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Audiological and genetic features of the *mt*DNA mutations

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Abstract

Conclusions—Significant difference in the incidence of mitochondrial DNA (mtDNA) mutations was found between the Chinese and USA populations. The identification of the *mt*DNA A1555G mutation in a large proportion of Chinese probands with nonsyndromic sensorineural hearing loss (NSHL) provides a molecular explanation for the high prevalence of aminoglycoside-induced deafness in China.

Objective—The aim was to characterize the audiological and genetic features of NSHL due to mutations in *mt*DNA.

Subjects and methods—The mtDNA and audiogram analyses were performed in 498 NSHL patients (290 from China and 208 from the USA) with and without history of aminoglycoside exposure. A PCR and restriction enzyme digestion protocol was used for mutational screening and the European Workshop on Genetic Hearing Loss criteria were applied for audiological classification.

Results—All Chinese probands (15.5%) with *mt*DNA mutation were found to carry the homoplasmic *mt*DNA A1555G mutation, whereas four probands (1.9%) from the USA were found to carry the *mt*DNA A1555G and two (1%) had *mt*DNA G7444A. Approximately 63% of the probands with *mt*DNA mutations had post-lingual hearing loss and 56.8% of them had a medical history of exposure to aminoglycosides. Hearing losses are bilateral, sensorineural, and symmetric. The main audiogram shapes found were sloping.

Keywords

Mitochondrial DNA; nonsyndromic sensorineural hearing loss; mutation; aminoglycoside-induced deafness

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Introduction

Hearing impairment is the most common disorder of sensorineural function and is an economically and socially important cause of human morbidity. Genetic factors are known to represent a major cause of hearing loss. The bulk (around 80%) of genetic deafness is nonsyndromic, which is often neuroepithelial in origin arising from defects in the function of the organ of Corti – the site of auditory transduction in the inner ear. To date, 59 loci involved in nonsyndromic deafness have been described (http://webhost.ua.ac.be/hhh/). Because of this extreme genetic heterogeneity, it had always been assumed that genetic hearing loss was caused by a very large number of equally rare genetic types whose specific identification in individual cases would remain an arduous task. It therefore came as surprise to learn that two forms of genetic deafness are much more frequent than all others, accounting for at least 30% of all genetic cases in many populations. One of these genes, the Connexin 26 (*GJB2*) gene, encodes a gap junction protein expressed in the cochlea and important for recycling potassium ions that flow into sensory hair cells as part of the transduction current [1]. Mutations in the *GJB2* gene have been found to be responsible for the commonest form of nonsyndromic recessive deafness in many populations (http://www.crg.es/deafness). The second common form of genetic deafness is the A1555G substitution in a mitochondrial ribosomal RNA gene, which causes increased susceptibility to aminoglycoside antibiotic-induced deafness as well as nonsyndromic hearing loss (NSHL) [2,3]. Since 1993 there have been numerous reports and studies showing that A1555G mutation is one of the most common mutations in the mitochondrial genome that can cause NSHL, often precipitated by use of aminoglycoside. The mitochondrial DNA (mtDNA) A1555G mutation has been reported in many ethnic groups, with more than 20% of deaf individuals carrying this mutation in some populations [4]. Susceptibility to aminoglycoside-induced hearing loss is maternally inherited in humans in a significant proportion of cases, particularly in the Chinese and Japanese populations [5–9]. However, these studies are case reports and have focused on familial cases. Moreover, previous observations on the audiograms of patients with mtDNA deafness (referred to all degrees of hearing loss) have shown that they exhibit considerable variations of their hearing loss [10,11], but the full range of phenotypic expression has not been well characterized – mainly due to the lack of consensus on audiological criteria and a small number of cases. This makes comparison difficult and results in limited information on the audiological characteristics of mtDNA deafness in most investigations.

In the present study, we screened DNA for the *mt*DNA mutations from two cohorts of deaf probands with nonsyndromic deafness from China and from the USA by a simple and reliable PCR restriction enzyme digestion protocol. Using the audiological classification criteria of genetic deafness proposed by the European Workshop on Genetic Hearing Loss (European Concerted Action Project on Genetics of Hearing Impairment, http://www.gendeaf.org, 1996), we analyzed audiograms of these patients in an attempt to provide a more accurate estimate of the contribution of these mutations to NSHL and to characterize the audiological features of patients with *mt*DNA deafness.

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Patients and methods

Subjects

All Chinese subjects were recruited from the Clinic for the Deaf in Beijing and Chengdu, China and the outpatient service of the Department of Otolaryngology, University of Miami. Patients recruited from the Florida area were of European ancestry or were mixed-Hispanics (a combination of at least two of the following races: White, Black, and Native American).

A total of 498 probands with nonsyndromic hearing loss were ascertained (290 from China and 208 from the USA). Both familial (248) and sporadic (250) cases have been identified. The age of the patients ranged from 7 years to 80 years. For each patient, the clinical and family history was obtained and complete physical examinations were performed by one of the investigators. A structured systems review was used to elicit evidence for syndromic forms of hearing loss such as Waardenburg syndrome, Pendred syndrome, Jervell and Lange-Nielseon syndrome, branchio-oto-renal syndrome, Alport syndrome, Norrie disease, Usher syndrome, and X-linked congenital fixation of the stapes [12,13]. Individuals were excluded from the study if the results of physical examination or routine investigations revealed a syndromal association. We also excluded from the analysis those patients with a recognized environmental cause such as infections or trauma. Information on exposure to known or possible ototoxic drugs was obtained. We are aware of some limitations to the study. History of aminoglycoside use was obtained by questionnaire and may therefore be subject to recall bias. Approval for human subjects for this study was obtained from the institutional review board (IRB) at the University of Miami. Informed consent was obtained for all participants.

DNA amplification and mutation screening

Genomic DNA was extracted from peripheral blood. By mutation screening, we have excluded *SLC26A4* (Pendred syndrome) and *GJB2* as deafness causative genes in the Chinese samples. The involvement of GJB2 in patients from the USA has been excluded. The primers pairs used for PCR amplification and method analysis of the *12S rRNA* and $tRNA^{Ser\,(UCN)}$ mutations were described previously by Pandya et al. [14]. In brief, DNA samples were tested for the presence of A1555G and A7445G mitochondrial mutations, by subsequent digestion of the PCR products with restriction enzymes. The A1555G mutation abolishes a site for the *Alw*26I enzyme. The undigested PCR product of 1605 bp is digested in normal individuals to yield bands of 1106, 293, and 206 bp, whereas in affected individuals, absence of the restriction site results in a larger band at 1399 bp and in the lower band at 206 bp. The PCR product obtained with primers for the nt7445 mutation is 662 bp. In unaffected individuals, digestion with the restriction enzyme *Xba*I results in two bands – 400 and 262 bp in size. The presence of A7445G abolishes the recognition sequence for this enzyme with absence of digestion after incubation with the enzyme. Because of the heterogeneity of mutations at the nucleotide 7445, we direct sequenced DNA from the individuals positive for the loss of an *Xba*I restriction site to screen for mutation at one of three adjacent base pairs, i.e. 7443, 7444, or 7445. Approximately 100 ng gelpurified PCR products were sequenced using the ABI PRISM BigDye Terminator Cycle Sequencing

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reaction kit. The sequencing reactions were subsequently analyzed in an automated ABI Prism 3100 sequencer.

Audiological classification criteria of genetic deafness proposed by the European Workshop on Genetic Hearing Loss

The results of the pure tone audiograms (PTAs) were analyzed using the audiological classification criteria of genetic deafness proposed by the European Workshop on Genetic Hearing Loss (http://www.gendeaf.org). All subjects were otoscopically examined, and pure tone audiometry was performed on all subjects. Air and bone conduction thresholds were measured at 250 Hz, 500 Hz, 1 kHz, 2 kHz, 4 kHz, 6 kHz, and 8 kHz.

Results

Contribution of the screened common mtDNA mutations to NSHL

A frequency estimated to be 15.5% (45/290) of NSHL cases was attributed to the homoplasmic *mt*DNA A1555G mutation in probands from China. Of the 208 NSHL patients from the USA, 4 were found to have the homoplasmic *mt*DNA A1555G mutation and 2 had the homoplasmic G7444A, giving a prevalence of *mt*DNA mutation of ~2.9%. Of the 51 deaf probands with mtDNA mutations, 18 (~35%) had a positive family history, whereas 33 (~65%) were sporadic cases. Twenty-nine Chinese probands (~64%; 29/45) with *mt*DNA mutations had a history of exposure to aminoglycosides, including gentamicin, streptomycin, and kanamycin. These subjects, due to infections or other illness, had received aminoglycosides (3–5 mg/kg/dose every 8 h for gentamicin, 15–25 mg/kg/dose every 12 h for streptomycin, 15 mg/kg/day every 8 h for kanamycin) at 1 year to 30 years. Hearing impairment usually occurred within 1–3 months after the administration of drugs. Comparison of incidence of mtDNA A1555G mutations between Chinese and USA probands is significant, with p values <0.001 (Table I).

Audiometric data of patients with mtDNA mutations

Audiometric data were available for 329 of 498 probands. A total of 33 of the probands (~62.8%; 32/51) with *mtDNA* mutations had post-lingual hearing loss. Approximately 68.6% (35/51) of patients with *mtDNA* had mild to moderate hearing loss and 31.4% (16/51) were found to have severe to profound hearing loss. Fourteen (88%, 14/16) of this latter group of probands had a medical history of exposure to aminoglycosides. For the patients without *mtDNA*, a total of 32% (89/278) had mild to moderate hearing loss and 68% (189/278) had severe to profound loss. Difference in distribution of degree of hearing loss among patients with and without mtDNA mutation is significant, with p values <0.001. Hearing losses associated with *mtDNA* mutation are bilateral and symmetric. The main audiogram shape found was mainly sloping (78.4% of the cases) and nonspecific (Table II). Results of the distribution of level of hearing loss in 29 deaf probands with and 22 with no history of aminoglycosides exposure are summarized in Table III. Fourteen of the 29 (48.3%) patients with a history of aminoglycosides exposure had severe or profound deafness whereas 2 of 22 of probands without drug exposure were found to have severe or profound hearing loss. Probands with history of aminoglycosides exposure are approximately 10 times more likely to have severe to profound hearing loss than probands

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without aminoglycosides exposure ($\chi^2 = 8.136$, $p = 0.004$, 95% confidence intervals = 2.031, 51.903; odds ratio = 10.267).

Variations in the severity of deafness and audiogram shapes were noticed within and between 10 families in which more than 2 affected persons had been tested. It was impossible to investigate the progression of hearing impairment in the present study because serial audiograms were only available in a few cases. In 54 families in which all family members were tested, individuals with various degree of hearing loss were found in 60% of the families. Audiogram shape showed intrafamilial and interfamilial variability.

Discussion

We first consider the prevalence of mtDNA mutations. Mitochondrial pathology plays an important role in both inherited and acquired hearing loss. Sensorineural hearing loss (SNHL) is present in 42–70% of individuals with mitochondrial disorders and can be syndromic and nonsyndromic [4,15,16]. *mt*DNA mutations have been identified in more than 3% of patients with SNHL [11,17]. The mitochondrial *12S rRNA (MTRNR1)* appears to be a hot spot for *mt*DNA mutations. The homoplasmic A1555G mutation of this rRNA has been associated with aminoglycoside-induced hearing loss and NSHL in many families of different ethnic origins [3,18–25]. In Spanish and Mongolian deaf probands, the 1555A-G mutation accounts for >20% of families with sensorineural deafness [3,18]. In the present study, we showed that all the deaf patients from China were found to carry the *mt*DNA A1555G mutation and we estimate that 15.5% of SNHL cases were attributed to the mutation. A total of four (1.9%) deaf probands from the USA carried the *mt*DNA A1555G mutation. Our findings indicate that the *mt*DNA A1555G is responsible for deafness in a large proportion of NSHL in China.

The mitochondrial *tRNA*$^{Ser\ (UCN)}$*(MTTS1)* is another hot spot for mtDNA mutations associated with NSHL. Four deafness-associated mutations – A7445G [26–28], 7472insC [29,30], T7510C [31], and T7511C [32–34] – have been identified in this gene. None of these mutations were detected in our sample. However, we have identified the G7444A mutation in 2 of 208 probands from the USA. The G7444A mutation in the mitochondrial COI/tRNA-Ser(UCN) genes was reported to influence the phenotypic expression of hearing loss associated with the A1555G mutation [14,35] and the visual loss caused by the primary LHON-associated mtDNA mutations [36]. However, the occurrence of the G7444A mutation in several unrelated subjects affected by hearing impairment strongly indicates that the mutation is directly involved in the pathogenesis of hearing impairment. Nuclear modifier gene(s) or aminoglycoside(s) may play a role in the phenotypic expression of the deafness-associated G7444A mutation in two Chinese pedigrees [37].

Mutations in *mt*DNA have also been found to be associated with both aminoglycoside-induced and nonsyndromic deafness [38,39]. These drugs are known to exert their antibacterial effects by directly binding to 16S ribosomal RNA (rRNA) in the 30S subunit of the bacterial ribosome, causing mistranslation or premature termination of protein synthesis [40,41]. Patients with hearing loss induced by aminoglycoside can be divided into two types: those who have received an ototoxic dose of aminoglycosides without evidence of genetic

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background as precipitating factor and those who are treated with a normal dose, sometimes one single dose, of aminoglycoside but with maternally transmitted predisposition to aminoglycoside ototoxicity.

The matrilineal transmission of aminoglycoside-induced deafness in the Chinese population was first reported in isolated pedigrees in the early 1990s and mutations in the *mt*DNA were suggested as the likely cause [5,6]. The most commonly used ototoxic drugs used in China are aminoglycoside antibiotics including streptomycin, gentamycin, and kanamycin. Aminoglycoside antibiotics were widely used and in many cases over-used nationwide in China from the 1960s to the 1980s, as they were considered cost-effective in controlling infections by a wide spectrum of bacteria. Despite the large number of reports on aminoglycoside-induced hearing loss in China and in other countries, aminoglycosides and a few new synthetic derivatives from traditional aminoglycosides, such as amikacin, netilmicin, etimicin, and isepamicin, are still being used in clinics all over China, especially in low income areas including mountainous areas.

The incidence of aminoglycoside-induced deafness has increased in recent years in China. Some studies of deaf-school populations have indicated that aminoglycoside antibiotics may account for 13–66% of profound deafness, with a prevalence of 0.035% [7]. Our data show that 88% of subjects with severe-profound *mt*DNA deafness carrying the homoplasmic A1555G mutation had exposure to aminoglycosides.

We now consider the audiological features of the mtDNA deafness. Previous observations on the audiograms have shown consistent phenotypes associated with mitochondrial hearing impairment: a post-lingual, bilateral, and symmetrical sensorineural hearing loss with a wide variability in the degree of hearing loss [10,11]. Previoius studies suggested that the hearing loss has a cochlear site of origin [11]. However, to date, most of the studies were conducted using a small number of subjects and only limited information is available on the audiological features of mitochondrial deafness. Moreover, because the qualitative terms describing the audiological characteristics such as the severity of hearing loss have been differently defined and reported by various investigators, there have been few detailed descriptions of the range of variability of the mtDNA deafness with regard to the degree and shape of audiograms. The audiological classification criteria of genetic deafness proposed by the European Workshop on Genetic Hearing Loss were defined on the basis of two large audiological studies on nonsyndromic hearing loss [42,43]. These criteria have been widely used in defining audiological features of genetic hearing loss and have been proved to be a valuable way to standardize the audiological results of genetic deafness from different researchers [44–46].

In the present study, the following features of the mtDNA deafness were observed: (a) the hearing impairment has a post-lingual onset; (b) the severity of hearing loss may vary greatly, ranging from mild to profound, but is more likely to be moderate (>40, <70 dB HL) or severe (>70, <95 dB HL) and symmetrical; (c) the majority of audiogram configurations are sloping and no specific audiograms have been identified. (d) There is a significant difference in the audiogram shapes between Chinese cases with A1555G mutation and

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without A1555G mutation and a poor correlation between the type of *mt*DNA mutations and the audiogram was found.

Audiometric configuration has been considered to be one feature that may help to indicate a hearing loss of genetic origin [42]. In the present study, the audiogram configurations for the majority of individuals with the mtDNA deafness were sloping, similar to those found in probands with post-lingual hearing impairment without *mtDNA* mutations. There was no difference in the audiogram shapes between Chinese cases with the A1555G mutation and other mtDNA deafness. However, specific genetic audiograms including the ascending and Ushaped configurations were not found in the present study. The results indicate that audiogram shapes found in the mtDNA deafness could not be differentiated from the audiograms occurring as a result of other environmental causes as well as from most genetic forms of hearing loss.

In conclusion, our data reveal a significant difference of incidence of *mt*DNA mutations between the Chinese and US populations. High prevalence of *mt*DNA mutations in NSHL provides a molecular explanation for the high prevalence of aminoglycoside-induced hearing loss in China. At the present time, it is not clear whether the aminoglycoside exposure in deaf probands without the mtDNA A1555G change simply reflects the frequent use of these drugs in China or whether they foreshadow additional causes of antibiotic sensitivity, possibly resulting from other nuclear or mitochondrial gene mutations. Intrafamilial variability observed in this study is consistent with a modifying influence of nuclear genes. All categories of hearing loss level were found with significant differences. The degree of mtDNA deafness that appears to be prevalent is moderate and severe. Hearing losses are bilateral, mild to profound, with a symmetric pattern and are more severe with aminoglycoside exposure. Audiograms associated with mtDNA deafness were usually sloping and nonspecific. Genetic backgrounds, particularly a maternal inheritance of hearing loss, should be carefully checked before the use of aminoglycosides in high risk populations. Because of the potential for preventing deafness in matrilineal relatives, we suggest that screening for the mtDNA A1555G mutation should be routinely performed in Chinese patients with hearing loss of uncertain cause.

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Table I

Mitochondrial mutations in deafness probands with nonsyndromic hearing loss from China and from the USA.

	Chinese probands (*n* = 290)		USA probands (*n* = 208)		
Mutation	No. of subjects	Prevalence of mutation (%)	No. of subjects	Prevalence of mutation (%)	*p* value
A1555G	45	15.5	4	1.9	<0.001
G7444A	0	0	2	1	
Total	45	15.5	6	2.9	

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Table II

Distribution of audiological features in 51 deafness probands with and 278 without mtDNA mutations.

		Audiological features							
		Degree of HL*				Audiogram shape*			
Status	Parameter	Mild	Moderate	Severe	Profound	Sloping	Residual	Flat	Other
With mtDNA mutations	No. of probands	8	27	10	6	40	8	3	0
	Prevalence (%)	15.7	52.9	19.6	11.8	78.4	15.7	5.9	0
Without mtDNA mutations	No. of probands	22	67	72	117	115	95	30	38
	Prevalence (%)	8.0	24.0	26.0	42.0	41.0	34.0	11.0	14.0

HL, hearing loss.

*Degree of hearing loss and audiogram shape are different between probands with and without mtDNA mutation at $p < 0.01$.

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Table III

Distribution of degree of hearing loss in 51 deafness probands with mtDNA mutations with and without history of aminoglycoside exposure.

	With history of AG exposure		Without history of AG exposure	
Degree of hearing loss	**No. of probands**	**Prevalence of type of hearing loss (%)***	**No. of probands**	**Prevalence of type of hearing loss (%)**
Mild	2	6.9	9	40.9
Moderate	13	44.8	11	50.0
Severe	8	27.6	2	9.1
Profound	6	20.7	0	0
Total	29	100	22	100

AG, aminoglycoside.

*Prevalence of type of hearing loss is different between probands with and without history of aminoglycoside exposure. Probands with history of AG exposure are 10 times more likely to have severe to profound hearing loss than probands without AG exposure ($\chi^2 = 8.136$, $p = 0.004$, 95% confidence intervals = 2.031, 51.903; odds ratio = 10.267).