; American Academy of Audiology; American Academy of Pediatrics; American Speech-Language-Hearing Association; Directors of Speech and Hearing Programs in State Health and Welfare Agencies. Year 2000 position statement: principles and guidelines for early hearing detection and intervention programs. *J Pediatr* 2000;106:798–817.
17. Baldwin CT, Hoth CF, Amos JA, da-Silva EO, et al. An exonic mutation in HuP2 paired domain gene causes Waardenburg's syndrome. *Nature* 1992;355:637–638.
18. Tassabehji M, Read AP, Newton VE, Harris R, et al. Waardenburg's syndrome patients have mutations in the human homologue of Pax-3 paired box gene. *Nature* 1992;355:635–636.
19. Hoth CF, Milunsky A, Lipsky N, Sheffer R, et al. Mutations in the paired domain of the human PAX3 gene cause Klein-Waardenburg syndrome (WS-III) as well as Waardenburg syndrome type I (WS-I). *Am J Hum Genet* 1993;52:455–462.
20. Tassabehji M, Newton VE, Read AP. Waardenburg syndrome type 2 caused by mutations in the human microphthalmia (MITF) gene. *Nat Genet* 1994;8:251–255.

21. Sánchez-Martín M, Rodríguez-García A, Pérez-Losada J, Sagrera A, et al. SLUG (SNAI2) deletions in patients with Waardenburg disease. *Hum Mol Genet* 2002;11:3231–3236.
22. Ederly P, Attie T, Amiel J, Pelet A, et al. Mutation of the endothelin-3 gene in the Waardenburg-Hirschsprung phenotype (Shah-Waardenburg syndrome). *Nat Genet* 1996;12:442–444.
23. Hofstra RM, Osinga J, Tan-Sindhunata G, Wu Y, et al. A homozygous mutation in the endothelin-3 gene associated with a combines Waardenburg type 2 and Hirschsprung phenotype (Shah-Waardenburg syndrome). *Nat Genet* 1996;12:445–447.
24. Pingault V, Bondurand N, Kuhlbrodt K, Goerich DE, et al. SOX10 mutations in patients with Waardenburg-Hirschsprung disease. *Nat Genet* 1998;18:171–173.
25. Melnick M, Bixler D, Silk K, Yune H, et al. Autosomal dominant branchiootorenal dysplasia. *Birth Defects Orig Artic Ser* 1975;5:121–128.
26. Fraser FC, Ling D, Clogg D, Nogrady B. Genetic aspects of the BOR syndrome-branchial fistulas, ear pits, hearing loss, and renal anomalies. *Am J Med Genet* 1978;2:241–252.
27. Heimler A, Lieber E. Branchio-Oto-Renal syndrome: reduced penetrance and variable expressivity in four generations of a large kindred. *Am J Med Genet* 1986;25:15–27.
28. Konig R, Fuchs S, Dukiet C. Branchio-oto-renal (BOR) syndrome: variable expressivity in a five-generation pedigree. *Eur J Pediatr* 1994;153:446–450.
29. Stratakis CA, Lin J-P, Rennert OM. Description of a large kindred with autosomal dominant inheritance of branchial arch anomalies, hearing loss and ear pits, and exclusion of the branchio-oto-renal (BOR) syndrome gene locus (chromosome 8q13.3). *Am J Med Genet* 1998;79:209–214.
30. RufRG, Xu PX, Silvius D, Otto EA, et al. SIX1 mutations cause Branchio-Oto-Renal syndrome by disruption of EYA1-SIX1-DNA complexes. *Proc Natl Acad Sci U S A* 2004;101:8090–8095.
31. Kalatzis V, Sahly I, El Amraoui A, Petit C. Eya1 expression in the developing ear and kidney: towards the understanding of the pathogenesis of Branchio-Oto-Renal (BOR) syndrome. *Dev Dyn* 1998;213:486–499.
32. Xu PX, Zheng W, Huang L, Maire P, et al. Six1 is required for the early organogenesis of mammalian kidney. *Development* 2003;130:3085–3094.
33. Zheng W, Huang L, Wei ZB, Silvius D, et al. The role of Six1 in mammalian auditory system development. *Development* 2003;130:3989–4000.
34. Williams CJ, Ganguly A, Considine E, McCarron S, et al. A-2aG transition at the 3' acceptor splice site of IVS17 characterizes the COL2A1 gene mutation in the original Stickler syndrome kindred. *Am J Med Genet* 1996;63:461–467.
35. Richards AJ, Yates JR, Williams R, Payne SJ, et al. A family with Stickler syndrome type 2 has a mutation in the COL11A1 gene resulting in the substitution of glycine 97 by valine in alpha 1 (XI) collagen. *Hum Mol Genet* 1996;5:1339–1343.
36. Vikkula M, Mariman EC, Lui VC, Zhidkova NI, et al. Autosomal dominant and recessive osteochondrodysplasias associated with the COL11A2 locus. *Cell* 1995;80:431–437.
37. Wilkin DJ, Mortier GR, Johnson CL, Jones MC, et al. Correlation of linkage data with phenotype in eight families with Stickler syndrome. *Am J Med Genet* 1998;80:121–127.
38. Yohay K. Neurofibromatosis types 1 and 2. *Neurologist* 2006;2:86–93.
39. National Institutes of Health Consensus Development Conference. Neurofibromatosis: conference statement. *Arch Neurol* 1988;45:475–478.
40. Phelps PD, Coffey RA, Trembath RC, Luxon LM, et al. Radiological malformations of the ear in Pendred syndrome. *Clin Radiol* 1998;53:268–273.
41. Reardon W, O'Mahoney CF, Trembath R, Jan H, et al. Enlarged vestibular aqueduct: a radiological marker of Pendred syndrome, and mutations of the PDS gene. *QJM* 2000;93:99–104.
42. Newton VE. Aetiology of bilateral sensori-neural hearing loss in young children. *J Laryngol Otol Suppl* 1985;10:1–57.
43. Arnos KS, Cunningham M, Israel J, Marazita ML. Innovative approach to genetic counseling services for the deaf population. *Am J Med Genet* 1992;44:345–351.
44. Rosenberg T, Haim M, Hauch AM, Parving A. The prevalence of Usher syndrome and other retinal dystrophy-hearing impairment associations. *Clin Genet* 1997;51:314–321.
45. Kimberling WJ, Moller CG, Davenport SL, Lund G, et al. Usher syndrome: clinical findings and gene localization studies. *Laryngoscope* 1989;99:66–72.
46. Neyroud N, Tesson F, Denjoy I, Leibovici M, et al. A novel mutation in the potassium channel gene KVLQT1 causes Jervell Lange-Nielsen cardioauditory syndrome. *Nat Genet* 1997;15:186–189.
47. Schulze-Bahr E, Wang Q, Wedekind H, Haverkamp W, et al. KCNE1 mutations cause Jervell and Lange-Nielsen syndrome. *Nat Genet* 1997;17:267–268.
48. Wolf B, Spencer R, Gleason T. Hearing loss is a common feature of symptomatic children with profound biotinidase deficiency. *J Pediatr* 2002;140:242–246.
49. Heller AJ, Stanley C, Shaia WT, Sismanis A, et al. Localization of biotinidase in the brain: implications for its role in hearing loss in biotinidase deficiency. *Hear Res* 2002;173:62–68.
50. Wander RJA, Jacobs C, Skjeldal OH. Refsum disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D, editors. The metabolic and molecular basis of inherited disease. New York: McGraw Hill, 1995:3301–3321.
51. van den Brink DM, Wanders RJ. Phytanic acid: production from phytol, its breakdown and role in human disease. *Cell* 2006;63:1752–1765.
52. Govan J. Ocular manifestations of Alport's syndrome: a hereditary disorder of basement membranes? *Br J Ophthalmol* 1983;67:493–503.
53. Barker DF, Hostikka SL, Zhou J, Chow LT, et al. Identification of mutations in the COL4A5 collagen gene in Alport syndrome. *Science* 1990;248:1224–1227.
54. Mohr J, Mageroy K. Sex-linked deafness of a possibly new type. *Acta Genet Statist Med* 1960;10:54–62.
55. Tranebjaerg L, Schwartz C, Eriksen H, Andreasson S, et al. A new X linked recessive deafness syndrome with blindness, dystonia, fractures, and mental deficiency is linked to Xq22. *J Med Genet* 1995;32:257–263.
56. Jin H, May M, Tranebjaerg L, Kendall E, et al. A novel X-linked gene, DDP, shows mutations in families with deafness (DFN-1), dystonia, mental deficiency and blindness. *Nat Genet* 1996;14:177–180.
57. Koehler CM, Leuenberger D, Merchant S, Renold A, et al. Human deafness dystonia syndrome is a mitochondrial disease. *Proc Natl Acad Sci U S A* 1999;96:2141–2146.
58. Usami S, Abe S, Akita J, Namba A, et al. Prevalence of mitochondrial gene mutations among hearing impaired patients. *J Med Genet* 2000;37:38–40.
59. Majamaa K, Moilanen JS, Uimonen S, Remes AM, et al. Epidemiology of A3243G, the mutation for mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes: prevalence of the mutation in an adult population. *Am J Hum Genet* 1998;63:447–454.
60. Kadowaki T, Kadowaki H, Mori Y, Tobe K, et al. A subtype of diabetes mellitus associated with a mutation of mitochondrial DNA. *N Engl J Med* 1994;330:962–968.
61. Cremers CW, Marres HA, van Rijn PM. Nonsyndromal profound genetic deafness in childhood. *Ann N Y Acad Sci* 1991;630:191–196.
62. Van Camp G, Willems PJ, Smith RJ. Nonsyndromic hearing impairment: unparalleled heterogeneity. *Am J Hum Genet* 1997;60:758–764.
63. Zelante L, Gasparini P, Estivill X, Melchionda S, et al. Connexin26 mutations associated with the most common form of non-syndromic neurosensory autosomal recessive deafness (DFNB1) in Mediterraneans. *Hum Mol Genet* 1997;6:1605–1609.
64. Estivill X, Fortina P, Surrey S, Rabionet R, et al. Connexin-26 mutations in sporadic and inherited sensorineural deafness. *Lancet* 1998;351:394–398.
65. Kelley PM, Harris DJ, Comer BC, Askew JW, et al. Novel mutations in the connexin 26 gene (GJB2) that cause autosomal recessive (DFNB1) hearing loss. *Am J Hum Genet* 1998;62:792–799.
66. Scott DA, Kraft ML, Carmi R, Ramesh A, et al. Identification of mutations in the connexin 26 gene that cause autosomal recessive nonsyndromic hearing loss. *Hum Mutat* 1988;11:387–394.
67. Zbar RI, Ramesh A, Srisailapathy CR, Fukushima K, et al. Passage to India: the search for genes causing autosomal recessive nonsyndromic hearing loss. *Otolaryngol Head Neck Surg* 1998;118:333–337.
68. Snoeckx RL, Huygen PL, Feldmann D, Marlin S, et al. GJB2 mutations and degree of hearing loss: a multicenter study. *Am J Hum Genet* 2005;77:945–957.
69. Vore AP, Chang EH, Hoppe JE, Butler MG, et al. Deletion of and novel missense mutation in POU3F4 in 2 families segregating X-linked nonsyndromic deafness. *Arch Otolaryngol Head Neck Surg* 2005;131:1057–1063.
70. Fischel-Ghodsian N. Mitochondrial mutations and hearing loss: paradigm for mitochondrial genetics. *Am J Hum Genet* 1998;62:15–19.
71. Hone SW, Smith RJ. Medical evaluation of pediatric hearing loss: laboratory, radiographic, and genetic testing. *Otolaryngol Clin North Am* 2002;35:751–764.
72. Zalzal GH, Shott SR, Towbin R, Cotton RT. Value of CT scan in the diagnosis of temporal bone diseases in children. *Laryngoscope* 1986;96:27–32.
73. Bamio D, Phelps P, Sirimanna T. Temporal bone computed tomography findings in bilateral sensorineural hearing loss. *Int J Pediatr Otorhinolaryngol* 1999;51:91–99.
74. Vore AP, Chang EH, Hoppe JE, Butler MG, et al. Deletion of and novel missense mutation in POU3F4 in 2 families segregating X-linked nonsyndromic deafness. *Arch Otolaryngol Head Neck Surg* 2005;131:1057–1063.
75. Middleton A, Hewison J, Mueller RF. Attitudes of deaf adults toward genetic testing for hereditary deafness. *Am J Hum Genet* 1998;63:1175–1180.
76. Arnos KS. The implications of genetic testing for deafness. *Ear Hear* 2003;24:324–331.
77. Arnos KS, Israel J, Cunningham M. Genetic counseling of the deaf—medical and cultural considerations. *Ann N Y Acad Sci* 1992;630:212–222.
78. Mohr P, Feldman JJ, Dunbar JL. The societal costs of severe to profound hearing loss in the United States. *Int J Technol Assess Health Care* 2000;16:1120–1135.
79. Downs MP, Yoshinaga-Itano C. The efficacy of early identification and intervention for children with hearing impairment. *Pediatr Clin North Am* 1999;46:79–87.

80. White KR. National Center for Hearing Assessment and Management website, 2006. <http://www.infanthearing.org>. Accessed 10 February 2007.
81. Yoshinaga-Itano C, Seday A, Coulter DK, Mehl AL. Language of early- and later-identified children with hearing loss. *J Pediatr* 1998;102:1161–1171.
82. Hone SW, Smith RJ. Medical evaluation of pediatric hearing loss: laboratory, radiographic, and genetic testing. *Otolaryngol Clin North Am* ;200235:751–764.
83. Norris VW, Arnos KS, Hanks WD, Xia X, et al. Does universal newborn hearing screening identify all children with GJB2 (connexin 26) deafness? Penetrance of GJB2 deafness. *Ear Hear* 2006;27:732–741.
84. Minoda R, Izumikawa M, Kawamoto K, Raphael Y. Strategies for replacing lost cochlear hair cells. *Neuroreport* 2004;15:1089–1092.
85. Shou J, Zheng JL, Gao WQ. Robust generation of new hair cells in mature mammalian inner ear by adenoviral expression of Hath1. *Mol Cell Neurosci* 2003;23:169–179.
86. Kawamoto K, Ishimoto S, Minoda R, Brough DE, et al. Math1 gene transfer generates new cochlear hair cells in mature guinea pigs in vivo. *J Neurosci* 2003;23:4395–4400.
87. Smith R, Bale J, White K. Sensorineural hearing loss in children. *Lancet* 2005;365:879–890.