Am. J. Hum. Genet. 65:141–150, 1999

A Gene for Fluctuating, Progressive Autosomal Dominant Nonsyndromic Hearing Loss, DFNA16, Maps to Chromosome 2q23-24.3

Kunihiro Fukushima,[1,*] Norio Kasai,[1,2,*] Yasuyoshi Ueki,[3,*] Kazunori Nishizaki,[1] Kennichi Sugata,[1] Satoshi Hirakawa,[3] Akemi Masuda,[1] Mehmet Gunduz,[1] Yoshifumi Ninomiya,[3] Yu Masuda,[1] Minako Sato,[4] Wyman T. McGuirt,[2] Paul Coucke,[5] Guy Van Camp,[5] and Richard J. H. Smith[2]

Departments of [1]Otolaryngology and [2]Molecular Biology and Biochemistry, Okayama University Medical School, Okayama, Japan; [3]Molecular Otolaryngology Research Laboratories, Department of Otolaryngology, University of Iowa, Iowa City; [4]Department of Otolaryngology, Keio University, Tokyo; and [5]Department of Medical Genetics, University of Antwerp, Antwerp

Summary

The sixteenth gene to cause autosomal dominant nonsyndromic hearing loss (ADNSHL), DFNA16, maps to chromosome 2q23-24.3 and is tightly linked to markers in the D2S2380-D2S335 interval. DFNA16 is unique in that it results in the only form of ADNSHL in which the phenotype includes rapidly progressing and fluctuating hearing loss that appears to respond to steroid therapy. This observation suggests that it may be possible to stabilize hearing through medical intervention, once the biophysiology of deafness due to DFNA16 is clarified. Especially intriguing is the localization of several voltage-gated sodium-channel genes to the DFNA16 interval. These cationic channels are excellent positional and functional DFNA16 candidate genes.

Introduction

Autosomal dominant nonsyndromic hearing loss (ADNSHL) is a heterogeneous disorder. Twenty-two loci have been identified (Hereditary Hearing Loss Homepage, Van Camp and Smith), and seven of the relevant genes have been cloned (in the following list, "DFN" denotes "deafness," "A" denotes "autosomal dominant," and the numerals denote the loci in the order in their discovery): DFNA1, *HDIA1* (MIM 124900 [Lynch et al. 1997]); DFNA3, *GJB2* (MIM 601544 [Denoyelle et al. 1998]); DFNA5, *DFNA5* (MIM 600994 [Van Laer et al. 1998]); DFNA8/12, *TECTA* (MIM 600994 [Verhoeven et al. 1998]); DFNA9, *COCH* (MIM 601369 [Robertson et al. 1998]); DFNA11, *MYO7A* (MIM 601317 [Liu et al. 1997]); and DFNA15, *POU4F3* (MIM 602459 [Vahava et al. 1998]) (table 1). Although, by definition, the phenotype in each case is limited to hearing impairment, some aspects of the hearing loss appear to be locus specific.

Both age at onset and audiometric configuration can be used to subclassify ADNSHL (see tables A1 and B1 [in Appendices A and B]). With respect to age at onset, DFNA3 (Chaib et al. 1994), DFNA8 (Kirschhofer et al. 1998), DFNA12 (Verhoeven et al. 1997), and DFNA13 (Brown et al. 1997) are prelingual—and presumably congenital—types of hearing loss. The hearing loss in DFNA3 and DFNA8 is moderate to severe is degree, nonprogressive, and predominantly high frequency. The DFNA12 loss also is moderate to severe and nonprogressive; however, the mid frequencies are affected, resulting in a "cookie-bite" type of audiogram in some hearing-impaired persons (Govaerts et al. 1998). A cookie-bite pattern also is seen in DFNA13 in childhood, but, by adulthood, age-related progression of the hearing loss flattens the audiometric curve.

DFNA1 (Leon et al. 1992), DFNA2 (Coucke et al. 1994), DFNA5 (Van Camp et al. 1995), DFNA6 (Lesperance et al. 1995), DFNA7 (Fagerheim et al. 1996), DFNA11 (Tamagawa et al. 1996), and DFNA14 (authors' unpublished data) are postlingual early-onset (i.e., age <~20 years) hearing losses. Among ADNSHL loci, DFNA1, DFNA6, and DFNA14 are unique in that the low frequencies are preferentially involved, resulting in an up-sloping audiometric curve; with regard to these loci, the loss begins at age ~10 years (Appendix B). Occasionally, a "hill-type" pattern is seen in DFNA6 during the 1st decade of life, reflecting involvement of the low and high frequencies, with initial sparing of the mid frequencies; however, as the mid frequencies become af-

Received February 11, 1999; accepted for publication May 6, 1999; electronically published June 4, 1999.

Address for correspondence and reprints: Dr. Richard J. H. Smith, Molecular Otolaryngology Research Laboratories, Department of Otolaryngology, University of Iowa, Iowa City, Iowa 52242. E-mail: richard-smith@uiowa.edu

*These authors contributed equally to this work.

0002-9297/99/6501-0019$02.00

Table 1

ADNSHL Loci

Locus	Location	Gene
DFNA1	5q31	HDIA1
DFNA2	1p32	
DFNA3	13q12	*GJB2*
DFNA4	DFNA19q13	
DFNA5	7p15	*DFNA5*
DFNA6	4p16.3	
DFNA7	1q21-q23	
DFNA8	11q	*TECTA*
DFNA9	14q12-q13	*COCH*
DFNA10	6q22-q23	
DFNA11	11q12.3-q21	*MYO7A*
DFNA12	11q22-q24	*TECTA*
DFNA13	6p21.3	
DFNA14	4p16	
DFNA15	5q31	*POU4F3*
DFNA16	2q24	
DFNA17	22q	
DFNA18	3q22	
DFNA19	10 pericentromeric	
DFNA20	Reserved	
DFNA21	Reserved	
DFNA22	Reserved	

fected, the audiogram flattens. DFNA2, DFNA5, DFNA7, and DFNA11 also have down-sloping audiometric curves. In DFNA2 (Marres et al. 1997; Kunst et al. 1998), DFNA5, and DFNA7, onset of hearing loss begins at age 5–15 years, with thresholds dropping to ~80 dB at frequencies >1,000 Hz. The rate of progression varies and is most rapid with DFNA7. With all of these loci, the final outcome is a gently sloping to flat audiometric curve, usually by the individual's mid 40s. The slope of the DFNA11 loss is more gradual in comparison with that of DFNA2, DFNA5, or DFNA7, although the loss in this case also is apparent during the 1st decade of life and is progressive.

DFNA4 (Chen et al. 1995*b*), DFNA9 (Manolis et al. 1996), and DFNA10 (O'Neill et al. 1996) are postlingual progressive late-onset (i.e., during or after the 3d decade of life) hearing losses. The loss begins during the 3d decade in the case of DFNA9, the 4th decade in the case of DFNA4, and the mid to late 5th decade in the case of DFNA10. Although bilateral amplification is required, DFNA9 hearing loss is the harbinger of a precipitous decline in word recognition, which correlates with a sharp decrease in communication ability and causes hearing aids to be of limited benefit.

Notably absent from this classification is fluctuating hearing loss. This type of loss generally is associated with autoimmune inner-ear disease (Tomiyama et al. 1995; Katsarkas 1996), Ménière disease (Filipo and Barbara 1997), and the dilated vestibular aqueduct (DVA) syndrome (Abe et al. 1997). However, it also can occur in persons with ADNSHL. In this report, we describe the localization of the first gene associated with fluctuating, progressive ADNSHL: DFNA16.

Subjects and Methods

Clinical Description

This family was ascertained through the Department of Otolaryngology, Okayama University Medical School. The pattern of inheritance is consistent with transmission of an autosomal dominant deafness-causing gene (fig. 1). Each affected person underwent pure-tone audiometry (PTA) and a complete physical examination, to exclude syndromic forms of hearing impairment. Additional tests performed to evaluate the hearing loss of affected persons included temporal-bone computed tomography and a western blot assay for anti–68-kD inner-ear protein antibodies. Several affected persons required in-patient treatment for sudden sensorineural hearing loss (SNHL). Because of the unique features of the hearing loss in this family, two cases will be described in detail.

Case 1 (*IV-6*).—An 11-year-old competitive swimmer was referred for an otolaryngological evaluation in early 1994 after a routine school health screen revealed probable elevated hearing thresholds. His general health was excellent, and his past medical history was unremarkable. As an infant, he had shown no evidence of developmental or mental delay, no noticeable hearing loss, and no delay in speech development. He had never experienced tinnitus or vertigo. Results of otoscopy were normal, as was the remainder of his physical examination, with the exception of the presence of nasal allergies.

PTA revealed a bilateral sloping SNHL predominantly affecting the higher frequencies (fig. 2*a*). No recruitment was observed either by self-recording audiometry (Jerger type I) or the short-increment sensitivity index (SISI) test (0% at 0.5, 1, 2, and 4 kHz). Acoustic brain-stem responses were observed at 70 dB in the left ear and at 80 dB in the right ear. Results of temporal-bone computed tomography were normal (fig. 3).

In April 1994, this individual first complained of left-ear tinnitus. Audiometry confirmed a decrease in hearing thresholds, and treatment with hydrocortisone, intravenous ATP, and vitamin B12 was initiated, resulting in a temporally related recovery of hearing thresholds, to pretreatment levels. A similar episode, also affecting the left ear, occurred 3 mo later, and again, the administration of oral steroids (prednisolone) was temporally associated with an improvement in hearing thresholds (fig. 2*b*). Acute fluctuations in hearing with or without tinnitus became common (diagnoses were made on December 7, 1994 [left ear], April 2, 1996 [left ear], May 7, 1996 [right ear], August 13, 1996 [right ear], October 11, 1996 [left ear], December 25, 1996 [right ear], May

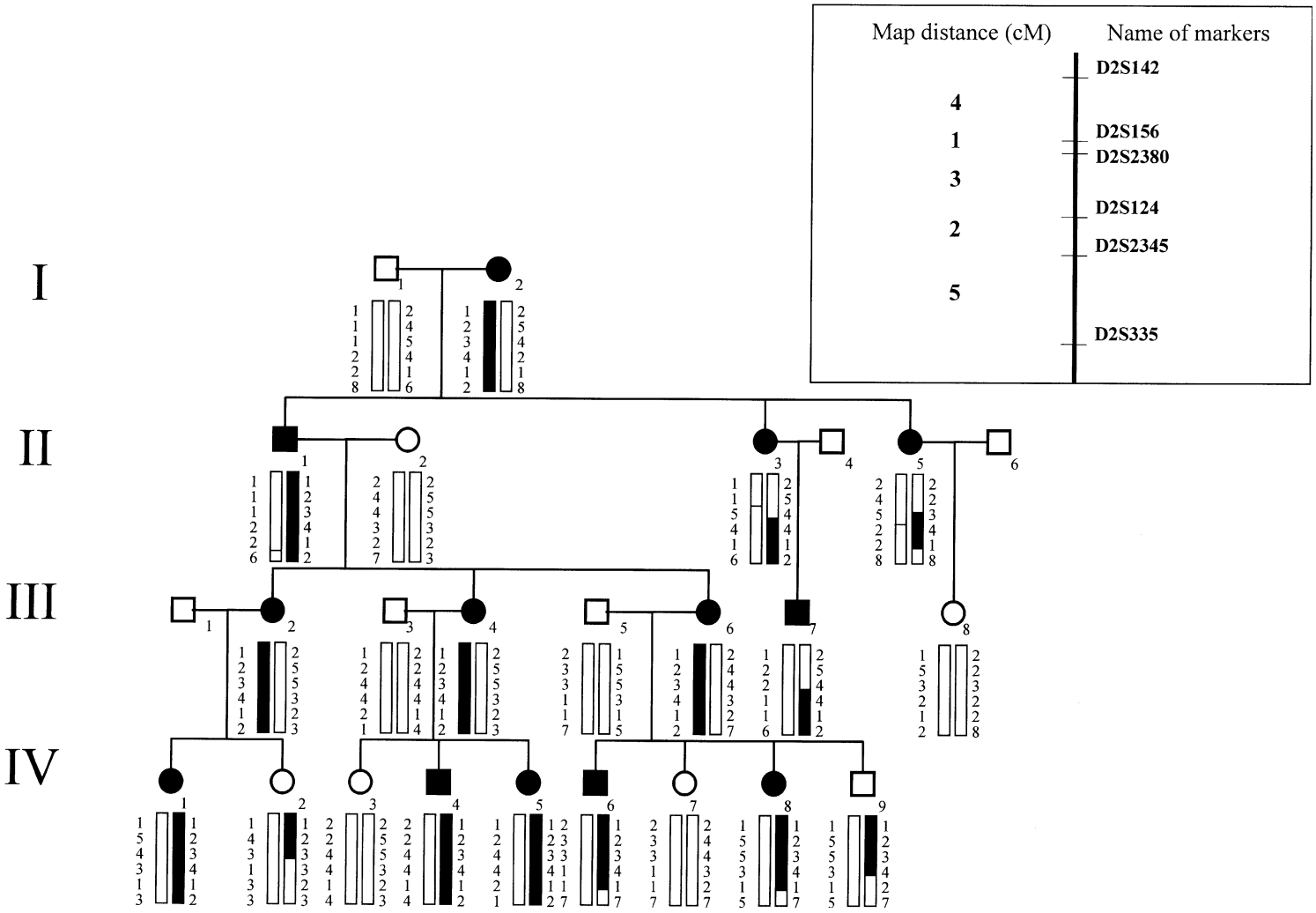

Figure 1 DFNA16 pedigree showing haplotypes assigned to minimize the number of recombination events (blackened circles denote affected females, and blackened squares denote affected males). The map and map distances are shown in the square at the upper right (National Center for Biotechnology Information, Entrez; Whitehead Institute for Biomedical Research/MIT Center for Genome Research). Paternal crossovers in II-1, II-3, and II-5 are indicated by a horizontal line; ages at last audiogram are as follows: IV-2, 15 years; IV-3, 21 years; IV-7, 16 years; IV-9, 11 years. Response to steroids was clinically documented in III-4, III-7, IV-1, IV-6, and IV-8; similar data were not available for III-4, III-6, IV-4, and IV-5; generations I and II were profoundly deaf with no recent fluctuations in hearing. IV-2 and IV-9 have critical recombinants that could affect the linked interval significantly; if IV-9 remains unaffected, the critical interval would be distal to marker D2S124 and would not include D2S2380. II-5 represents a double recombination event (confirmed several times).

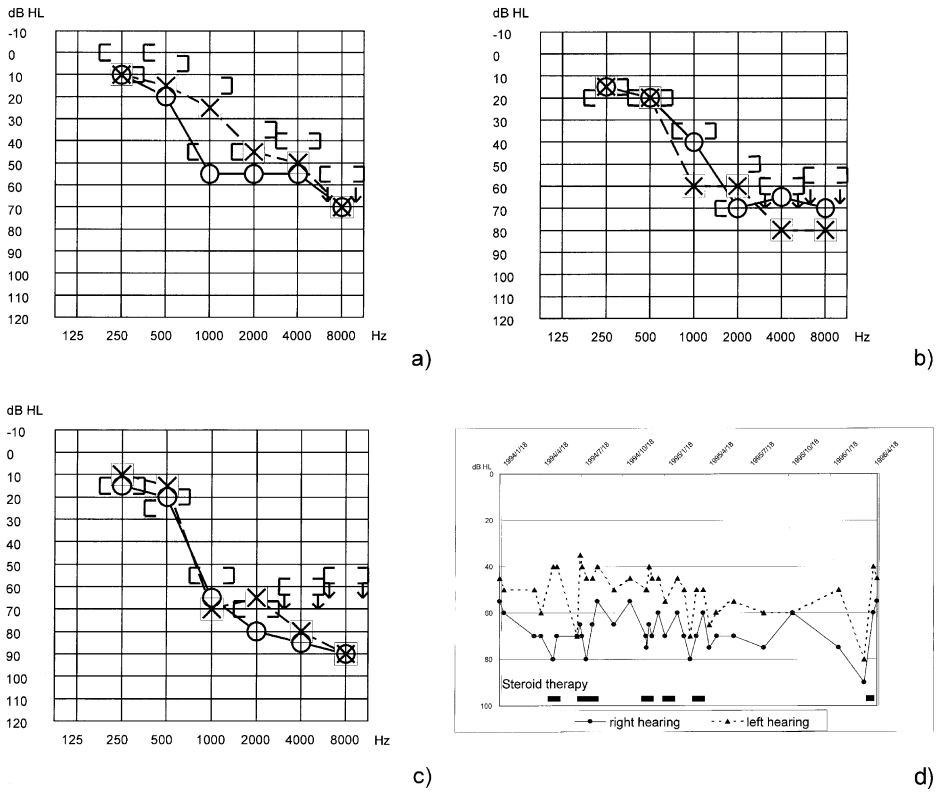

Figure 2 Audiogram of IV-6 at initial presentation (*a*) and after the second (*b*) and last (*c*) episode of fluctuating hearing loss. The graph summarizes chronological changes in hearing levels over a 27-mo period (circles and triangles represent right- and left-ear hearing levels, respectively, at 2,000 Hz pure-tone stimulus, and horizontal bars at the bottom (*d*) indicate periods of steroid therapy.

8, 1997 [right ear], and August 15, 1997 [both ears]) (fig. 2*d*). Most of these episodes occurred during swimming season, suggesting a possible relationship between physical stress and hearing loss; however, the most recent episode, in February 1998, followed a flulike infection. Tinnitus was severe, and the hearing loss was bilateral (fig. 2*c*). Again, a temporal response to corticosteroids (hydrocortisone) was seen.

Case 2 (*IV-8*).—The younger sister of the boy described in case 1 was referred for an otolaryngological evaluation after she failed a preschool hearing screen at age 6 years. Her history was unremarkable for developmental or medical problems, and there were no complaints of either hearing loss or delays in language development. Audiometry revealed a sloping, high-frequency SNHL; SISI was 0% in the right ear and 5%–10% in the left ear (fig. 4*a*).

On February 15, 1995, she experienced her first episode of acute hearing loss and promptly was put on a regimen of therapy with betamethasone. By March 1, 1995, her hearing had recovered. A second episode of hearing loss occurred in June 1996; recovery again was temporally associated with the use of steroids. This cycle repeated itself in August 1996, September 1996, October 1996, March 1997, May 1997, July 1997, and March 1998. The last episode followed the same flulike illness that had affected her brother (fig. 4).

In an expanded investigation into the extended family, all hearing-impaired persons stated that they had had normal or nearly normal hearing until age 9–10 years. Two persons did report some vertigo, but this had not been associated with episodes of acute hearing loss. All hearing-impaired females who had been pregnant reported acute hearing loss and tinnitus immediately after parturition. One hearing-impaired woman (III-4) who suspected a relationship between physical stress and hearing loss tried to avoid extremely rigorous activities by her children (IV-4 and IV-5). Their hearing loss was not as severe as that of their cousins (IV-6 and IV-8), and they reported few episodes of fluctuation (fig. 5).

Genotyping

Genomic DNA was extracted from peripheral-blood samples obtained from consenting family members, by established procedures (Grimberg et al. 1989). After

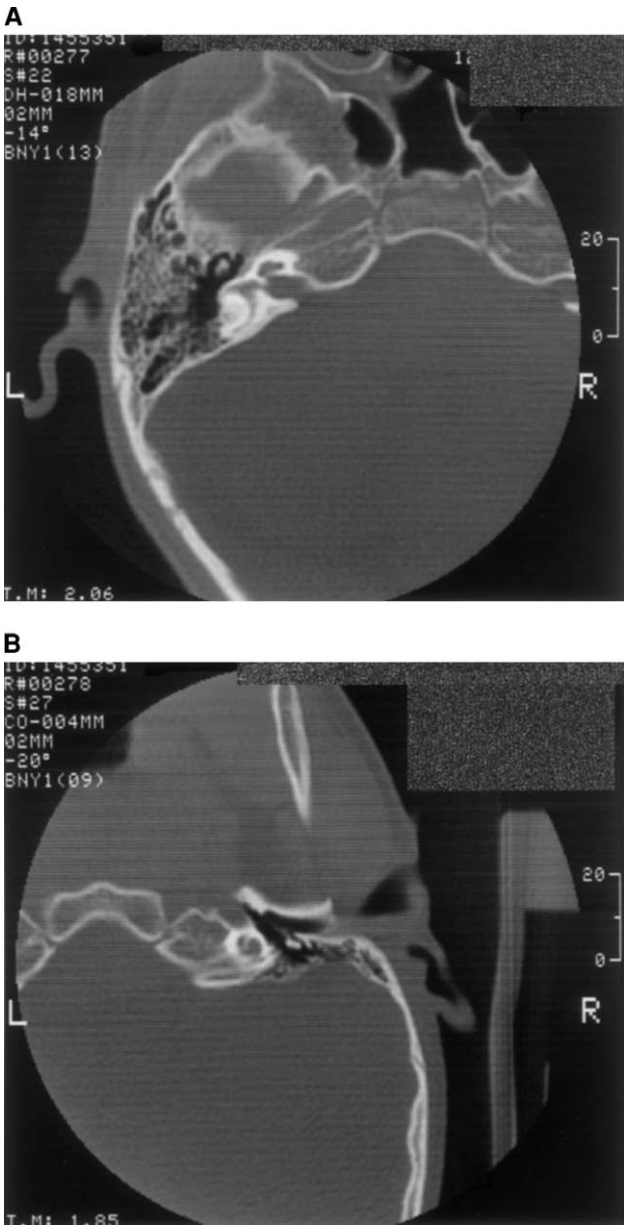

Figure 3 Computed tomography of temporal bone of IV-6 in axial (*a*) and sagittal (*b*) planes, showing no evidence of a dilated vestibular aqueduct.

linkage to known deafness-causing loci was excluded (Hereditary Hearing Loss Homepage, Van Camp and Smith), a genomewide screen was performed with 386 markers spaced an average of 10 cM apart (MapPairs human screening set, version 8.0). PCR reactions were performed as described elsewhere (Brown et al. 1997). After PCR amplification, samples were electrophoresed on a 6% denaturing polyacrylamide gel. Bands were stained by SYBERGREEN (10 ml of 1:10,000) at room temperature for 30 min and were visualized by Fluorlmager SI (Molecular Dynamics). Alleles were scored manually by two investigators; when there were discrepant or ambiguous results, the scoring was repeated.

Linkage Analysis

Two-point and multipoint linkage analysis was performed by FASTLINK (Cottingham et al. 1993). Liability classes were assigned, with 50% penetrance for subjects of age $\leq$10 years and with 90% penetrance for subjects of age >10 years. The disease-allele frequency was set at .0001, with the recombination fractions (θ) in males and females being considered to be equal. First, two-point LOD-score analysis was performed first between the disease allele and each marker; then four-point LOD-score analysis was performed with markers on chromosome 2q.

Results

Linkage to the known deafness-causing loci (both dominant and recessive) was excluded. Two-point genomewide linkage analysis was performed, and only two loci, one on chromosome 2 and the other on chromosome 18, showed possible linkage (LOD score >2.0). Additional markers were examined in both of these areas. A multipoint LOD score of 4.08 ($\theta = 0$) was obtained with D2S2345, over the D2S2380-D2S124-D2S2345-D2S335 interval (fig. 6).

Discussion

DFNA16 is the 16th ADNSHL-causing gene to be mapped and is characteristically unique when compared with all previously characterized deafness-causing loci. Persons in the pedigree that we studied have fluctuating and, at times, rapidly progressive SNHL. These features of DFNA16 hearing loss suggest that an understanding of the relevant biophysiology may reveal ways to prevent the fluctuation, thereby preserving, at some level, residual hearing.

Fluctuating SNHL is rare, accounting for <5% of all SNHL of unknown etiology. In children, it is usually diagnosed in association with either congenital cytomegalovirus (CMV) infection (Fowler et al. 1997) or bony abnormalities of the inner ear, the latter most commonly being a DVA (Abe et al. 1997). The prevalence of SNHL in persons with asymptomatic congenital CMV is <10%, and, of this fraction, 20%–30% experience fluctuating high-frequency hearing loss. In the pedigree that we studied, there is no evidence consistent with either this diagnosis or any other type of acquired hearing loss.

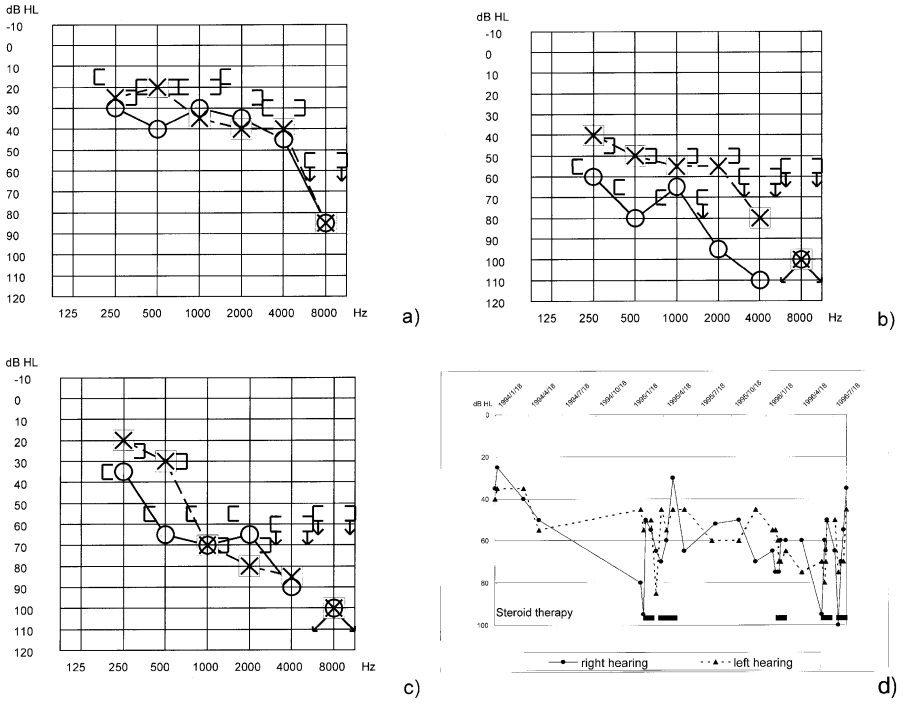

Figure 4 Audiogram of IV-8 at initial presentation (*a*) and after second (*b*) and last (*c*) episode of fluctuating hearing loss. The graph summarizes chronological changes in hearing levels over a 30-mo period (circles and triangles represent right- and left-ear hearing levels, respectively, at 2,000 Hz pure-tone stimulus, and horizontal bars at the bottom indicate periods of steroid therapy (*d*).

DVA is defined as an enlargement of the endolymphatic duct and sac and is diagnosed by computed-tomographic examination of the temporal bones (Abe et al. 1997). In as many as 80% of persons with DVA, fluctuation in hearing occurs. This abnormality also is a feature of branchiootorenal syndrome (Chen et al. 1995*a*), Pendred syndrome (Reardon et al. 1997), and DFNB4 (Li et al. 1998). In this pedigree, there was no evidence of syndromic hearing loss, and, although there was marked fluctuation in hearing, normal temporal-bone anatomy was documented in the two persons (cases 1 and 2) who underwent thin-cut computed tomography.

In adults, fluctuating hearing loss is most commonly seen in Ménière syndrome (Filipo and Barbara 1997) and autoimmune inner-ear disease (Tomiyama et al. 1995; Katsarkas 1996). The former is characterized by both fluctuating SNHL that is often unilateral and predominantly in the low frequencies and vertigo that can last for minutes to hours, and it is accompanied by nausea and vomiting, as well as by constant or intermittent tinnitus, which typically increases in intensity, either before or during the vertiginous attacks. Several families have been described in which a Ménière-syndrome gene appears to be segregating (Morrison 1995); however, in this pedigree the phenotype is inconsistent with this diagnosis. It is conceivable that other mutations of the deafness-causing gene in this family could result in classic Ménière syndrome. Phenotypic variability associated with deafness-causing genes is well documented, and an allelic variant of the gene *COCH* is known to produce Ménière-like symptoms (authors' unpublished data).

Autoimmune inner-ear disease is characterized by bilateral progressive asymmetric hearing loss (Veldman 1997). Approximately 65% of affected persons are middle-age women (Hughes et al. 1988), 25%–50% of whom describe fluctuation in hearing and the presence of vertigo, which initially may suggest the diagnosis of Ménière syndrome. The autoimmune reaction may occur

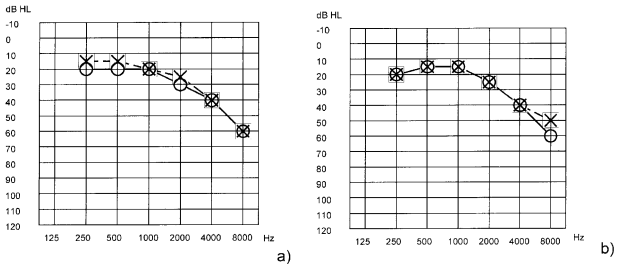

Figure 5 Audiograms of IV-4 at age 16 years and IV-5 at age 13 years. (Compare these results with those for IV-6 at age 13 years [fig. 2*c*] and IV-8 at age 10 years [fig. 4*c*].)

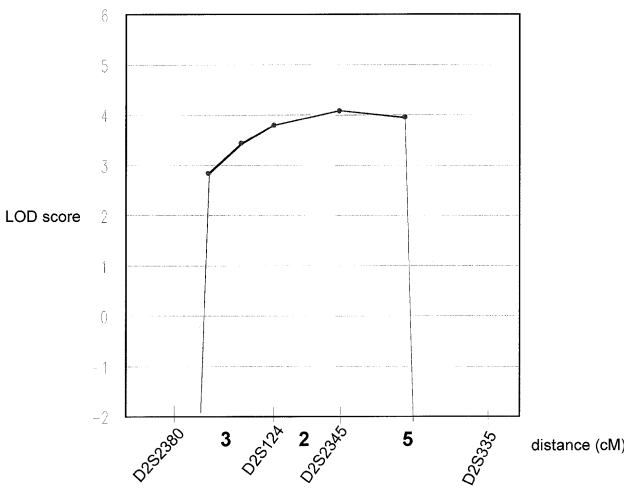

Figure 6 Multipoint-LOD-score results over interval defined in figure 1.

either as part of the symptom complex of multisystemic, non–organ-specific disease that occurs with rheumatoid arthritis, Wegener granulomatosis, polyarteritis nodosa, and systemic lupus erythematosis or as an organ-specific process, which has been referred to as "primary autoimmune inner-ear disease." The diagnosis is facilitated by the detection of an anti–68-kD antibody by western blot. In a study of 279 persons with rapidly progressive SNHL, 32% were positive for this antibody, and, of those in whom the hearing loss was progressing during the time of testing, 89% had a positive western blot (Gottschlich et al. 1995). In this pedigree, although the SNHL seemed to improve with corticosteroid administration, the possibility of autoimmune inner-ear disease appears unlikely, for several reasons: two individuals tested by western blot while hearing loss was progressing were negative for the anti–68-kD antibody; the family history is negative for other autoimmune diseases; and the age at onset is unusually early.

Corticosteroid therapy is the only treatment that has proved effective in the treatment of sudden SNHL (Wilson et al. 1980; Moskowitz et al. 1984). Recommended daily prednisone doses in adults are in the 60–80-mg range, with a gradual decrease during the course of several weeks. A response to therapy is more likely in persons with hearing loss in the 40–80-dB range, and, if the symptoms recur after the dosage has been decreased, then resumption of prednisone, at a dosage of 40 mg/d for 1 mo, and an autoimmune work-up are recommended (Harris and Ruckenstein 1996). Although the mechanism of action of prednisone is not known, it is an anti-inflammatory drug that suppresses the immune response. It also has a mineralocorticoid effect on fluid and electrolyte balance, which is interesting in view of the genes that have been mapped to the DFNA16 interval.

The DFNA16 interval is defined conservatively by D2S2380 (centromeric) and D2S335 (telomeric) (see the legend to fig. 1) on 2q23-q24.3, a chromosomal region that includes three voltage-gated sodium channels—SCN1A, SCN2A1, and SCN3A (Malo et al. 1991; GeneMap '99). Cationic channels play an important role in hearing, and mutations in three voltage-gated potassium-channel genes—*KVLQT1* (Neyroud et al. 1997), *KCNE* (Tyson et al. 1997), and *KCNQ4* (Kubisch et al. 1999)—are known to cause hearing loss (*KVLQT1* and *KCNE1* result in Jervell and Lange-Nielsen syndrome, and *KCNQ4* results in DFNA2). Few data have been reported on sodium channels; however, intracochlear application of tetradotoxin, a sodium-channel blocker, does affect cochlear response to electric stimulation (Santos-Sacchi 1993), and sodium channels appear to be important for inner-ear fluid regulation (Mizuta et al. 1995).

The demonstration that SCN1A, SCN2A1, and SCN3A are cochlear expressed makes them excellent positional and functional candidate genes for DFNA16. If one of these voltage-gated sodium channels is implicated—because the phenotype includes fluctuating and, at times, rapidly progressive SNHL—perhaps micromanipulation of the inner-ear environment by round-window catheters can stabilize hearing. The clinical possibilities implicit in the unique features of the DFNA16 phenotype make this localization noteworthy.

Acknowledgments

The authors thank the family for making this study possible. Drs. Yoshida and Take provided some of the clinical data, and S. Fukuda and the staff of Kanariya-Gakuen facilitated follow-up of the hearing-impaired children. This research was supported by a Ministry of Health and Welfare of Japan grant (to K.F.); by Ministry of Education, Science, Sports and Culture grant for scientific research (B)09470372 (to Y.M.); by the Flemish Fund for Scientific Research (FWO-Vlaanderen) (support to G.V.C.); and by National Institutes of Health grant R01DC03544 (to R.J.H.S.). G.V.C. holds a research position at FWO-Vlaanderen.

Appendix A

ADNSHL Loci Classified on the Basis of Age at Onset of Hearing Loss

In the following list, the congenital losses are stable; all others are progressive.

Congenital:
DFNA3

DFNA8/12
DFNA13
Early onset (age <20 years):
DFNA1
DFNA2
DFNA5
DFNA6
DFNA7
DFNA11
DFNA14
DFNA16
Late onset (age ⩾20 years):
DFNA4
DFNA9
DFNA10

Appendix B

ADNSHL Loci Classified on the Basis of Audiometric Profile

In the following list, DFNA1 is quickly progressive, with severe to profound SNHL at age <30 years; DFNA6, and DFNA 14 are slowly progressive, with some hearing present throughout life; DFNA6, DFNA7, DFNA8/12, and DFNA12 have more than one audiometric profile; and DFNA16 entails fluctuating hearing loss.

Low frequency (up sloping):
DFNA1
DFNA6
DFNA14
Mid frequency (cookie bite):
DFNA12
DFNA13
High frequency (up sloping):
DFNA2
DFNA3
DFNA5
DFNA7
DFNA9
DFNA10
DFNA16
High/low frequency (hill shape):
DFNA6
All frequencies (flat):
DFNA4
DFNA7
DFNA11
DFNA8/12

Electronic-Database Information

GeneMap '99, http://www.ncbi.nlm.nih.gov/genemap
Hereditary Hearing Loss Homepage, Guy Van Camp & Richard Smith, http://dnalab-www.uia.ac.be/dnalab/hhh
National Center for Biotechnology Information, Entrez, http://www.ncbi.nlm.nih.gov/Entrez
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim
Whitehead Institute for Biomedical Research/MIT Center for Genome Research, http://www-genome.wi.mit.edu

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