was still just 35 years old. He had no other clinical disorders such as myoclonus or family history of HL or neurological disorders. It should also be noted that recently the m.7472insC mutation was identified in gastric cancer tissues.[23] This report suggested that somatic mtDNA mutations may have an important role in the progression of gastric cancer.

In conclusion, the present extended screening system by use of a suspension array for major mtDNA mutations was demonstrated to be powerful, because we could detect both major causative and unexpected mtDNA mutations. The present system is helpful for both the diagnosis and epidemiological studies. Detecting mtDNA mutations in the early stage of HL could be meaningful both to select the optimal therapeutic strategies for the patients and to provide appropriate genetic counseling.

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ORIGINAL ARTICLE

Mitochondrial DNA haplogroup associated with hereditary hearing loss in a Japanese population

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Abstract

Conclusion: Haplogroup D4b, especially subhaplogroup D4b2, may be one of the modifiers associated with the phenotypic expression of hereditary hearing loss (HL). *Objectives:* The present study investigated the association between suspected hereditary HL and 12 major mtDNA haplogroups in a Japanese population. Besides the mutations of mitochondrial DNA, many modifiers including environmental factors and genetic polymorphisms are involved in HL. *Methods:* The subjects comprised 373 unrelated Japanese patients with suspected hereditary HL and 480 controls. Twenty of the 373 patients were excluded from the study because the m.1555A>G or the m.3243A>G mutation had been detected in them. The mitochondrial haplotypes were classified into 12 major Japanese haplogroups (i.e. F, B, A, N9a, N9b, M7a, M7b, G1, G2, D4a, D4b, and D5). The frequency of each haplogroup in patients with HL was compared with that of the controls using the chi-squared test. *Results:* The frequency of the HL patients carrying the mitochondrial haplogroup D4b was significantly higher than that of the controls (37/353 [10.5%] vs 31/480 [6.5%]; OR 1.70 [95% CI 1.03–2.79, $p = 0.036$]) and evidence for enhancement was found in subhaplogroup D4b2 (32/353 [9.1%] vs 24/480 [5%], OR 1.89 [95% CI 1.09–3.28, $p = 0.021$]).

Keywords: *Mitochondrial DNA polymorphisms, modifiers, haplotype*

Introduction

Sensorineural hearing loss (HL) is the most common sensory disorder in humans, affecting about 1.9 per 1000 children at birth; and the ratio of patients with HL increases with age [1]. It is assumed that patients with suspected hereditary HL include not only those carrying the pathogenic mutations but also those with a multitude of intrinsic and extrinsic factors [2]. In fact, previous studies have revealed that HL is correlated with genetic polymorphisms in somatic genes [3,4]. Many pathogenic mitochondrial DNA (mtDNA) mutations are well known to cause HL [5-7]. Just as in the case of genetic polymorphisms in somatic genes, it is natural to consider that mtDNA polymorphisms could be associated with the phenotypic expression of HL. However, no association study between mtDNA haplogroups and HL has been performed. In this study, we focused on the correlation between mitochondrial haplogroups (i.e., a set of tightly-linked mtDNA polymorphisms) and hereditary HL. We performed a case-control study on the association between 12 major mitochondrial haplogroups and suspected hereditary HL in a Japanese population, based on the comprehensive analysis of polymorphisms in the coding region of the mtDNA.

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Table I. Demographic features of the patients with hearing loss (HL).

Feature		Value
Sex	Male	144 (38.6%)
	Female	229 (61.4%)
Age at onset of HL (years)	Newborn or 0	31 (8.3%)
	1–3	23 (6.2%)
	4–10	80 (21.4%)
	11–20	43 (11.5%)
	21–30	39 (10.5%)
	31–40	50 (13.4%)
	41–50	37 (9.9%)
	51–60	31 (8.3%)
	61–70	12 (3.2%)
	71–80	5 (1.3%)
	Unknown	22 (5.9%)
Mode of inheritance	Autosomal dominant	92 (24.7%)
	Autosomal recessive	52 (13.9%)
	Maternal	47 (12.6%)
	X-linked	0
	Sporadic	179 (48.0%)
	Unknown	3 (0.8%)
Type of audiogram	High-frequency steeply sloping	80 (21.4%)
	High-frequency gently sloping	104 (27.9%)
	Flat	39 (10.5%)
	U-shaped (cookiebite)	39 (10.5%)
	Reverse U-shaped	4 (1.1%)
	Low frequency	39 (10.5%)
	Deafness	21 (5.6%)
	Others	43 (11.5%)
	Unknown	4 (1.1%)
	Total	373

Material and methods

Study population

The study population comprised 373 unrelated Japanese patients with suspected hereditary HL and 480 controls. The patients had visited the outpatient clinic of the Department of Otolaryngology, University Hospital of Medicine, Tokyo Medical and Dental University. Background characteristics of these patients are shown in Table I and were described previously [7]. These patients were suspected of having hereditary HL because they had a family history of it or because they had no other apparent cause of HL. We had previously detected the m.1555A>G and the m.3243A>G mutations in a total of 20 of these patients [7]. Because these mutations are located in mtDNA and thought to contribute strongly to the phenotypic expression of HL, we excluded these 20 patients from the case-control analysis. The average age of the remaining 353 patients was 40.9 ± 18.6 years, with an age range between 1 and 84 years; and the study group comprised 138 males and 215 females. As controls, 480 individuals with no manifestation of HL were selected from the National Institute of Health and Nutrition and were enrolled in this study. The control subjects comprised 143 males and 337 females. Their average age was 52.5 ± 12.3 years, with an age range between 23 and 85 years.

The study protocol complied with the Declaration of Helsinki. It was also approved by the Committee on the Ethics of Human Research of the Tokyo Metropolitan Institute of Gerontology, the Institutional Review Board (IRB no. 68) of Tokyo Medical and Dental University, and the Committee on the Ethics of Human Research of the National Institute of Health and Nutrition. This study was carried out only after obtaining the written informed consent from each individual and/or the parents in the case of children.

Selection of mitochondrial polymorphisms for haplogroup classification

By using our mtSNP database (http://mtsnp.tmig.or.jp/mtsnp/index.shtml) and phylogenetic tree of the Japanese [8], we selected 151 polymorphic sites that have been useful for classification of mitochondrial haplogroups. We selected a further 32 mtSNPs that define the 12 major haplogroups (i.e. F, B, A, N9a, N9b, M7a, M7b, G1, G2, D4a, D4b, and D5) found in Japan (Table II).

Genotyping of polymorphisms

The DNA samples were purified from the blood by using a standard procedure. In all, 186 genotypes of mtDNA polymorphisms were determined (G&G Science Corporation, Fukushima, Japan) by a method that combines the PCR and sequence-specific oligonucleotide probes with the use of suspension array technology (Luminex® 100™; Luminex, Austin, TX, USA) [9]. Details of the methodology used for genotyping, including the primers and probes for haplotyping, were given previously [10]. To confirm the accuracy of genotyping by this method, we subjected 91 DNA samples whose entire sequence

Table II. Polymorphic sites characteristic of 12 major haplogroups.

Haplogroup	Polymorphisms
F	3970C>T (ND1: syn), 13928G>C (ND5: S531T), 10310G>A (ND3: syn)
B	8272 (9 bp deletion in noncoding region)
A	663A>G (12S rRNA), 8794C>T (ATP6: H90Y)
N9a	5231G>A (ND2: syn), 12358A>G (ND5: T8A), 12372G>A (ND5: syn)
N9b	5147G>A (ND2: syn), 11016G>A (ND4: S86N), 14893A>G (Cytb: syn)
M7a	2772C>T (16S rRNA), 4386T>C (tRNA-Gln)
M7b	4071C>T (ND1 syn), 4048G>A (ND1: D248N), 6680T>C (CO1: syn), 12811T>C (ND5 Y159H)
G1	709G>A (12S rRNA), 4833A>G (ND2: T122A), 5108T>C (ND2: syn), 8200T>C (CO2: syn), 15497G>A (Cytb: G251S)
G2	709G>A (12S rRNA), 4833A>G (ND2: T122A), 5108T>C (ND2: syn), 13563A>G (ND5: syn), 7600G>A (CO2: syn)
D4a	4883C>T (ND2: syn), 5178C>A (ND2: L237M), 3010G>A (16S rRNA), 14979T>C (Cytb: I78T), 8473T>C (ATP8: syn)
D4b	4883C>T (ND2: syn), 5178C>A (ND2: L237M), 3010G>A (16S rRNA), 1382A>C (12S rRNA)
D5	4883C>T (ND2: syn), 5178C>A (ND2: L127), 10397A>G (ND3: syn)

Cytb, cytochrome b; syn, synonymous substitution.

of the mitochondrial genome had been determined by direct sequencing to the Luminex method. In each instance, the genotype determined by the Luminex sequence-specific oligonucleotide hybridization assay system was identical to that determined by the direct sequencing.

Statistical analysis

The frequency of each haplogroup in patients with suspected hereditary HL and in controls was compared by using chi-squared tests of JMP version 8 (SAS Institute Japan, Tokyo, Japan). The p value, odds ratio (OR), and 95% confidence intervals (CIs) were calculated. A p value < 0.05 was considered statistically significant.

Results

Twelve common mtDNA haplogroups accounted for 77.6% and 73.3% of haplogroups in the patients with HL and the controls, respectively. The numbers of patients with HL and controls belonging to each haplogroup are shown in Table III. Comparing the patients with the controls, we calculated that the frequency of the patients belonging to the mitochondrial haplogroup D4b was significantly higher than that of the controls (OR 1.70 [95% CI 1.03–2.79], $p = 0.036$), as shown in Table IV. With regard to the other 11 haplogroups, we did not find any significant difference between the 2 groups. Next, as the subdivision of D4 into D4a and D4b had been proposed earlier on the basis of distinctive mutational motifs [11], we subclassified these patients and controls belonging to haplogroup D4b. Five (1.4%) of the 37 patients belonging to haplogroup D4b were assigned to haplogroup D4b1, and the other 32 patients (9.1%) to haplogroup D4b2. Seven (1.5%) of the 31 controls belonging to haplogroup D4b were assigned to haplogroup D4b1, and the other 24 controls (5.0%) to haplogroup D4b2. The frequency of the HL patients in the haplogroup D4b2 subgroup was significantly higher (OD 1.89 [95% CI 1.09–3.28], $p = 0.021$) than that for the control group, whereas the frequencies of the patients and the controls belonging to haplogroup D4b1 were low and did not differ significantly.

Table III. Haplogroup distribution in patients with hereditary hearing loss (HL) and in controls.

Haplogroup	HL patient, % (*n*)	Control, % (*n*)
F	9.1 (32)	6.9 (33)
B	14.7 (52)	11.7 (56)
A	6.8 (24)	7.3 (35)
N9a	3.4 (12)	2.9 (14)
N9b	3.1 (11)	2.1 (10)
M7a	7.4 (26)	9.0 (43)
M7b	6.2 (22)	5.0 (24)
G1	3.4 (12)	4.8 (23)
G2	2.0 (7)	3.1 (15)
D4a	7.9 (28)	8.6 (42)
D4b	10.5 (37)	6.5 (31)
D5	3.1 (11)	5.4 (26)
Others	22.4 (79)	26.7 (128)
Total	100 (353)	100 (480)

Table IV. Chi-squared test for haplogroup/subhaplogroup D4b, D4b1, and D4b2.

Haplogroup/subhaplogroup	*p* value	OR (95% CI)
D4b	0.036	1.70 (1.03–2.79)
D4b1	0.96	1.03 (0.32–3.27)
D4b2	0.021	1.89 (1.09–3.28)

Discussion

We examined the association between suspected hereditary HL and each of 12 major mitochondrial haplogroups in a Japanese population. Among the 12 major mitochondrial haplogroups, haplogroup D4b was associated with the pathogenesis of hereditary HL in the patients with presumed HL. In particular, subhaplogroup D4b2 accounted for this association. No association was found between patients with HL and subhaplogroup D4b1.

Mitochondrial haplogroup D4b is characterized by m.514delCA and m.8020G>A, and subhaplogroup D4b2 by m.1382A>C, m.8964C>T, and m.9824T>A, according to our previous study [8]. One or several of these polymorphisms may influence the expression of hereditary HL. Three of them, namely m.8020G>A, m.8964C>T, and m.9824T>A polymorphisms, are located in the genes encoding proteins involved in oxidative phosphorylation, and these three substitutions are synonymous ones. Of the five polymorphisms characterizing haplogroup D4b2, one of them, namely the m.1382A>C polymorphism, is located in the 12S rRNA gene, and this polymorphism may possibly affect the secondary structure of 12S rRNA. Previous studies have demonstrated that several mutations represented by m.1555A>G or m.1494C>T are associated with nonsyndromic HL, possibly due to a change in the secondary structure of 12S rRNA [12]. Besides, it has been revealed that mitochondrial 12S rRNA variants also could be associated with nonsyndromic HL [13]. The gene encoding mitochondrial 12S rRNA is considered a hot spot for mutations associated with HL. We suppose that this m.1382A>C polymorphism could also be a polymorphism associated with HL. Previous studies suggest that the phenotypic expression of the deafness-associated 12S rRNA mutations might be modulated by the mitochondrial haplotype [14,15].

Being a polymorphism characterizing haplogroup D4b associated with HL, m.514delCA is located in the mtDNA control region and may be a functional polymorphism. Although the m.514delCA is a sporadic substitution, it was previously reported that the mtDNA content in the skeletal muscle is lower in subjects with m.514$(CA)_4$ than in those with m.514$(CA)_5$ [16]. The mtDNA content is significantly associated with mitochondrial function such as citrate synthase activity in the skeletal muscle and the VO_2 peak [17]. This m.514$(CA)_n$ repeat may be also associated with HL, because mitochondrial function plays an important role in maintaining the function of the inner ear [18]. Therefore, we propose this polymorphism to be a candidate affecting the phenotypic expression of hereditary HL.

If modulating factors such as nuclear modifier genes, environmental factors or mitochondrial haplotypes are related to the phenotypic expression, we should consider the existence of these modifiers as being at play in hereditary HL. Several nuclear DNA polymorphisms have previously been demonstrated to be associated with HL [3,19]. Therefore, it is natural that mtDNA polymorphisms would also be thought to be associated with HL, because cells of the inner ear contain many mitochondria [18]. As a haplogroup is a group of similar haplotypes, the mitochondrial haplogroup could modulate the phenotypic expression of hereditary HL.

Our previous study demonstrated that subhaplogroup D4b2 is related to longevity [20]. We can speculate that the m.1382A>C, which is a subhaplogroup D4b2-specific polymorphism, might affect the functionality of the 12S rRNA, thereby conferring resistance against reactive oxygen species (ROS) or decreasing the production of ROS in the mitochondria. This matter seems to be contradictory to the results of the present study showing that subhaplogroup D4b2 enhanced the phenotypic expression of hereditary HL. We suppose that the mechanism underlying the ROS effect on the inner ear is not entirely the same as that for the lifespan. It should be noted that (1) the sample size of the present study was relatively small, especially as we had divided the subjects into 12 mitochondrial haplogroups, and (2) the problem of multiple comparisons remains. Further extensive studies are necessary to understand the functional link between mitochondrial haplogroups and hereditary HL.

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