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Inherited Nonsyndromic Hearing Loss

An Audiovestibular Study in a Large Family With Autosomal Dominant Progressive Hearing Loss Related to DFNA2

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Objective: To study nonsyndromic progressive sensorineural hearing loss (SNHL) with significant linkage to the DFNA2 locus on chromosome 1p in a Dutch kindred.

Design: A 6-generation family with 194 family members was studied. Of the presumably affected persons, 43 were examined in detail to obtain audiograms and 37 underwent vestibulo-ocular examination.

Results: Regression analysis showed significant and equal linear progression in SNHL with age (by about 1 dB per year) at all frequencies. Offset values were close to zero at the low frequencies (0.25, 0.5, and 1 kHz) but increased systematically with the frequency. It is likely that they represent congenital high-frequency SNHL: about

15 dB at 2 kHz, 30 dB at 4 kHz, and 50 dB at 8 kHz. Bilateral caloric weakness was not observed. A significant finding was that 25% to 35% (depending on the exclusion criteria) of the patients showed an increased vestibulo-ocular reflex (hyperreactivity) as measured by rotatory responses. Forty-one patients showed significant linkage to the 1p locus.

Conclusions: Including the present family, 4 families have been reported to show linkage to chromosome 1p. Statistical analysis of the audiological data shows a progression of 1 dB per octave per year in this type of progressive SNHL.

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ABOUT 16 hereditary nonsyndromic types of sensorineural hearing loss (SNHL) have been described. Based on characteristics such as age at onset and shape of the audiogram, 8 autosomal dominant inherited forms have been distinguished clinically.¹

So far, 11 genes have been localized that are responsible for autosomal dominant hearing loss.² This number exceeds the number of clinically different forms of autosomal dominant nonsyndromic hearing loss reported in the literature. In 2 different unrelated families (1 Indonesian and 1 American) whose affected persons showed different audiological phenotypes, 1 of the diseased genes has been linked to chromosome 1p.³ In a Costa Rican family with 45 persons affected by autosomal dominant low-frequency hearing loss, the gene has been localized on chromosome 5q.⁴ In these reports, data on the vestibular function of the affected persons were lacking, as was the case in many other reports on inherited nonsyndromic hearing loss. It may be relevant to the differential diagnosis of these types of he-

reditary hearing loss to be aware of any possible otoneurological (dys)function. Recent developments in gene linkage and identification are an overwhelming power to stimulate refinement of the previous clinical classification of genetic types of SNHL. These new developments also provide more insight into the pathogenesis of these nonsyndromic diseases, which constitute about 50% to 75% of all inherited forms of hearing loss.

A clinical study was performed on a large, 6-generation, Dutch family to define the type of autosomal dominant inherited hearing loss and to examine vestibular function. Audiograms were analyzed to evaluate hearing loss and progression. Gene linkage analysis was also performed. The results proved to be important to the process of defining the gene.⁵

RESULTS

PEDIGREE

After having gained insight into the pedigree, 109 persons were examined. The anamnesis of the 85 persons who were not examined disclosed that only 3 had im-

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PATIENTS AND METHODS

Several patients diagnosed as having SNHL at the Department of Otorhinolaryngology at the University Hospital Nijmegen, Nijmegen, the Netherlands, were members of the same family. Family members were approached by 1 of the probands. Genealogical studies enabled us to complete a pedigree of 6 generations (**Figure 1**) with 222 family members, 194 of whom were alive. All the family members living in the Netherlands were invited to participate in a clinical and genetic linkage study (N=179), and informed consent was obtained. Participants underwent clinical examination by the authors, who are experienced in the field of genetic hearing loss and audiometric testing. A selected sample of persons was also referred for vestibular examination.

AUDITORY SYSTEM

Audiometric examination comprised pure-tone audiometry, using Interacoustic type AC5 equipment (Asseus, Denmark) calibrated according to the International Organization for Standardization 389 and 8253-1 standards in a sound-treated room.^{6,7} Air-conduction thresholds were measured in decibel hearing level. The bone-conduction threshold also was measured to exclude conductive hearing loss. The shape of the audiogram was classified by using (with some minor modifications) the terms and definitions given by Liu and Xu,⁸ which were based on previous classifications by Fisch in 1955⁹ and Paparella et al in 1975.¹⁰ Subjects with a perceptive hearing loss of 25 dB or higher on

the High Fletcher Index (average loss at 1000, 2000, and 4000 Hz) with a suspected hereditary origin also were referred for vestibular examination.

VESTIBULAR AND OCULOMOTOR SYSTEM

Vestibular tests were performed with the patient in the dark with the eyes open; eye movements were recorded with DC electro-oculography. Velocity step tests were performed with a rotatory chair (Toennies, Freiburg im Breisgau, Germany).

To characterize the vestibulo-ocular reflex, the following variables were used: initial velocity, time constant, and "Gesamtamplitude," or cumulative eye displacement. The methods used, including those of the caloric test and computer analysis, have been described in detail in previous reports.¹¹⁻¹⁴

Gaze positions were tested to investigate the presence of gaze-evoked nystagmus. Saccades, smooth pursuit, and horizontal optokinetic nystagmus responses were elicited and analyzed as reported previously.¹⁵

If the subjects were unable to participate personally, information was obtained by telephone or by heteroanamnesis. Whenever possible, data and audiograms were requested from the treating ear, nose, and throat physician.

A 20-mL venous blood sample was obtained from the participants for gene-linkage studies; the methods and results of the gene-linkage studies have been reported elsewhere.¹⁵

Because it is thought that this type of autosomal dominant nonsyndromal inherited hearing loss is of monogenic origin, karyotypes were not performed.

paired hearing (CIII-3, DIV-14, DV-17); no audiograms were available for these 3 persons.

HEARING

Hearing impairment was found in 59 of the 109 participants (High Fletcher Index ≥ 25 dB). However, in 16 of them there may have been another explanation for their hearing loss than a genetic defect (eg, otitis, noise exposure, or trauma). This group also included a number of persons whose hearing thresholds were below 95%, compatible with age-related presbycusis (International Organization for Standardization 7029).¹⁶ This determination was made before genotyping the family members. No members of this group had offspring with hearing impairment.

In the remaining 43 persons, strong evidence existed that they were suffering from a hereditary form of hearing impairment based on their position in the pedigree and their negative otological history. No other characteristic features were found during physical examination.

Most of the audiograms were classified as the sharply sloping high-frequency sensorineural type: 37 patients, of whom the youngest was aged 44 years, showed this shape bilaterally, and 2 patients had a gently sloping audiogram on 1 side.⁸ Residual hearing was found in the 4 oldest patients (73-81 years). An almost

flat audiogram was found in 1 patient (CIII-9). Another person (CV-23) had SNHL that was too severe for her age (64 years) compared with the other affected family members. In the genetic-linkage study, she and person CIV-21, who had a midfrequency-type audiogram, could not be linked, so they were regarded as possible phenocopies and were excluded from further statistical analysis of the audiograms.

Pure-tone averages (PTAs; mean dB HL at 500, 1000, and 2000 Hz) (**Figure 2**), calculated for each patient per ear, did not disclose any significant left-right differences. The hearing threshold data (n=474) were plotted against age for the right and left ear separately. There was a linear relation between threshold and age by first approximation (**Figure 3**). It is clear from Figure 3 that the frequencies relate to parallel regression lines. The offset value, ie, the extrapolation value obtained at age 0 years, increased systematically with the frequency. The annual threshold increase was close to 1 dB per year at all frequencies. The average threshold increase (audiogram slope) at any age was about 8 dB per octave below 2 kHz and about 14 dB per octave above 2 kHz.

VESTIBULO-OCULAR FUNCTION

Vestibulo-ocular examination was performed on 37 of the affected persons whose audiogram had been ob-

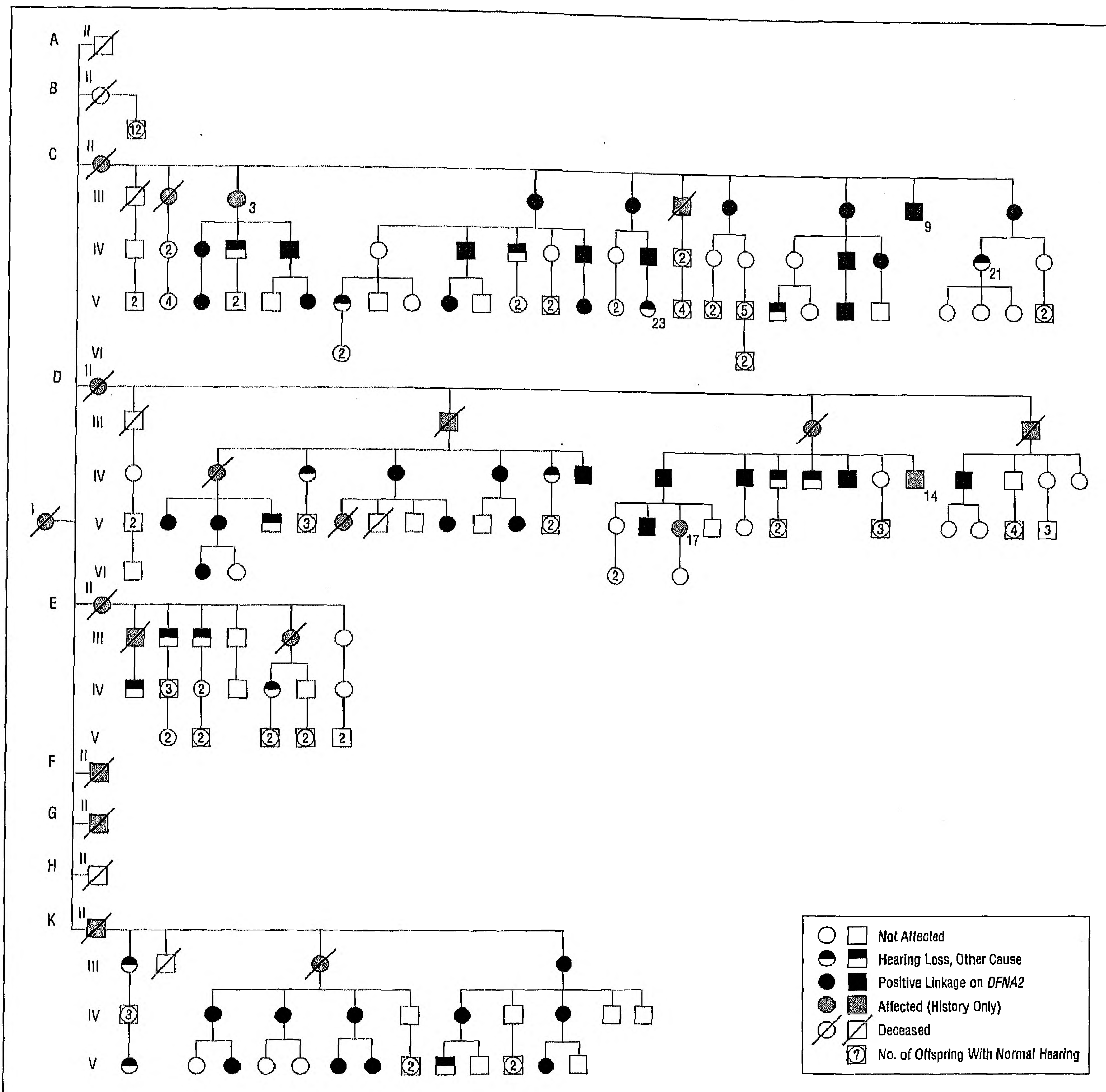


Figure 1. Pedigree of a family with high-frequency sensorineural hearing loss.

tained. None of them showed any spontaneous or gaze-evoked nystagmus, and their smooth pursuit and optokinetic responses were normal. Saccades were normal, except in 1 patient who showed unilateral abduction palsy. In the latter patient, a remarkable downbeating postrotatory response (apart from a normal horizontal nystagmus response) was the only vestibular abnormality observed.

The velocity step responses showed vestibular hyperreactivity (VH; any variable value $>97.5\%$) in 13 patients (35%, significant with $P < .001$). Transient vertigo was mentioned by 2 patients; 1 of them showed VH. It was interesting that 4 patients with VH mentioned that they suffered from motion sickness.

Based on our own normal values for response level, only 3 patients had significant unilateral caloric hyporeflexia (including 2 patients with areflexia). In a bino-

mial distribution for 70 observations (ie, 2×35 caloric responses), this was not significant for a chance to occur of $P \leq .03$. Furthermore, no patients experienced bilateral weakness.

The vestibular findings did not differ significantly between males and females, different generations, different age groups, or family branches within the pedigree.

COMMENT

Owing to increasing awareness of the hereditary aspects of hearing loss, more than 50 autosomal dominant hereditary syndromes with hearing loss have been described to date.² Based on genetic linkage studies, more than 10 nonsyndromal autosomal dominant inherited types have been identified (DFNA1-DFNA11). We be-

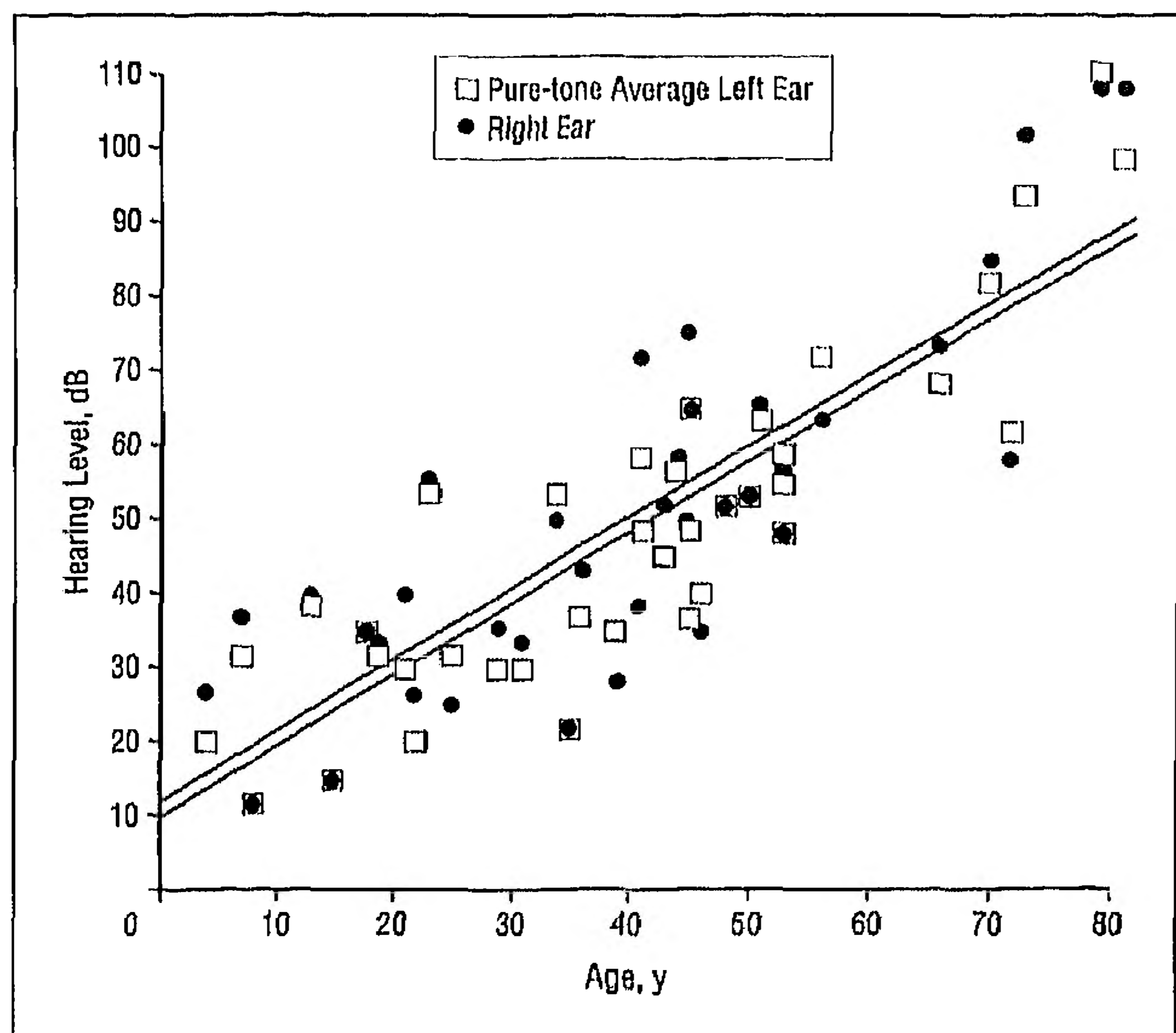


Figure 2. Linear progression with age.

lieve that a clinical diagnosis of autosomal dominant hearing loss can be simplified by taking care that the following criteria are fulfilled: the anamnesis must show evidence of hearing loss in at least 3 generations without any indications of an acquired origin; there must be objective audiological proof of hearing loss in at least 2 generations; and there must be at least 1 case of father-son transmission in the family. Our findings in the present family satisfy these criteria. The lack of any other characteristic supports the nonsyndromic aspect of this form of hearing loss.

The affected family members had a type of SNHL that was most pronounced at the higher frequencies and showed significant progression by an average of about 1 dB per year at all frequencies. The regression analysis indicated that at the middle and high frequencies, there was a substantial offset threshold: about 15 dB at 2 kHz, 30 dB at 4 kHz, and 50 dB at 8 kHz. It is likely that this SNHL is congenital, unless progression occurred much more rapidly at these frequencies during the first years of life. This disorder is one of the nonsyndromal autosomal dominant types of congenital high-frequency SNHL with progression at all frequencies. Owing to the apparent linear progression at all frequencies, the shape of the audiogram presumably will be preserved in every person from early childhood onward, whereas the extent of the SNHL will steadily increase until the threshold becomes saturated at the limit of the audiometric scale, first at the high frequencies and later at the low frequencies. Profound deafness with some residual hearing at the lower frequencies is the final stage.

The slow progression and the intersubject and interear variations were such that there was large variation in the age at which the average hearing threshold at the speech frequencies would indicate that the patient might benefit from the use of a hearing aid. Some of the patients might need a hearing aid starting at the age of 5 years, while others might not need any until the age of 40 years. In the latter case,

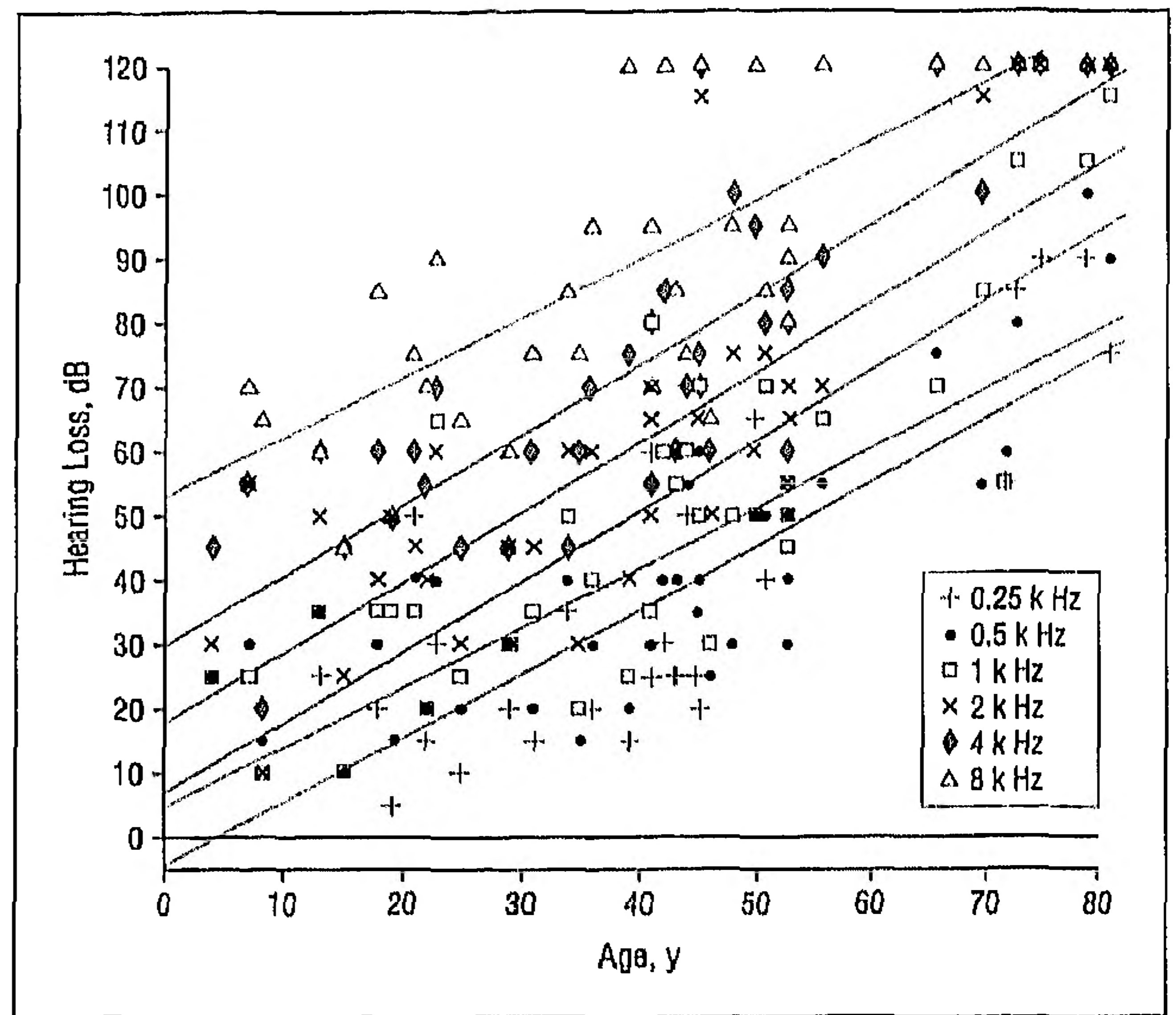


Figure 3. Pure-tone threshold (left ear) of all patients plotted against age.

the lower frequencies remain unaffected for a long time and the patient may be unaware of any hearing impairment for several decades, as was confirmed by some of our patients.

An elaborate audiometric analysis was performed in a different family about 30 years ago by Huizing et al.¹⁷ These authors observed differences in the rate of progression per frequency. The high frequencies showed increased thresholds in the early stages, followed by the low frequencies in the third decade of life.

These variations in audiometric characteristics provide support for the existence of different autosomal dominant nonsyndromic forms of hearing loss. On a gene level, different syndromes also seem to exist. The gene responsible for the hearing loss in the family described by Huizing et al (*DFNA5*) is located on chromosome 7p.¹⁶ A gene responsible for another form of high-frequency SNHL has been located on chromosome 1p (*DFNA2*).² Genetic-linkage studies on the present family led to localization of the diseased gene to the *DFNA2* locus on chromosome 1p.⁵ Unfortunately, it was impossible to perform a comparative analysis between the different families linked to *DFNA2* owing to the use of different audiometric methods. Resemblance between progression with age is present, but there is some difference between the date of onset.

The vestibular system was functional throughout life in our patients, although we found diminished or absent caloric excitability on 1 side in 15% to 17% of the patients. However, as already stated, for absolute response levels, only 3 patients (9%) showed significant unilateral caloric impairment, which may have been a false-positive finding. Given the impressively symmetrical hearing impairment in most patients, it is remarkable that we did not find any patients with bilateral caloric weakness.

In the patients with VH (35%), the vestibular system was working "too well," ie, the gain of the

vestibulo-ocular reflex was higher than usual, and about 31% of the patients with this finding reported suffering from motion sickness under certain conditions. The finding of VH in this disorder is puzzling. A hyperactive vestibulo-ocular reflex is a central abnormality, which has been reported in vestibulocerebellar dysfunction, multiple sclerosis, the hyperventilation syndrome, and idiopathic spasmodic torticollis.^{12,14,19,20}

CONCLUSIONS

The hearing loss analyzed in this family can be defined as a progressive high-frequency SNHL. Genetic linkage studies showed a positive linkage to the *DFNA2* locus. Because families with a positive linkage on *DFNA2* who live on different continents have been described, it is expected that this locus will play an important role in gene identification in inherited non-syndromal autosomal dominant hearing loss.

Statistical analysis of the audiological data shows a progression of 1 dB per octave per year in this type of progressive SNHL. This might be a clinical diagnostic criterion of the diseased gene on *DFNA2*. Similar analysis of audiological data from other families with linkage on *DFNA2* is necessary to support this conclusion, which can be of utmost importance for genetic counseling and carrier planning.

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