Ⅴ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

○ はこの研究に関連した論文・著書

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Ⅵ. 研究成果の刊行物・別刷

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ORIGINAL ARTICLE

Anatomical feature of the middle cranial fossa in fetal periods: Possible etiology of superior canal dehiscence syndrome

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Abstract

Conclusion: Different from adults, the superior semicircular canal (SSC) protrudes into the cranium during the fetal period. This might cause adhesion of the membranous labyrinth to dura as the bony labyrinth develops much later than the membranous labyrinth. This adhesion interferes with ossification and leads to a bony defect in the SSC. *Objectives:* The purpose of this study was to investigate a possible etiology of superior canal dehiscence syndrome (SCDS) from a view point of ontogeny. *Methods:* Forty-two adult cadavers and 4 fetal cadavers were used for macroscopic observation of the middle cranial fossa (MCF). In addition, six fetuses underwent computed tomography (CT) examinations. The volume data of the CT obtained from four adults were also used for comparison. Using these CT data, we investigated the anatomic relationship between the MCF and SSC. *Results:* The SSC and the cochlea in fetuses protruded into the cranium in macroscopic anatomy and CT examination. On the other hand, the SSC of all adults was completely or mostly buried in the temporal bone.

Keywords: *Fetus, hearing loss, superior semicircular canal, vertigo*

Introduction

The superior semicircular canal (SSC) is situated in the most superior part of the inner ear approximating to the middle cranial fossa (MCF), but rarely shows dehiscence of the bony roof of the SSC. The presence of this dehiscence is known to both anatomists and otologists [1]; however, disorders relating to superior canal dehiscence (SCD) were unknown for many years. Minor et al. first reported the relationship between dehiscence of bone overlying the SSC and pressure-induced vertigo or hearing loss [2]. This pathology is named superior canal dehiscence syndrome (SCDS) and its clinical features, diagnosis, and treatment have been investigated [3–5]. However, the etiology of the bony dehiscence itself is still unclear. The height and angle of the SSC were estimated by an imaging study in patients with and without SCD, and no statistically significant difference was reported [6].

With the progress of high resolution computed tomography (HRCT), detection of this dehiscence has become easier using coronal section of the HRCT, and patients having this dehiscence without symptoms of vertigo or hearing loss have been reported [7]. The presence of this dehiscence as well as SCDS has also been reported among pediatric populations [8,9]. According to a report on cadavers with SCD, the shape of the bony defect itself was consistent with the congenital bony defect based on mathematical analysis [10]. These data indicate that the cause of this dehiscence is attributable to a congenital defect; therefore, anatomic analysis during the fetal period might be a clue to solving this problem. In this study, we aimed to investigate the anatomic relationship between the MCF and SSC. We report

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characteristic features of the fetus and discuss our hypothesis of the etiology of SCDS.

Material and methods

Forty-two adult and 6 fetal cadavers were enrolled for this study. These fetuses were provided by courtesy of the Department of Clinical Anatomy, Tokyo Medical and Dental University. The fetuses were aged 16, 18, 20, 26, 26, and 28 weeks, respectively, and the ages were estimated by biparietal diameters.

Macroscopic observation

In three of these fetuses (aged 16, 20, and 26 weeks), the crania had already been opened and the other fetus (aged 18 weeks) had half of the head specimen; therefore, a total of seven temporal bones were examined. In the adult cadavers, the crania were opened without damaging the skull base, and then the brains were removed with extreme care while observing the MCF.

Image analysis of the temporal bone

Volume data of the CT were obtained using a cone-beam CT scanner (Aquitomo®, Morita Co. Ltd, Kyoto and MSX-100CT®, Shimadzu Co. Ltd, Kyoto, Japan). To obtain high resolution images, the CT's X-ray was collimated to 0.5 mm (Aquitomo®) and 0.25 mm (MSX-100CT®), so the voxel data were obtained with minimum 0.125 and 0.016 mm^3. Volume data obtained from four adults (two men aged 20 and 43 years, and two women aged 29 and 54 years) were used for image analysis. These four adults underwent CT examination for screening of a disease and did not have any disorder in either the middle ear or inner ear. The CT examinations were performed for the six fetuses in the same manner.

These data were transferred to a personal computer. Using image software (One View®, Morita Co. Ltd), three-dimensional (3D) images and multiplanar images, which were perpendicular or parallel to the SSC, were reconstructed. Analyzing these images, we studied the anatomic relationship between the MCF and SSC.

All protocols were approved by the Ethics Reviewing Committee (Tokyo Medical and Dental University No. 1060) and the CT examinations of the four adults were carried out only after obtaining written informed consent.

Results

Macroscopic anatomy of the MCF

Several eminences and ridges were observed in the MCF in all 42 adult cadavers and they corresponded mainly with the sulcus of the temporal lobe. There was no bony eminence that completely reflected the contour of the SSC, in other words, most of the SSC was completely or mostly buried in the temporal bone. Thus, it was difficult to detect the SSC from the MCF (Figure 1).

In contrast, four fetuses had an MCF with a smooth surface and no ridges as were seen in the MCF in adults (Figure 2). Instead, a large protrusion perpendicular to the petrous ridge was observed in the posterior part of the temporal bone. This protrusion was observed symmetrically on both sides of the MCF but was not observed in the adult MCF. In addition to this protrusion, another slight protrusion was also observed that was situated slightly anterior to the internal

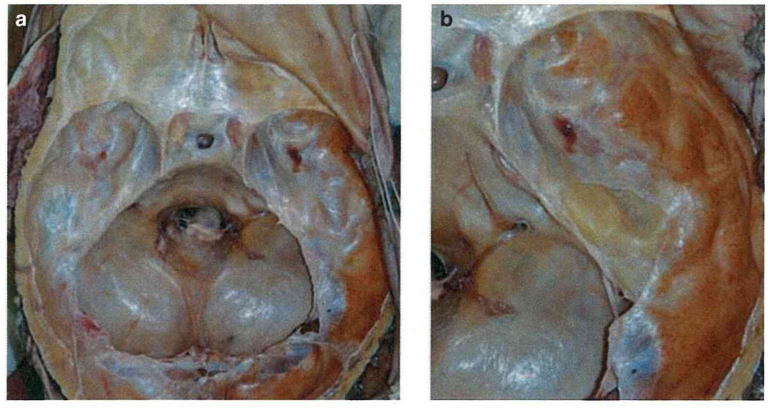

Figure 1. The middle cranial fossa (MCF) of an adult cadaver. The cranial fossa covered with dura (a). Several eminences and ridges are observed in the MCF and the surface shape of the MCF is not symmetrical. It is difficult to detect the exact location of the superior semicircular canal (SSC) even though the dura has been removed (b).

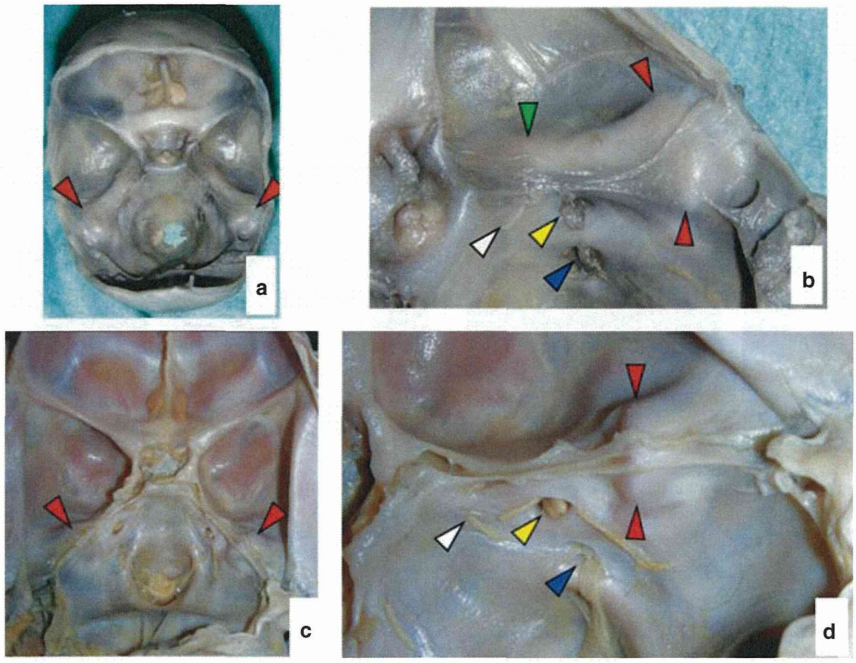

Figure 2. Skull base of fetal cadavers aged 16 weeks (a, b) and 26 weeks (c, d). These middle cranial fossas (MCFs) have a smooth and symmetrical surface as compared with those of adults. Apparent protrusion is observed in the posterior part of the temporal bone (red arrowheads). This protrusion is observed at the posterior end of the MCF in the fetus aged 16 weeks and is observed relatively anterior in the fetuses aged 26 weeks (b, d). There is another slight protrusion (green arrowhead), which is situated anterior to the internal auditory canal (yellow arrowheads). The latter protrusion is not apparent at 26 weeks. These protrusions were solid on palpation; however, other surfaces were elastic and soft. White arrowheads, abducens nerve; blue arrowheads, jugular foramen and IX–XI cranial nerves.

auditory canal and was also observed symmetrically on both sides. Soft and thick fibrous tissue, which was thought to be developing dura, covered the skull base. The skulls were very soft and assumed to have been in a stage before complete ossification. However, the abovementioned protrusions were solid on palpation and apparently different from the other skull components.

Image analysis of the temporal bone

The three-dimensional images from the fetus are shown in Figure 3. A large protrusion observed in the posterior part of petrous bone was clearly reconstructed on the CT. Coronal images of this large protrusion revealed that this protrusion was precisely consistent with the SSC. The fetus aged 16 weeks had

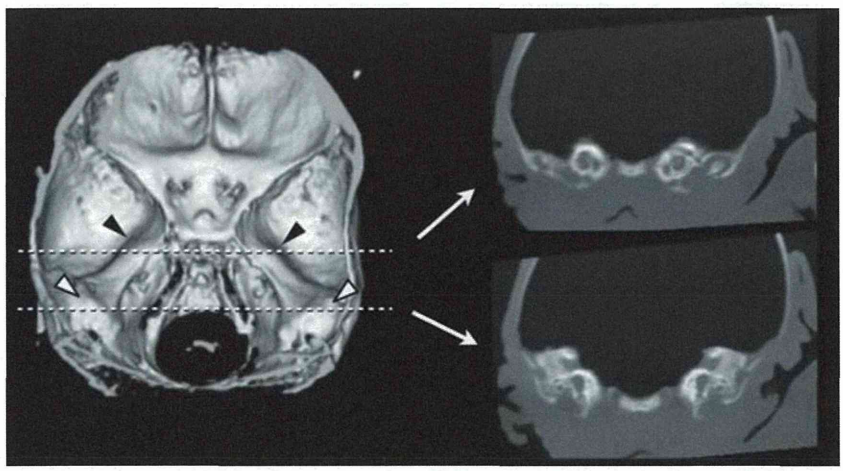

Figure 3. Three-dimensional reconstructed image from a fetus aged 16 weeks. Large protrusions (white) are reconstructed symmetrically in the posterior part of petrous bone. Slight protrusions (black arrowheads) are also reconstructed. Coronal images were made along the dotted lines. These images indicate that the large protrusions correspond to the superior semicircular canal (SSC) and the slight protrusions correspond to the cochlea.

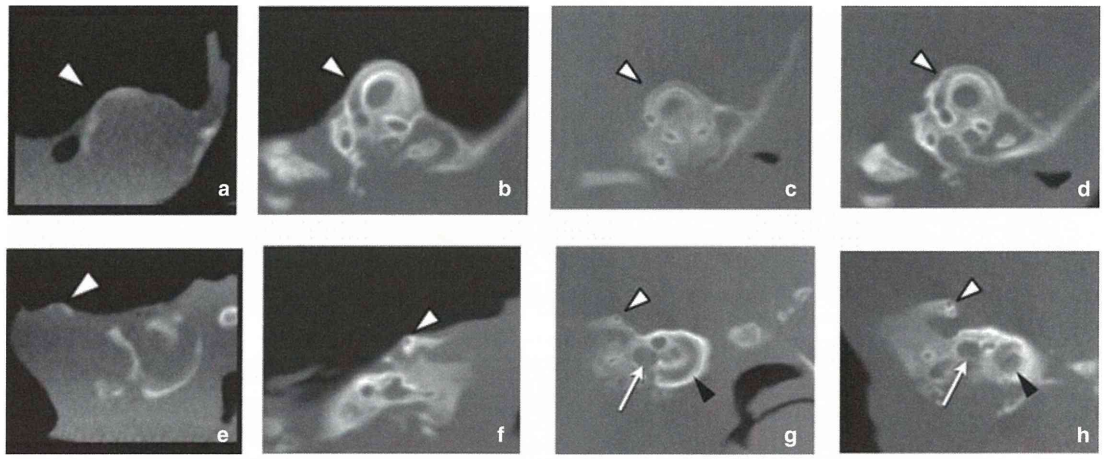

Figure 4. Images of the right fetal superior semicircular canal (SSC). Sections parallel to the SSC (a–d) and those perpendicular to the SSC (e–h) are reconstructed. Most of the SSC protrudes into the middle cranial fossa (MCF) (white arrowheads). Ossification is not completed in the fetus aged 16 weeks (a, e). Fetuses aged 26 weeks (b, f) and (c, g), and 28 weeks (d, h). White arrows, internal auditory canal; black arrowheads, cochlea.

not matured so we could not clearly identify the inner ear structure from the CT image; however, the protrusions corresponded precisely to the SSC. Moreover, most of the SSC was situated in the cranium (Figure 4). The other protrusion of anterior part of the MCF corresponded completely with the cochlea on both sides (Figure 3). As shown in the figures, the relative sizes of the inner ears were large and filled most of the petrous bone, especially in the fetus aged 16 weeks.

On the other hand, there was no protrusion seen in CT examinations of adults. In the vertical and axial section image of the SSC, the arc of the SSC rather was located entirely in the temporal bone other than protruding into the cranium (Figure 5). Furthermore, the inner ears of adults were relatively smaller than those of fetuses.

Discussion

Congenital bony defect of the temporal bone has well documented anatomic characteristics and occurs in the bony labyrinth and other areas of the temporal bone [11]. When we consider the cause of the dehiscence of the SSC, we notice unique anatomic findings of the SSC, which are not observed in the other semicircular canals. The SSC is located very close to the MCF; however, the distance between the SSC and MCF differs in each individual [12]. The SSC is believed to cause the arcuate eminence, which is a bony protrusion into the MCF. Although a previous study demonstrated that the arcuate eminence was not derived from the SSC in adults, the present study revealed a significant protrusion of the SSC into the

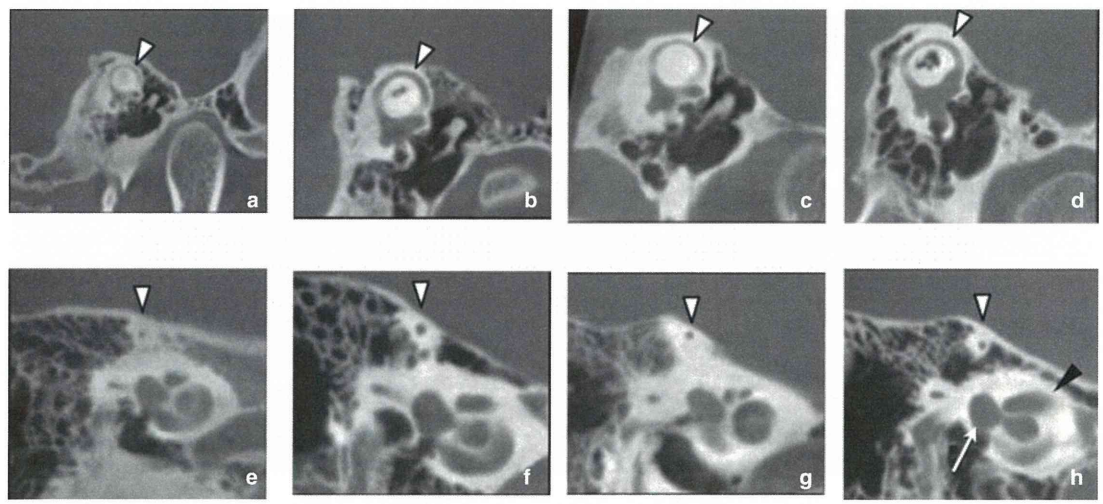

Figure 5. Images of the right adult superior semicircular canal (SSC). Sections parallel to the SSC (a–d) and those perpendicular to the SSC (e–h) are reconstructed. The SSC is encased in the middle cranial fossa (MCF) (white arrowheads). The SSC is well ossified and mostly surrounded by air cells. White arrow, internal auditory canal; black arrowhead, cochlea.

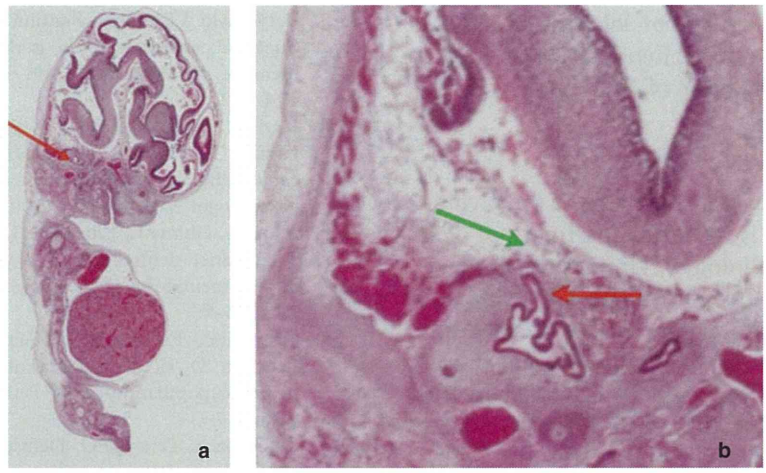

Figure 6. (a) Histological section of the fetus aged 8 weeks; (b) enlarged image. The superior semicircular canal (SSC) (red arrow) is growing and is very close to the developing brain. Dura mater (green arrow), which arises mainly from paraxial mesoderm, is also developing between the SSC and brain. When the SSC is too close to the brain, development of the cartilage covering the superior part of the SSC becomes immature, leading to a bony defect.

MCF during the fetal period [12,13]. Furthermore, previous studies revealed the presence of an idiopathic dehiscence of the bone overlying the SSC [10,14]. In the present study, the fetal skull base was very soft, which implied that the temporal bone was completely ossified. Nevertheless, dura was observed even in the fetus aged 16 weeks.

Considering these data, we aimed to clarify the cause of the bony roof dehiscence of the SSC and to indicate the pathophysiology of SCDS based on the fetal temporal bone study. The membranous labyrinth of the inner ear is formed at an early stage of embryonic development and the osseous labyrinth has already developed to a size similar to that in the adult by 21 weeks of fetal age [15,16]. During the fetal period, the inner ears are relatively much larger than the other organs, including the cerebrum and the cranium, which continue growing after birth. Therefore, the size of inner ear is much larger compared with the other skull components including the petrous bone.

Due to this size disproportion, the SSC protrudes directly to the MCF during the fetal period (Figures 2 and 3). This protrusion might cause adhesion of the membranous labyrinth to dura before complete ossification of the bony labyrinth. These anatomic characteristics could hamper ossification of the bone overlying the SSC causing the dehiscence. This is in contrast to the anatomic findings for the other semicircular canals, whose surrounding structures, namely mastoid air cell, start developing well after the bony labyrinth has been completely ossified.

To confirm our hypothesis, we investigated histological sections of embryos, which were provided courtesy of the Evolutionary Anatomy in the Research Department of Cell and Developmental Biology, the University College London (Figure 6). The mesenchyme enclosing the otocyst becomes chondrified to form the otic capsule in the eighth week. The SSC is close to the developing brain. Dura mater arising mainly from the paraxial mesoderm also develops between the SCC and brain (Figure 6b). When the SCC is too close to the developing dura, cartilage formation covering the superior part of the SSC may be disturbed, leading to a bone defect on the roof of the SSC. An enlarged superior petrosal sinus was also reported to be a cause of SCD and this was also explained in the same manner [17].

According to our hypothesis, since the dehiscence exists at birth, people having SCD may show clinical symptoms immediately after birth or complain of characteristic symptoms in their youth [8,9,18]. However, most SCDS patients are adults and often develop symptoms after episodes of barotrauma or loud sounds [19,20]. The possible explanation is as follows. The congenital bony dehiscence itself does not cause SCDS because it has been suggested that the dura of the MCF is tightly attached to the membranous labyrinth. The dura mater seems to play a role in plugging the dehiscence; therefore changes in the pressure of the inner ear and/or intracranial space do not interfere with the sensory organs in the inner ear. SCDS might develop as a syndrome when attachment of the dura comes off the membranous labyrinth by various causes, such as minor head trauma or barotrauma.

In the present study, the cochlea also protruded slightly into the MCF like the SSC. However, we did not encounter spontaneous cochlear dehiscence and 'cochlear dehiscence syndrome' has not been reported yet. Further investigation is needed to

make sure of the mechanism of labyrinthine bone defect. However, the above hypothesis could be proved concerning the genesis of SCD and SCDS.

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ORIGINAL ARTICLE

Extended screening for major mitochondrial DNA point mutations in patients with hereditary hearing loss

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Hearing loss (HL) is the most common sensory disorder in humans. Many patients with mitochondrial diseases have sensorineural HL (SNHL). The HL of these patients manifests as a consequence of either syndromic or nonsyndromic mitochondrial diseases. Furthermore, the phenotypes vary among patients even if they are carrying the same mutation. Therefore, these features make it necessary to analyze every presumed mutation in patients with hereditary HL, but the extensive analysis of various mutations is laborious. We analyzed 373 patients with suspected hereditary HL by using an extended suspension-array screening system for major mitochondrial DNA (mtDNA) mutations, which can detect 32 other mtDNA mutations in addition to the previously analyzed 29 mutations. In the present study, we detected 2 different mtDNA mutations among these 373 patients; m.7444G>A in the *MT-CO1* gene and m.7472insC in the *MT-TS1* gene in 1 patient (0.3%) for each. As these two patients had no clinical features other than HL, they had not been suspected of having mtDNA mutations. This extended screening system together with the previous one is useful for the genetic diagnosis and epidemiological study of both syndromic and nonsyndromic HL.
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Keywords: hereditary hearing loss; mitochondrial DNA; mutation; suspension array

INTRODUCTION

We can find many patients with hearing loss (HL) among those with mitochondrial DNA (mtDNA) mutations. These patients are classified into two categories; those having only HL (nonsyndromic HL) and those with HL plus other symptoms of mitochondrial disease (syndromic HL). Furthermore, as the severities and phenotypes of mitochondrial diseases vary from patient to patient, we often find mtDNA mutations in unexpected cases.[1] The fact that there are many cases without any apparent family history makes it more difficult to diagnose mitochondrial diseases.[2] Sensorineural HL (SNHL) is the most common sensory disorder in humans, having a prevalence of 2.7 per 1000 in children under 5 years of age.[3] The frequency of patients with HL caused by mtDNA mutations increases with age, because mitochondrial diseases usually become aggravated with age. Therefore, it is necessary to analyze many different suspected mutations in mtDNA, but it is very exhaustive to examine these muations one by one.

Previously, we reported the results of extensive and rapid screening for major 29 major point mutations of mtDNA in patients with hereditary HL by using a suspension array technology.[4] Our previous survey of 373 patients with suspected HL by use of this screening system revealed the m.1555A>G mutation in 11 patients, the m.3243A>G mutation in 9 patients, and the m.8348A>G, m.11778G>A and m.15498G>A mutations in 1 patient each. In the present extended study, we increased the number of mutations that could be detected from 29 to 61. We examined the applicability of this extended screening system for genetic diagnosis of hereditary HL by analyzing these same 373 patients with suspected hereditary HL.

MATERIALS AND METHODS

Patients

The study population included 373 unrelated Japanese patients with suspected hereditary HL, who visited the outpatient clinic of the Department of Otolaryngology, University Hospital of Medicine, Tokyo Medical and Dental University. The subjects included patients with a family history of HL and those with no apparent cause of HL, even though they did not have any apparent family history of HL. Their detailed demographic and audiometric features are shown in Table 1. The average age of them was 40 years, with a range between 1 and 77 years.

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

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Table 1 Demographic features of HL patients

Sex	
Male (%)	144 (38.6)
Female (%)	229 (61.4)
Onset age 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 (100)

Abbreviation: HL, hearing loss.

Extended screening of mtDNA pathological mutation by use of suspension-array technology

DNA samples were purified from the blood by using a standard procedure. The mtDNA from each patient was analyzed with the previously described extended suspension array-based screening system.[5] The targets of the present analysis were 32 mtDNA mutations in 15 genes: 1 in each of *MT-TQ* (*tRNA^{Gln}*), *MT-TW* (*tRNA^{Trp}*), *MT-TC* (*tRNA^{Cys}*), *MT-TH* (*tRNA^{His}*), *MT-TL2* (*tRNA$^{Leu(CUN)}$*), *MT-ND6* and *MT-CYB* genes; 2 in each of *MT-TN* (*tRNA^{Asn}*), *MT-ATP6*, *MT-TG* (*tRNA^{Gly}*) and *MT-TE* (*tRNA^{Glu}*) genes; 3 in the *MT-ND3* gene; 4 in the *MT-CO1* gene; and 5 in each of the *MT-TI*(*tRNA^{Ile}*) and *MT-TS1* (*tRNA$^{Ser(UCN)}$*) genes as shown in Table 2. The mtDNA mutations reported in our previous study were within the DNA fragments amplified by multiplex PCR for mtDNA haplotyping, which was mainly designed for anthropological purposes. For the present study, we newly designed a second multiplex PCR system to analyze the 32 additional mtDNA mutations (including m.7445, which is known to cause of HL).

Comparison of results between suspension array and direct DNA sequencing

DNA sequencing was carried out by using an Applied Biosystems 3130 × l Genetic Analyzer (Applied Biosystems, Foster City, CA, USA), a BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems) and Sequencher version 4.2.2 (Gene Codes, Ann Arbor, MI, USA) to compare the sequences with the revised Cambridge reference sequence,[6,7] while following the standard procedure.[8,9]

Table 2 List of 32 mutations examined by use of the extended suspension array-based system for the detection of mtDNA mutation detection system

Nucleotide position (m)	*Nucleotide change*	*Amino acid change*	*Locus*	*Clinical phenotype*
4269	A>G		MT-TI	Encephalopathy/FICP
4295	A>G		MT-TI	MHCM
4298	G>A		MT-TI	CPEO/MS
4300[a]	A>G		MT-TI	MICM
4320	C>T		MT-TI	MHCM
4332	G>A		MT-TQ	MELAS/encephalopathy
5537	A>insT		MT-TW	MILS
5698	G>A		MT-TN	CPEO/MM
5703	G>A		MT-TN	CPEO/MM
5814	T>C		MT-TC	Encephalopathy
7443[b]	A>G	Ter-G	MT-CO1	DEAF
7444[b]	G>A	Ter-K	MT-CO1	LHON/SNHL/DEAF
7445[b]	A>C	Ter-S	MT-CO1	DEAF
7445[a]	A>G	Ter-Ter	MT-CO1	SNHL
7472[b]	C>insC		MT-TS1	PEM/AMDF
7497[a]	G>A		MT-TS1	MM/exercise intolerance
7510	T>C		MT-TS1	SNHL
7511[a]	T>C		MT-TS1	SNHL
7512[a]	T>C		MT-TS1	PEM/MERRF + MELAS
8993	T>C	L>P	MT-ATP6	NARP/MILS
8993	T>G	L>R	MT-ATP6	NARP/MILS
9997	T>C		MT-TG	MHCM
10010	T>C		MT-TG	PEM
10158[a]	T>C	S>P	MT-ND3	MILS
10191	T>C	S-P	MT-ND3	ESOC/Leigh-like disease/MILS
10197[a]	G>A	A-T	MT-ND3	MILS/dystonia/stroke
12147	G>A		MT-TH	MERRF + MELAS/cerebral edema
12297	T>C		MT-TL2	Dilated cardiomyopathy
14568[b]	C>T	G-S	MT-ND6	LHON
14709[a]	T>C		MT-TE	MM + DMDF/encephalomyopathy
14710	G>A		MT-TE	Encephalomyopathy + retinopathy
15243	G>A	G>E	MT-CYB	MHCM

Abbreviations: AMDF, ataxia, myoclonus and deafness; ATP6, ATP synthase F_0 subunit 6; CO1, cytochrome *c* oxidase subunit I; CPEO, chronic progressive external ophthalmoplegia; CYB, cytochrome *b*; DEAF, maternally inherited deafness or aminoglycoside-induced deafness; DMDF, diabetes mellitus + deafness; ESOC, epilepsy, strokes, optic atrophy and cognitive decline; FICP, fatal infantile cardiomyopathy, plus a MELAS-associated cardiomyopathy; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy and ragged-red fibers; MHCM, maternally inherited hypertrophic cardiomyopathy; MICM maternally inherited cardiomyopathy; MILS, maternally inherited Leigh syndrome; MR, mental retardation; MS, multiple sclerosis; mtDNA, mitochondrial DNA; NARP, neurogenic muscle weakness, ataxia and retinitis pigmentosa; ND, NADH dehydrogenase subunit; SNHL, sensorineural hearing loss; PEM, progressive encephalomyopathy.
Abbreviations and information about mutations are annotated in the MITOMAP database.
[a]Mutation reported as both homoplasmic and heteroplasmic.
[b]Mutation reported as homoplasmic.

RESULTS AND DISCUSSION

In the present extended study, 2 of the 32 mtDNA mutations, m.7444G>A and m.7472insC, were detected by the screening system, each in 1 patient out of the 373 patients with SNHL. The median fluorescent intensities for the m.7444G>A mutation and the 7472insC mutation are displayed in scatter diagrams (Figure 1). When the median fluorescent intensity values for the wild-type signals were below the cut-off values, we regarded the mutations as homoplasmic. The m.7444G>A mutation was homoplasmic and the 7472insC mutation was heteroplasmic. On the basis of the

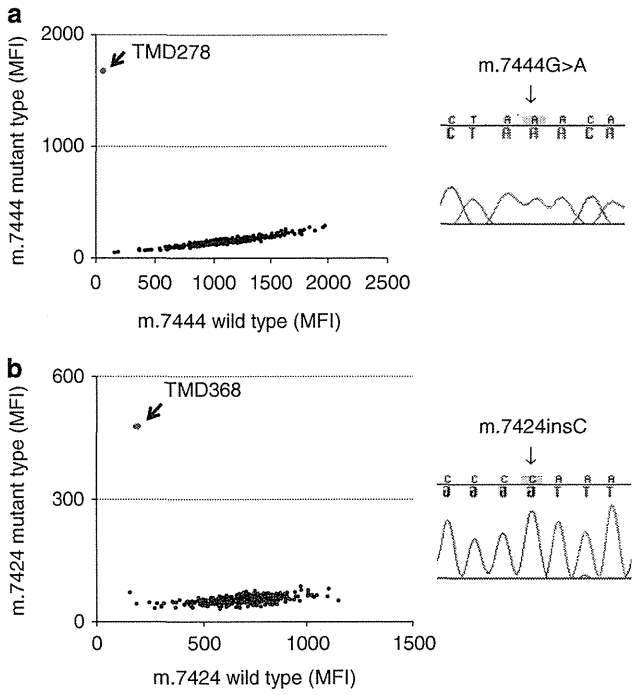

Figure 1 Scatter diagrams with mutant median fluorescent intensity values on the y axis and wild-type ones on the x axis and electropherograms of DNA sequences for the m.7444G>A homoplasmic mutation (**a**) and the m.7472insC heteroplasmic mutation (**b**). All 373 DNA samples were analyzed by the m.7444G>A and m.7472insC mutation detection systems, using universal 96-well plates. Later on, each result was merged into the two separate scatter diagrams. Red circles indicate median fluorescent intensity values for mutation-positive DNAs.

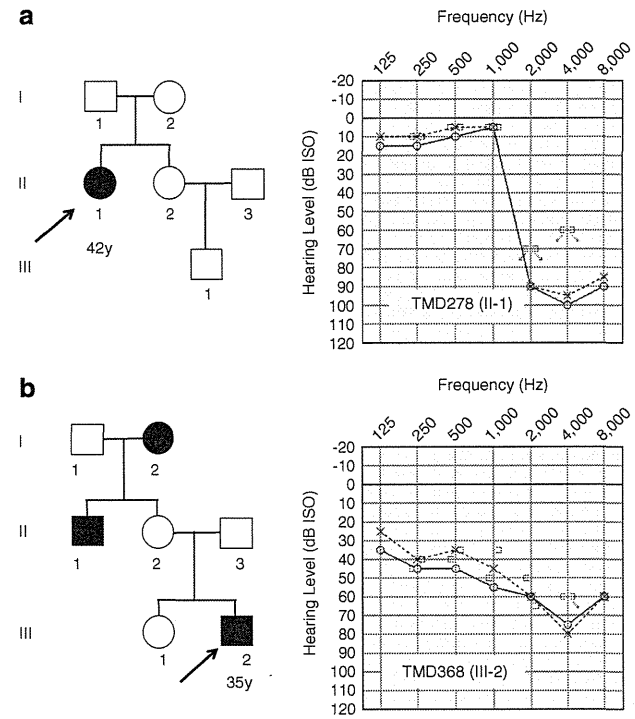

Figure 2 Pedigrees of the families and audiograms of patient TMD278 (**a**) and patient TMD368 (**b**). Clinical features are depicted: black-filled circles or squares as individuals with deafness. Arrows indicate probands. Symbols on pure tone audiograms: dB, decibels; ISO, international standards organization.], left-ear bone conduction; [, right-ear bone conduction; O, right-ear air conduction; X, left-ear air conduction.

Table 3 Mitochondrial DNA mutations detected in 373 patients with hereditary HL screened by the previous and present detection system

mtDNA mutation	*Number*	*Frequency (%)*
Previous study (Kato, 2010)		
m.1555A>G	11	2.9
m.3243A>G	9	2.4
m.8348A>G	1	0.3
m.11778G>A	1	0.3
m.15498G>A	1	0.3
Present study		
m.7444G>A	1	0.3
m.7472insC	1	0.3
Undetected	348	93.3
Total	373	100

Abbreviation: HL, hearing loss.

chromatogram, the mutation load was estimated as 59%. None of the other 30 mutations were detected in these patients with SNHL. We summarized the mtDNA mutations detected by the previous and the present analytical systems in Table 3.

SNHL is one of the most common disorder in patients with mitochondrial diseases,[10] which is represented by the mutations of the homoplasmic m.1555A>G and the heteroplasmic m.3243A>G.[11–16] We previously reported that not only these mutations but also other mutations could be detected in the patients with either nonsyndromic or syndromic hereditary HL. The m.7444G>A mutation was earlier reported as a cause of aminoglycoside-induced and nonsyndromic HL.[17] However, patient TMD278, carrying this mutation, had no history of aminoglycoside injection in her detailed clinical history. On the other hand, we should mention that this mutation characterizes haplogroup V7 and H40b, and there is no direct evidence that these haplogroups tend to have HL.[18] Furthermore, it was also reported that the m.7444G>A mutation is a secondary mutation found in patients with Leber's hereditary optic neuropathy (LHON) and that this mutation has an additional role in the pathogenesis of LHON.[19,20] Primary mutations, m.11778G>A, m.3460G>A and m.14484T>C can cause LHON. However, these mutations had already been examined in our previous study and the patient TMD278 was negative for them. With regard to her clinical data, she had high-tone SNHL as shown in Figure 2a, although she was 42 years of age. The onset of her HL occurred during her childhood, after which the HL became progressive. She had started wearing hearing aids 3 years before visiting our clinic. Her clinical feature seemed sporadic because she had neither other clinical disorders such as LHON nor a family history of HL.

The m.7472insC was reported as a pathogenic heteroplasmic mutation within the coding region of $tRNA^{Ser(UCN)}$. This mutation was previously reported to be associated with progressive myoclonus epilepsy or syndromic disorders including HL, ataxia and myoclonus in previous reports.[21] The phenotypes of this mutation, however, vary even among individuals within the same family.[22] The audiogram of TMD368 showed moderate SNHL (Figure 2b), although this patient