REVIEW ARTICLE
At the Speed of Sound: Gene Discovery in the Auditory System

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As auditory genes and deafness-associated mutations are discovered at a rapid rate, exciting opportunities have arisen to uncover the molecular mechanisms underlying hearing and hearing impairment. Single genes have been identified to be pathogenic for dominant or recessive forms of nonsyndromic hearing loss, syndromic hearing loss, and, in some cases, even multiple forms of hearing loss. Modifier loci and genes have been found, and investigations into their role in the hearing process will yield valuable insight into the fundamental processes of the auditory system.

Introduction

Over the past 5 years, remarkable progress has been made in the identification of new loci for nonsyndromic hearing impairment (NSHI) and in the cloning of deafness genes (fig. 1; table 1). To date, 77 loci have been reported for nonsyndromic deafness: 40 autosomal dominant, 30 autosomal recessive, and 7 X-linked (Hereditary Hearing Loss Homepage). In addition, 51 auditory genes have been identified: 15 for autosomal dominant NSHI loci, 9 for autosomal recessive NSHI loci, 2 for X-linked NSHI loci, 5 mitochondrial, and ⩾32 genes for syndromic hearing loss (note that some genes cause multiple forms of deafness) (table 1). Although significant advances have been made, there is no doubt that many more genes await discovery. Identifying these genes and characterizing the proteins they encode will increase our knowledge of the molecular processes involved in the auditory system and will improve our understanding of how such processes can become altered and lead to hearing impairment.

Hearing loss is a common sensory disorder in the human population. The incidence of congenital hearing loss is estimated at 1 in 1,000 births, of which approximately equal numbers of cases are attributed to environmental and genetic factors (fig. 2) (Morton 1991; Gorlin et al. 1995). Environmental factors leading to hearing loss include acoustic trauma, ototoxic drugs (e.g., aminoglycosides), and bacterial and viral infections. Of the hearing-loss disorders attributable to ge-

netic causes, ~70% are classified as nonsyndromic and the remaining 30% as syndromic. Hundreds of syndromic forms of deafness have been described, and the underlying genetic mutation has been identified for many of the more common forms (table 1) (Gorlin et al. 1995; Steel and Kros 2001). Among the many disorders classified as syndromic hearing loss, the pathology varies widely, but, in nonsyndromic deafness, the defect is generally sensorineural.

Nonsyndromic hearing impairment can be further subdivided by mode of inheritance: ~77% of cases are autosomal recessive, 22% are autosomal dominant, 1% are X-linked, and <1% are due to mitochondrial inheritance (fig. 2) (Morton 1991). Dominant loci are denoted with the prefix "DFNA," recessive loci with "DFNB," X-linked loci with "DFN," and modifying loci with "DFNM." Generally, patients with autosomal recessive hearing impairment have prelingual and profound deafness, and patients with autosomal dominant hearing impairment have progressive and postlingual hearing impairment. This observation may be explained by the complete absence of functional protein in patients with recessive disorders, whereas, in patients with autosomal dominant disorders, dominant mutations may be consistent with initial function and subsequent hearing impairment due to accumulation of pathology.

Genes Involved in Deafness

The cochlea is an intricate organ composed of dozens of cell types and specialized regions required for the normal process of hearing. Of the genes responsible for deafness, many of the encoded proteins have been shown to be expressed within the cochlea and can be grouped into functional categories that are instructive in providing insight into the biology of hearing (fig. 3).
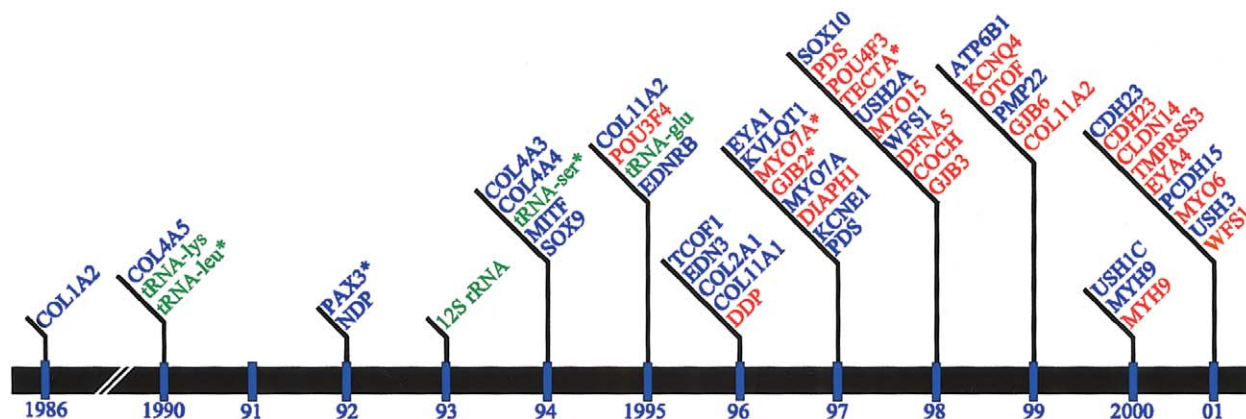
Figure 1   Timeline indicating the years in which genes were identified as causing deafness. Genes are listed in chronological order within the year in which mutations were first identified as causing nonsyndromic (*red*), syndromic (*blue*), or mitochondrial (*green*) deafness. An asterisk (*) indicates that mutations in a particular gene cause multiple forms of deafness in that classification (for example, *MYO7A*, which is colored red and has an asterisk, causes both dominant and recessive nonsyndromic deafness). See table 1 for disorders associated with each gene.

Hair-Cell Structure

The intricate nature of the sensory epithelium and its highly organized stereocilia necessitates that a precise structure be maintained to ensure proper function. This is supported by the number of deafness-associated mutations in genes encoding structural proteins found in hair cells. Two unconventional myosin genes, *MYO7A* (MIM 276903) and *MYO15* (MIM 602666), have been shown to play a critical role in the structural integrity of the stereocilia (table 1) (reviewed by Friedman et al. [1999]). In addition to the important function of *MYO7A* in the inner ear, as evidenced by its etiology in DFNA11 (MIM 601317) and DFNB2 (MIM 600060]), its involvement in Usher syndrome type 1B (USH1B [MIM 276903) demonstrates that similar macromolecular interactions are required for proper function in both the ear and eye. Also, the human orthologs for the genes mutated in the mouse waltzer (*Cdh23;* Mouse Genome Informatics [MGI] accession number 1890219) and Ames waltzer (*Pcdh15;* MGI accession number 1891428) have recently been identified in persons with Usher syndrome type 1D (USH1D [MIM 601067]) (Bolz et al. 2001; Bork et al. 2001) and Usher syndrome type 1F (USH1F [MIM 605514]) (Ahmed et al. 2001; Alagramam et al. 2001), respectively. Another myosin gene, *MYO6* (MIM 600970), found to result in the disorganization and fusion of stereocilia in Snell's waltzer mouse when defective (Self et al. 1999; Melchionda et al. 2001), accounts for nonsyndromic autosomal dominant hearing loss in an Italian family (Melchionda et al. 2001). Though the predicted role of *MYO6* in anchoring the stereocilia is crucial in the ear, a lack of phenotype in the eye demonstrates that this function is not necessary for vision.

Extracellular Matrix

Comparable to the fundamental role of structural proteins in the proper functioning of the stereocilia, the importance of extracellular matrix genes to other structures in the ear is illustrated by mutations in these genes that affect hearing (table 1). Several collagens are important for integrity in many organ systems, and the inner ear is no exception (table 1). Similarly, disruption of usherin (MIM 276901), a laminin homolog and part of the extracellular matrix in the cochlea and Buchs membrane of the eye, results in Usher syndrome type 2A (USH2A [MIM 276901]) (Eudy et al. 1998). DFNA9 (MIM 601369), a dominant nonsyndromic deafness disorder with vestibular pathology, is caused by mutations in *COCH* (MIM 603196), which encodes a secreted protein (Robertson et al. 1998). The presence of the mutant protein causes a loss of cells in the spiral ligament and limbus and the accumulation of acidophilic deposits in the nerve channels and supporting tissues of the organ of Corti, perhaps leading to compression or blockage of the cochlear nerve. The importance of the tectorial membrane, which is composed of an extracellular matrix, in the conduction of sound is supported by the findings that mutations in *TECTA* (MIM 602574), which codes for the tectorial membrane protein α-tectorin, are etiologic for both the dominant DFNA8/12 (MIM 601543, MIM 601842) (Verhoeven et al. 1998) and recessive DFNB21 (MIM 603629) (Mustapha et al. 1999) nonsyndromic deafness disorders.

Ion Homeostasis

The primary organization of compartmentalization and ionic balance of fluids in the ear has been highlighted
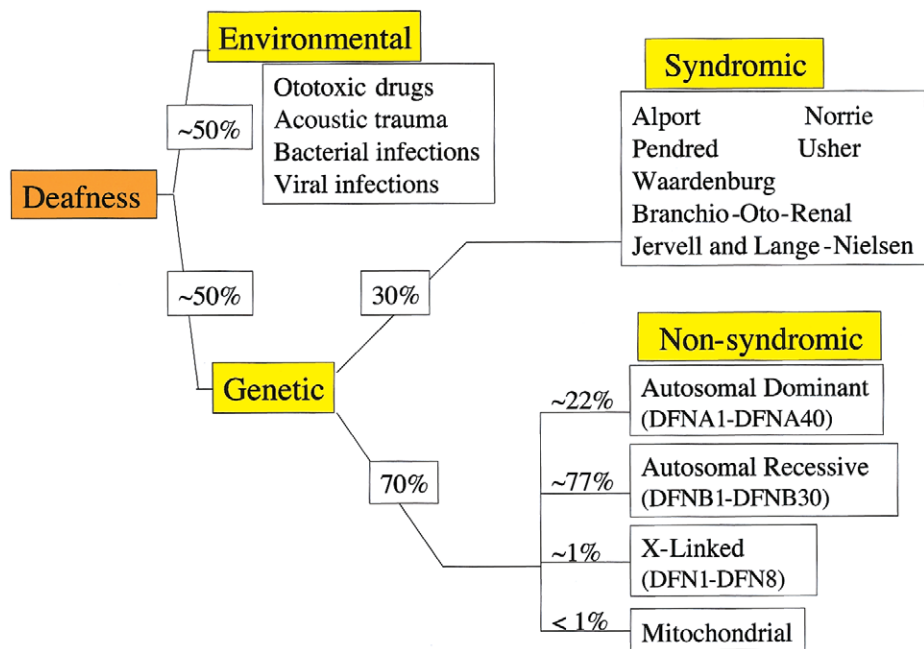
Figure 2 Classification of etiologies of deafness. Some examples of environmental causes of deafness and of more-common forms of syndromic deafness disorders are listed.

by the number of gap junctions and ion channels found to control critical transport of different molecules. Mutations in the gap junction subunits, connexins, are etiologic in several types of nonsyndromic deafness, with *GJB2* (encoding connexin 26 [MIM 121011]) being responsible for as much as 50% of profound congenital nonsyndromic recessive deafness in some populations (Rabionet et al. 2000). Several potassium channels, including *KCNQ4* (MIM 603537) and *KCNE1* (MIM 176261), are also crucial because of their role in K$^+$ recycling (reviewed by Steel [1999]). With the ion flux created by the aforementioned proteins, it is critical to keep inner ear fluids separate to maintain a resting potential. The discovery of pathogenic mutations in *CLDN14* (MIM 605608) in DFNB29 (MIM 605608) identified a tight junction protein involved in compartmentalization of endolymph (Wilcox et al. 2001).

Transcription Factors

As with other biological pathways, transcription factors are essential in hearing, and defects in these proteins help to elucidate critical components in this process. One pathway has been partially defined by the discovery of interactions between *MITF* (MIM 156845), *PAX3* (MIM 193500), and *SOX10* (MIM 602229), which have been found to be defective in different types of Waardenburg syndromes (types I [MIM 193510], II [MIM 193500], III [MIM 148820], and IV [MIM 277580]). *MITF* is known to be a key player in the regulation of melanocyte de-

velopment which, when interrupted, disrupts pigmentation as well as hearing function (Tachibana et al. 1996). It has since been discovered that *SOX10* and *PAX3* synergistically transactivate *MITF* and that pathogenic mutations in *SOX10* or *PAX3* disrupt their binding to and induction of the *MITF* promoter (Bondurand et al. 2000; Potterf et al. 2000).

Another family of transcription factors, the *EYA* genes, is critical in embryonic development. Although it has been known that branchio-oto-renal (BOR [MIM 113650]) and branchio-otic (BO [MIM 602588]) syndromes are allelic disorders resulting from mutations in *EYA1* (MIM 601653) (Abdelhak et al. 1997; Vincent et al. 1997), it has just recently been discovered that DFNA10 (MIM 601316) is due to mutations in *EYA4* (MIM 603550), which is predicted to function in the mature organ of Corti (Wayne et al. 2001). The absence of syndromic features associated with DFNA10 is intriguing and is suggestive of redundancy during embryogenesis or of various functions affected differentially by known mutations.

Miscellaneous

Some proteins associated with hearing loss do not fit into any summary categories and may represent the first members of new groups of proteins whose importance is only now being appreciated. Mutations in a novel serine protease gene, *TMPRSS3* (MIM 605511), were found in DFNB8/10 (MIM 601072 and MIM 605316)

Table 1

Chronological List of Deafness Genes Identified Since 1986

Number and Gene	Map Position	Type of Hearing Loss[a]	Disorder	Date First Reported	Reference
1. *COL1A2* (MIM 120160)	7q22.1	SHL	Osteogenesis imperfecta (MIM 166200)	July 1986	Sykes et al. 1986
2. *COL4A5* (MIM 303630)	Xq22	SHL	Alport syndrome (MIM 104200 and MIM 203780)	June 1990	Barker et al. 1990
3. *tRNA-leu* (MIM 590050)	Mitochondrial	SHL	Myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS [MIM 540000])	December 1990	Goto et al. 1990
			Diabetes mellitis and deafness (MIM 520000)	August 1992	van den Ouweland et al. 1992
4. *tRNA-lys* (MIM 590060)	Mitochondrial	SHL	Myoclonic epilepsy and ragged-red fiber disease (MERRF [MIM 545000])	June 1990	Shoffner et al. 1990
5. *PAX3*	2q35	SHL	Waardenburg syndrome type I	February 1992	Tassabehji et al. 1992
			Waardenburg syndrome types I and III	March 1993	Hoth et al. 1993
6. *NDP* (MIM 310660)	Xp11.3	SHL	Norrie disease (MIM 310600)	June 1992	Berger et al. 1992
				June 1992	Chen et al. 1992
7. *12S rRNA* (MIM 561000)	Mitochondrial	NSHL	Mitochondrial deafness (MIM 221745)	July 1993	Prezant et al. 1993
8. *COL4A3* (MIM 120070)	2q36-q37	SHL	Alport syndrome	September 1994	Mochizuki et al. 1994
9. *COL4A4* (MIM 120131)	2q36-q37	SHL	Alport syndrome	September 1994	Mochizuki et al. 1994
10. *tRNA-ser* (MIM 590080)	Mitochondrial	NSHL + SHL	Sensorineural deafness (MIM 590080)	October 1994	Reid et al. 1994
			Progressive myoclonic epilepsy, ataxia, and hearing loss (MIM 590080)	August 1995	Tiranti et al. 1995
			Palmoplantar keratoderma and deafness (MIM 590080)	January 1998	Sevior et al. 1998
11. *MITF*	3p14.1-p12.3	SHL	Waardenburg syndrome type II	November 1994	Tassabehji et al. 1994
12. *SOX9* (MIM 114290)	17q24.3-q25.1	SHL	Campomelic dysplasia (MIM 114290)	December 1994	Foster et al. 1994
13. *COL11A2*	6p21.3	NSHL + SHL	Stickler syndrome (STL2 [MIM 604841])	February 1995	Vikkula et al. 1995
			DFNA13 (MIM 601868)	December 1999	McGuirt et al. 1999
14. *POU3F4* (MIM 300039)	Xq21.1	NSHL	DFN3 (MIM 304400)	February 1995	de Kok et al. 1995
15. *tRNA-glu* (MIM 590025)	Mitochondrial	SHL	Maternally inherited diabetes and deafness (MIM 590025)	May 1995	Hao et al. 1995
16. *EDNRB* (MIM 131244)	13q22	SHL	Waardenburg syndrome type IV	December 1995	Attie et al. 1995
17. *TCOF1* (MIM 154500)	5q32-q33.1	SHL	Treacher Collins (MIM 154500)	February 1996	Dixon 1996
18. *EDN3* (MIM 131242)	20q13.2-q13.3	SHL	Waardenburg syndrome type IV	April 1996	Edery et al. 1996
19. *COL2A1* (MIM 120140)	12q13.11-q13.2	SHL	Stickler syndrome (STL1 [MIM 108300])	June 1996	Williams et al. 1996
20. *COL11A1* (MIM 120280)	1p21	SHL	Stickler syndrome (STL2)	September 1996	Richards et al. 1996
21. *DDP* (MIM 304700)	Xq22	NSHL	DFN1 (MIM 304700)	October 1996	Jin et al. 1996
22. *EYA1*	8q13.3	SHL	BOR syndrome	February 1997	Abdelhak et al. 1997
23. *KVLQT1* (MIM 192500)	11p15.5	SHL	Jervell and Lange-Nielsen Syndrome (JLNS1 [MIM 220400])	February 1997	Neyroud et al. 1997
24. *MYO7A*	11q12.3-q21	NSHL + SHL	DFNA11	March 1997	Liu et al. 1997*c*

			DFNB2	June 1997	Liu et al. 1997*b*
			DFNB2, USH1B	June 1997	Weil et al. 1997
25. *GJB2*	13q12	NSHL	DFNB1	May 1997	Kelsell et al. 1997
			DFNA3	May 1998	Denoyelle et al. 1998
26. *DIAPH1* (MIM 602121)	5q31	NSHL	DFNA1 (MIM 124900)	November 1997	Lynch et al. 1997
27. *KCNE1*	21q22.1-q22.2	SHL	Jervell and Lange-Nielsen Syndrome (JLNS2 [MIM 220400])	November 1997	Tyson et al. 1997
				November 1997	Schulze-Bahr et al. 1997
28. *PDS*	7q31; 7q21-34	NSHL + SHL	Pendred syndrome (MIM 274600)	December 1997	Everett et al. 1997
			DFNB4	March 1998	Li et al. 1998
29. *SOX10*	22q13	SHL	Waardenburg syndrome type IV	February 1998	Pingault et al. 1998
30. *POU4F3* (MIM 602460)	5q31	NSHL	DFNA15 (MIM 602459)	March 1998	Vahava et al. 1998
31. *TECTA*	11q22-q24	NSHL	DFNA8, DFNA12	May 1998	Verhoeven et al. 1998
			DFNB21	March 1999	Mustapha et al. 1999
32. *USH2A*	1q41	SHL	USH2A	June 1998	Eudy et al. 1998
33. *MYO15*	17p11.2	NSHL	DFNB3 (MIM 600136)	June 1998	Wang et al. 1998
34. *DFNA5* (MIM 600994)	7p15	NSHL	DFNA5 (MIM 600994)	October 1998	Van Laer et al. 1998
35. *COCH*	14q12-q13	NSHL	DFNA9	November 1998	Robertson et al. 1998
36. *GJB3* (MIM 603324)	1p34	NSHL	DFNA2	December 1998	Xia et al. 1998
37. *ATP6B1* (MIM 192132)	2cen-q13	SHL	Distal renal tubular acidosis associated with sensorineural deafness (MIM 267300)	January 1999	Karet et al. 1999
38. *KCNQ4*	1p34	NSHL	DFNA2	February 1999	Kubisch et al. 1999
39. *OTOF* (MIM 603681)	2p22-p23	NSHL	DFNB9 (MIM 601071)	April 1999	Yasunaga et al. 1999
40. *PMP22* (MIM 601097)	17p11.2	SHL	Charcot-Marie-Tooth disease (MIM 118220)	June 1999	Kovach et al. 1999
41. *GJB6* (MIM 604418)	13q12	NSHL	DFNA3	September 1999	Grifa et al. 1999
42. *USH1C* (MIM 605242)	11p15.1	SHL	Usher syndrome type 1C (USH1C [MIM 605242])	September 2000	Verpy et al. 2000
				September 2000	Bitner-Glindzicz et al. 2000
43. *MYH9*	22q13	NSHL + SHL	May-Hegglin (MIM 155100) and Fechtner (MIM 153640) syndromes	September 2000	The May-Hegglin/Fechtner Syndrome Consortium 2000
			DFNA17 (MIM 603622)	November 2000	Lalwani et al. 2000
44. *CDH23*	10q21-q22	NSHL + SHL	USH1D	January 2001	Bolz et al. 2001
			USH1D and DFNB12	January 2001	Bork et al. 2001
45. *CLDN14*	21q22	NSHL	DFNB29	January 2001	Wilcox et al. 2001
46. *TMPRSS3*	21q22.3	NSHL	DFNB8, DFNB10	January 2001	Scott et al. 2001
47. *EYA4*	6q22-q23	NSHL	DFNA10	February 2001	Wayne et al. 2001
48. *PCDH15* (MIM 605514)	10q21-22	SHL	USH1F	July 2001	Ahmed et al. 2001
				August 2001	Alagramam et al. 2001
49. *MYO6*	6q13	NSHL	DFNA22 (MIM 600970)	September 2001	Melchionda et al. 2001
50. *USH3*	3q21-q25	SHL	USH3	October 2001	Joensuu et al. 2001
		SHL	Wolfram syndrome	October 1998	Inoue et al. 1998
				December 1998	Strom et al. 1998
51. *WFS1*	4p16	NSHL	DFNA6/14	October 2001	Bespalova et al., in press

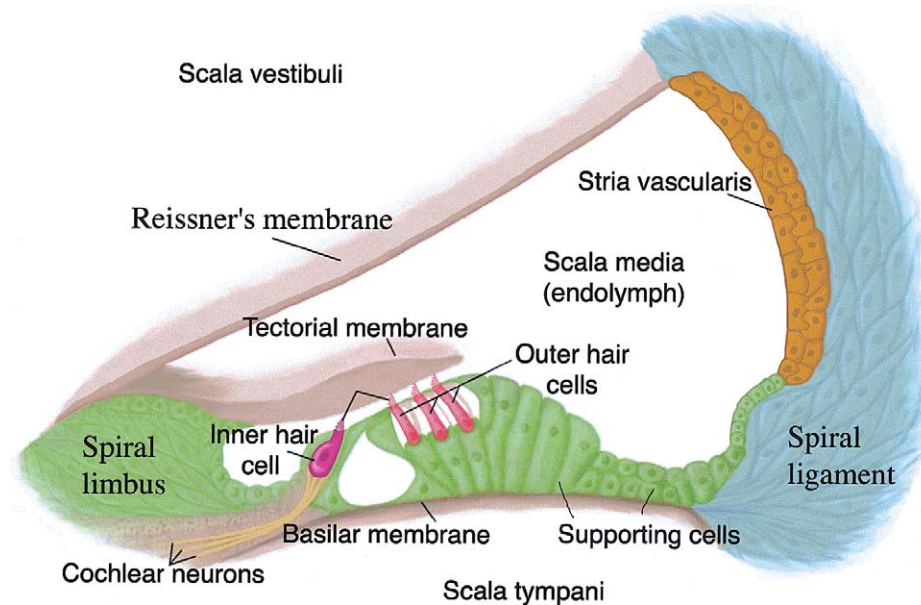[a] SHL = syndromic hearing loss; NSHL = nonsyndromic hearing loss.

Figure 3 Cross section of the cochlear duct, showing the major regions found within the cochlea. Selected genes and the regions in which they are expressed are as follows: endolymphatic duct: *PDS;* hair cells: *DIAPH1, POU4F3, MYO6, MYO7A, MYO15, KCNQ4, OTOF, USH1C, MYH9, CDH23,* and *CLDN14;* extracellular matrix: *USH2A;* Reissner's membrane: *MYH9* and *CDH23;* spiral ligament: *COCH, MYH9,* and *NDP;* spiral limbus: *COCH, GJB2, GJB3, GJB6,* and *ATP6B1* (interdental cells); stria vascularis: *NDP, KCNE1* (marginal cells), and *KVLQT1* (marginal cells); supporting cells: *GJB2, GJB3,* and *GJB6;* and tectorial membrane: *TECTA.* (Adapted with permission from Steel [1999].)

and were correlated with the allelic difference observed in the age at onset between DFNB8 and DFNB10 (Scott et al. 2001). *TMPRSS3* is the first example of a dysfunctional protease causing deafness, indicating that critical regulators of pathways in the inner ear are activated through proteolytic cleavage. Homozygous and compound heterozygous mutations in another novel gene, *USH3* (MIM 276902), have recently been shown to underlie Usher syndrome type 3 (USH3 [MIM 276902]) (Joensuu et al. 2001). *USH3* encodes a protein containing two predicted transmembrane domains with unknown function and is expressed in many tissues, including the retina (Joensuu et al. 2001). Mutations in another gene, *WFS1* (MIM 606201), responsible for Wolfram syndrome (MIM 606201), an autosomal recessive disorder characterized by diabetes mellitus, optic atrophy, and often, deafness, has recently been found to be responsible for the dominant nonsyndromic deafness disorder, DFNA6/14 (Bespalova et al., in press). *WFS1* encodes a protein, called "wolframin," containing nine putative transmembrane domains with unknown function (Bespalova et al., in press). Interestingly, it is not known why some *WFS1* mutations selectively affect low-frequency hearing (DFNA6/14), whereas other *WFS1* mutations affect higher frequencies, as in the hearing loss associated with Wolfram syndrome (Bespalova et al., in press).

Phenotypic Diversity

Gene discovery in the auditory system has provided many examples that illustrate that mutations in one gene may give rise to quite variable phenotypes. For example, mutations in a single gene can lead to both syndromic and nonsyndromic hearing loss (as is the case with *COL11A2* [MIM 120290], *MYH9* [MIM 160775], *MYO7A, PDS* [MIM 274600], *CDH23* [MIM 605516], and *WFS1* [MIM 606201]). Moreover, mutations in a single gene can cause both dominant and recessive forms of nonsyndromic hearing loss (e.g., *GJB2* for both DFNA3 [MIM 601544] and DFNB1 [MIM 220290]), and *TECTA* for DFNA8/12 and DFNB21). These examples of phenotypic diversity demonstrate how the type of mutation, the position of the mutation within the gene, and allelic combinations (i.e., compound heterozygosity) can affect the overall clinical presentation.

MYO7A *Mutations in DFNA11, DFNB2, and USH1B*

MYO7A mutations result in a range of human disease phenotypes. A single *MYO7A* mutation causes deafness in an autosomal dominant nonsyndromic form (DFNA11) (Liu et al. 1997*c*) and at least four mutations result in a recessive nonsyndromic form (DFNB2) (Liu et al. 1997*b;* Weil et al. 1997). Further, ≥41 mutations

cause an autosomal recessive syndromic form of deafness that is accompanied by retinitis pigmentosa (USH1B) (Weil et al. 1995; Weston et al. 1996; Adato et al. 1997; Levy et al. 1997; Liu et al. 1997a, 1998; Janecke et al. 1999). Although MYO7A genotype-phenotype correlations are, in general, difficult to synthesize coherently, it has been hypothesized that many of the recessive MYO7A mutations are pathogenic by loss of function (Liu et al. 1998; Janecke et al. 1999). In contrast, the DFNA11-associated MYO7A mutation is likely to have a dominant negative effect; all DFNA11 patients have a 9-bp deletion in exon 22, which encodes a coiled-coil domain important for homodimerization (Liu et al. 1997c). The precise mechanisms by which the majority of MYO7A mutations lead to hearing loss are not yet known, and the way in which mutations in the same gene result in both syndromic and isolated hearing impairment remains to be determined. The possibility that tissue-specific differences in the function of MYO7A may result in distinct mutations having variable effects in the eye but similar effects in the inner ear is under consideration (Liu et al. 1998).

CDH23 Mutations in DFNB12 and USH1D

CDH23 mutations cause recessive hearing loss in both nonsyndromic (DFNB12 [MIM 601386]) and syndromic (USH1D) forms. Interestingly, a correlation between mutation and phenotype seems to exist: six missense CDH23 mutations lead to amino acid substitutions and are found in families with DFNB12, whereas two nonsense and two splice-site mutations lead to truncated CDH23 protein and are found in families with typical and atypical USH1D (Bork et al. 2001).

GJB2 Mutations in DFNB1 and DFNA3

Mutations in GJB2 (encoding connexin 26), are pathogenic in both autosomal dominant (DFNA3) and autosomal recessive (DFNB1) forms of hearing loss (Kelsell et al. 1997; Denoyelle et al. 1998). More than 50 GJB2 mutations have been identified and account for as much as 50% of all congenital cases of nonsyndromic hearing impairment, with a high prevalence of three mutations (35delG, 167delT, and 235delC) in specific populations (white, Ashkenazi Jewish, and Asian, respectively) (Connexins and Deafness Homepage). The severity of hearing loss and the likelihood of progression are variable, even with a single mutation, complicating predictions of phenotype in the setting of genetic counseling.

PDS Mutations in DFNB4 and Pendred Syndrome

Mutations in PDS, encoding an anion transporter named "pendrin" which is proposed to function in endolymphatic fluid homeostasis (Everett et al. 1999), cause recessive hearing loss in both nonsyndromic (DFNB4 [MIM 600791]) and syndromic (Pendred syndrome [MIM 274600]) forms (Everett et al. 1997; Li et al. 1998). At least 47 different PDS mutations, most of which are specific to individual families, are associated with either DFNB4 or Pendred syndrome and are thought to adversely affect fluid homeostasis, resulting in the cochlear malformations and temporal bone anomalies that eventually lead to hearing loss (Campbell et al. 2001 and references therein). Mutations that abrogate ion transport in the chloride-iodide transport protein, pendrin, cause syndromic hearing loss in Pendred syndrome, whereas apparently less-severe mutations that decrease ion flow are responsible for isolated hearing loss in DFNB4 (Scott et al. 2000).

TECTA Mutations in DFNA8/12 and DFNB21

Mutations in TECTA, encoding α-tectorin, are responsible for nonsyndromic hearing loss in both dominant (DFNA8/12) (Verhoeven et al. 1998; Alloisio et al. 1999; Balciuniene et al. 1999) and recessive (DFNB21) (Mustapha et al. 1999) types. DFNB21-affected family members, who have prelingual severe-to-profound sensorineural deafness, harbor a splice-site mutation predicted to lead to a truncated α-tectorin protein. DFNA8/DNFA12-affected members, who demonstrate prelingual and stable midfrequency hearing loss, have missense mutations that replace conserved amino acid residues within the zona pellucida domain of α-tectorin (Verhoeven et al. 1998; Alloisio et al. 1999). Affected members of another family with DFNA12, who, interestingly, also have significant linkage to the DFNA2 locus (MIM 600101), show a later-onset progressive hearing loss and have a mutation in a different domain of α-tectorin, the zonadhesion/von Willebrand domain, resulting in replacement of a cysteine with a serine in one of the von Willebrand repeats (Balciuniene et al. 1999). One possible explanation for the observed spectrum of hearing phenotypes, ranging from prelingual to late-onset progressive in families with the dominant form of hearing loss, may lie in the position of the mutation in the protein (i.e., the particular domain affected). This may differentially alter the ability of α-tectorin to interact with certain molecules and may thus result in various degrees of improper assembly of the noncollagenous tectorial matrix (Balciuniene et al. 1999). Another fascinating possibility is that the difference in phenotypes is due to modification of TECTA by a gene at another locus (e.g., DFNA2) (Balciuniene et al. 1999).

Modifier Genes

Modifier genes influence the expression or function of other genes. Several modifier loci and their genes for hereditary hearing loss have been discovered in both

humans and mice. In the mouse, modifier genes have been identified as a result of divergent phenotypes attributed to the genetic background of various strains.

tub *and* moth1

Tubby mice are homozygous for an autosomal recessive mutation (*tub/tub* [MGI accession number 98868]) causing adult-onset insulin-resistance–associated obesity and early-onset cochlear and retinal degeneration (Ikeda et al. 1999). Obesity is observed in tubby mice after age 12 wk, although abnormal electroretinograms and auditory brain stem responses are detectable as early as age 3 wk (Ikeda et al. 1999). Although it is known that the *tub* gene encodes a transcription factor (Boggon et al. 1999), the exact mechanisms by which the *tub* allele leads to the tubby phenotypes have not been elucidated. A genetic modifier of tubby hearing, *moth1* (MGI accession number 1346024), can worsen or prevent the tubby hearing impairment, depending on the type of *moth1* allele and on whether one or both copies of the allele are present (Ikeda et al. 1999). A dominant *moth1* allele protects the tubby mouse against hearing loss in one strain (CAST/Ei.B6; *tub/tub*), whereas a recessive *moth1* allele worsens the deafness in a different tubby strain (C57BL/6; *tub/tub*) (Ikeda et al. 1999).

dfw *and* mdfw

Another example of a deafness modifier gene in mice is *mdfw* (modifier of deaf waddler [MGI accession number 1202391]), for which two different alleles have been identified (Noben-Trauth et al. 1997). Deaf waddler mice are homozygous for an autosomal recessive mutation (*dfw* [MGI accession number 105368]), exhibit highly unbalanced and uncontrolled movements by age 2 wk, and are profoundly deaf by age 3 wk as a result of progressive hair-cell degeneration (Lane 1987; Street et al. 1995; Noben-Trauth et al. 1997). *dfw* encodes an ATPase pump (*Atp2b2* [MGI accession number 105368]) that is required for maintenance of low cytosolic Ca^{2+} by pumping Ca^{2+} out of both auditory and vestibular hair cells (Kozel et al. 1998; Street et al. 1998). Interestingly, in one strain (CBy), heterozygotes for *dfw²ʲ* exhibit abnormal auditory brain stem responses (ABR) and age-dependent progressive hearing loss, whereas in another strain (CBy/CAST/Ei) only about one-quarter of *dfw²ʲ* heterozygotes displayed increased ABR thresholds (Noben-Trauth et al. 1997). This difference in penetrance of the hearing impairment in the two strains has been attributed to a naturally occurring modifier, *mdfw,* mapped to chromosome 10 (Noben-Trauth et al. 1997). The dominant CAST/Ei-derived *mdfw* allele protects *dfw* heterozygotes from hearing loss, whereas the recessive CBy-derived *mdfw* allele permits hearing loss in the *dfw* heterozygotes.

DFNB26 *and* DFNM1

Autosomal recessive, nonsyndromic, sensorineural hearing loss has been mapped to 4q31 in a large consanguineous Pakistani family and has been designated "DFNB26" (MIM 605428) (Riazuddin et al. 1999). Of interest, seven family members homozygous for the mutant DFNB26 haplotype were found to have normal hearing. A second linkage analysis identified a deafness modifier gene (*DFNM1* [MIM 605429]), mapped to 1q24, which is thought to suppress the DFNB26 deafness in these individuals. Identification of these two genes (*DFNB26* and *DFNM1*) will lead to an understanding of the interaction of their gene products and facilitate elucidation of the pathway that leads to the DFNB26 phenotype.

Mitochondrial Modifier Locus

A mouse model of hearing loss modified by a mitochondrial locus has been identified. A mitochondrial allele, causing presbycusis, or age-related hearing loss, has been shown to interact with a nuclear locus (*ahl* [MGI accession number 87972]) on mouse chromosome 10 (Avraham 2001). Mice with both copies of the A/J *ahl* allele were found to have more-severe hearing loss than mice with a single allele (Johnson et al. 2000).

The Future of Auditory Research

The past decade has witnessed impressive advancements in auditory research. With both the human and mouse genomes sequenced to near completion and the advent of gene chip technology, gene discovery and functional genomics in the auditory system will continue at a rapid pace. To this end, we are ever closer to an enhanced understanding of the hearing process, which will lead to increased availability of diagnostic and presymptomatic genetic testing options, early intervention, and disease-based treatments.

Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Connexins and Deafness Homepage, http://www.iro.es/deafness/

Hereditary Hearing Loss Homepage, http://www.uia.ac.be/dnalab/hhh/

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for genes: *12S rRNA* [MIM 561000], *ATP6B1* [MIM 192132], *CDH23* [MIM 605516], *CLDN14* [MIM 605608], *COCH* [MIM 603196], *COL11A1* [MIM 120280], *COL11A2* [MIM 120290], *COL1A2* [MIM 120160], *COL2A1* [MIM 120140], *COL4A3* [MIM 120070], *COL4A4* [MIM 120131],

COL4A5 [MIM 303630], *DDP* [MIM 304700], *DFNA5* [MIM 600994], *DIAPH1* [MIM 602121], *EDN3* [MIM 131242], *EDNRB* [MIM 131244], *EYA1* [MIM 601653], *EYA4* [MIM 603550], *GJB2* [MIM 121011], *GJB3* [MIM 603324], *GJB6* [MIM 604418], *KCNE1* [MIM 176261], *KCNQ4* [MIM 603537], *KVLQT1* [MIM 192500], *MITF* [MIM 156845], *MYH9* [MIM 160775], *MYO15* [MIM 602666], *MYO6* [MIM 600970], *MYO7A* [MIM 276903], *NDP* [MIM 310600], *OTOF* [MIM 603681], *PAX3* [MIM 193500], *PCDH15* [MIM 605514], *PDS* [MIM 274600], *PMP22* [MIM 601097], *POU3F4* [MIM 300039], *POU4F3* [MIM 602460], *SOX10* [MIM 602229], *SOX9* [MIM 114290], *TCOF1* [MIM 154500], *TECTA* [MIM 602574], *TMPRSS3* [MIM 605511], *tRNA-glu* [MIM 590025], *tRNA-leu* [MIM 590050], *tRNA-lys* [MIM 590060], *tRNA-ser* [MIM 590080], *USH1C* [MIM 605242], *USH2A* [MIM 276901], *USH3* [MIM 276902], *WFS1* [MIM 606201]; nonsyndromic deafness disorders: DFNA1 [MIM 124900], DFNA2 [MIM 600101], DFNA3 [MIM 601544], DFNA5 [MIM 600994], DFNA8 [MIM 601543], DFNA9 [MIM 601369], DFNA10 [MIM 601316], DFNA11 [MIM 601317], DFNA12 [MIM 601842], DFNA13 [MIM 601868], DFNA15 [MIM 602459], DFNA17 [MIM 603622], DFNA22 [MIM 600970], DFNB1 [MIM 220290], DFNB2 [MIM 600060], DFNB3 [MIM 600316], DFNB4 [MIM 600791], DFNB8 [MIM 601072], DFNB9 [MIM 601071], DFNB10 [MIM 605316], DFNB12 [MIM 601386], DFNB21 [MIM 603629], DFNB29 [MIM 605608], DFN1 [MIM 304700], DFN3 [MIM 304400], sensorineural deafness [MIM 590080]; and syndromic deafness disorders: Alport syndrome [MIM 104200, 203780], BO syndrome [MIM 602588], BOR syndrome [MIM 113650], campomelic dysplasia [MIM 114290], Charcot-Marie-Tooth disease [MIM 118220], diabetes mellitus and deafness [MIM 520000], distal renal tubular acidosis associated with sensorineural deafness [MIM 267300], Fechtner syndrome [MIM 153640] , JLNS1 [MIM 220400], JLNS2 [MIM 220400], maternally inherited diabetes and deafness [MIM 590025], May-Hegglin syndrome [MIM 155100], mitochondrial deafness [12S rRNA] [MIM 221745], MERRF [MIM 545000], MELAS [MIM 540000], Norrie disease [MIM 310600], osteogenesis imperfecta [MIM 166200], palmoplantar keratoderma and deafness [MIM 590080], Pendred syndrome [MIM 274600], progressive myoclonic epilepsy, ataxia and hearing loss [MIM 590080], STL1 [MIM 108300], STL2 [MIM 604841], Treacher Collins [MIM 154500], USH1B [MIM 276903], USH1C [MIM 605242], USH1D [MIM 601067], USH1F [MIM 605514], USH2A [MIM 276901], USH3 [MIM 276902], Waardenburg syndrome type I [MIM 193500], Waardenburg syndrome type II [MIM 193510], Waardenburg syndrome type III [MIM 148820], Waardenburg syndrome type IV [MIM 277580], and Wolfram syndrome [MIM 606201])

Mouse Genome Informatics (MGI), http://www.informatics .jax.org/ (for *ahl* [MGI accession number 87972], *Atp2b2* [MGI accession number 105368], *cdh23* [MGI accession number 1890219], *mdfw* [MGI accession number 1202391], *moth1* [MGI accession number 1346024],

Pcdh15 [MGI accession number 1891428], and *tub* [MGI accession number 98868])

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