Letters to the Editor

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A New Locus for Nonsyndromic Hereditary Hearing Impairment, DFNA17, Maps to Chromosome 22 and Represents a Gene for Cochleosaccular Degeneration

To the Editor:

Over the past several decades, the proportion of the population with hearing impairment attributed to genetic factors has increased as modern medicine has become both more adept at controlling maternal and pediatric infections and better educated about the iatrogenic causes of hearing impairment. At present, as much as one-half of all congenital hearing impairment is considered to have an underlying genetic component (Arnos et al. 1992; Brookhouser 1994; Cohen and Gorlin 1995; Fraser 1995), making hereditary hearing impairment (HHI) one of the most common inherited human deficits.

Cochleosaccular degeneration (CSD) is the most common histopathologic finding in cases of profound congenital HHI. It is estimated to occur in ~70% of cases (Ormerod 1960; Bergstrom 1980; Gulya and Juhlin 1992). CSD was described first by Scheibe in 1892 and is more commonly known as "Scheibe dysplasia." It affects structures that are derived from the pars inferior of the otocyst. Thus, the membranous cochlea and saccule are affected, but the osseous labyrinth, the membranous utricle, and the semicircular canals are normal.

Because there is no clinically available test to diagnose CSD, postmortem histologic examination of the temporal bone is required. The histopathology of CSD is characterized by a loss of neurosensory hair cells and their supporting cells in the cochleae and sacculae. Cochlear and vestibular nerve atrophy varies and ranges from none to severe. Reissner's membrane and the saccular wall are typically collapsed. The stria vascularis is atrophic with inclusion of abnormal periodic acid-Schiff–positive material. The pathology in the cochlea is typically most severe in the basal turn, with progressive preservation of normal architecture toward the apex. Occasionally, endolymphatic hydrops is present, indicating a disturbance in ionic and osmotic regulation.

Although CSD is relatively common, its molecular pathogenesis remains to be deciphered. Genetic analysis of families with HHI associated with CSD represents a potential route toward identification of genes responsible for intact and functional membranous structures within the cochlea. First, histopathology offers physical evidence of the specific tissues that the disease gene affects. Second, it may provide clues to the functions of the mutant gene. Finally, animals with similar histopathology serve as excellent models for CSD-associated hearing impairment. Previously, no nonsyndromic HHI loci had been associated with CSD, and, with the exception of the DFNA9 locus, there were no nonsyndromic HHI loci that had been both genetically mapped and histologically characterized (Manolis et al. 1996).

Here we present the first reported mapping of a gene responsible for CSD. The family transmitting this mutant gene is a previously described, multigenerational, nonconsanguineous American family with autosomal dominant HHI (Lalwani et al. 1997).

The family studied was identified through the temporal-bone database at the House Ear Institute in Los Angeles. Institutional-review-board approval was obtained for the human-research protocols from the House Ear Institute and the National Institute on Deafness and from Other Communication Disorders at the National Institutes of Health. Eighteen members of the family were enrolled in the study, of whom eight are affected. Extensive medical histories were obtained, and audiological evaluations were performed as described elsewhere (Lalwani et al. 1997). In addition, temporal bones and the brain stem, removed at autopsy from the proband, were analyzed as described elsewhere (Lalwani et al. 1997).

The family has been described in detail previously (Lalwani et al. 1997). In summary, the affected family members exhibit nonsyndromic HHI with an autosomal dominant mode of transmission; there was no pigmentary abnormality in any of the affected individuals. Initially, the hearing impairment would begin at age 10 years and would involve only the high frequencies; by the 3d decade of life, affected family members had moderate to severe deafness. Histologic examination of the proband's temporal bone exhibited classic CSD, with degeneration of the organ of Corti, the saccular epithelium, and the stria vascularis. In addition, there was

asymptomatic loss of neurons and gliosis in the inferior olivary nucleus.

Genomic DNA was extracted from whole blood by standard phenol extraction. Samples were quantified by spectrophotometry and were diluted to 25 ng/μl, for amplification by PCR. A 10-cM genome scan was produced with the ABI Prism Linkage Mapping Set, version 1.0 (PE Applied Biosystems), consisting of fluorescently labeled markers detecting microsatellite polymorphisms (Weber and May 1989; Reed et al. 1994). Fine mapping was accomplished with fluorescently labeled MapPairs from Research Genetics.

PCR used 50 ng of genomic DNA in a 10-μl reaction. The final reaction consisted of 1 × PCR Perkin-Elmer buffer; 2 pmol of fluorescently labeled forward primer; 2 pmol of reverse primer; 50 μM each of dCTP, dGTP, dTTP, and dATP; 2.0 mM $MgCl_2$; and 0.25 U of Ampli*Taq* Gold DNA Polymerase (PE Applied Biosystems). Reactions were started, at 95°C for 12 min, to activate the polymerase. Thirty-four cycles of amplification were completed in the following protocol: 94°C for 45 s, 57°C for 45 s, and 72°C for 60 s. Samples were maintained at 72°C for 10 min, for extension. Products were resolved on 4.25% denaturing polyacrylamide gels (6 M urea) and were visualized on a 377 prism (PE Applied Biosystems).

The FASTLINK program package enabled calculation of two-point and multipoint LOD scores over the entire genome (Cottingham et al. 1993; Schäffer et al. 1994). A dominant mode of inheritance with complete penetrance was assumed. A phenocopy rate of 0.1% was assumed, since this is the incidence of congenital hearing impairment in the United States. The phenotype of individuals <10 years old (V:1 and V:3 are 4 and 8 years old, respectively) was assumed to be unknown, since hearing loss begins at this age in this family.

Previous SIMLINK analysis had shown that the family could generate a maximum LOD score of 4.033, with a mean ± SD of 2.872 ± 0.036 (Boehnke 1986; Lalwani et al. 1997). Genomic scanning at 10-cM intervals identified on chromosome 22 a region with a LOD score >3.0 and exclusion of the remainder of the genome; fine mapping of the region by means of eight additional markers in the linked region was performed. A maximum LOD score of 3.98 was obtained at D22S283 (table 1). Haplotypes were then constructed to determine the critical recombination events (fig. 1). The centromeric recombination occurs in individual IV:6, between markers D22S689 and D22S280. The telomeric recombination occurs between markers D22S282 and D22S444 in several individuals (III-4, IV-7, IV-8, and IV-11). These critical crossovers define a linked region spanning a 16.89–22.97-cM interval, which includes D22S280 near the centromere and D22S282 near the telomere. This region corresponds to the cytogenetic bands 22q12.2-22q13.3.

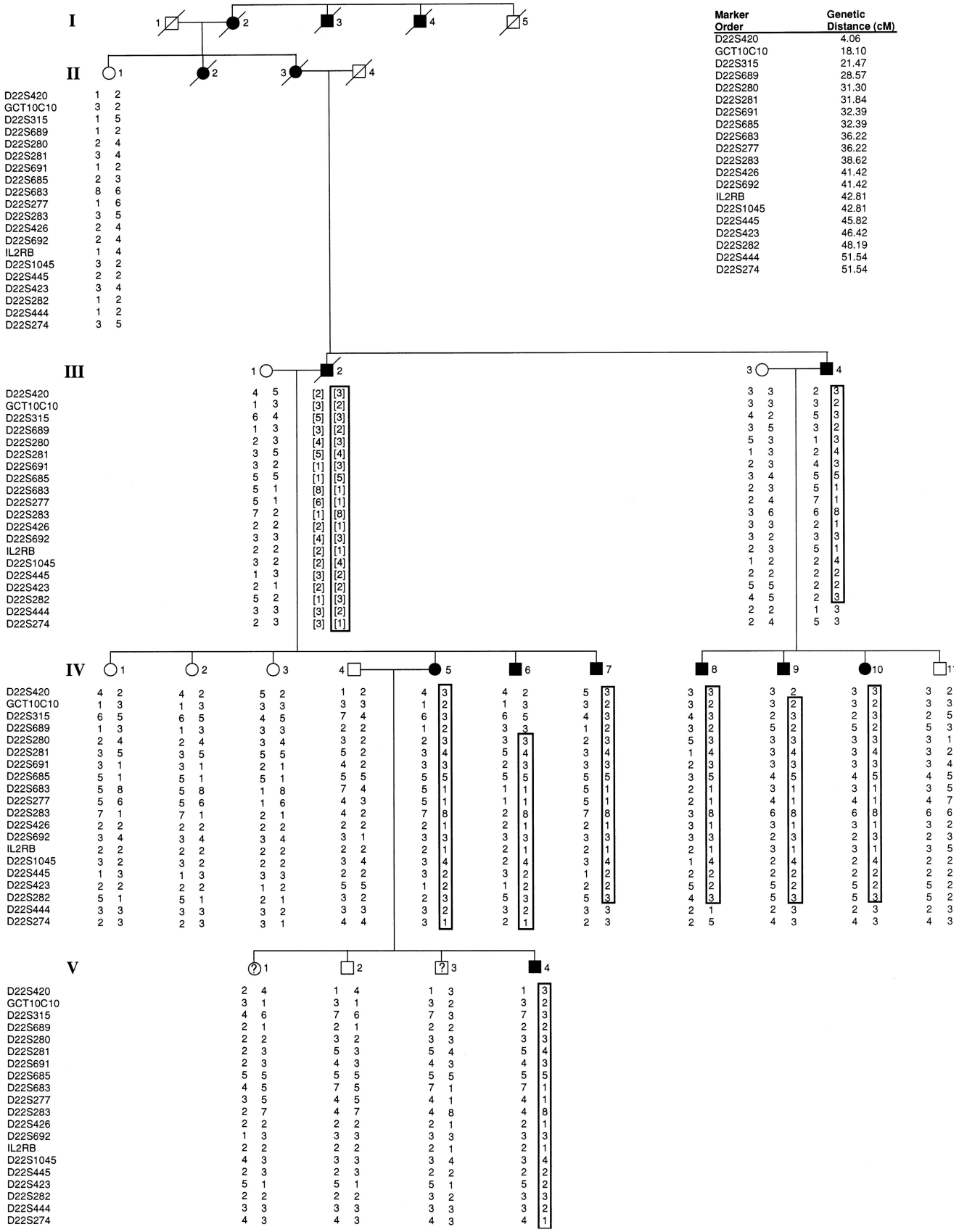
Table 1

Two-Point LOD Scores Calculated across Linkage Region, with Relative Genetic Distances, According to the Marshfield Medical Research Foundation Genetic Map

Marker	LOD Score at θ = 0	.1	.2	Genetic Distance (cM)
D22S420	−∞	.93	.86	4.06
GCT10C10	−∞	1.86	1.57	18.10
D22S315	−∞	1.90	1.47	21.47
D22S689	−∞	2.04	1.76	28.57
D22S280	3.22	2.55	1.84	31.30
D22S281	3.22	2.93	2.39	31.84
D22S691	2.87	2.26	1.59	32.39
D22S685	2.16	1.72	1.26	32.39
D22S683	3.53	2.81	2.03	36.22
D22S277	3.52	2.89	2.21	36.22
D22S283	3.98	3.26	2.49	38.62
D22S426	3.78	3.06	2.28	41.42
D22S692	1.91	1.48	1.02	41.42
IL2RB	3.30	2.94	2.39	42.81
D22S1045	3.33	2.65	1.92	42.81
D22S445	2.06	1.79	1.44	45.82
D22S423	1.14	.88	.63	46.42
D22S282	2.99	2.27	1.50	48.19
D22S444	−∞	−1.44	−.30	51.54
D22S274	−∞	−1.57	−.51	51.54

Two individuals, V:1 and V:3, who are <10 years old, were classified as unknown and therefore did not contribute to the LOD score. Individual V:1 does not carry the disease haplotype, and her audiogram is completely normal. Her brother, V:3, is 8 years old and currently has a normal audiogram. However, he carries a portion of the disease haplotype. If he does become affected as he ages, the linked region will be defined by flanking markers D22S689 and D22S423, encompassing a 14.52–17.85-cM region. On the other hand, if he remains unaffected, the linked region will be narrowed to 1.77–5.72 cM, flanked by markers D22S445 and D22S444.

Remarkable progress has been made in the identification of genes responsible for nonsyndromic HHI. To date, the locations of 18 autosomal dominant, 20 autosomal recessive, and 8 X-linked hearing-loss genes have been identified (Hereditary Hearing Loss). Here, we report identification of DFNA17, a new locus for autosomal dominant nonsyndromic HHI, on chromosome 22q12.2-q13.3. Typically, autosomal dominant HHI is characterized by postlingual onset of hearing loss, in contrast to the prelingual onset of deafness observed in autosomal recessive cases. DFNA17 is characterized by high-frequency hearing loss that begins at age 10 years, progresses to severe deafness by the 3d decade, and involves all frequencies. This auditory phenotype is



Marker Order	Genetic Distance (cM)
D22S420	4.06
GCT10C10	18.10
D22S315	21.47
D22S689	28.57
D22S280	31.30
D22S281	31.84
D22S691	32.39
D22S685	32.39
D22S683	36.22
D22S277	36.22
D22S283	38.62
D22S426	41.42
D22S692	41.42
IL2RB	42.81
D22S1045	42.81
D22S445	45.82
D22S423	46.42
D22S282	48.19
D22S444	51.54
D22S274	51.54

	I	II	III 1	III 2	III 3	III 4
D22S420	1 2	1 2	4 5	[2] [3]	3 3	2 3
GCT10C10		3 2	1 3	[3] [2]	3 3	3 2
D22S315		1 5	6 4	[5] [3]	4 2	5 3
D22S689		1 2	1 3	[3] [2]	3 5	3 2
D22S280		2 4	2 3	[4] [3]	5 3	1 3
D22S281		3 4	3 5	[5] [4]	1 3	2 4
D22S691		1 2	3 2	[1] [3]	2 3	4 3
D22S685		2 3	5 5	[1] [5]	3 4	5 5
D22S683		8 6	5 1	[8] [1]	2 3	5 1
D22S277		1 6	5 1	[6] [1]	2 4	7 1
D22S283		3 5	7 2	[1] [8]	3 6	6 8
D22S426		2 4	2 2	[2] [1]	3 3	2 1
D22S692		2 4	3 3	[4] [3]	3 2	3 3
IL2RB		1 4	2 2	[2] [1]	2 3	5 1
D22S1045		3 2	3 2	[2] [4]	1 2	2 4
D22S445		2 2	1 3	[3] [2]	2 2	2 2
D22S423		3 4	2 1	[2] [2]	5 5	2 2
D22S282		1 2	5 2	[1] [3]	4 5	2 3
D22S444		1 2	3 3	[3] [2]	2 2	1 3
D22S274		3 5	2 3	[3] [1]	2 4	5 3

	IV 1	IV 2	IV 3	IV 4	IV 5	IV 6	IV 7	IV 8	IV 9	IV 10	IV 11
D22S420	4 2	4 2	5 2	1 2	4 [3]	4 2	5 [3]	3 [3]	3 2	3 [3]	3 2
GCT10C10	1 3	1 3	3 3	3 3	1 [2]	1 3	3 2	3 2	3 2	3 2	3 3
D22S315	6 5	6 5	4 5	7 4	6 [3]	6 5	4 3	4 3	2 3	2 3	2 5
D22S689	1 3	1 3	3 3	2 2	1 [2]	3 3	1 2	3 2	5 2	5 2	5 3
D22S280	2 4	2 4	3 4	3 2	2 [3]	3 [3]	2 3	5 3	3 3	3 3	3 1
D22S281	3 5	3 5	5 5	5 2	3 [4]	5 4	3 4	1 4	3 4	3 4	3 2
D22S691	3 1	3 1	2 1	4 2	3 [3]	2 3	3 3	2 3	3 3	3 3	3 4
D22S685	5 1	5 1	5 1	5 5	5 [5]	5 5	5 5	3 5	4 5	4 5	4 5
D22S683	5 8	5 8	1 8	7 4	5 [1]	1 1	5 1	2 1	3 1	3 1	3 5
D22S277	5 6	5 6	1 6	4 3	5 [1]	1 1	5 1	2 1	4 1	4 1	4 7
D22S283	7 1	7 1	2 1	4 2	7 [8]	2 8	7 8	3 8	6 8	6 8	6 6
D22S426	2 2	2 2	2 2	2 2	2 [1]	2 1	2 1	3 1	3 1	3 1	3 2
D22S692	3 4	3 4	3 4	3 1	3 [3]	3 3	3 3	3 3	2 3	2 3	2 3
IL2RB	2 2	2 2	2 2	2 2	2 [1]	2 1	2 1	2 1	3 1	3 1	3 5
D22S1045	3 2	3 2	2 2	3 4	3 [4]	2 4	3 4	1 4	2 4	2 4	2 2
D22S445	1 3	1 3	3 3	2 2	3 [2]	3 2	1 2	2 2	2 2	2 2	2 2
D22S423	2 2	2 2	1 2	5 5	1 [2]	1 2	2 2	5 2	5 2	5 2	5 2
D22S282	5 1	5 1	2 1	3 2	2 [3]	5 3	5 3	4 3	5 3	5 3	5 2
D22S444	3 3	3 3	3 2	3 3	3 [2]	3 2	3 3	2 1	2 3	2 3	2 3
D22S274	2 3	2 3	3 1	4 4	3 [1]	2 1	2 3	2 5	4 3	4 3	4 3

	V 1	V 2	V 3	V 4
D22S420	2 4	1 4	1 3	1 [3]
GCT10C10	3 1	3 1	3 2	3 [2]
D22S315	4 6	7 6	7 3	7 [3]
D22S689	2 1	2 1	2 2	2 [2]
D22S280	2 2	3 2	3 3	3 [3]
D22S281	2 3	5 3	5 4	5 [4]
D22S691	2 3	4 3	4 3	4 [3]
D22S685	5 5	5 5	5 5	5 [5]
D22S683	4 5	7 5	7 1	7 [1]
D22S277	3 5	4 5	4 1	4 [1]
D22S283	2 7	4 7	4 8	4 [8]
D22S426	2 2	2 2	2 1	2 [1]
D22S692	1 3	3 3	3 3	3 [3]
IL2RB	2 2	2 2	2 1	2 [1]
D22S1045	4 3	3 3	3 4	3 [4]
D22S445	2 3	2 3	2 2	2 [2]
D22S423	5 1	5 1	5 1	5 [2]
D22S282	2 2	2 2	3 2	3 [3]
D22S444	3 3	3 3	3 3	3 [2]
D22S274	4 3	4 3	4 3	4 [1]

Figure 1 Haplotypes of chromosome 22. Haplotypes for individual III:2, the proband, are inferred from the haplotypes of his children and wife. The disease haplotypes are boxed.

also shared by other previously mapped autosomal dominant nonsyndromic loci, including DFNA2, DFNA5, DFNA7, and DFNA9. High-frequency hearing loss that progresses to involve all frequencies is typical of presbycusis, or hearing loss associated with aging. Considered the most common form of hearing impairment, age-associated hearing impairment is thought to have a multifactorial etiology, with heredity being an important contributing factor. Therefore, the gene responsible for DFNA17, as well as other nonsyndromic HHI genes associated with progressive hearing loss, may provide critical insights into an understanding of the molecular pathophysiology of presbycusis.

The genes responsible for hearing impairment, at seven of the autosomal dominant nonsyndromic HHI loci, have been identified during the past 2 years (Lalwani and Castelein 1999). Mutations in an unconventional myosin gene, myosin VIIA, have been demonstrated to be responsible for DFNA11 (Liu et al. 1997). In the same year, mutations in the diaphanous gene were shown to be the pathogenic cause of DFNA1 (Lynch et al. 1997). In the first 6 mo of 1998, mutations in connexin 26, TECTA, and POU4F3 were found to be responsible for DFNA3, DFNA8/12, and DFNA15, respectively (Denoyelle et al. 1998; Vahava et al. 1998; Verhoeven et al. 1998). These genes have a wide variety of functions, including intercellular communication via gap-junction formation by connexin 26, regulation of actin polymerization by diaphanous-gene, transcription regulation by POU4F3, tectorial membrane constitution by TECTA, and, finally, anchoring of the actin cytoskeleton by myosin VIIA. The wide range of functions subserved by the DFNA genes reflects the heterogeneity of genes involved in nonsyndromic deafness (DFN).

Although the pace of the mapping and identification of mutated genes that cause nonsyndromic HHI has been rapid, their biologic role in the determination of cochlear structure and function is largely unknown. The absence of temporal-bone histologic data from families that have been used for mapping studies has hindered our understanding of the effects of the mutant hearing genes. The DFNA17 family was identified by histologic examination of the temporal bone of the proband, unlike most families with HHI, who are identified initially by clinical symptoms. Hearing impairment in the DFNA17 family is associated with CSD, considered to be the most common cause of profound congenital hearing impairment, accounting for 70% of cases with HHI. DFNA17 represents the first nonsyndromic gene for CSD. However, CSD is likely genetically heterogeneous, because a variety of clinical forms of HHI can lead to the common histopathologic manifestation. DFNA9 is the only other DFN locus for which the human temporal-bone histopathology has been reported. Affected individuals in this family exhibit mucopolysaccharide depositions in the neural channels of the inner ear (Khetarpal et al. 1991; Khetarpal 1993), and the gene for hearing impairment in this family maps to 14q12-13 (Manolis et al. 1996).

DFNA17 maps to a relatively large genetic region of 16.89–22.97 cM, which is typical for mapping studies that comprise families similar in size to the DFNA17 family. Unfortunately, this region is too large for positional cloning. Alternative approaches to identification of the mutated gene include investigation of cloned genes in the linked region and investigation of mouse models of deafness mapped to syntenic regions. There are many expressed sequence tags and genes that have been mapped to 22q12.2-13.3 and that thus represent potential candidate genes for DFNA17 (Science/The Human Gene Map). The history of the search for hearing-impairment genes has demonstrated that it is difficult to predict a candidate gene on the basis of its known or putative function (e.g., PDS, a putative sulfate-transporter gene, has been found to be associated with hearing impairment). Therefore, it is difficult to select, for mutation analysis, a candidate gene expressed in the DFNA17 region.

A sample of the genes expressed in the linked region includes those for metalloproteinase inhibitor 3 precursors, sodium/glucose cotransporter 1, α-*N*-acetylgalactosaminidase precursor, platelet-derived growth factor, and nonmuscle myosin heavy-chain A (NMMHC-A). Because mutations in two myosin genes are known to cause hearing impairment (Liu et al. 1997; Wang et al. 1998), this class of genes deserves particular attention as potential candidates. Thus the nonmuscle myosin within the linked region represents a strong candidate for DFNA17 (Saez et al. 1990; Simons et al. 1991; Toothaker et al. 1991). Human NMMHC-A is a class II conventional myosin, unlike unconventional myosins VIIA and 15, which have been shown to cause hearing impairment. However, NMMHC-A is not a traditional striated-muscle-cell myosin, since it is expressed in the rat intestine, testis, liver, lung, thymus, kidney, and heart and not in striated muscle (Simons et al. 1991). Recently it has been shown that NMMHC-A is also expressed in the cochlea (authors' unpublished data).

Another approach toward identification of the DFNA17 gene is to use mouse models of deafness that map to the syntenic region in the mouse. Human myosin VIIA and myosin 15 have been identified by initial characterization of the homologous mouse models (Liu et al. 1997; Wang et al. 1998). The mouse syntenic region for DFNA17 includes chromosomes 11 and 15. No mouse deafness models have yet been reported that map to a region syntenic with the human DFNA17. One mouse deafness model—dominant spotting, or kit—displays histology that resembles that of human CSD (Bock and Steel 1983; Steel and Bock 1983), but the gene for this mouse phenotype maps to the homologous region of

human chromosome 4. Other animal models for CSD include Dalmatian dogs, Hedlund white mink, and the deaf white cat (Mair 1973; Steel and Bock 1983). However, none of these loci have been mapped, because of the unavailability of genetic markers for these species. Furthermore, unlike the family in the present study, these animal models of CSD are associated with skin-pigment abnormalities due to a lack of melanocytes.

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Electronic-Database Information

URLs for data in this article are as follows:

Hereditary Hearing Loss, http://dnalab-www.uia.ac.be/dnalab/hhh
Marshfield Medical Research Foundation, http://www.marshmed.org/genetics (for genetic distances)
Science/The Human Gene Map, http://www.ncbi.nlm.nih.gov/cgi-bin/SCIENCE96/chr?22

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