REVIEW ARTICLE

CURRENT CONCEPTS

Newborn Hearing Screening — A Silent Revolution

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HEARING LOSS IS AN ETIOLOGICALLY HETEROGENEOUS TRAIT WITH many known genetic and environmental causes.[1] Historically, some environmental causes of hearing loss, such as rubella embryopathy, have been epidemic in nature, establishing that the incidence of congenital deafness can vary widely at various times and among populations. Other important environmental causes of hearing loss include prematurity, prenatal and postnatal infections, head trauma, subarachnoid hemorrhage, and pharmacologic ototoxicity. Genetic causes account for at least 50 to 60 percent of childhood hearing loss in developed countries and can be classified according to the pattern of inheritance, the presence (syndromic) or absence (nonsyndromic) of distinctive clinical features, or the identification of the causal mutation. Because hearing is so critical to the normal development and acquisition of language, we review prelingual hearing loss, which is either present at birth or begins before the age of five years, when language has normally been acquired.

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PREVALENCE OF HEARING LOSS IN NEWBORNS

The initiation of screening of newborns for hearing defects in this country can largely be attributed to the career-long efforts of the audiologist Marion Downs. As long ago as 1964,[2] she showed that severe-to-profound hearing loss could reliably be detected by behavioral hearing screening of neonates. She found such losses in 17 of 17,000 infants,[3] a figure identical to contemporary estimates for severe-to-profound bilateral hearing loss. For every such infant, one or two are born with lesser but clinically significant degrees of hearing loss.[4]

Before the implementation of universal newborn hearing screening — beginning in Rhode Island in 1989,[5] Hawaii in 1990,[6] and Colorado in 1993[7,8] — two important developments were required. The first was the application of objective noninvasive physiological tests for hearing loss that could be administered by nonprofessional personnel.[9] The second was the demonstration that the early detection of hearing loss influences the educational outcome of affected infants.[10] When these prerequisites were met, the endorsement of universal newborn hearing screening by the National Institutes of Health Consensus Development Conference in 1993 led to the gradual spread of programs throughout the nation during the next 10 years.

Two complementary screening techniques are now in widespread use: the automated auditory brain-stem response measures average neural response to a large number of repeated sound signals of the same pitch and intensity, whereas measurement of spontaneous or sound-induced otoacoustic emissions detects sound produced by movements of outer hair cells of the cochlea. Both methods have acceptable sensitivities and specificities and are often used together in two-stage screening protocols. However, in patients with auditory neuropathy, the hair-cell response — measured by the otoacoustic emissions — may be completely normal, whereas the

auditory brain-stem response is abnormal because of asynchrony in the transmission of neural signals. Thus, two-stage screening protocols in which the auditory brain-stem response is used only to confirm abnormal otoacoustic-emissions responses may fail to detect this form of hearing loss. Differences in diagnostic criteria, completeness of follow-up, and screening protocols have contributed to the variation in the reported incidence of deafness at birth. In England, where compliance with confirmatory testing is high, permanent childhood hearing loss is defined as a bilateral sensorineural loss of 40 dB or more, and the reported incidence is 1.33 per 1000 newborns. In the United States, a sensorineural loss of 35 dB or more in either ear is typically the threshold used to identify patients who are referred for confirmatory testing, and because 30 to 40 percent of detected losses are unilateral, 1.86 per 1000 seems to be a reasonable overall estimate for the incidence at birth (Fig. 1).[11-13] Nonetheless, estimates vary and some may be higher,[14] reflecting true etiologic, as well as diagnostic, differences. The prevalence of permanent sensorineural hearing loss continues to increase during childhood and reaches a rate of about 2.7 per 1000 children before the age of five years and 3.5 per 1000 during adolescence. For every 10 infants with permanent hearing loss at birth, similar losses develop in another 5 to 9 children before the age of nine years.[12]

When universal programs to screen newborns for hearing defects were first implemented, the test failure rates ranged from 2 to 4 percent. Among newborns failing the screening tests, 85 to 90 percent were determined later to have normal hearing; this was considered to be an acceptable performance standard for well-established programs. However, the high proportion of infants with normal hearing who failed screening led to criticism that unwarranted parental anxiety elicited by the test failure would outweigh the benefits of the program. To minimize such anxiety, the euphemism "refer" was adopted to characterize failed screening tests. With time, the testing characteristics of these programs have improved dramatically, and many hospitals now have a failure rate of less than 0.5 percent, only about half of which is due to infants who actually have normal hearing.

With the advent of newborn screening, the average age at which hearing loss is confirmed has dropped from 24 to 30 months to 2 to 3 months.[15] Infants in whom remediation is begun within six months are able to maintain language and social and emotional development that is commensurate with their physical development, in striking contrast to those whose hearing loss is first detected after six months of age. This observation does not depend on the mode of communication: it applies to children who are identified early as having hearing loss and who speak, sign, or use both modes of communication.[16]

Given the improvements in the test characteristics of these screening programs, the term "refer" should be replaced with the word "fail" to describe the results of a screening test that indicates a hearing loss. The health care professional responsible for the screening program should meet with the parents of infants who fail the screening test to review its importance, reinforcing the need for prompt audiologic confirmation and emphasizing the potential for the normal development of language with prompt and appropriate intervention. In hospitals in which the personnel and facilities are available, audiologic confirmation before discharge is feasible for infants who fail the screening test. The initiation of programs that facilitate the immediate confirmation of a hearing loss would also permit prompt initiation of genetic evaluation, counseling, and testing and would serve as model programs for the delivery of these services.

Early hearing detection and intervention programs have been established in every state in the union, are mandated in at least 39 states, and provide audiologic screening for nearly 93 percent of all newborn infants.[17,18] In addition to identifying infants who will benefit from early intervention, these programs should be able to provide valuable epidemiologic data on secular trends in the incidence of genetic and environmental causes of hearing loss, as well as variation in specific forms of hearing loss between populations. An extraordinarily successful newborn screening program has been implemented in Poland; as of the summer of 2004, 99 percent of infants were screened before leaving the hospital.[19] Although newborn screening programs are under way in other European countries, none has had success similar to that in Poland. Better hearing for persons of all nations is an achievable, important goal, given that a disabling hearing impairment affects about 4.2 percent of the world's population, with two thirds of such persons living in developing countries.

Infection is an important contributing cause of

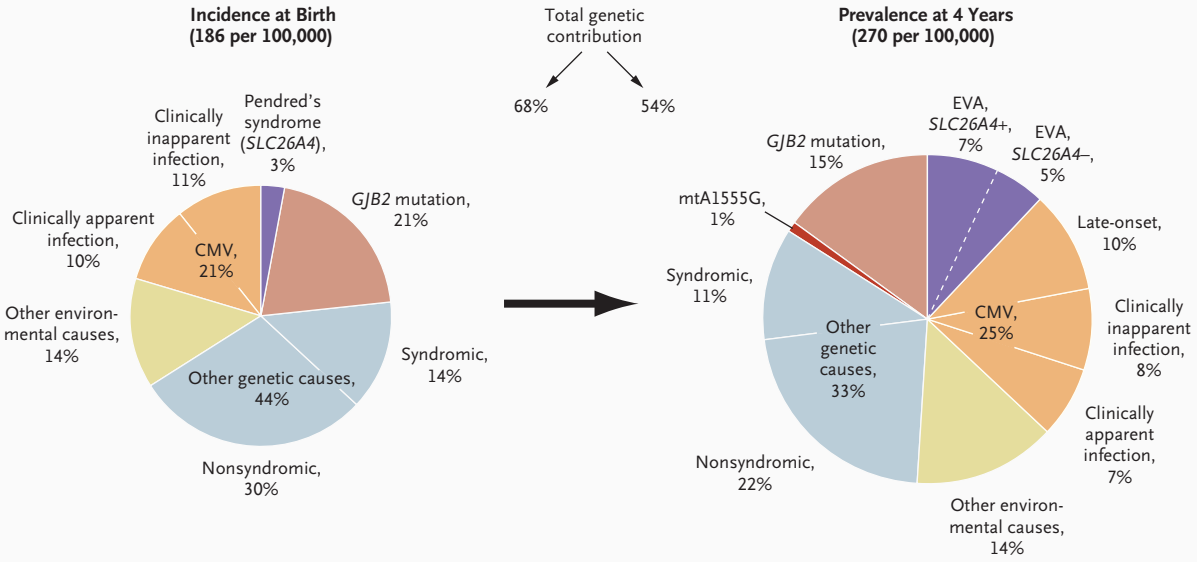

Figure 1. Estimates of Causes of Deafness at Birth and at Four Years in the United States.

The incidence of deafness at birth in the United States, and its prevalence at four years of age, were obtained by adjusting estimates from the United Kingdom[11,12] (where, in contrast with the United States, follow-up is nearly complete) to include unilateral hearing loss. The overall proportion of genetic cases at four years of age was estimated by sentinel phenotype analysis.[13] Estimates for specific causes were obtained from previously published data (as documented in the Supplementary Appendix, available with the full text of this article at www.nejm.org). No studies were available in which universal newborn testing was performed for more than one specific cause of deafness in the same population sample. CMV denotes cytomegalovirus, mtA1555G the mitochondrial A1555G mutation, and EVA enlargement of the vestibular aqueduct.

deafness worldwide. Hearing disorders related to the acquired immunodeficiency syndrome, which include both sensorineural and conductive losses, overwhelm South Africa, and congenital rubella infection, often accompanied by hearing loss, is the most common birth defect in India.[20]

The success of newborn screening in developed countries has had enormous personal, societal, and economic benefit. Although finding the resources to implement solutions in developing countries is a major problem, standardizing screening and intervention programs for the detection and treatment of newborns remains an important goal.

LIMITATIONS OF EXISTING SCREENING PROGRAMS

Existing universal screening programs to identify hearing defects in newborns in the United States still do not enjoy the extraordinarily high follow-up rates for positive test results that characterize most metabolic screening programs for newborns. Another limitation is that some forms of early-onset hearing loss are not apparent at birth. To address this issue, the Joint Committee on Infant Hearing has identified a series of 10 risk indicators that should prompt the continued monitoring of hearing status, even if the results of newborn screening are normal (Table 1).[21] Most of the risk factors are highly relevant features of the clinical, family, or medical history, but it is important to recognize that many, and perhaps most, cases of late-onset hearing loss may not have any of these risk factors. Testing protocols should also be standardized to permit the comparison and aggregation of data from different sites and to avert the failure to identify infants with specific forms of hearing loss, such as auditory neuropathy.[22] Finally, most screening programs have lacked an etiologic focus, which may compromise meaningful interpretation of the results of early intervention.

GENETIC CAUSES OF SYNDROMIC HEARING LOSS

More than 300 forms of syndromic hearing loss, in which distinctive associated clinical features are a constant (or at least an occasional) feature, have been characterized.[23] In many cases several genes

Table 1. Risk Indicators for Audiologic Monitoring for Progressive or Delayed-Onset Sensorineural Hearing Loss, Conductive Hearing Loss, or Both, in Infants (29 Days through 2 Years of Age) with Normal Hearing on Newborn Screening.*

Parental or caregiver concern regarding child's hearing, speech, language, or developmental delay
Family history of permanent hearing loss in childhood
Stigmata or other findings associated with a syndrome known to include a sensorineural or conductive hearing loss or eustachian-tube dysfunction
Postnatal infections associated with sensorineural hearing loss, including bacterial meningitis
In utero infections such as cytomegalovirus infection, herpes, rubella, syphilis, and toxoplasmosis
Neonatal indicators such as hyperbilirubinemia at a serum level requiring exchange transfusion, persistent pulmonary hypertension of the newborn associated with mechanical ventilation, and conditions requiring the use of extracorporeal-membrane oxygenation
Syndromes associated with progressive hearing loss such as neurofibromatosis, osteopetrosis, and some forms of Usher's syndrome
Neurodegenerative disorders such as Hunter's syndrome or sensory neuropathies such as Friedreich's ataxia and Charcot–Marie–Tooth syndrome
Head trauma
Recurrent or persistent otitis media with effusion for at least 3 months

* Information is from the Joint Committee on Infant Hearing.[21]

that can cause the same phenotype or a closely related one have been identified. In other cases, observed variation in the severity or clinical findings can be attributed to different mutations of the same gene, resulting in a genotype–phenotype correlation. Some of the main recognized forms of syndromic deafness are summarized in Table 2.

Among syndromic entities, Pendred's syndrome is a relatively common form of autosomal recessive deafness with an onset in infancy or early childhood. Although the specific step in the transport of iodide across the thyrocyte that is defective in Pendred's syndrome has now been identified, the resulting thyromegaly that defines the syndrome may not be apparent until adolescence or adult life, thus complicating attempts to anticipate the hearing loss from syndromic features.[24] Structural abnormalities of the cochlea, ranging from Mondini malformations (the cochlea lacks the normal two and a half turns) to enlargement of the vestibular aqueduct, are almost invariably found; the latter can occur with deafness in the absence of thyroid disease.[25] Patients with Pendred's syndrome typically carry two *SLC26A4* mutations, but 61 percent of persons with nonsyndromic enlargement of the vestibular aqueduct are found to carry a single mutation,[26] implying a risk ratio in excess of 30 for the 1.7 percent of the population who are heterozygous for *SLC26A4*. These observations suggest that some cases of nonsyndromic enlargement of the vestibular aqueduct result from an interaction between a single *SLC26A4* mutation and a second mutation involving another gene.[27] In a recent study, this disorder was found in 20.8 percent of 810 children with sensorineural hearing loss. Virtually all the children became symptomatic after birth, and the mean age at referral was 5.8 years.[28] It seems reasonable to assume that at least a third, or 7 percent, of these children had prelingual deafness and would have benefited from early detection and intervention.

GENETIC CAUSES OF NONSYNDROMIC HEARING LOSS

Most cases of genetic hearing loss are nonsyndromic (not associated with distinctive clinical features). The search for specific genes for nonsyndromic as well as syndromic forms of deafness has met with astonishing success, resulting in the identification of more than 110 chromosomal loci and at least 65 genes (available at http://webhost.ua.ac.be/hhh).

Nonsyndromic forms of hearing loss can also be distinguished by their pattern of inheritance and often by the age at onset, progression, and audiologic characteristics of the hearing loss or by associated otologic findings such as vestibular dysfunction. Four terms are used to distinguish different forms of nonsyndromic hearing loss. When new loci are mapped, those showing dominant transmission are designated by DFNA,

followed by an accession number. DFNB refers to recessive forms, DFN to X-linked genes, and DFNM to genes that modify the expression of other genetic forms of hearing loss. When the causal genes are identified, their names are often used to supplement or replace the DFN terms. Examples of forms of dominant and recessive nonsyndromic hearing loss for which the genes have been identified are shown in Tables 3 and 4, respectively.

Because of the degree of heterogeneity of hearing-loss genes, it came as a surprise that mutations in a single gene, *GJB2,* account for 30 to 50 percent of all cases of profound nonsyndromic hearing loss in many populations.[29] *GJB2* encodes connexin 26, a hexameric gap-junction protein widely expressed in supporting cells and connective tissues of the cochlea. The connexin hexamers on the surface of adjacent cells bind together to form intercellular channels purportedly allowing recycling of potassium ions from hair cells to the stria vascularis (Fig. 2), where they are actively pumped back into the cochlear endolymph.[30] The maintenance of a high endocochlear potential by potassium recycling is of critical importance for sound perception.

Although deafness caused by mutation of *GJB2* was first thought to be profound in degree and congenital in onset, it is now known to show considerable phenotypic variation,[31,32] including well-documented cases in which affected infants showed no hearing loss on screening. Because all such cases are retrospective, it is not clear whether the hearing in these infants was actually normal at birth or whether they had subclinical losses. Establishing the full range of expressivity of *GJB2* mutations is an important research priority. Although more than 100 mutations involving *GJB2* have been identified, a single variant, designated 35delG, accounts for up to 70 percent of all pathologic mutations in many populations.[33]

Most cases of genetic deafness result from mutations involving a single gene, but a small and growing number are being identified in which hearing loss is determined by mutations in two independent genes. For example, DFNB1 can result from two mutations involving *GJB2,* two mutations in the closely linked *GJB6* gene, or a combination of mutations involving both genes (the combination of mutations accounts for about 8 percent of DFNB1 cases).[33] *GJB6* is a gene with sequence similarity to *GJB2* and is also expressed in the cochlea; its product, connexin 30, can form heteromeric gap-junction channels with connexin 26 subunits, thus explaining the observed cases of digenic transmission. Digenic transmission also provides an explanation for a substantial proportion of deaf persons who are heterozygous for mutations in *GJB2,* in apparent contradiction to the rules of recessive inheritance.

The mating pattern of deaf persons who communicate by sign language is characterized by a very high frequency of marriages among the deaf (assortative mating), often extending over many generations, which brings together rare deafness genes of all types with a much greater frequency than would be observed if marriages occurred at random with respect to deafness. As the frequency of deafness in the ancestors of deaf persons increases, there is a progressive increase in the frequency of persons who by chance are heterozygous for DFNB1 but are deaf owing to some other genetic cause. Finally, rare DFNB1 mutations have been identified that show a dominant pattern of transmission and thus represent another explanation for deafness in persons who are heterozygous for *GJB2.* Most of these persons, however, have distinctive dermatologic findings and would be properly classified as having a syndromic form of deafness.

CAUSE OF THE HIGH PREVALENCE OF DEAFNESS FROM MUTATIONS IN *GJB2*

There are several possible causes of the high frequency of *GJB2* deafness, including recurrent mutation, population bottlenecks, heterozygous advantage, and founder effects (origin from a common ancestor).[34] More recently, it has been suggested that a combination of the increased genetic fitness (i.e., fertility) of the deaf population that began when sign language was introduced in Western countries 400 years ago and the resulting linguistic homogamy (mate selection based on the mode of communication) that occurred at least in part from the establishment of residential schools for the deaf has resulted in a doubling of the frequency of *GJB2* deafness in the United States during the past 200 years.[35] Computer simulation studies have shown that this mechanism will preferentially amplify the most common recessive gene for deafness in a population, and a similar mechanism may well account for the extraordinary acceleration in human evolution that occurred after the first appearance of genes for speech 150,000 to 200,000 years ago.[36]

Table 2. Selected Forms of Syndromic Hearing Loss.*

Disorder	Features	Pattern of Inheritance	Relative Frequency†	No. of Loci	Comments	OMIM No.
Alport's syndrome	Hematuria with progressive renal failure, progressive late-onset high-frequency sensorineural hearing loss; anterior lenticonus and macular flecks	XL or AR	1%	3	Results from mutations in 1 of 3 collagen genes expressed in glomerular basement membrane	301050
Alström's syndrome	Truncal obesity beginning in childhood; progressive retinal dystrophy involving cones and rods; type 2 diabetes; progressive sensorineural hearing loss, acanthosis nigricans, and cardiomyopathy can begin in infancy	AR	Common in Acadians of Nova Scotia and Louisiana	1	Results from mutations involving *ALMS1* at 2p13, discovered at the breakpoint of a chromosomal translocation; *ALMS1* expressed ubiquitously at low levels and encodes a 4169–amino acid protein of unknown function	203800
Type 4 Bartter's syndrome	Polyhydramnios and prematurity with metabolic acidosis and high renin and aldosterone levels, with salt wasting, normal blood pressure, and renal failure; caused by mutations in the chloride-channel genes *BSND*, *CLCNKA*, and *CLCNKB* expressed in the kidney and stria vascularis	AR or digenic	Most common in consanguineous Middle Easterners	3	Three genes acting alone or in combination; *CLCNKB* deletions from unequal crossing-over; digenic homozygotes for mutations of both *CLCNK* loci have been described; murine knockouts exhibit nephrogenic diabetes	602522 602023 602024
Biotinidase deficiency	Seizures; hypotonia; ataxia; organic acidemia; alopecia associated with sensorineural hearing loss; in 75% of affected patients	AR	1/60,000‡	1	One of metabolic diseases screened for at birth in many states; preventable form of hearing loss with prompt biotin supplements	253260
Branchio-oto-renal (BOR) syndrome	Hearing loss; preauricular pits; malformed pinnae; branchial fistulae; renal anomalies ranging from structural malformations to agenesis	AD	2%	1	BOR (*EYA1*) gene product interacts with 128 other proteins; defects in several lead to somewhat similar syndromes	113650
DFNA17	Sensorineural hearing loss; with or without nephritis; cataracts; platelet anomalies; leukocyte inclusions; hemorrhagic tendency	AD	Rare	1	*MYH9* mutations can cause dominant Alport's syndrome with features of Fechtner's syndrome or Sebastian syndrome, or isolated sensorineural hearing loss	603622
DFNA22	Dominant mutations of *MYO6* can cause a progressive postlingual sensorineural hearing loss associated with hypertrophic cardiomyopathy, sudden death, arrhythmias, and long-QT interval	AD	Rare	1	*MYO6* expressed in heart and cochlea, participates in intracellular transport, anchoring of organelles, or both; other mutations cause DFNA22, a form of nonsyndromic sensorineural hearing loss	606346
Fabry disease	Vascular skin lesions; abdominal pain; nephropathy with renal failure; corneal dystrophy; angina; cardiomyopathy, high-frequency sensorineural hearing loss; treatment by renal transplantation or enzyme replacement	XL	1/40,000‡	1	Deficiency of α-galactosidase; high-frequency sensorineural hearing loss; in 78% of cases progressive or sudden onset; may have isolated cardiomyopathy, arrhythmia, and sudden death	301500

Jervell and Lange–Nielsen syndrome	Profound sensorineural hearing loss with prolongation of QT interval, syncope, and risk of sudden death	AR	0.25–0.5%	2	Genes encode subunits of potassium channels; carriers also at risk for sudden death; treatment effective	220400
Nance deafness	Congenital fixation of stapes foot plate with mixed hearing loss; distinctive CT findings of dilated internal auditory canal and poor separation of basal cochlear turn	XL	>1%	1	Gene defects in *POU3F4*, which encodes a DNA-binding transcription factor; deletions common; perilymphatic "gusher" often complicates stapes surgery; mild hearing loss in some female carriers	304400
Pendred's syndrome	Sensorineural hearing loss; goiter; cochlear malformations; high risk of nonsyndromic enlarged vestibular aqueduct in carriers, which is seen in 20% of children with late-onset hearing loss	AR	4–10%	1	Iodine transport defect diagnosed by perchlorate discharge test in those homozygous for Pendred's syndrome (*SLC26A4*); sensorineural hearing loss with variable onset and severity	274600
Renal tubular acidosis	Dehydration, growth failure, metabolic acidosis with alkaline urine, nephrocalcinosis and rickets; variable hearing loss	AR, frequent consanguinity	Found in inbred North Africans	>2	Defects in proton-pump genes *ATP6B1* or *ATP6N1B* expressed in kidney and stria vascularis; additional loci probable	267300 602722
Treacher Collins syndrome	Conductive hearing loss with malformed ossicles, microtia, cleft palate; micrognathia, downward slanting eyes, coloboma of the eyelid	AD	1%	1	Frequent absence of a family history possibly reflecting new mutations or mild expression in a parent	154500
Usher's syndrome	Sensorineural hearing loss; vestibular symptoms; retinitis pigmentosa		4–6%	12	Commonest cause of deafness with blindness; early diagnosis of retinitis pigmentosa possible with electroretinography; cochlear implants effective; sign language recommended because eventual blindness may require finger spelling; some mutations cause only sensorineural hearing loss	Type 1, 276900, 276904, 601067 602097, 602083, 606943 Type 2, 276901, 276905, 605472 Type 3, 276902
	Type 1, profound hearing loss; vestibular symptoms; retinitis pigmentosa beginning in first decade	AR	(60)	7		
	Type 2, stable moderate-to-severe hearing loss; retinitis pigmentosa in first to second decade	AR	(30)	4		
	Type 3, progressive hearing loss; variable vestibular symptoms; variable onset of retinitis pigmentosa	AR	(10)	1		
Waardenburg's syndrome	Neural crestopathy with hearing loss in one or both ears; patches of eye, skin, hair hypopigmentation; occasional Hirschsprung's disease, spina bifida		1–4%	9	Hearing loss caused by defective migration of pigment cells to stria vascularis; infrequent bowel movements common; Hirschsprung's disease with obstruction or gastrointestinal dyskinesia seen; *WS* genes include hierarchy of regulatory and structural genes controlling migration and function of neural-crest cells	Type 1, 193500 Type 2, 193510 600193, 600193, 608890 Type 3, 148820 Type 4, 277580
	Type 1, white forelock; dystopia canthorum; synophoris; pinched nares	AD	Common	1		
	Type 2, dystopia absent	AD or AR	Less common	4		
	Type 3, limb defects in *WS1* homozygotes	AD	Very rare	1		
	Type 4, increased incidence of Hirschsprung's disease in carriers and homozygotes	AR	Rare	3		

* OMIM denotes Online Mendelian Inheritance in Man, XL X-linked, AR autosomal recessive, and AD autosomal dominant.
† Unless otherwise noted, relative frequency is among persons with hearing loss. Values in parentheses are the proportions of the total relative frequency for the disorder.
‡ Relative frequency is the rate in the entire population.

Table 3. Cloned Autosomal Dominant Hearing-Loss Genes.*

DFN	Locus	Gene	Protein	Function, Expression, and Comments	Hearing Loss	OMIM No.
DFNA1	5q31	*DIAPH1*	Diaphanous	"Private" mutation; wide tissue expression; actin polymerization	Moderate-to-profound, postlingual, low-frequency, progressive deafness; hair-cell defect; onset 1st to 4th decade	124900
DFNA2	1p34–p35.1	*GJB3*	Connexin 31	Gap junction; milder in female patients	Moderate-to-severe, postlingual, high-frequency, progressive deafness with tinnitus; K^+-recycling defect; onset 4th to 6th decade	600101
		KCNQ4	Potassium channel	Expressed in outer hair cells; auditory pathway; common; dominant negative mutations	Moderate, postlingual, high-frequency, progressive deafness with vertigo; K^+-recycling defect	
DFNA3	13q11–q12	*GJB2*	Connexin 26	Dominant changes with PPK, KID, or Vohwinkel's syndromes and tinnitus	Moderate-to-profound, prelingual deafness; K^+-recycling defect; may be some hearing at birth	601544
		GJB6	Connexin 30	Dominant negative; can show skin findings of KID syndrome	Moderate-to-profound, prelingual, high-frequency progressive deafness; K^+-recycling defect	604418
DFNA4	19q13.33	*MYH14*	Myosin 14	Expressed in cochlea; mutations found in 1% of 300 deaf subjects	Moderate-to-profound, fluctuating, progressive deafness; hair-cell defect	600652
DFNA5	7p15	*DFNA5*	DFNA 5	Orphan gene; unknown function; mouse knockout model has normal hearing	Moderate-to-severe, postlingual, high-frequency, progressive deafness	600994
DFNA6/14	4p16.1	*WFS1*	Wolframin	C-terminal missense changes cause commonest low-level hearing loss; recessive inactivating and truncating Wolfram changes can show high-level hearing loss	Moderate-to-severe, prelingual, low-frequency hearing loss with tinnitus; widely expressed in cochlea	600965
DFNA8/12	11q22–q24	*TECTA*	α Tectorin	Dominant negative; truncation or splice-site changes in recessive DFNB21; additive digenic interaction with one of the DFNA2 genes	Severe, prelingual or postlingual, U-shaped or high-frequency, progressive hearing loss; tectorial membrane defect	601543
DFNA9	14q12–q13	*COCH*	Cochlin	Expressed in spiral ligament and limbus; can include vertigo; aids and implants help; mouse knockout model has normal hearing	Moderate-to-profound, postlingual, progressive high-frequency deafness with tinnitus, vertigo, poor balance, and endolymphatic hydrops; onset 2nd to 7th decade	601369
DFNA10	6q23	*EYA4*	Eyes absent 4	Can also cause sensorineural hearing loss, then cardiomyopathy with heart failure	Moderate-to-severe, postlingual, progressive, U-shaped hearing loss; onset, 1st to 4th decade; defective transcription factor	601316

ENVIRONMENTAL CAUSES OF PRELINGUAL HEARING LOSS

Congenital cytomegalovirus infection has replaced rubella embryopathy as the most prevalent environmental cause of prelingual hearing loss in the United States. A retrospective study, using DNA extracted from blood spots from newborns, showed that 10 percent of infants with congenital hearing loss and 35 percent of those with moderate-to-severe late-onset loss were infected with cytomegalovirus at birth.[37] The incidence of the infection in newborns varies with maternal age, parity, and socioeconomic status, ranging from 0.1 to 2 percent, and hearing loss is present at birth in 3.9 percent of all infants with the virus. How-

Table 3. (Continued.)

DFN	Locus	Gene	Protein	Function, Expression, and Comments	Hearing Loss	OMIM No.
DFNA11	11q13.5	*MY07A*	Myosin 7A	Unconventional myosin; can cause USH1B or recessive DFNB2; forms stereocilia in hair cells	Moderate-to-severe, postlingual, progressive, high-frequency hearing loss; onset, 1st to 6th decade; hair-cell defect	601317
DFNA13	6p21.3	*COL11A2*	Collagen 11α2	Can also cause Stickler's, Marshall's, and OSMED phenotypes	Moderate-to-severe, postlingual, U-shaped hearing loss; tectorial membrane defect	601868
DFNA15	5q31	*POU4F3*	Pou domain 4F3	Transcription factor; *POU3F4* causes X-linked Nance deafness (see syndromic forms)	Moderate-to-severe, postlingual, progressive hearing loss with onset by 5th decade; defective hair-cell transcription factor	602459
DFNA17	22q11.2	*MYH9*	Myosin 9	Unconventional myosin; atrophic stria vascularis; Scheibe's dysplasia; endolymphatic hydrops; causes Fechtner's, Sebastian's, and Epstein's syndromes	Moderate-to-profound, postlingual, progressive high-frequency deafness; hair-cell defect	603622
DFNA20/26	17q25.3	*ACTG1*	Actin γ1	Filament forms cytoskeleton; impaired motility, organelle transport; cytokinesis; interacts with products of many deafness genes; *Jackson-shaker* mouse model	Moderate, postlingual, progressive hearing loss; defect in intracellular cytoskeletal protein	604717
DFNA22	6q13	*MYO6*	Myosin 6	Unconventional myosin; changes impede myosin movement; cardiomyopathy; arrhythmia; heart failure in some; recessive *DFNB37* has variable RP and vestibular symptoms	Moderate-to-profound, postlingual, progressive hearing loss; onset by 5th decade; hair-cell defect	606346
DFNA28	8q22	*TFCP2L3*	Tfcp2l3	DNA-binding transcription factor; 4793 bp with 16 exons	Moderate-to-severe, postlingual, progressive hearing loss; onset by 5th decade; defective transcription factor	608641
DFNA36	22q11.2	*TMC1*	Tmc1	Transmembrane hair-cell protein; *Beethoven* mouse model; DFNB7 recessive form	Moderate-to-profound, postlingual, rapidly progressive deafness by 3rd decade; defective transmembrane protein in hair cells	606705
DFNA48	12q13–q15	*MYO1A*	Myosin 1A	Unconventional myosin; mutations in 8 of 230 patients; moderate-to-severe hearing loss with variable penetrance	Moderate-to-severe, postlingual, progressive hearing loss; probable hair-cell defect	607841
CRYM	16p13.11–p12.3	*CRYM*	μ Crystallin	Cytosolic thyroid hormone–binding protein; lens protein changes in 2 of 192 patients with nonsyndromic hearing loss; expressed in spiral ligament and limbus	Moderate-to-severe prelingual deafness by 2nd decade; possible K^+-recycling defect	123740

* OMIM denotes Online Mendelian Inheritance in Man, PPK palmoplantar keratoderma, KID keratitis ichthyosis deafness, OSMED otospondylomegaepiphyseal dysplasia, RP retinitis pigmentosum.

ever, 84 percent of newborns with congenital cytomegalovirus infection lack distinctive clinical findings so that the virus is not recognized as the cause in those with a hearing loss at birth. In children with clinically apparent and subclinical infections, the cumulative prevalence of hearing loss by the age of six years is 36 and 11 percent, respectively.[38] The hearing loss can be unilateral, fluctuating, or progressive in nature, and its onset can be delayed for months or even years.[39,40] In cases not recognized at birth, it can be difficult, if not impossible, to establish a retrospective diagnosis with certainty because seropositive infants may have been infected postnatally.

Table 4. Cloned Autosomal Recessive Hearing-Loss Genes.*

DFN	Locus	Gene	Protein	Function, Expression, and Comments	Hearing Loss	OMIM No.
DFNB1	13q11–q12	*GJB2* *GJB6*	Connexin 26 Connexin 30	Gap-junction subunits; form homo- and heteromers; potassium recycling; expressed in supporting cells; 30–40% of genetic deafness, monogenic or digenic; also autosomal dominant and syndromic	Profound, some moderate-to-severe, usually prelingual; some pass newborn screening	220290
DFNB2	11q13.5	*MYO7A*	Myosin 7A	Unconventional myosin; some mutations cause USH1B; others, only nonsyndromic hearing loss	Profound, prelingual, and with balance disorders in USH1B	600060
DFNB3	17p11.2	*MYO15A*	Myosin 15A	Unconventional myosin, 2% incidence in Benkala, Bali; *shaker 2* mouse model	Profound, prelingual; hair-cell defect	600316
DFNB4	7q31	*SLC26A4*	Pendrin	Chloride and iodine transport; expressed in thyroid, cochlea; some homozygotes do not have thyroid disease; 30× risk of EVA in heterozygous carriers	Variable high-frequency hearing loss frequently postlingual; enlarged vestibular aqueduct in 20% of postlingual hearing loss	600791
DFNB6	3p21	*TMIE*	Tmie	Transmembrane protein; cochlea; required for muturation of hair cells; *spinner* mouse model	Profound, prelingual; transmembrane protein	600971
DFNB7/11	9q13–q21	*TMC1*	Tmc1	Expressed in inner and outer hair cells; *deafness* mouse shows degeneration of organ of Corti; stria vascularis; dominant gain-of-function mutations cause DFNA36; also autosomal dominant	Profound, prelingual; hair-cell defect	600974
DFNB8/10	21q22.3	*TMPRSS3*	Tmprss3	Expressed in spiral ganglion, supporting cells, and stria vascularis; 344 amino acid protein includes LDLRA and SRCR domains and a critical serine protease domain	DFNB8: profound, prelingual, expressed in stria vascularis DFNB10: moderate and progressive, postlingual	601072
DFNB9	2p22–p23	*OTOF*	Otoferlin	Expressed in inner hair cells, spiral ganglion, and semicircular canals; auditory neuropathy in some cases	Flat auditory brain-stem response; otoacoustic emissions acceptable; auditory neuropathy	601071
DFNB12	10q21–q22	*CDH23*	Otocadherin	Expressed in stereocilia and hair-bundle formation; interacts with myosin 7A and harmonin; some mutations cause USH1D	High-frequency loss; profound with *ATP2B2* modifier; hair-cell defect	601386
DFNB16	15q15	*STRC*	Stereocilin	Expressed only in hair cells; tandem duplication leads to gene deletions	Postlingual and stable, high-frequency loss	603720
DFNB18	11p15.1	*USH1C*	Harmonin	Causes Arcadian USH1C or nonsyndromic hearing loss by alternate splicing; forms scaffold proteins in cilia with myosin 7A and otocadherin	Profound, prelingual; hair-cell defect; mutation spliced out of retinal transcript	602092

Pharmacologic ototoxicity is another important environmental cause of prelingual hearing loss. In the United States, 10 percent of persons attributing their deafness to this cause have mutations involving the mitochondrial 12S ribosomal (rRNA) gene including the A1555G substitution, which is associated with extreme sensitivity to aminoglycoside ototoxicity.[41] One case in 20,000 to 40,000 births is a reasonable estimate of the prevalence of the A1555G mutation as a cause of prelingual deafness in the United States. In Spain, this mutation accounts for 15 to 20 percent of cases of familial nonsyndromic hearing loss, and hearing loss develops in many older family members even in the absence of documented exposure to aminoglycosides.[42]

Table 4. (Continued.)

DFN	Locus	Gene	Protein	Function, Expression, and Comments	Hearing Loss	OMIM No.
DFNB21	11q22–q24	*TECTA*	α Tectorin	Expressed in tectorial membrane; many dominant mutations cause DFNA8 and 12; also autosomal dominant	Profound, postlingual, progressive with high U-shaped loss	602574
DFNB22	16p12.2	*OTOA*	Otoancorin	Extracellular protein at apex of sensory epithelium	Moderate, prelingual; hair-cell defect	607039
DFNB23	10q21–q22	*PCDH15*	Protocadherin	Causes USH1F or nonsyndromic hearing loss; *Ames waltzer* mouse model	Profound, prelingual; hair-cell defect	609533
DFNB67	6p21.3	*TMHS*	Tmhs	Transmembrane protein localized to hair cells; vestibular findings in *hurry–scurry* mouse model	Profound, prelingual; hair-cell defect	609427
DFNB29	21q22.3	*CLDN14*	Claudin 14	In tight junction at hair cells and supporting cells; expressed in inner and outer hair cells and kidney	Profound, prelingual; hair-cell defect	605608
DFNB30	10p11.1	*MYO3A*	Myosin 3A	Unconventional myosin; expressed in cochlea and eye, but no visual symptoms; earlier onset in homozygotes with nonsense mutations than in compound heterozygotes with splice-site defects	Profound, prelingual, progressive with high-frequency loss; hair-cell defect	607101
DFNB31	9q32–q34	*WHRN*	Whirlin	Acts to lengthen stereocilia tips; *whirler* mouse model	Prelingual; hair-cell defect	607084
DFNB36	1p36.1–p36.1	*ESPN*	Espin	Actin-bundling; short stereocilia; *jerker* mouse model	Profound, prelingual; hair-cell defect and vertigo	609006
DFNB37	6q13	*MYO6*	Myosin 6	Unconventional myosin; hypertrophic cardiomyopathy may occur with DFNA22; also autosomal dominant	Profound, prelingual; hair-cell defect, vertigo, and possibly retinitis pigmentosum	607821
DFNB28	22q13.1	*TRIOBP*	Triobp	Actin-binding cytoskeletal protein; long isoform expressed in cochlea, brain, and eye	Profound prelingual; hair-cell defect	609823

* OMIM denotes Online Mendelian Inheritance in Man.

IMPROVING DETECTION OF LATE-ONSET PRELINGUAL HEARING LOSS

Audiologic screening is available for hearing loss caused by hundreds of different genetic mutations, but it cannot detect forms of deafness that are not expressed at birth. The best way to detect cases of prelingual hearing loss that either are not present at birth or are associated with subclinical hearing losses would be to perform molecular genetic tests on blood spots from all newborns to identify those at risk for the most frequent causes of late-onset loss and to add infants to the group who should receive continued audiologic monitoring. Tests for *GJB2* deafness and the mitochondrial A1555G mutation are commercially available, and although *SLC26A4* is a large gene with 21 exons, 70 percent of persons who are heterozygous for Pendred's syndrome and 91 percent of those who are homozygous could readily be identified by the screening of a limited number of exons. If screening for these three causes of late-onset hearing loss was performed, together with a test for the presence of cytomegalovirus, we estimate that the follow-up of at-risk infants should result in the presymptomatic detection of nearly 60 percent of all infants in whom late-onset prelingual hearing loss develops, as well as an immediate etiologic diagnosis for at least 40 percent of those with congenital loss.

The use of molecular testing alone to detect genetic hearing loss is not currently feasible because of the many uncertainties that would arise in the interpretation of test results. As an adjunct to audiologic screening, however, such tests would

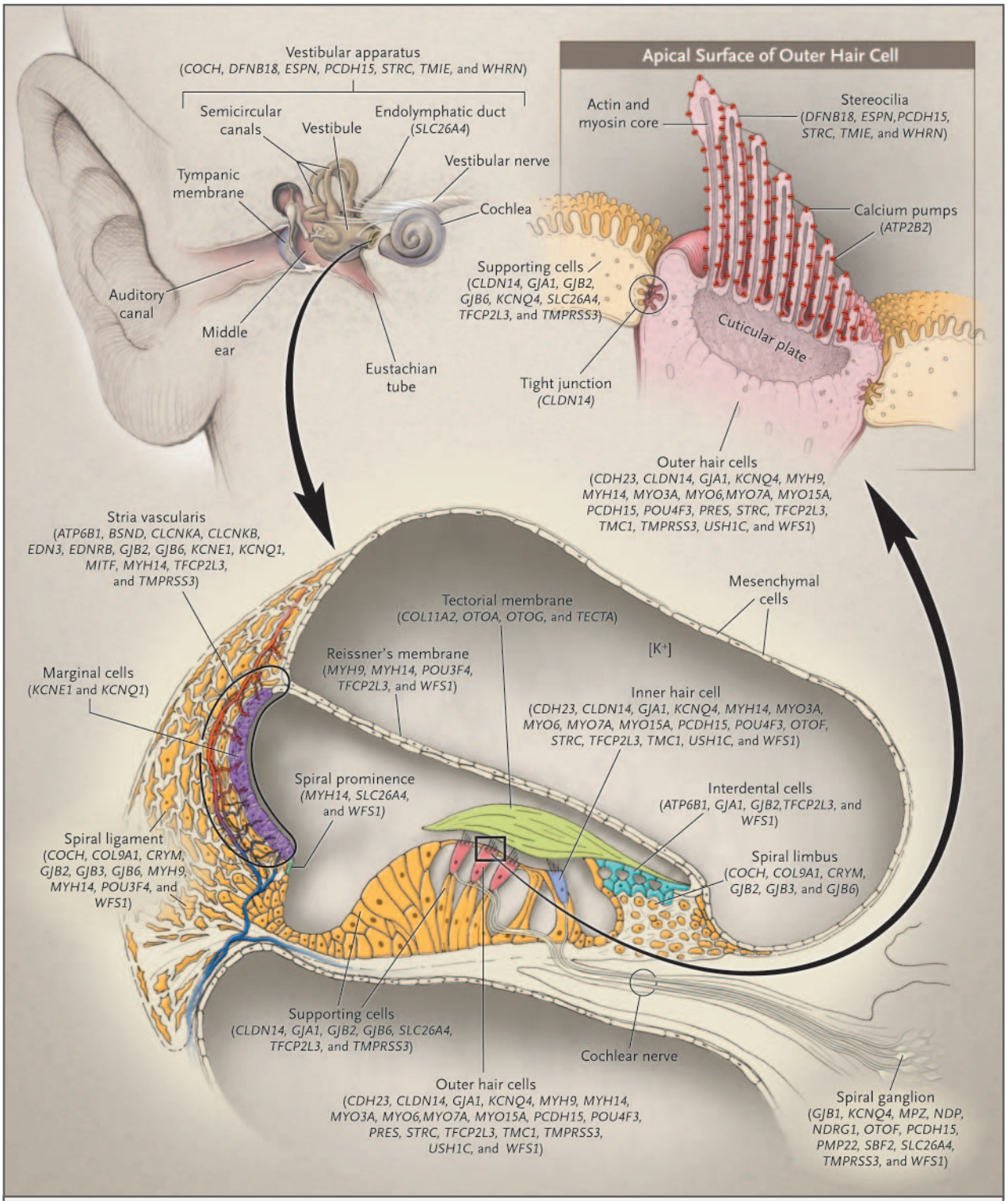

Figure 2. View of the Outer, Middle, and Inner Ear with a Cross-Sectional View of the Cochlear Duct and a View of Hair Cells.
The genes related to deafness and the locations of the products they encode are shown. The Hereditary Hearing Loss Homepage (www.webhost.ua.ac.be/hhh/) gives an interactive view of the expression of these genes.

provide a powerful and unprecedented strategy for identifying infants at risk for the development of prelingual hearing loss.

There are many benefits of moving from the mere detection of hearing loss to the identification of its cause.[43] These include disease prevention, improved therapy, improved interpretation of the results of early intervention, and the psychological benefits of understanding the true cause of a disease. In general, cochlear implants have been successful in allowing speech to develop, even in children with profound hearing loss.[44] In some cases the results have been disappointing, and a precise genetic diagnosis may help to identify infants in whom the procedure will not be as useful. As shown in Figure 2, a growing number of genetic causes for auditory neuropathy are being identified in addition to hyperbilirubinemia, and the improved detection of these genetic causes may lead to the development of more effective treatments. In addition, the successful induction of hair-cell regeneration in guinea pigs[45] and gene silencing by RNA interference in the mouse provide support for the hope that specific forms of genetic deafness in humans may someday be addressed by similar forms of gene therapy. Such treatments would probably be disease-specific and require a precise etiologic diagnosis.

Despite the recommendations of professional organizations[46] and the Joint Committee on Infant Hearing,[21] in most screening programs systematic genetic evaluation and counseling are not a routine part of the approach to infants with confirmed hearing loss, even though specific genetic abnormalities are the most common cause of prelingual hearing loss and specific genetic tests are becoming available for a growing number of deafness genes. In the future, the use of molecular diagnostic DNA chips that are already being developed will permit routine, simultaneous testing for mutations involving many genes. When a specific form of syndromic deafness can be identified clinically, testing could be limited to the relevant set of mutations that are known to cause the syndrome. Positive test results are typically highly accurate, although ambiguities may exist in the interpretation of specific or newly recognized mutations. Negative results may not always rule out the diagnosis of the particular disorder or other genetic causes of deafness. Even if the test procedure involves DNA sequencing of coding regions of a deafness gene, regulatory mutations in noncoding regions cannot be ruled out as a potential cause or risk factor. Furthermore, the interpretation of test results for persons who are apparently heterozygous can often be problematic. When the goal of implementing extremely-low-cost genomic DNA sequencing (the so-called $1,000 genome sequence[47]) becomes a reality, many but not all of these ambiguities will be resolved. Despite current limitations, the ever-expanding use of diagnostic molecular testing of all infants identified with hearing loss is rapidly becoming the standard of care and represents an important advance in the clinical management of cases of deaf infants.

In summary, the astonishing spread of universal programs to screen newborns for hearing defects throughout the world has truly been a revolution in health care. Although these programs have been successful, they would greatly benefit from the standardization of testing protocols, the immediate confirmation of abnormal screening tests, the introduction of an etiologic focus, and the improved identification of infants at risk for late-onset prelingual hearing loss. By conducting molecular tests on all infants for just four important causes of hearing loss, the most common genetic and environmental causes of congenital deafness could be established shortly after birth, and infants at risk for the most common genetic, environmental, and preventable causes of late-onset prelingual hearing loss could be identified.

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