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Familial Progressive Sensorineural Deafness Is Mainly Due to the mtDNA A1555G Mutation and Is Enhanced by Treatment with Aminoglycosides

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Summary

Hearing loss involves both genetic and environmental factors. A mutation (A1555G) in the mtDNA has been associated with aminoglycoside-induced and nonsyndromic sensorineural deafness. The pathological significance of this mutation in Caucasoid families has not been established, and its relationship with antibiotic treatment is not well understood. We studied 70 Spanish families with sensorineural deafness (36 congenital and 34 late onset) for the mtDNA A1555G mutation. The A1555G mutation was found in 19 families with maternally transmitted deafness but not in the other 51 families or in 200 control subjects. In 12 families all the patients with the A1555G mutation who received aminoglycosides became deaf, representing 30.3% of the deaf patients in these families. None of the deaf patients from seven other families received aminoglycosides. Overall, only 17.7% of the patients with deafness and the A1555G mutation had been treated with aminoglycosides. The age at onset of deafness was lower (median age 5 years, range 1–52 years) in those treated with aminoglycosides than in those who did not receive antibiotics (median age 20 years, range 1–65 years) ($P <$ .001). The mtDNA of these families belongs to haplotypes common in Europeans. These data indicate that the A1555G mutation accounts for a large proportion of the Spanish families with late-onset sensorineural deafness, that the A1555G mutation has an age-dependent penetrance for deafness (enhanced by treatment with aminoglycosides), and that mtDNA backgrounds probably do not play a major role in disease expression.

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Introduction

Hearing loss affects ~1/1,000 infants, 5% of people <45 years of age, and 30% of subjects >70 years of age (Nance and Sweeney 1975; Cohen and Gorlin 1995; Van Camp et al. 1997). In ~50% of cases of profound deafness in childhood there is probably a genetic predisposition (Brown 1969; Morton 1991). In adult patients, presbycusis is the most common cause of hearing loss and also involves genetic and hereditary factors (Nadol 1993; Gorlin 1995). Hereditary deafness is a heterogeneous group of disorders with different patterns of inheritance (18% autosomal dominant, 80% autosomal recessive, and ~2% X linked) (Konigsmark 1969; Cohen and Gorlin 1995). Hearing loss of genetic origin can be conductive or sensorineural and can form part of a syndrome, with other clinical abnormalities (30%), or it may be the sole clinical symptom (70%) (Cohen and Gorlin 1995).

The number of genes involved in deafness is unknown but is estimated to be several hundred (Steel and Brown 1994; Petit 1996). The genetic bases of some syndromic forms of deafness have been discovered during recent years, and they include some of the genes that cause Waardenburg syndrome (Tassabehji et al. 1992, 1994), Norrie disease (Berger et al. 1992), and Usher syndrome (Weil et al. 1995). Nonsyndromic sensorineural hearing loss is also genetically determined, and linkage studies have localized >30 genes involved in autosomal dominant, autosomal recessive, and X-linked hearing loss (Petit 1996; Van Camp et al. 1997). Two genes involved in nonsyndromic sensorineural deafness (*POU3F4* at Xq21.1 and *MYOVIIA* at 11q13.5) already have been identified (Guilford et al. 1994; de Kok et al. 1995). Positional cloning and candidate-gene approaches are being undertaken to identify the other genes. Recently, mutations in the connexin-26 (*GJB2*) gene (Kelsell et al. 1997; Zelante et al. 1997) and in the *MYOVIIA* gene (Liu et al. 1997; Weil et al. 1997) have been detected in autosomal recessive sensorineural deafness.

It is likely that the interaction of genes with environmental factors plays an important role in the development of deafness, especially for late-onset cases. Most ototoxic substances are found in high concentrations in the inner ear and cause hearing loss by damaging the cochlea, in particular the auditory hair cells and the stria vascularis (Nadol 1993). Aminoglycoside antibiotics are well known for their ototoxicity, which affects ~25% of the patients who receive these drugs (Hawkins 1976). Recent work has shown that aminoglycosides produce an enhancement of the N-methyl-D-aspartate (NMDA)–receptor activity, resulting in hair-cell death through an excitotoxic mechanism (Basile et al. 1996).

Some sensorineural nonsyndromic and antibiotic-induced hearing losses show a mitochondrial mode of inheritance, being transmitted only through females. The relationship between deafness and mitochondrial mutations has been defined for mitochondrial syndromes associated with hearing impairment and also for nonsyndromic sensorineural deafness.

The A1555G mutation in the mitochondrial 12S rRNA has been associated with aminoglycoside-induced and nonsyndromic sensorineural deafness (Prezant et al. 1993). The pathological significance of this mutation in congenital and late-onset–deafness families has not been established, and its relationship with antibiotic treatment is not well understood. To investigate both the role played by the A1555G mutation in hereditary deafness and its relationship with aminoglycoside treatment, we have analyzed 70 unrelated and unselected Spanish families suffering from sensorineural hearing loss. We have found the A1555G mutation in the 19 pedigrees with progressive and maternally transmitted deafness. The study revealed that the A1555G mutation is the most common cause of late-onset familial sensorineural deafness in our families and that it originated independently in several lineages. Moreover, the study shows that aminoglycosides accelerate the development of deafness and that factors other than aminoglycosides probably contribute to deafness, in the presence of this predisposing mutation.

Patients and Methods

Patients and Families

We collected 70 Spanish families with severe sensorineural inherited hearing loss. The limiting criteria used in the selection of the families were that the deafness (congenital or progressive) had to be nonsyndromic and that the family had to have at least two affected members. Forty-two families were from clinical centers, and 28 were obtained through advertisements in the public media. The collection and analysis of samples was performed in accordance with the approved ethics rules for genetic studies. Informed consent for analysis was obtained from all members of the families that participated in the study. Families with deafness were classified as autosomal dominant, autosomal recessive, X linked, or mitochondrial (only maternal transmission), in accordance with the patterns of transmission of deafness. Pedigree analyses showed a segregation pattern of deafness consistent with maternal transmission, for 19 of the 70 families. For these 19 families the information regarding the onset and progression of hearing loss, the history of treatment with antibiotics, and the presence of other factors involved in deafness was collected from at least one member from each nuclear family, which implies several members from each of the pedigrees. For all the families with children, the information was ascertained from the parents (mainly the mother). For adult affected patients, the information was obtained from at least one relative from the same generation. We screened for the A1555G mutation in the index cases from the 70 deafness families and in all the available samples (58 affected and 44 at risk) from the 19 families consistent with maternal inheritance. The controls for the molecular analysis of the A1555G mutation were 200 normal subjects from the general population, who were originally from different regions of Spain. The controls for haplotype and phylogenetic analyses were 237 subjects from several western European countries, including Spain.

mtDNA Studies

The A1555G mutation was analyzed by amplification of mtDNA, by PCR using 50 ng of DNA and 10 pmol of each primer (5′-GCT CAG CCT ATA TAC CGC CAT CTT CAG CAA-3′ [sense] and 5′-TTT CCA GTA CAC TTA CCA TGT TAC GAC TGG-3′ [antisense]), by digestion of the amplified 339-bp fragment, with the restriction enzyme *Hae*III, and by electrophoresis on a 3% agarose gel. The antisense oligonucleotide was modified by changing the penultimate nucleotide from T to G (underlined), which created the restriction site *Hae*III (GGCC/CCGG) if the G at position 1555 of the 12S rRNA was present in the patient. The PCR product contains another *Hae*III site, which serves as a control of enzyme digestion. Normal subjects have two fragments, of 216 bp and 123 bp, and the affected patients have fragments of 216 bp, 93 bp, and 30 bp, owing to the creation of a *Hae*III site by the A1555G mutation. The presence of the A1555G mutation was confirmed by sequencing of the PCR products, with a 373A DNA sequencer and the cycle dye terminator DNA sequencing kit (Applied Biosystems). Two point mutations in the tRNA(Ser), at nt 7445 and 7472, and possible deletions or duplications of the mtDNA (Reid et al. 1994; Tiranti et al. 1995) also were studied.

Haplotype and Phylogenetic Analyses

The entire mtDNA of 10 patients from 10 unrelated pedigrees (S1–S10) was amplified in nine overlapping fragments, by PCR, as described elsewhere (Torroni et al. 1996). Each of the nine PCR segments was digested with 14 restriction endonucleases (*Alu*I, *Ava*II, *Bam*HI, *Dde*I, *Hae*II, *Hae*III, *Hha*I, *Hin*cII, *Hin*fI, *Hpa*I, *Msp*I, *Mbo*I, *Rsa*I, and *Taq*I). All subjects were screened for several European-specific polymorphisms, including a *Bst*NI site at nt 13704, an *Acc*I site at nt 15254, two *Nla*III sites, at nt 4216 and 4577, a *Bfa*I site at nt 4917, and an A/G polymorphism at nt 12308 in the tRNA(Leu) gene (Torroni et al. 1997). Restriction fragments were resolved by electrophoresis on NuSieve plus SeaKem agarose (FMC BioProducts) gels. This procedure allows both the screening of ~20% of the sequence variation in each mtDNA and the definition of haplotypes.

The phylogenetic relationships between the haplotypes of the patients and those found in 237 European control subjects were inferred by parsimony analysis. The dendrograms were rooted by use of the African haplotype AF71 (the so-called African outgroup), which is a member of the African-specific haplogroup L and already has been used as an outgroup (Torroni et al. 1994). Maximum-parsimony trees were generated by random addition of sequences, by use of the "Tree Bisection and Reconnection" algorithm (phylogenetic analysis using parsimony) (Swofford 1993). The analysis was terminated at 1,000 trees, after 140 replications.

Statistical Analyses

Log-transformed ages at onset of deafness were compared between the group of deaf patients who received aminoglycosides and (*a*) the group of relatives with deafness and the A1555G mutation who were not treated with antibiotics, by use of the two-way (relation and treatment with aminoglycosides) analysis of variance, and (*b*) the entire group of deaf but untreated patients, by use of Student's *t*-test for independent data. χ^2 Tests were used to compare differences between groups of patients and at-risk individuals and also between the deafness families collected from clinical centers and those ascertained through advertisements in the public media. The statistics package SPSS 6.1.3 was used for calculations. The penetrance of the mtDNA A1555G mutation was calculated as the complementary function of the cumulative proportion of survival. This was calculated for the A1555G patients treated with aminoglycosides, for those untreated, and for all the subjects with the A1555G mutation.

Results

Maternally Transmitted Progressive Sensorineural Deafness

Among the 70 families, 36 had congenital deafness, and in 34 the hearing loss was progressive. Nineteen (27.1%) of the 70 pedigrees showed a segregation pattern of deafness that was consistent/compatible with maternal transmission, whereas 40 (57.1%) were recessive, 10 (14.3%) were dominant, and 1 (1.4%) was X linked. There were differences between the deafness families collected from clinical centers and those ascertained through advertisements in the public media, with a larger number of congenital families from the clinical centers ($P < .02$) and a larger number of mitochondrial cases from advertisements in the media ($P < .001$). The 19 families with maternal transmission included a total of 214 deaf patients and 215 subjects (the unaffected children and siblings of a woman with a mitochondrial mutation) "at risk" of developing deafness (fig. 1). The 19 families were from different regions of Spain, and there was no consanguinity.

The affected subjects of the 19 families with maternally inherited deafness presented with bilateral and sensorineural hearing loss as the sole clinical symptom. Most of the patients had late-onset/progressive deafness, but in eight patients, from six different families, deafness started at <2 years of age. There was a wide variability in the age at onset of deafness within each family. The age at onset of deafness was within the range of 1–65 years (mean $\pm$ SD = 20.7 $\pm$ 18.6) and was <40 years in 82.5% of the cases. Audiometric studies of 20 affected individuals showed severe to profound sensorineural bilateral deafness at 40 dB, at 250 Hz, and at 110 dB, at 8,000 Hz. No other clinical alterations, including CNS or neuromuscular problems, cardiomiopathy, or diabetes, were observed in the patients. Biochemical studies of 12 deaf patients failed to detect hyperglycemia or other abnormalities.

Familial Sensorineural Deafness and Treatment with Aminoglycosides

In 12 (52.6%; S2, S4, S6–S11, S14, S16, S18, and S19) of the 19 families with maternally inherited deafness, all the patients that received aminoglycosides became deaf (one to seven patients per family), but these patients represent only 30.3% of the affected family members (fig. 1). The relationship between deafness and treatment with aminoglycosides was absolute in only three pedigrees (S2, S7, and S8). In families S4, S11, and S14, 30%–50% of the deaf patients received antibiotics. However, in six other families (S6, S9, S10, S16, S18, and S19) only 1–3 patients with deafness, of 4–26, received aminoglycosides. There were several cases in

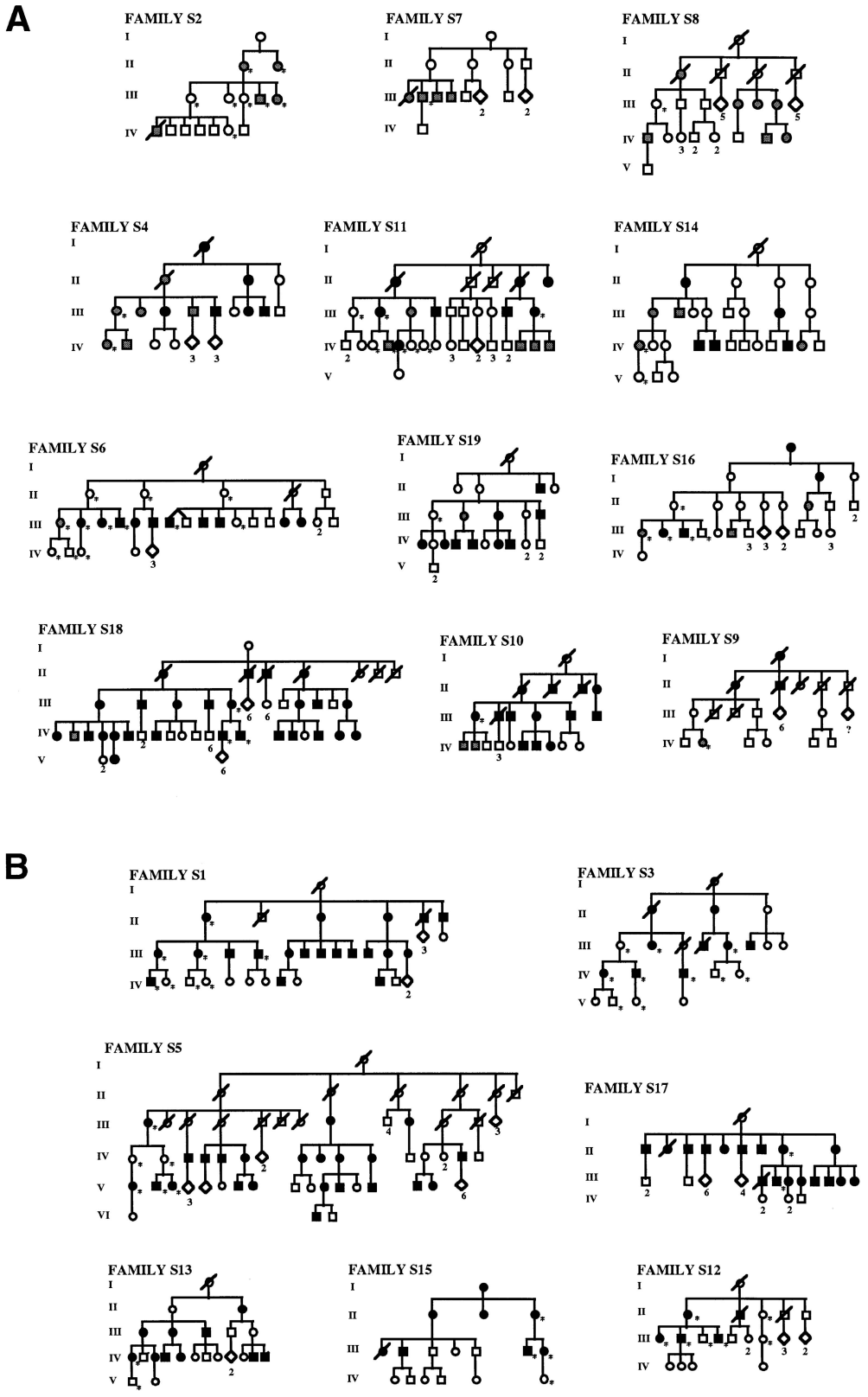

Figure 1 Nineteen Spanish pedigrees affected by maternally inherited deafness and harboring the A1555G mutation in the 12S rRNA gene of the mtDNA. *A,* Twelve pedigrees with deafness related to treatment with aminoglycoside antibiotics, for at least one affected subject. *B,* Seven pedigrees with deafness not related to aminoglycoside treatment. Blackened symbols indicate patients who have developed sensorineural deafness and were not treated with aminoglycosides. Gray-shaded symbols indicate deaf patients who have received antibiotic treatment. An asterisk (*) indicates the patients from whom DNA samples were obtained. A number beneath a symbol indicates the number of descendants. The A1555G mutation was found in all the deaf patients analyzed and in their maternal relatives.

which hearing loss developed before the clinical introduction of aminoglycosides. In family S4 patient I-1 developed deafness at 20 years of age (in 1910), and in family S9 two patients (I-1 and II-1) became deaf in 1916 and 1936, respectively. Finally, in seven families (S1, S3, S5, S12, S13, S15, and S17; 5–23 deaf patients/family) there was no record of aminoglycoside administration.

Mitochondrial A1555G Mutation in Progressive Deafness

An adenine-to-guanine transition at nt 1555 of the mtDNA (the A1555G mutation) (Prezant et al. 1993) in the 12S rRNA gene was found in homoplasmia in all the subjects (102 patients) analyzed from the 19 families with maternally transmitted deafness (fig. 2). The A1555G mutation was not found in 200 control subjects or in the index patients from the 51 families with a Mendelian pattern of inheritance of deafness. Deafness was reported in 214 (49.9%) of the 429 patients who were expected to have received the A1555G mutation from their A1555G-positive mothers. A previously unknown nucleotide change in the mtDNA (C→T transition at nt 1537 of the 12S rRNA) was detected in family S4 (fig. 2). Since this change eliminates a restriction site for the enzyme *Nsi*I, digestion with this enzyme was used to study the other affected families and the normal subjects. The change was present in homoplasmia in all maternally related family members from family S4 and was not found in the other families or in 50 normal subjects.

Age at Onset and Penetrance of the A1555G Mutation

The age at onset of deafness in the patients treated with aminoglycosides was lower (mean ± SD = 11.1 ± 12.1 years, median 5 years, range 1–52 years) than in those who did not receive antibiotics, when either the patients from all the families (mean ± SD = 21.2 ± 17.6 years, median 16 years, range 1–65 years) ($t = 2.84$; $P = .006$) or only those from the families with a record of exposure to aminoglycosides (mean ± SD = 24.8 ± 17.4 years, median 20 years, range 1–65 years) ($F = 21.2$; $P < .001$) were considered. The probabilities that an individual with the A1555G mutation develops hearing loss by a certain age are shown in figure 3. The probabilities of deafness at 30 years of age are 96.5% in the treated group and 39.9% in the untreated group.

One hundred thirty-seven at-risk patients (with the A1555G mutation) from the families with aminoglycoside treatment (age range 1–84 years, mean ± SD = 32.3 ± 21.3 years) and 78 at-risk subjects from the families without a record of aminoglycoside treatment (age range 1–80 years, mean ± SD = 31.0 ± 22.2) were asymptomatic at the time of the study or did not develop deafness during their lifetime. Both the similar proportion of deaf patients (47.1% with antibiotic treatment and 54.1% without), with respect to the at-risk subjects, in the two groups of families and the similar mean age of the at-risk subjects in the two groups demonstrate the strong role of the A1555G mutation in causing deafness, regardless of treatment with aminoglycosides.

Phylogenetic Analysis of mtDNAs with the A1555G Mutation

The mtDNA haplotypes for 10 unrelated patients belonging to families S1–S10 were determined. Haplotype analysis revealed that these subjects harbored five different haplotypes described in Europeans (haplotypes 1, 2, 64, 109, and 123; fig. 4). Haplotypes 1, 2, and 64 are members of haplogroup H (Torroni et al. 1994) and were present in eight families (S2, S3, and S5–S10) with the A1555G mutation. Haplogroup H is the most common in western Europeans and reaches a frequency of >50% on the Iberian peninsula. Family S4 belongs to haplogroup V, which is common on the Iberian peninsula, with a frequency of 20%. Both haplogroup H and haplogroup V are European specific (Torroni et al. 1996). Finally, the haplotype observed in family S1 belongs to haplogroup L, which is African specific but not uncommon in some southern European populations (Spanish and southern Italian) (Torroni et al. 1994; Chen et al. 1995). The parsimony tree of the mtDNA haplotypes in the 10 sensorineural deafness patients is shown in figure 4. This maximum-parsimony tree includes the five haplotypes observed in the patients and those described elsewhere in 237 European controls. The length of this tree is 374 steps, and it has consistency and retention indices of .837 and .904, respectively.

Discussion

Common progressive (late-onset) deafness probably is due to the combined action of mutations in susceptibility genes (mitochondrial or nuclear) and environmental factors. Unfortunately, the link between gene abnormalities and environmental influences in causing disease is still poorly understood. We have detected the mitochondrial A1555G mutation in 19 Spanish pedigrees (27.1% of the total families studied) affected with progressive sensorineural deafness. This mutation previously had been reported only in a few families, either in combination with aminoglycoside treatment (two Chinese [Prezant et al. 1993], three Japanese [Hutchin et al. 1993], and two Mongolian [Pandya et al. 1997] pedigrees) or in the absence of antibiotic treatment (one Arab-Israeli pedigree [Prezant et al. 1993] and one Zairean pedigree [Matthijs et al. 1996]). More recently, it also has been

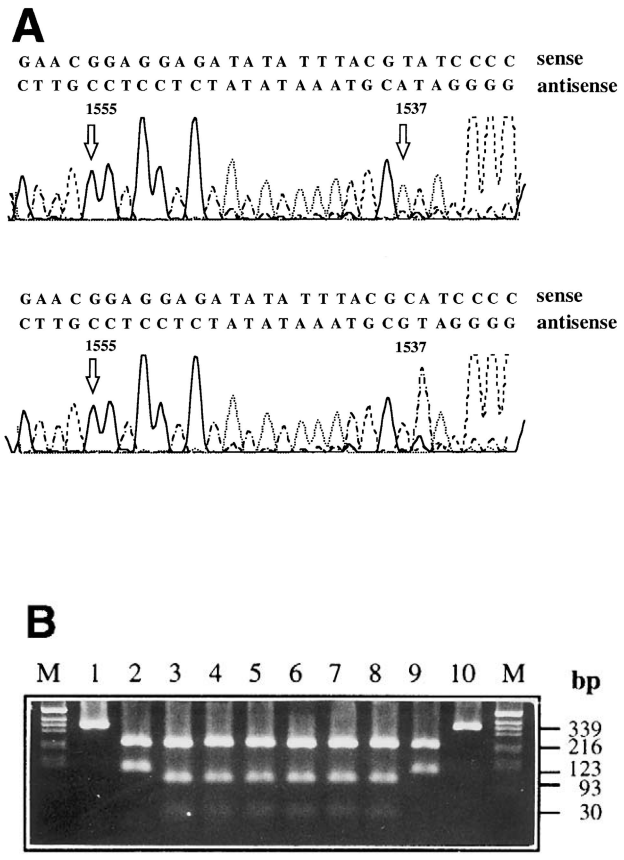

Figure 2 *A,* Identification of the A1555G mutation and the nucleotide change 1537T, in the 12S rRNA of the mtDNA. *Top,* Partial sequence of the 12S rRNA gene, showing the 1555 A→G transition, with the T at nt 1537, in one affected member (III-1) of family S4. *Bottom,* Partial sequence showing the common C at nt 1537 and the A1555G mutation, in a deaf patient (II-1) from family S2. The antisense chromatograms are shown. *B,* Detection of the mtDNA A1555G mutation in patients affected by maternally transmitted sensorineural deafness. The analysis of the A1555G mutation was performed by PCR amplification of a segment of the mitochondrial 12S rRNA gene and by digestion with the restriction enzyme *Hae*III. Lane M, Molecular-weight marker. Lanes 1 and 10, Undigested control samples. Lanes 2 and 9, Digested control samples. Lanes 3–8, Index cases of families S1–S6. The digested samples from control subjects have two fragments, of 216 bp and 123 bp. The samples from affected patients have fragments of 216 bp, 93 bp, and 30 bp, owing to the creation of a *Hae*III site by the A1555G mutation.

detected in two Spanish families (El-Schahawi et al. 1997) and in five Japanese families, with several subjects having progressive deafness without treatment with aminoglycosides (Usami et al. 1997). The phylogenetic analysis of the mtDNA haplotypes that was performed here revealed that the A1555G mutation in the Spanish families is the product of at least five independent mutational events. Because 6 of the 10 pedigrees harbored the most common European haplotype (haplotype 2), it is also likely that at least some of the A1555G mutations in haplotype 2 represent independent mutational events rather than a single mutational event transmitted, by descent, to the 6 pedigrees.

The detection of the mutation in patients with mtDNA haplotypes that are very divergent indicates that the A1555G mutation is the primary mtDNA factor contributing to sensorineural deafness and that mitochondrial genetic background probably does not play a major role in disease expression. This is further supported by the haplotype distribution of the A1555G mutation among affected Spanish families, which is similar to that found in the general Spanish population, indicating that there is no association between certain haplogroups and maternally transmitted sensorineural deafness.

The A1555G mutation occurs in a highly conserved region of the mitochondrial 12S rRNA, where the mRNA is decoded. It has been postulated that the A1555G mutation elongates the tRNA binding region on the ribosome, with an adverse effect on the fidelity of the translation of the mRNA, leading to hair-cell death (Prezant et al. 1993). Both the strong association between the A1555G mutation and sensorineural deafness and the lack of association with a specific haplogroup strongly support the hypothesis that this mitochondrial change is the main cause of deafness.

Whereas the relationship between the A1555G mutation and deafness after treatment with aminoglycosides is absolute, only 17.7% of the deaf patients that have this mutation received these antibiotics, and in several cases deafness occurred before the introduction of aminoglycosides into clinical practice, ~50 years ago. Thus, in seven of the families presented here and in the Arab-Israeli pedigree (Prezant et al. 1993) and the Zai-

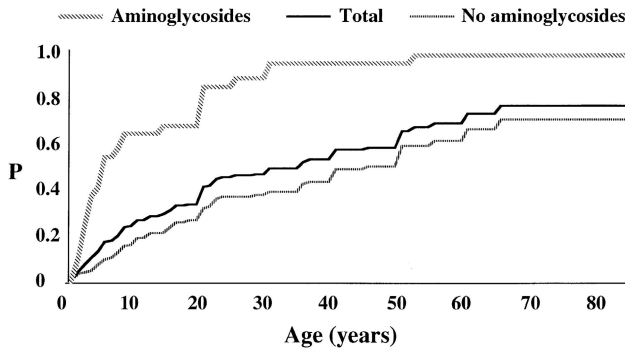

Figure 3 Graph of the probability that an individual possessing the mtDNA A1555G mutation will develop hearing loss by a certain age. The patients were grouped into those treated with aminoglycosides, those untreated, and the total number of patients. The curves represent the complementary function of the cumulative proportion of survival. This allows estimation of the age-dependent penetrance of the A1555G mutation. The median time to deafness was 5.63 years for the treated group, 40.99 years for the untreated group, and 30.83 years for the total.

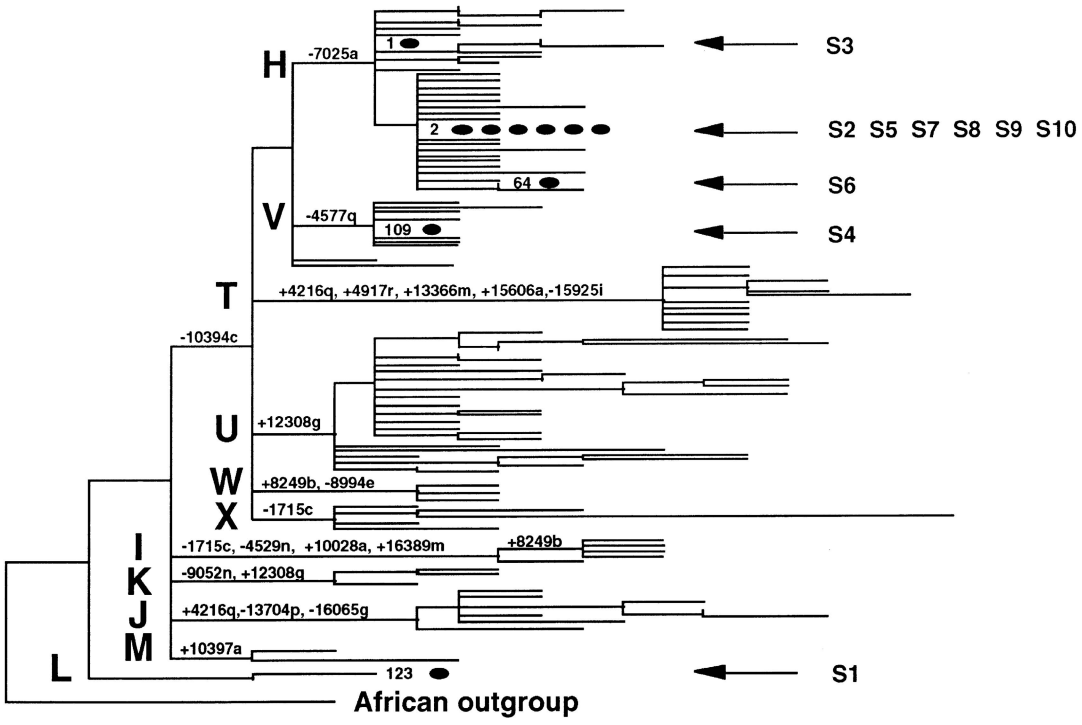

Figure 4 Phylogenetic tree of mtDNA haplotypes of patients with sensorineural deafness and the A1555G mutation. This maximum-parsimony tree includes five different haplotypes (1, 2, 64, 109, and 123) observed in the 10 unrelated patients from pedigrees S1–S10 (*blackened ovals*) and the haplotypes described elsewhere for 237 European controls. The patients' haplotypes are defined by the following mutations, relative to the reference sequence (GenBank D38112): for S1 (haplogroup L), +3592h, +10394c, +13803e, +16389g/−16390b, and +16517e; for S2, S5, S7, S8, S9, and S10 (haplogroup H), −7025a and +16517e; for S3 (haplogroup H), −7025a; for S4 (haplogroup V), −4577q; and, for S6 (haplogroup H), −7025a, +3846c/−3849e, and +16517e. The tree was rooted by use of a Senegalese haplotype ("African outgroup") belonging to the African-specific haplogroup L (Torroni et al. 1994). "H," "I," "J," "K," "L," "M," "T," "U," "V," "W," and "X" indicate major haplotype groupings (haplogroups), and the numbers associated with the lowercase letters indicate the sites for the restriction enzymes that define the specific haplogroups. The restriction enzymes correspond to the following code: a, *Alu*I; b, *Ava*II; c, *Dde*I; e, *Hae*III; g, *Hin*fI; h, *Hpa*I; k, *Rsa*I; i, *Msp*I; m, *Bam*HI; n, *Hae*II; p, *Bst*NI; q, *Nla*III; and r, *Bfa*I. The horizontal-branch lengths are proportional to the number of mutational events that separate the haplotypes, with the exception of the 16517 *Hae*III site. In the parsimony analysis, this hypervariable site was assigned half the weight assigned to all other sites.

rean pedigree (Matthijs et al. 1996) there was no record of treatment with aminoglycosides. Interestingly, only on rare occasions, the A1555G mutation has been detected in sporadic cases of aminoglycoside-induced deafness (Fischel-Ghodsian et al. 1993, 1997; Hutchin et al. 1993). Therefore, treatment with these antibiotics clearly is not indispensable for the development of hearing loss associated with the A1555G mutation. Since it has been shown that aminoglycosides cause hair-cell death through enhancement of NMDA-receptor activity (Basile et al. 1996), it is possible that aminoglycoside ototoxicity and the A1555G mutation follow different pathogenic pathways, which converge in hair-cell death and the deafness phenotype.

Is the A1555G mutation alone enough to produce hearing loss? Since not all the patients with the A1555G mutation became deaf (50% penetrance by 30 years of age, 88% penetrance by 65 years of age), other factors must contribute to the development of deafness in the affected subjects. With regard to the Arab-Israeli pedigree, the action of a recessive modifying nuclear gene on the A1555G effect had been suggested (Prezant et al. 1993) (also suggested for the Zairean pedigree; Matthijs et al. 1996). One important difference between the A1555G families described here and the Arab-Israeli family is that hearing loss is mainly congenital in the latter (Prezant et al. 1993) but is progressive and of later onset in the Spanish families. It is likely that this reflects either different modifying factors (genetic or environmental) in the two genetic backgrounds or the presence of a major nuclear gene in the Arab-Israeli family.

In conclusion, this study shows that the A1555G mutation is a major factor in progressive inherited deafness (with age-dependent penetrance) and that its penetrance can be enhanced by treatment with aminoglycosides. We also show that the A1555G mutation is much more com-

mon (27.1% of all Spanish families with sensorineural deafness, 55.9% of those with progressive deafness) than was suspected previously. This finding suggests that this mutation also might be common in affected families of other European populations and that screening for the A1555G mutation should be performed routinely in molecular-diagnostic centers. One of the reasons why, in the past, the A1555G mutation had been rarely observed in deaf families of European descent is probably due to a bias, toward congenital cases, in the ascertainment of families. Since the nonsyndromic-deafness families studied here were selected randomly and include both families with congenital deafness and those with progressive deafness, it is likely that the figures previously published for patterns of inheritance of hearing loss (mainly based on congenital cases) are incorrect. The identification of the A1555G mutation in families with deafness, the presymptomatic detection of this mutation in maternally related subjects, and the avoidance of aminoglycosides by individuals who are positive for the A1555G mutation should help in the prevention of deafness.

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