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THE GENETICS OF DEAFNESS

Walter E. Nance*

Department of Human Genetics,Virginia Commonwealth University, Richmond, Virginia

Deafness is an etiologically heterogeneous trait with many known genetic and environmental causes. Genetic factors account for at least half of all cases of profound congenital deafness, and can be classified by the mode of inheritance and the presence or absence of characteristic clinical features that may permit the diagnosis of a specific form of syndromic deafness. The identification of more than 120 independent genes for deafness has provided profound new insights into the pathophysiology of hearing, as well as many unexpected surprises. Although a large number of genes can clearly cause deafness, recessive mutations at a single locus, GJB2 or Connexin 26, account for more than half of all genetic cases in some, but not all populations. The high frequency may well be related to the greatly improved social, educational, and economic circumstances of the deaf that began with the introduction of sign language 300–400 years ago, along with a high frequency of marriages among the deaf in many countries. Similar mechanisms may account for the rapid fixation of genes for speech after the first mutations appeared 50,000–100,000 years ago. Molecular studies have shown that mutations involving several different loci may be the cause for the same form of syndromic deafness. Even within a single locus, different mutations can have profoundly different effects, leading to a different pattern of inheritance in some cases, or isolated hearing loss without the characteristic syndromic features in others. Most cases of genetic deafness result from mutations at a single locus, but an increasing number of examples are being recognized in which recessive mutations at two loci are involved. For example, digenic interactions are now known to be an important cause of deafness in individuals who carry a single mutation at the Connexin 26 locus along with a deletion involving the functionally related Connexin 30 locus. This mechanism complicates genetic evaluation and counseling, but provides a satisfying explanation for Connexin 26 heterozygotes who, for previously unknown reasons, are deaf. A specific genetic diagnosis can sometimes be of great clinical importance, as in the case of the mitochondrial A1555G mutation which causes gene carriers to be exquisitely sensitive to the ototoxic effects of aminoglycosides. This potentially preventable genetic-environmental interaction was the most common cause of genetic deafness in countries where these antibiotics were used indiscriminately in the past. Advances in genetic knowledge along with the use of cochlear implants have posed unique ethical dilemmas for society as well as the deaf community. Since most deaf children are born to hearing parents, it seems likely that deaf culture, and intermarriages among those born with deafness will recede during this century. Will future critics view this as one of the medical triumphs of the 21st Century, or as an egregious example of cultural genocide? On the other hand, genetics can provide empowering knowledge to the deaf community that for the first time can allow many deaf couples to know whether their children will be hearing or deaf even before they are conceived.
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INTRODUCTION

Astonishing success has been achieved during the past decade in identifying genes for deafness so that any current account of this research must be regarded as a "work in progress." For the first half of the 20th Century, geneticists argued about whether two, three, or perhaps four genes could explain the inheritance of deafness, and whether these genes were dominant or recessive. More than 120 independent genes have been identified which can be the cause of hearing loss, and it now seems likely that this number may rise to include 1% of all human genes, or about 300. The goal of this review is to highlight some of the results and significance of this rapidly expanding body of knowledge, and to suggest some of the directions that future research may take.

GENETIC EPIDEMIOLOGY OF DEAFNESS

Deafness has many recognized genetic and environmental causes. In this country, profound hearing loss occurs in about 0.8–1.0 per 1,000 births, but the incidence is known to vary with time and place. Many previous studies have suggested that about 50% of profound deafness is genetic in etiology. However, during the last rubella pandemic in 1964, the estimated proportion of genetic cases fell to about 10%. Estimates of this type are obtained by the collection and analysis of the distribution of affected relatives in the families of deaf probands, or index cases. The method of analysis involves the reasonable assumption that all nuclear families with more than one affected individual ("multiplex cases") are genetic in origin. The task is then to estimate what proportion of the "simplex cases" with only one affected individual, are also genetically determined. We know that simplex cases could represent true sporadic cases of environmentally caused deafness in which the chance of another affected child is very low. Alternatively, they could represent "chance isolated genetic cases" in which, by chance, there is only one affected child. The process of analysis is analogous to estimating the size of an iceberg from the part that is above water and knowledge of the density of ice and water. If only families with two or more affected children are considered to be genetic, the true proportion will be underestimated. On the other hand, assuming that all simplex cases of deafness are caused by sporadic, nongenetic factors would lead to the absurd conclusion that all deaf children in one-child families have nongenetic hearing loss. Data emerging from newborn hearing screening programs suggest that for every child with profound hearing loss, one to two

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*Correspondence to: Walter E. Nance, M.D., Ph.D., Department of Human Genetics, Virginia Commonwealth University, Richmond, VA 23298. E-mail: nance@hsc.vcu.edu
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are born with lesser, but clinically significant, degrees of hearing loss. Much less is known about the contribution of genetic factors to this latter group of patients and systematic studies of these cases are badly needed. Although the genes that ultimately cause a child to be deaf are present from the time of conception, not all forms of genetic deafness are necessarily expressed at birth. Many families have been observed in which the hearing loss appears to have been delayed in onset; there are others in which there is a variable rate of progression. Genetic hearing loss can be classified in many ways, including the mode of inheritance, the age of onset, audiologic characteristics, presence or absence of vestibular dysfunction, and the location and/or identity of the causal gene(s). The analysis of large collections of family data have suggested that at among genetic cases, approximately 77–88% are transmitted as autosomal recessive traits, 10–20 % as dominants, and 1–2% as X-linked traits [Rose et al., 1977]. The frequency of mitochondrial deafness is quite variable and can range from less than 1% to more than 20% in some populations. Some forms of genetic deafness have distinctive audiologic findings including conductive, low, mid-tone, or high-frequency hearing losses, or evidence for vestibular dysfunction. Finally, in 20–30% of cases, there may be other associated clinical findings that permit the diagnosis of a specific form of syndromic deafness.

CLASSIFICATION OF GENETIC DEAFNESS

Syndromic Deafness

Nearly 400 forms of deafness have been identified in which the presence of associated clinical findings permits the diagnosis of a specific form of syndromic deafness. In many of these syndromes, the hearing loss is a mild or inconstant feature. Some other syndromes are quite rare. However there are several well-characterized entities in which hearing loss is a frequent or constant, and often the most clinically significant, feature. A few instructive examples of the later group are described below. More comprehensive reviews and up to date information is available on several Internet sites and elsewhere [Gorlin et al., 1995; Hereditary Hearing Loss Homepage, 2000; Keats et al., 2002; Online Mendelian Inheritance in Man, 2002].

The Branchio-Oto-Renal (BOR) Syndrome

The branchio-oto-renal syndrome refers to the association of sensori-neural or mixed hearing loss with persistent branchial cleft fistulas, prehelical pits, malformations of the pinna, deformities of the inner ear which may include the Mondini malformation and stapes fixation along with renal anomalies including dysplasia or adysplasia, polycystic kidneys, and malformations of the calyces [Melnick et al., 1976]. About 80% of gene carriers have some degree of hearing loss, which can have a delayed onset. The trait was mapped to band 13.3 on the long (q) arm of chromosome 8 (i.e., 8q13.3), and later shown to result from mutations involving the EYE1 gene [Abdelhak et al., 1997]. This gene is homologous to the Eya gene in Drosophila, which is required for the normal formation of its compound eye by activating downstream targets. These findings prompted a closer examination of the eyes of human subjects with EYA1 missense mutations and have revealed cataracts and anterior segment anomalies in some cases. It is remarkable that knowledge of the phenotype produced by Eya in the fruit fly was of relevance to the clinical findings in humans. The BOR syndrome is transmitted as a dominant trait such that an affected individual has a 50% chance of transmitting the trait to each child.

Waardenburg Syndromes

These disorders account for at least 1–2% of individuals with profound hearing loss. Bilateral or unilateral hearing loss of variable severity occurs in association with defects in tissues and structures derived from neural crest cells. The most conspicuous findings are pigmentary abnormalities which can include brilliant blue eyes, complete or segmental heterochromia, lateral displacement of the inner canthi of the eyes, a pinched nose, synophorys, and variable patches of cutaneous hyper- or hypopigmentation [Waardenburg, 1951]. Gastrointestinal symptoms such as chronic constipation, are common and some patients report symptoms of gastrointestinal dyskinesia or a history of Hirschsprung disease. The incidence of neural tube defects is increased and limb defects may be seen. The disorder is genetically heterogeneous, and mutations involving at least eight loci can contribute to the phenotype. Waardenburg Syndrome, Type 1 (WS1) can result from any one of more than 50 different mutations involving the PAX3 gene on 2q35. The PAX3 gene produces a DNA binding protein that regulates the MITF locus on 3q12, among other down stream targets. Mutations in MITF, in turn, give rise to WS2A, which is distinguished clinically from WS1 primarily by the absence or less frequent occurrence of the eyelid anomaly dystopia canthorum, and a higher frequency of deafness and heterochromia [Hughes et al., 1994; Liu et al., 1995]. Some WS2A patients exhibit generalized hypopigmentation (albinoidism) with or without freckling. This phenotypic variant has been termed Tietz Syndrome. Additional dominantly inherited WS2 variants have been localized to chromosomes 1p21–p13.3 (WS2B) and 8p23 (WS2C). Mutations involving the vasoactive peptide endothelin–3 (END3) on 20q13.2 or its receptor, ENDRB on 13q22, can also cause the features of WS, commonly in association with Hirschsprung disease [McCallion and Chakravarti, 2001]. Homozygotes exhibit the full syndrome, while heterozygotes may only develop Hirschsprung disease. Single mutations involving the DNA binding SOX10 locus on 22q13 can also lead to combined features. These phenotypic variants have been designated WS4 or the Shah-Waardenburg syndrome. Finally, homozygous carriers of deletions involving the SLUG transcription factor on 8q11 have a form of WS2 that shows recessive transmission [Sanchez-Martin et al., 2002] The gene product of MITF is also a DNA binding regulatory protein. Its downstream targets include SLUG and the tyrosinase gene (TYR), which codes for the enzyme required for normal pigment formation that is deficient in one form of generalized albinism [Tachibana et al., 1994]. Families have been reported in which the digenic interaction between a mutation at the MITF locus with a mild abnormality at the TYR locus resulted in the features of WS2 along with ocular albinism [Morell et al., 1997]. These important observations show how pigment abnormalities are incorporated as a component of WS and illustrate how phenotypic variation in a syndrome can result from the effects of modifier genes at other loci. It is tempting to speculate that interactions of this type could in part explain why only about 20–30% of those who carry a PAX3 mutation develop profound bilateral hearing loss [Pandya et al., 1996]. WS3 refers to the presence of limb defects in association with other features of WS. It can result from homozygosity for two PAX3 mutations; from particular PAX3 mutations in single dose; or from small chromosomal deletions involving the PAX3 locus. In the cochlea, neural crest cells are known to contribute to the intermediate layer of the stria vascularis, and it thus seems likely that the cause of deafness in WS may be related to a defect

in the ability of the stria to maintain the critical endocochlear potential that is required for the hair cells to function normally. The successful cloning of PAX3 illustrates three powerful and complementary techniques that have been used to map human genes. First, the gene was localized to the long arm of chromosome 2 by testing Waardenburg families for highly variable genetic marker genes located throughout the genome. The goal was to identify markers located close to the WS locus. A particular allele at this marker locus was always transmitted in the families along with the WS1 trait. Markers in the 2q35 region met this criteria, and by invoking what might be characterized as "guilt by association" the approximate chromosomal location of the WS1 gene could be inferred The next important clue was the description of a rare case of WS1 in a Japanese boy who was found to have a small inverted segment on the long arm of chromosome two. This knowledge effectively localized the gene to one of the two break points of the inversion. Finally, the recognition that a coat color mutation in the mouse, known as "Splotch" mapped to the homologous region of the mouse genome served to focus attention on the human homolog of Splotch as a candidate gene for WS1. The discovery that pathologic mutations in PAX3 cosegregated with the WS in many, but not all families, confirmed the fact that PAX3 mutations can cause WS, and provided the first clear indication that mutations at other loci might also cause similar syndromes. The information that is emerging about the intricate hierarchy of genes that determine the Waardenburg syndromes is providing a dazzling glimpse of the interacting network of genes that control the development and function of the ear.

Usher Syndromes

This eponym refers to the syndromic association of deafness with retinitis pigmentosa (RP), a progressive degeneration of the retina that leads to loss of night vision, restriction of the visual fields, and ultimately, blindness. The incidence in this country has been estimated to be 4.4 per 100,000 [Boughman et al., 1983], but the syndrome accounts for 2–4% of all cases of profound deafness, and 50% of the deaf-blind population. Usher syndrome is both phenotypically and genetically heterogeneous. Approximately 40% of affected patients show a profound congenital hearing loss, with vestibular dysfunction and an early onset of RP, often within the first decade of life, that is characteristic of Usher Syndrome Type 1 (USH1); 57% with USH2 have a less severe hearing loss, with a later onset of RP and can usually communicate orally; in the remaining 3% with USH3, the severity of the hearing loss is variable and can be progressive [Rosenberg et al., 1997]. To date, six genes for USH1 have been mapped (USH1A-G), and of these, four have been identified, as has one of three USH2 loci and one USH3 locus. Mutations involving the MYO7A gene have been shown to be the cause of USH1B. However, two forms of nonsyndromic deafness (NSD), the dominantly inherited DFNA11 and the recessive DFNB2 also map to the same region, 11q13.5, and have been shown to result from other alleles at the MYO7A locus. Another recessive form of NSD, DFNB18, maps to 11p15.1, the same location as USH1C, which codes for the protein harmonin. In this case, molecular studies have provided an interesting explanation for the differences between the mutations which cause USH1C and those which only cause deafness (ie.,DFNB18). Although genes are composed of linear sequences of nucleotides at a particular site on a given chromosome, typically, the sequences are not continuous. Instead, the coding sequence, which specifies the amino acid sequence of the protein product, is normally interrupted by noncoding sequences known as introns. After the genetic message has been transcribed, these introns must be spliced out to form the mature messenger RNA. Expression of the enzymes required for this process can vary from tissue to tissue such that some exons (as well as introns) may also be spliced out in some tissues but not in others. The coding sequence is not altered but the message can be drastically edited to skip specific exons in particular tissues resulting in the synthesis of proteins that can differ in length. It is as if each article in a scientific journal had a different editor who used different rules to determine whether an abstract, acknowledgements, footnotes, references, figures, or tables should be included in the published version. This feature of gene expression greatly expands the different ways a single gene can be expressed in different tissues or at different times during development. Returning to the phenotypic differences in harmonin mutations, in at least one subject with isolated hearing loss (ie., DFNB18), the mutation occurs in an exon of the gene that is normally spliced out and not expressed in the retina [Ouyang et al., 2002]. Any patient who is homozygous or even a compound heterozygote for a mutation of this type would be expected to show deafness without RP, providing a satisfying explanation for at least some of the striking phenotypic differences that can be seen between different mutations involving the same gene.

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Jervell, Lang-Neilsen Syndromes (JLNS)

This syndrome refers to the association of sensori-neural deafness and prolongation of the QT interval on the electrocardiogram, reflecting a defect in cardiac repolarization. This in turn can lead to recurrent attacks of syncope, ventricular arrythmia, and sudden death. In some cases, syncopal attacks have been precipitated by fright. The syndrome is a rare recessive trait accounting for perhaps one per thousand children with profound deafness. However, when informed about this entity, many superintendants of schools for the deaf can recall having seen, during their careers, students who died suddenly of unexplained causes. Patients with JLNS should be under the care of a knowledgeable cardiologist, since treatment with beta-adrenergic blockers or other drugs is effective in most cases. In a second, much more frequent condition, the Ward-Romano syndrome, prolongation of the QT interval, recurrent syncope, and sudden death can be seen in the absence of hearing loss. It has been shown that in at least some cases, Ward-Romano patients are heterozygous for genes that cause JLNS when present in the homozygous state. Thus, the parents and other hearing relatives in the extended family of a JLNS patient may be at risk for syncope and sudden death. Mapping studies have shown that the gene (KVLQT1), which causes JLNS1 and the Ward-Romano

syndrome, is a member of a large family of potassium channel genes, a discovery that has provided a profound insight into the physiology of hearing [Neyroud et al., 1997]. The transduction of sound waves into a neural signal is initiated by the physical deflection of the hair cells of the cochlea, which mechanically opens ion channels in the hair cells and allows the passive inward flow of potassium ions from the high potassium environment of the surrounding endolymphatic fluid. The high potassium concentration is in turn maintained by active transport through potassium channels, such as those involved in the JLNS syndromes, that are located in the stria vascularis at the outer periphery of the coiled cochlear duct. Like a battery, this system stores potential energy in the high potassium concentration of the endolymph for use by the hair cells during sound transduction [Davis, 1965]. One possible reason for this evolutionary adaptation may be to avoid the need for active potassium transport in the cilia. Decreasing the energy requirements of the hair cells may dramatically increase their sensitivity to external sounds by allowing them to function in a microenvironment that is devoid of turbulent blood flow. Imagine the cacophony that would be produced if a capillary bed were required in the basal membrane that supports the hair cells, in order to provide the energy required for active potassium transport in the cillia! In addition to the JLNS1 locus on chromosome 11p15.5, recessive mutations involving another potassium channel gene, KCNE1, at the JLN2 locus on chromosome 21q22.1, can produce an identical phenotype. The expression of another potassium channel gene, KCNQ4, is limited to the outer hair cells. Although it does not contribute to homeostasis of the endolymph, mutations in the gene can cause a relatively common dominant form of progressive hearing loss (DFNA2) that typically begins in the first two decades of life, initially involves the high frequencies, and progresses to become a profound loss within about a decade.

Biotinidase Deficiency

This autosomal recessive trait results from the deficiency of an enzyme required for the normal recycling of the vitamin biotin. Infants with severe deficiency are therefore entirely dependent on dietary sources of the vitamin for their nutritional requirements and typically develop skin rashes, seizures, hair loss, hypotonia, vomiting, and acidosis within the first few months of life. This may progress to coma and death. If untreated, 75% of affected infants develop hearing loss, which may be profound, and persists despite the subsequent initiation of treatment [Wolf et al., 2002]. Since the symptoms of the disease, including the hearing loss, can be completely prevented by presymptomatic diagnosis and the administration of supplemental biotin, this disease has been included in many newborn screening programs throughout the world. The resulting data have shown that the incidence of affected homozygotes with severe enzyme deficiency is about is about 1 in 60,000. Boitinidase deficiency is an example of a completely preventable form of genetic deafness. Some treatments for hearing loss, such as hearing aides or cochlear implants, are generally effective for a wide range of affected individuals regardless of the etiology of their hearing loss. However, as illustrated by biotinidase deficiency, treatments that depend upon knowledge of the nature of the gene defect are likely to be very specific in their theraputic relevance, even though they may be highly effective. Thus there is no indication that supplemental biotin would improve the hearing of anyone other than the 1–1.5 % of hearing impaired infants estimated to have biotinidase deficiency. This disease also illustrates another important strategy that has been particularly useful for mapping human genes for deafness. The term polymorphism refers to regions of the genome in which common sequence variations are found. Although some polymorphisms, such as the sickle cell gene, are maintained at high frequency in the population by the selective advantage they confer to heterozygous carriers, most polymorphisms have no detectable clinical effects and many are not even located within the coding sequences of genes. These genetic markers have been useful for mapping genes, and some are so variable that it is unusual for an individual to be homozygous for exactly the same allele or variant. This feature has been used to map genes for rare recessive traits by "homozygosity mapping." We know that deaf individuals who are the offspring of consanguineous matings carry two alleles for deafness that must be identical because they are both copies of the same gene carried by one of the common ancestors. To localize a gene, therefore, all we need to do is type a sample of consanguineous probands for a large number of polymorphic markers, and look for the chromosomal region where all of the affected individuals are homozygous or "identical by descent." In the case of biotinidase deficiency, the analysis of data from 18 consanguinious probands allowed the localization of the gene to a very small region on 3p25 that was only about 0.036 % of the length of the entire genome [Blanton et al., 2000]. Many rare forms of recessive NSD have only been observed in a single family and homozygosity mapping has been of particular value for mapping these loci.

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Pendred Syndrome

This autosomal recessive disorder is characterized by neuorsensory deafness, goiter, and malformation of the inner ear. It is probably the commonest form of syndromic deafness and accounts for approximately 7.5% of all individuals with profound hearing loss [Fraser, 1965]. The goiter results from a specific defect in the organification of iodine which may be demonstrated by the abnormal release of radioactive iodine trapped by the thyroid after the administration of perchlorate. Unfortunately, this highly specific test is not widely available. The goiter may be delayed in onset and clinically unapparent, and is usually not associated with hypothyroidism. A variety of malformations of the inner ear can be demonstrated radiographically in 86% of cases, including Mondini malformation and malformations of the vestibular canals, but the most characteristic finding is dilation of the vestibular acqueduct [Reardon et al., 2000]. The hearing loss is usually profound, but can be variable in its onset, rapidly progressive, and even unilateral. The successful cloning of the gene for Pendred Syndrome, SLC26A4, showed that it was a member of a family of genes involved in sulfate transport, but functional studies of pendrin, the protein product of the gene, suggest that it is primarily involved in the transport of iodine and chloride ions. As in the case of

Usher Syndrome, a form of nonsyndromic deafness, DFNB4 can also result from mutations in the Pendred gene. Cochlear abnormalities are also present in DFNB4, and it is not clear how many of these cases may have unapparent thyroid disease, since testing with the perchlorate discharge test has not been reported in these patients.

Congenital Fixation of the Stapes Footplate With Perilymphatic Gusher

Many examples of this association have been described, suggesting that it may be the commonest form of X-linked deafness. Affected males can have either a mixed or neurosensory deafness. In cases with a conductive component, a congenital fixation of the stapes footplate is found at the time of surgery but attempts to mobilize the footplate typically lead to a profuse flow of endolymphatic fluid, which effectively prevents remediation [Nance et al., 1971]. Computerized tomography shows dilation of the internal auditory meatus with an abnormal communication between the subarachnoid space and the cochlear endolymph which accounts for the "gusher" at the time of stapes surgery. Carrier females may show a mild hearing loss and less severe abnormalities of the inner ear. After the locus was mapped to Xq21.1, affected males were found to carry mutations involving a DNA binding regulatory gene, POU3F4 [de Kok et al., 1995]. In many families, the mutation has been shown to be a deletion, which can vary greatly in size, and can sometimes involve nearby genes for mental retardation and choroideremia. In such cases, symptoms of two or all three diseases may be present in affected family members, a phenomenon known as a contiguous gene syndrome.

Alport Syndromes

Alport Syndrome refers to the association of neurosensory hearing loss with progressive nephritis. The latter begins with hematuria and can lead to progressive renal failure and death. About 50% of affected individuals develop a progressive bilateral hearing loss, which usually begins in the second decade of life, involves the high frequencies initially, and may become incapacitating. Ocular findings can include congenital cataracts, spherophakia, retinal flecks, and anterior lenticonus. The latter two findings are seen in about 85% and 25% of affected individuals and are highly characteristic of the syndrome. Renal biopsy shows irregular thickening of the glomerular basement membranes. The disease results from mutations involving one or the other of three tissue specific polypeptide subunits of collagen that are encoded by the COL4A3, COL4A4, and COL4A5 genes. The latter is determined by an X-linked gene at Xq22 while the genes coding for the first two collagens are located adjacent to each other on 2q35. Typically males with the X-linked form of Alport syndrome are more severely affected than females, who may never develop end stage renal disease. The three collagen subunits are expressed in the basilar membrane, spiral ligament, and basement membranes of the stria vascularis. However, interpretation of the molecular basis of the hearing loss is complicated by the fact that renal failure, dialysis, and ototoxic drugs that may be used for treatment can all contribute to hearing loss. The overall incidence of Alport Syndrome is about 1 in 10,000, with the X-linked form being more common than both of the autosomal variants. About 8,000 individuals with glomerulonephritis progress to end stage renal disease each year and make a substantial contribution to the 13,500 renal transplants that are performed annually.

Nonsyndromic Deafness

About 70–80% of genetic deafness is nonsyndromic. At least 33 recessive, 41 dominant, and five sex-linked loci have been mapped Among these, 31 of the causal genes have been identified. The dominant loci are identified by the symbol and numbers DFNA1–41; the recessive loci are designated DFNB1–33, and DFN1–5 refers to the X-linked loci. A current listing of the mapped genes and identified loci, along with references, can be found at the Hereditary Hearing Loss Homepage (http://dnalab-www.uia.ac.be/dnalab/hhh/). Several important examples of nonsyndromic deafness that have been identified to date are described in greater detail below.

Connexin Deafness

In view of the large number of loci already identified, the knowledge that most cases of genetic deafness are caused by mutations involving a single gene in many populations came as an astonishing surprise. The Connexins are a family of genes that code for the subunits of gap junction proteins. Gap junctions form when the hexameric hemi-connexins on the surface of two adjacent cells "dock" to form a complete gap junction. The resulting channels permit the flow of ions and small molecules between the cells. At least 14 mammalian Connexins have been identified, and are designated by numbers that refer to their molecular size. Connexin 26 (also termed CX26 and GJB2), for example, has a molecular weight of 26,000 Daltons. The different Connexins vary in the tissues and developmental stages at which they are expressed. Furthermore, some are capable of forming heteromeric as well as homomeric connexins. Thus the clinical effects of a mutation may well depend on the degree of redundant expression of other Connexins as well as its pattern of expression within an organ or tissue. Seven of these genes are either known to be the cause of human deafness, or are expressed in the ear. More than 80 different mutations of the CX26 gene have been reported [The Connexin-Deafness Homepage, 2002]. Many are "private" mutations, having been observed in only one or a few pedigrees, but examples of very common alleles have also been identified in several populations including the 35delG mutation in Caucasians, the 167delT allele in Ashkenazi Jews, the 235delC allele in Asian populations, and the R143W mutation in Ghana. Most pathologic mutations are recessive, but at least six exhibit dominance. Similarly, Connexin deafness is usually not associated with other features, but characteristic dermatologic findings have been reported in association with specific mutations, including palmoplantar hyperkeratosis in association with the dominant G59A allele [Heathcoat et al., 2000], mutilating keratoderma (Vorwinkle Syndrome) in association with the D66H allele [Maestrini et al., 1999], and three dominant alleles associated with the keratoderma-ichytheosis-deafness (KID) syndrome [Richard et al., 2002]. In addition, hearing loss occurs with dermatologic abnormalities in some mutations involving CX30 and CX31, and with neurologic abnormalities in X-linked Charcot-Marie–Tooth disease caused by the CX32 gene. In most large studies, deaf probands are encountered who are apparent CX26 heterozygotes. Since the reported frequency of heterozygotes in the general population has exceded 3% in some studies, the heterozygosity could be unrelated to the hearing loss. Alternatively, dominance or an unidentified second pathologic CX26 allele could be the explanation. Recently, it has been reported that a 342 kb deletion spanning the CX30 locus can interact with a single recessive CX26 mutation to cause deafness [del Castillo et al., 2002]. The CX26 and CX30 genes are located within about 40 kb of each other on 13q11. Although the CX26 locus is not involved in the deletion, it is still not clear whether the deafness arises because the CX26 and

CX30 proteins interact, or whether the deletion itself perturbs the expression of the adjacent normal CX26 gene. In Spain, this deletion accounted for two thirds of 33 deaf probands who were apparent CX26 heterozygotes. In this country, 17 of 625 (2.7%) deaf probands were found to carry the CX30 deletion, including one affected homozygote, and the deafness in 17.7% of deaf CX26 heterozygotes could be explained by this mechanism [Nance et al., 2002].

Why mutations involving the Connexins are such a common cause of deafness is not clear. There is little to suggest they have a high mutation rate, or that there is a selective advantage for connexin carriers, as in the case of sickle cell disease. Population bottlenecks and founder effects can explain why some genes have a high prevalence, and could have contributed to the high frequency of the 167delT and R143W mutations in Ashkenazi Jews and Ghana, but these effects are usually associated with small or relatively closed populations. One interesting possibility is that the high frequency has resulted from the greatly improved social and economic circumstances of the deaf combined with intense assortative mating among the deaf. Both of these trends began with the introduction of sign language and the establishment of residential schools for the deaf about 300 years ago. An analysis of a large nationwide collection of pedigree data on deaf families collected 100–200 years ago suggests that the relative frequency of connexin deafness in this country at that time cannot have been greater than about 17% [Nance et al., 2000]. Contemporary estimates suggest that this frequency may have doubled in the past 200 years. Marriages between individuals with precisely the same type of recessive deafness can only have deaf offspring, and are termed "noncomplementary matings." Since the frequency of these marriages is proportional to the fourth power of the respective gene frequency, only the commonest forms of deafness will make an appreciable contribution to these matings. Thus the combination of improved fertility (i.e., genetic fitness) and assortative mating is a mechanism that will selectively amplify the commonest form(s) of recessive deafness in the population, along with "modifier genes", such as the CX30, deletion which can interact with the major gene. [Nance et al., 2002b]. In countries without a long tradition of sign language or intermarriage among the deaf, such as India and Mongolia, CX26 mutations are present, but Connexin deafness occurs at a very low frequency. The Bengkala village in Bali provides a striking contrast. The frequency of recessive DFNB3 deafness in the 2185 villagers is 2%; 17% of the hearing subjects are gene carriers, and all deaf by deaf matings are noncomplementary as might be expected [Friedman et al., 1995]. The dramatic increase in the frequency of this gene was accompanied by the development of an indigenous sign language, now learned both by the deaf and hearing villagers. In many primitive populations, the genetic fitness of the deaf is close to zero. Although "gene drift" undoubtedly played a role in the initial survival of the original DFNB3 mutation, it is difficult to escape the conclusion that the combination of improved fitness and assortative mating that followed the invention of a sign language, must also have contributed to the dramatic increase in the frequency of deafness in the population. Clearly, this mechanism can increase the frequency of recessive genes for deafness other than the Connexins. It also seems likely that precisely the same forces led to the rapid fixation of genes for speech [Lai et al., 2001] when they first arose in the human species and subsequently contributed to the explosive evolution of the human brain that has occurred during the past 50,000–100,000 years. The evolutionary biologist Stephen Gould popularized the idea that during specific periods the pace of evolution has suddenly accelerated [Gould and Eldredge, 1977]. The combination of intense assortative mating with improved fitness associated with the acquisition of speech may be the mechanism accounting for at least one such event in human evolution [Nance and Pandya, 2002b].

". . .the combination of improved. . .genetic fitness. . .and assortative mating is a mechanism that will selectively amplify the commonest form(s) of recessive deafness in the population. . ."

Mitochondrial A1555G mutation

The A1555G mutation in the mitochondrial 12S ribosomal RNA gene was first shown to be a cause of deafness in a large Arab-Israeli pedigree with matrilineal transmission of a severe to profound hearing loss that typically began in infancy or early childhood [Jabber et al., 1992]. Molecular testing revealed a homoplastic substitution in the 12S ribosomal RNA gene. Similar pedigrees with the same mutation have been reported from Spain, where the mutation appears to be a remarkably common cause of deafness [Estivill et al., 1998], and from Italy, but the onset of hearing loss occurs later in these families. In other countries such as the United States, China, South Africa, and Mongolia, A1555G deafness has been virtually confined individuals who have been exposed to aminoglycoside antibiotics. The explanation for the great variation in the phenotypic expression of this mutation is not known with certainty. Data support the idea that the risk and expression of hearing loss in subjects who carry the A1555G substitution can be strongly influenced, either by other nuclear or mitochondrial genes or by environmental factors such as exposure to aminoglycosides. In this country where aminoglycosides are used selectively, but often in high doses, only about 15% of all patients whose hearing loss is attributed to aminoglycosides are found to carry the A1555G mutation [Fischel-Ghodsian et al., 1997]. In contrast, in Mongolia, where aminoglycosides were widely used in the past, the A1555G mutation was the commonest identifiable cause of deafness in a survey of students at the school for the deaf in Ulanbaatar in 1997 [Pandya et al., 1997]. Other mutations in the same mitochondrial gene have been identified in patients with aminoglycoside ototoxicity who lack the A1555G substitution, including a delT961Cn mutation [Casano et al., 1999], but little is known about their prevalence. When a molecular diagnosis can be established, aminoglycoside ototoxicity is a trait with a high potential for preventing the recurrence of deafness among matrilineal relatives. Whether all patients, or perhaps all Hispanic patients, admitted to neonatal intensive care units should be screened for relevant mitochondrial mutations before the administration of aminoglycosides is an issue that would depend critically on the population prevalence of the mutations. Unfortunately, these data represent an important gap in existing knowledge.

Dominantly inherited low frequency hearing loss (DFNA6, 14, & 38)

Dominantly inherited low frequency hearing loss was first reported in a large kindred whose impairment was generally confined to frequencies less than 2000 cps. A pseudolongitudinal analysis of the audiologic findings within the family provided little evidence for progression with age. Affected family members were not severely incapacitated and the children responded well to preferential classroom placement [VUHDSG, 1968]. The gene in this family was mapped to 4p16.3 [Lesperance et al., 1995]. Two other forms of dominantly inherited hearing loss, one of which exhibited progression, were subsequently mapped to the same region and designated DFNA14 and DFNA38. However, when DFNA6 was found to arise from mutations in the Wolfram Syndrome I gene (WFS1), DFNA14 and DFNA38 were shown to be the consequence of allelic mutations at the same locus [Bespalova, et al., 2001]. Mutations involving this locus are now thought to explain most cases of dominantly inherited low frequency hearing loss. However, one additional gene, DFNA1, which led to a rapidly progressive hearing loss beginning in the low frequencies, was identified in a single large Costa Rican kindred, mapped to 5q31, and later shown to result from a mutation in the human homolog of the diaphanous gene in drosophila [Lynch, et al., 1997]. Wolfram syndrome is a complex recessive trait. The hallmarks are diabetes mellitus and insipidus, optic atrophy, and deafness, but a variety of neuropsychiatric symptoms can also be seen including seizures, ataxia, retardation, depression, violent behavior, and suicide in some patient populations. Typically the hearing loss in affected homozygotes has been progressive beginning with the high frequencies. Diabetes mellitus and hearing loss have been shown to occur with higher frequency in heterozygous carriers. Carrier status does not appear to be a major risk factor for psychiatric disease and suicide, but the possibility that some alleles have these effects has not been excluded [Crawford et al., 2002]

MOLECULAR BASIS OF HEARING AND DEAFNESS

As new genes for deafness have been mapped and cloned, analysis of their base pair sequence has frequently allowed the structure and function of their protein products to be inferred. Molecular and histologic studies of m-RNA synthesis have allowed determination of the developmental stage, tissues, and cells in which these genes are expressed, resulting in an ever more detailed understanding of the molecular basis of hearing.

Transcription Factors

Several large classes of proteins are known which are typically required to initiate the transcription of messenger RNA (m-RNA). Some bind to specific sites within the promoter region of the gene, while others are involved in specific interactions with other proteins in the complete transcription complex. An abnormal phenotype can result from an abnormal base pair sequence in the promoter region or from a deficiency or abnormality in the transcription factor. Seven forms of deafness are known to be the result of mutations of transcription factors. Defects in PAX3, MITF, and SOX10 cause three forms of Waardenburg. Mutations involving the POU4F3 and POU3F4 genes cause a dominant form of progressive hearing loss (DFNA15) and the X-linked syndrome of congenital fixation of the stapes footplate respectively. Finally, mutations involving the EYA1 and EYA4 genes are the cause of the Branchio-oto-renal syndrome and a dominantly inherited form of late onset hearing loss (DFNA10) respectively. Since these defective transcription factors act on both copies of a diploid target gene, all of these traits exhibit dominant transmission.

Intracellular proteins

Atypical Myosins

Mutations involving four different atypical myosins have been shown to be the cause of deafness. Different mutations in MYO7A can cause dominant or recessive NSD or Usher syndrome, type 1B. Mutations involving MYO6 and MYH9 both lead to progressive forms of dominant hearing loss (DFNA22 & DFNA17) while MYO15 defects underlie a profound congenital form of recessive NSD (DFNB3).

Structural Proteins

Two genes, DIAPH1 and STRC are highly expressed in the hair cells where they act to promote actin polymerization in the hair cells, and the production of Sterocilin, a component of the microvillar proteins respectively. Defects in the former result in the progressive dominantly inherited hearing loss of DFNA1 on 5q31, while the latter is associated with recessive deafness, DFNB16 on 15q15. The OTOF and TCOF1 are both intracellular proteins which are thought to be involved in the trafficking of intracellular organels. Otoferlin is located in the cytoplasm and anchored to the cell membrane while the Treacle protein is involved in nuclear-cytoplasmic trafficking. TCOF1 is located on 5q31, and its mutations are the cause of Treacher Collins Syndrome. Defects in OTOF cause a form of recessive NSD, DFNB9 on 2p23.

Transmembrane Proteins

Channelopathies

Mutations involving at least three members of the Connexin family of gap junction proteins Cx26, Cx30, and Cx43 are known to cause hearing loss. Two potassium channel genes, KVLQT1 and KCNE1, are essential for maintaining the normal homeostasis of the cochlear endolymph. Defects in these genes cause two forms of the recessive Jervelle, Lange-Nielsen Syndrome (JLN1 & 2). As noted previously, mutations in another potassium channel gene, KCNQ4, can cause DFNA2 but do not contribute to homeostasis of the endolymph. One other gene for deafness, SLC26A4, the cause of Pendred Syndrome, is a membrane-bound protein that is involved in ion transport, and the fixation of iodine in the thyroid gland. Prestin, the putative molecular motor protein of the outer hair cells, is a member of this same family of genes. A unique attribute of the outer hair cells is their ability to change their length in response to sound stimuli. This property is thought to greatly amplify and help resolve the transmission of sound waves along the basal membrane. Mutations in this gene have been identified in deaf probands, although the mode of inheritance is not yet clear [Liu et al., 2002].

Cell Adhesion

Two genes for deafness involve genes that are required for normal cell adhesion. CDH23, on 10q21, is a member of a calcium dependant family of genes, the cadherins, that mediate cell adhesion. It is abnormal in USH1D as well as in families with recessive DFNB12. The claudins are another a large family of genes that form tight junctions that bind homologous as well as heterologous cells together. A mutation in CLDN14 on 21q22.3 is responsible for the recessive deafness in DFNB29.

Other transmembrane proteins

The functions of the transmembrane USH3 and TMC1 proteins that are defective in USH3 on 3q21 and domi-

nant or recessive forms of NSD (DFNB7/11, DFNBA36) on 9q13 are not as well established but TMPRSS3, which causes a recessive form of NSD on 21q22.3, codes for a transmembrane protein with protease activity.

Extracellular Proteins

Mutations involving three collagen genes, COL2A1, COL11A2, and COL11A1 are the cause of the three recognized forms of Stickler Syndrome, while mutations involving COL4A5, COL4A3, and COL4A4 cause the autosomal and sex linked forms of Alport Syndrome. The gene that causes USH2A codes for an extracellular matrix protein, while TECTA, the gene defective in DFNA8/12 on 11q22, codes for a component of the tectorial membrane. Otoancorin, the product of the OTOA gene, is thought to anchor the apical surface of the hair cells to the tectorial membrane, and is defective in DFNB22 on16p12.2.

Energy Production

Both nuclear and cytoplasmic genes are active in the mitochondria, the site of oxidative phosphorylation in the cell. Hearing loss can be a part of a large number of complex neurologic syndromes that involve deletions in the mitochondrial DNA or point mutations involving mitochondrial t-RNSs. The A1555G substitution in the 12S mRNA gene and the A7445G substitution in the t-RNA Ser(UNC) gene are examples of two mitochondrial mutations that can lead to hearing loss alone. Finally, DDP the Deafness/Dystonia peptide is the product of a gene on Xq22 that is responsible for the deafness, blindness, retardation, and dystonia seen in the Tranebjaerg syndrome. The protein product of this gene is normally transported into the mitochondria, but its precise function there has not been identified.

SOCIAL AND ETHICAL ASPECTS OF GENETIC DEAFNESS

Advances in human genetics have raised many ethical issues such as privacy, autonomy, prenatal diagnosis, stem cell research, and the rights of children, that are just as applicable to deafness as they are to other genetic traits. In addition, there are issues that are particularly relevant, if not unique, to deafness.

Attitudes of the Deaf and Hearing Communities

The contrasting attitudes of the deaf and hearing communities about genetic issues have been highlighted in a number of recent surveys [Stern et al., 2002; Middleton et al., 1998]. Many deaf individuals reject the medical model of deafness as a disability that needs to be "fixed." Most express no preference for hearing or deaf children, but many would prefer a deaf child and relatively few express a preference for hearing children. The attitudes of the deaf community towards genetic testing and the use of prenatal diagnosis, including the selective abortion of either deaf or hearing fetuses, tend to be more polarized than those of hearing parents. In contrast, the birth of a deaf child is often the supreme tragedy in the lives of hearing parents, who would do anything to restore the child's hearing. There are few other human traits for which such divergent attitudes are held.

"Geneticists have generally discounted Bell's concerns about the mating structure of the deaf population. . . . However it now appears. . .this mechanism may have contributed to an increase in the frequency of the most common form of recessive deafness. . ."

The Legacy of Alexander Graham Bell

Bell's involvement with the Eugenics movement may have had a lasting influence on the attitudes of the deaf community towards genetics. Bell was an educator of the deaf who devoted most of his professional career to promoting the welfare of deaf children. In 1883, 17 years before the rediscovery of Mendel's work, he published a Memoir of the National Academy of Sciences in which he speculated that the continued intermarriage among the deaf might someday result in the formation of a deaf variety of the human race [Bell, 1883]. Although some of Bell's genetic proposals cannot withstand modern criticism, his perceptions about the effect of the mating structure of the deaf population on the frequency of deafness may well have been correct. To avoid this effect, Bell advocated the closing of residential schools for the deaf in favor of what is now called mainstreaming. In this instance, he was actually advocating more random mating, as opposed to the selective breeding commonly associated with eugenics. Geneticists have generally discounted Bell's concerns about the mating structure of the deaf population believing that the effect would be negligible in view of the large number of genes involved in deafness. However, it now appears that this mechanism may have contributed to an increase the frequency of the most common form of recessive deafness during the last 200 years. Thus, Bell's prediction forces us to consider what attitude we should take towards the pattern of marriages that may have contributed to this increase. Assortative mating among the deaf is not the only example in which the marriage patterns of a population can have a profound influence on the frequency of specific genetic diseases. The frequencies of Tay-Sachs disease and Sickle Cell Anemia in this country are much higher than they would be if marriages occurred at random, and unless we are also prepared to abolish racial and ethnic homogamy, there would appear to be no rational genetic basis for prohibiting marriages among the deaf. It now seems likely that Bell's goal will be achieved not through the mainstreaming of deaf children but because of the widespread use of cochlear implants. This development almost certainly represents a much greater threat to deaf culture than genetic testing. Deaf culture may well disappear in our country by the end of this century. If that does occur, who among us can predict whether it will be viewed as one of the medical triumphs of the 21st Century, or as an egregious example of cultural genocide?

Genetic Counseling

Genetic counselors are medical specialists who are especially skilled in the evaluation, diagnosis, and counseling of patients with certain genetic traits. In some cases, medical geneticists also become intimately involved in the treatment and long-term follow-up of patients with specific genetic diseases. In the case of hereditary deafness, geneticists can assist in the establishment of a specific etiologic diagnosis. In some cases, this may result in the diagnosis of a form of syndromic deafness for which specific treatments or diagnostic tests are indicated. The Jervelle, Lange-Neilsen Syndromes, Usher Syndromes, Branchio-

oto-renal Syndrome, and Alport Syndromes are examples of genetic forms of deafness in which serious complications involving other organ systems may arise. Even when a diagnosis of nonsyndromic deafness is made, an increasing number of genetic tests can diagnosis a specific form of NSD. These tests can be of particular value in confirming a genetic etiology in families where there is only one affected child and no history of deafness in the family. Connexin testing has rapidly become the standard of care for the management of such cases. In the future, it will become increasingly useful to establish a specific genetic etiology in order to provide prognostic information about the natural history of deafness in a family, and options for specific therapy. Some forms of nonsyndromic deafness are progressive, while others are remarkably stable. Some have a conductive component that may be amenable to surgical treatment. Finally, reliable information about the chance that deafness will recur in the immediate family or in the children of the proband can only be provided if the genetic form of deafness and its mode of inheritance are known. If this knowledge is provided in a way that it can be understood and integrated by the patient it can help dispel misconceptions and feelings of guilt and allow the parents to focus on planning for their child's future. For deaf adults, information about the cause of a trait that has had such an important influence on their lives can be empowering. In the past, deaf couples have never known how, why, or even if their children would be deaf, as they are, or hearing. For some, this uncertainty must be like not knowing what race your child will be. Increasingly, couples can receive answers to these questions prospectively. Much is known about the genetics of profound deafness. In comparison, much less is known about the causes of lesser degrees of clinically significant hearing loss. Many of these children may have one or the other of the several hundred genetic syndromes that have been described in which hearing loss is a less conspicuous or inconstant feature. In many ways, these children are more in need of the expertise in dysmorphology that a geneticist brings to the evaluation of such children than those who have a clear cut diagnosis. Finally, as the training of audiologists incorporates more knowledge about genetics they should be increasingly able to recognize families who would benefit from genetic evaluation and counseling, and to understand and reinforce information provided to their patients during counseling.

FUTURE DIRECTIONS

In the recent past, the state of our knowledge was such that we lumped many forms of nonsyndromic deafness together; assumed that each form of syndromic deafness was caused by a single gene; believed that dominance and recessivity were intrinsic properties of genes, and had little insight into the heterogeneity of mutations and the molecular mechanisms involved in their effects. We used descriptive terms such as reduced penetrance variable expressivity, multifactorial transmission, and stochastic variation to explain away examples of unexpected gene expression. We are now gaining a much more sophisticated understanding of genetic heterogeneity, and the factors which influence the expression of genes, their interactions with each other, and with the environment. In the immediate future we can expect to see more of the same as additional genes for deafness are discovered and we listen to the incredible stories they have to tell. The coincident development of the newborn hearing movement (Karl White, this volume) during this new era of genetics provides an unparalleled opportunity for synergistic interactions between these two streams of medical and scientific progress. The time will come when the application of existing "gene chip" technologies or other methods currently under development, will make it possible to perform molecular genetic screening tests on blood samples from newborn infants at low cost for a virtually unlimited number of gene mutations that can cause deafness. The question then arises, "What gene defects should we screen for and why?" Would it be important to know that an infant has inherited a gene that may cause hearing loss when he or she is 50 years old? One option would be to focus on forms of hearing loss that may not be expressed at birth and could therefore be missed in current audiologic newborn screening programs. Another possible criterion would be to screen for very common forms of deafness, or for forms that are associated with other serious and/or preventable clinical complications. Examples of the former might include hearing loss resulting from CMV infection or Pendred Syndrome. Examples in the latter group would include Connexin deafness, the mitochondrial A1555T mutation, genes for the JLN syndrome, and possibly one or more forms of Usher Syndrome. Screening for a limited array of traits such as these could be performed with the newborn blood spots that are already collected for existing metabolic screening programs. If programs of this type are implemented in this country, it would be highly desirable to collect pilot data on the frequency of the traits and the sensitivity and specificity of the tests. In this way, it should be possible to incorporate the new tests into existing screening programs. Programs of this type should be viewed as a complement to and not a substitute for existing newborn hearing screening programs. They would identify additional high-risk infants who deserve close follow-up, and accelerate an etiologic diagnosis in others. In view of the complexities surrounding the interpretation of even the simplest test results, it would not even be possible to contemplate a newborn molecular screening program without a preexisting audiologic screening program. For example, some deaf individuals are found to carry only a single Cx26 mutation. As noted previously, it is now known that many of these individuals also carry a deletion of the Cx30 gene. However, others are undoubtedly simply heterozygous carriers of a single Cx26 mutation. Without evidence that a newborn infant has normal hearing, it would be difficult to draw the conclusion that the test result merely indicated heterozygosity with any degree of certainty. In view of the rapidly expanding body of relevant genetic knowledge about genetic deafness, the American College of Medical Genetics has recommended that all infants with confirmed hearing losses who are identified in newborn screening programs, should be referred to a geneticist for clinical evaluation, the performance of indicated genetic tests, and counseling [Nance et al., 2000], and has developed detailed practice guidelines for the evaluation of such infants [Genetic Evaluation of Genetic Hearing Loss Ex-

". . .information about the cause of a trait that has had such an important influence on their lives can be empowering. In the past, deaf couples have never known how, why, or whether their children would be deaf"

pert Panel, 2002]. Unfortunately, although most states support genetic clinics and programs at their academic medical centers, these genetic programs have not, in general, been incorporated as an integral part of the newborn hearing screening movement, and the proportion of infants who are referred for evaluation is quite low. If all cases were referred, and if limited molecular screening programs were established, it would provide an unparalleled opportunity to collect population-based data on the prevalence and natural history of specific forms of both genetic and environmental deafness.

As noted previously, there are a very limited number of forms of genetic deafness for which specific therapy is currently available. It seems likely that many more preventive or curative treatments may someday be developed, but will only be applicable to specific forms of genetic deafness, thus emphasizing the importance of an accurate diagnosis. On the other hand, some forms of treatment, such as hearing aids and cochlear implants, are of benefit to hearing-impaired individuals with a wide range of genetic etiologies, and it is to be hoped that other therapeutic approaches such as the use of stem cell technology to replace hair cells may, in a similar manner, benefit a wider range of affected individuals. The prospects for new discoveries and improved treatments are bright, and it is an exciting time to be a geneticist interested in hearing loss.

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