Available online at www.sciencedirect.com
ScienceDirect
Biochemical and Biophysical Research Communications 348 (2006) 200–205
BBRC
www.elsevier.com/locate/ybbrc

Extremely low penetrance of deafness associated with the mitochondrial 12S rRNA T1095C mutation in three Chinese families

Pu Dai [a,1], Yongyi Yuan [a,1], Deliang Huang [a,1], Yaping Qian [b], Xin Liu [a], Dongyi Han [a,*], Huijun Yuan [a], Xinjiang Wang [b], Wie-Yen Young [a,*], Min-Xin Guan [b,c,*]

[a] *Department of Otolaryngology, Chinese PLA General Hospital, Beijing, China*
[b] *Division and Program in Human Genetics and Center for Hearing and Deafness Research, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA*
[c] *Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH 45229, USA*

Received 4 July 2006
Available online 17 July 2006

Abstract

Mutations in mitochondrial DNA (mtDNA) have been found to be associated with sensorineural hearing loss. We report here the clinical, genetic, and molecular characterization of three Chinese pedigrees (a total of 43 matrilineal relatives) with aminoglycoside-induced impairment. Clinical evaluation revealed the variable phenotype of hearing impairment including audiometric configuration in these subjects, although these subjects shared some common features: being bilateral and sensorineural hearing impairment. Strikingly, only probands of these Chinese pedigrees exhibited severe to profound hearing loss. Mutational analysis of the mtDNA in these pedigrees showed the presence of homoplasmic 12S rRNA T1095C mutation, which has been associated with hearing impairment in several families. Sequence analysis of the complete mitochondrial genomes in these pedigrees showed the identical homoplasmic T1095C mutation and distinct sets of mitochondrial DNA (mtDNA) variants belonging to haplogroups M11C. Despite the presence of several highly evolutionarily conservative variants in protein-encoding genes and 16S rRNA gene, the extremely low penetrance of hearing loss with the T1095C mutation implies that the mitochondrial variants may not play an important role in the phenotypic expression of the T1095C mutation in these Chinese families. However, the history of exposure to aminoglycosides in these three hearing-impaired subjects suggested that the aminoglycosides very likely are the cause of hearing loss.

Keywords: Hearing loss; Mitochondrial 12S rRNA; Mutation; Variant; Haplotype; Penetrance; Chinese

Mutations in mitochondrial 12S rRNA have been shown to be associated with both aminoglycoside-induced hearing loss [1,2]. Of these, the C1494T mutation in the 12S rRNA gene has been associated with both aminoglycoside-induced and nonsyndromic hearing loss in two Chinese families [3–5], while the A1555G mutation in the highly conserved A-site of the 12S rRNA has been associated with both aminoglycoside-induced and nonsyndromic hearing loss in many families worldwide [6–19]. Furthermore, the T1095C mutation has also been shown to be associated with hearing impairment [19–23]. In fact, the occurrence of the T1095C mutation in these several genetically unrelated subjects affected by hearing impairment strongly indicates that this mutation is involved in the pathogenesis of hearing impairment, including aminoglycoside ototoxicity. This T-to-C transition disrupted an evolutionarily conserved base-pair at stem loop of the helix 25 of 12S rRNA [24]. This nucleotide is also located at the P-site of ribosome, suggesting an important role in the initiation of mitochondrial protein synthesis [20]. The alteration of the tertiary or quaternary structure of this rRNA by the T1095C mutation may lead to impairing mitochondrial protein synthesis, thereby causing the

* Corresponding authors. Fax: +1 513 636 3486.
E-mail addresses: hdy301@263.net (D. Han), ywy301@163.net (W.-Y. Young), min-xin.guan@cchmc.org (M.-X. Guan).
[1] These authors contributed equally to this work.

0006-291X/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbrc.2006.07.031

mitochondrial dysfunction associated with hearing impairment [23].

To further understand the pathogenesis of maternally inherited aminoglycoside-induced and nonsyndromic hearing loss, a systematic and extended mutational analysis of mitochondrial 12S rRNA has been initiated at Department of Otolaryngology of the Chinese PLA General Hospital [14–17]. In the present study, we report the clinical, molecular, and genetic characterization of three Chinese pedigrees with aminoglycoside-induced hearing loss. Clinical and genetic evaluation revealed extremely low penetrance of hearing loss in these Chinese families. Mutational analysis of 12S rRNA has led to the identification of the T1095C mutation in those families. To understand the role of mitochondrial haplotypes in the phenotypic expression of the A1555G mutation, we performed PCR-amplification of fragments spanning entire mitochondrial genome and subsequent DNA sequence analysis in the matrilineal relatives of those families.

Subjects and methods

Subjects and audiological examinations. As the part of genetic screening program for the hearing impairment, three Chinese families were ascertained through the Otology Clinic at Chinese PLA General Hospital. A comprehensive history and physical examination were performed to identify any syndromic findings, the history of the use of aminoglycosides, genetic factors related to the hearing impairment in members of these pedigrees. An age-appropriate audiological examination was performed and this examination included pure-tone audiometry (PTA) and/or auditory brainstem response (ABR), immittance testing, and Distortion product otoacoustic emissions (DPOAE). The PTA was calculated from the sum of the audiometric thresholds at 500, 1000 and 2000, 4000 and 8000 Hz. The severity of hearing impairment was classified into five grades: normal < 26 Decible (dB); mild $= 26$–40 dB; moderate $=$ 41–70 dB; severe $= 71$–90 dB; and profound > 90 dB. Informed consent was obtained from participants prior to their participation in the study, in accordance with the Cincinnati Children's Hospital Medical Center Institutional Review Board and Ethnic Committee of Chinese PLA General Hospital.

Mutational analysis of mitochondrial genome. Genomic DNA was isolated from whole blood of participants using Puregene DNA Isolation Kits (Gentra Systems). Subject's DNA fragments spanning the entire mitochondrial 12S rRNA gene were amplified by PCR using oligodeoxynucleotides corresponding to positions 618–635 and 1988–2007 [25]. The entire mitochondrial genomes of three subjects carrying the T1095C mutation were PCR-amplified in 24 overlapping fragments by use of sets of the light-strand and the heavy-strand oligonucleotide primers, as described elsewhere [25]. Each fragment was purified and subsequently submitted for sequence analysis as described above. The resultant sequence data were compared with the updated consensus Cambridge sequence (GenBank Accession No.: NC_001807) [26].

Results and discussion

To further elucidate the molecular basis of aminoglycoside ototoxicity, we have performed a mutational analysis of the mitochondrial 12S rRNA gene in a cohort of Chinese subjects, who were diagnosed for aminoglycoside ototoxicity by the Otology Clinic at the Chinese PLA General Hospital. First, DNA fragments spanning mitochondrial 12S rRNA were PCR-amplified from each affected subject and were then purified and subsequently analyzed by DNA sequencing. Of variants in this 12S rRNA gene, the T1095C mutation in the 12S rRNA gene was found in three subjects apparently in the homoplasmy (data not shown). In fact, those three subjects, as shown in Table 1, had been administered aminoglycosides (3–5 mg/kg/dose every 8 h for gentamicin or 15–25 mg/kg/dose every 12 h for streptomycin or 7.5 mg/kg/every 18 h for kamamycin) for various illnesses at the ages of less than 2 years. They began suffering bilateral hearing impairment within three months after drug administration. As illustrated in Fig. 1, audiological evaluation showed that all those subjects showed the loss of the high frequencies and their hearing impairment was symmetric. Those subjects, as shown in Table 1, exhibited a variable severity of hearing impairment and audiometric configuration: subject BJ215 III-10 suffered from severe hearing loss (70 dB at right and left ears; with flat-shaped pattern), subject BJ216 III-4 exhibited a profound hearing loss (>100 dB at both ears; with flat-shaped pattern), and subject BJ217-III-4 had profound hearing loss (96 dB at right ear, and 100 dB at left ear; with slope-shaped pattern).

A comprehensive history and physical examination as well as audiological examination were performed to identify any syndromic findings, the history of the use of aminoglycosides, genetic factors related to the hearing impairment in all available members of three Chinese families carrying the T1095C mutation. These families are living in Inner Mongolia, Northern China. In fact, comprehensive family medical histories of those probands and other members of these Chinese families showed no other clinical abnormalities, including diabetes, muscular diseases, visual dysfunction, and neurological disorders. Strikingly, as shown in Fig. 2, only probands exhibited aminoglycoside-induced hearing loss, while none of other 40 matrilineal relatives including the proband's mother in those families had hearing deficit. As shown in Table 1, other four Chinese subjects carrying the T1095C mutation suffered from severe to mild hearing impairment and variable audiometric configuration [22,23]. Similarly, other 20 Chinese pedigrees carrying the A1555G mutation exhibited extremely low penetrance of hearing loss, ranging from 4% to 18% [14,17]. By contrast, the average penetrance (including aminoglycoside-induced deafness) of three Mongolia pedigrees carrying the A1555G mutation is ~62.5% [10], while ~59% and 67% of matrilineal relatives from BJ110 and BJ105 families exhibited hearing loss, respectively [15,16]. The extremely low penetrance of hearing loss in these Chinese families carrying the T1095C mutation strongly suggests the T1095C mutation itself is not sufficient to produce the clinical phenotype. Therefore, other modifier factors including the aminoglycosides, nuclear genes, and mitochondrial haplotypes are necessary for the phenotypic manifestation of the T1095C mutation.

To understand the role of mitochondrial haplotypes in the phenotypic expression of the T1095C mutation, we performed a PCR-amplification of fragments spanning

Table 1
Summary of clinical data for seven Chinese subjects carrying the T1095C mutation

Subject	Gender	Audiometric configuration	Use of aminoglycosides	Age at onset (yr)	PTA (dB) right ear	PTA (dB) left ear	Level of hearing impairment
BJ215-III-10	M	Flat	Yes	1.5	70	70	Severe
BJ216-III-4	M	Flat	Yes	<1	>100	>100	Profound
BJ217 III-4	M	Slope	Yes	<1	96	100	Profound
[a]#78	M	Slope	Yes	4	62	55	Severe
#81	M	U-shaped	No	10	58	58	Moderate
#101	M	Hill-shaped	No	35	26.6	26.6	Mild
[b]BJ112	F	Cookie bite	No	<1	53	38	Moderate

[a] Zhao et al. [23].
[b] Wang et al. [22].

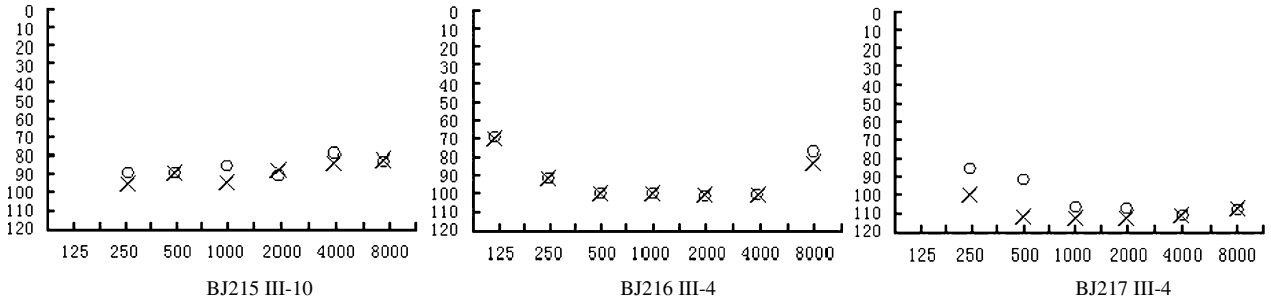

Fig. 1. Air conduction audiogram of three affected subjects with the T1095C mutation. Symbols: X-left, O-right ear.

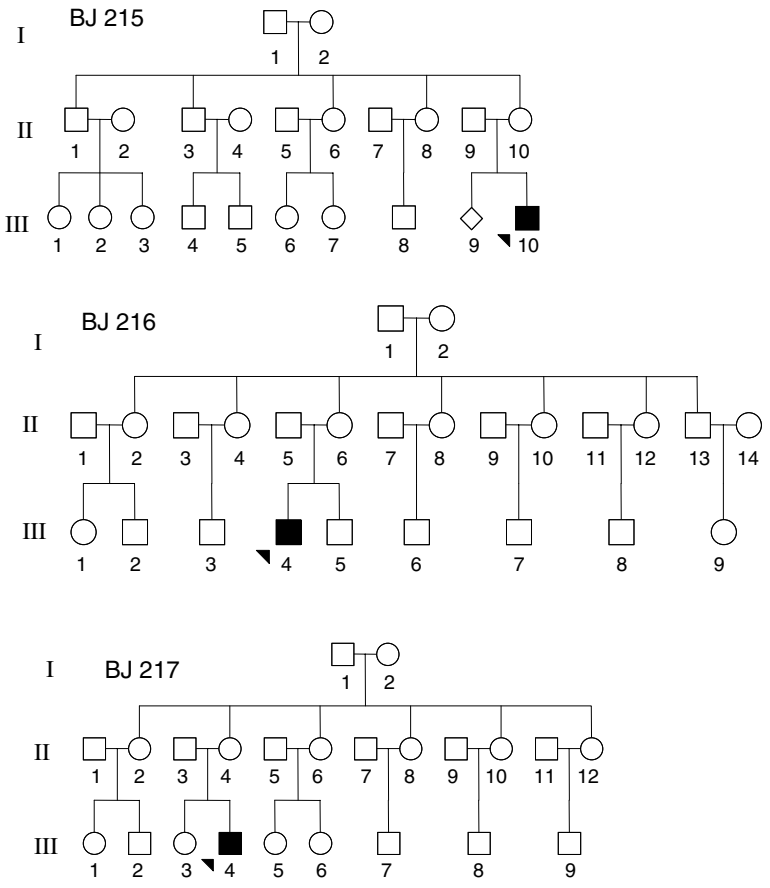

Fig. 2. Three Chinese pedigrees with aminoglycoside-induced hearing loss. Hearing-impaired individuals are indicated by filled symbols. Arrow denotes probands.

entire mitochondrial genome and subsequent DNA sequence analysis in three probands. In addition to the identical T1095C mutation, as shown in Table 2, these subjects exhibited 17 distinct polymorphisms and 30 identical variants belonging to Eastern Asian haplogroup M11 [27]. Similarly, other three mitochondrial genomes with T1095C mutation also belong to haplogroup M11 [22,23]. This suggested that the T1095C mutation in these six subjects may occur from the same origin. Of nucleotide changes in these mitochondrial genomes, there are 11 known variants in the D-loop, one novel (C739T) and two known variants in 12S rRNA gene, one novel (A2883G) and one known variants in the 16S rRNA gene, one novel variant T10007C in $tRNA^{Gly}$ gene, 16 known and 4 novel silent variants in the protein-encoding genes as well as 9 missense mutations (2 novel and 7 known) in the protein-encoding genes [28]. These missense mutations are the A4638G (I57V) in the ND2 gene, the A8108G (I175V) in the CO2 gene, the A8701G (T59A) and A8860G (T112A) in A6 gene, the

Table 2
mtDNA variants in three Chinese pedigrees with the T1095C mutation

Gene	Position	Replacement	[a]Conservation (H/B/M/X)	[b]CRS	BJ215	BJ216	BJ217	[c]Previously reported
D-loop	73	A to G		A	G	G	G	Yes
	146	T to C		T		C	C	Yes
	198	C to T		C	T		T	Yes
	200	A to G		A	G	G		Yes
	215	A to G		A	G	G	G	Yes
	263	A to G		A	G	G	G	Yes
	318	T to C		T	C	C	C	Yes
	326	A to G		A	G	G	G	Yes
	489	T to C		T	C	C	C	Yes
	16173	C to T		C			T	Yes
	16223	C to T		C	T		T	Yes
12S rRNA	739	C to T	C/A/A/—	C			T	No
	750	A to G	A/A/G/—	A	G	G	G	Yes
	1095	T to C	T/T/T/T	T	C	C	C	Yes
	1438	A to G	A/A/A/G	A	G	G	G	Yes
16S rRNA	2706	A to G	A/G/A/A	A	G	G	G	Yes
	2833	A to G	A/A/A/A	A			G	No
ND2	4738	A to G (Ile to Val)	I/T/T/T	A		G		No
	4769	A to G		A	G	G	G	Yes
	5187	C to T		C		T		No
	5192	A to G		A		G		No
CO1	6531	C to T		C	T	T	T	Yes
	7028	C to T		C	T	T	T	Yes
CO2	7642	G to A		G	A	A	A	Yes
	8108	A to G (Ile to Val)	I/I/I/I	A	G	G	G	Yes
	8188	A to G		A			G	No
A6	8701	A to G (Thr to Ala)	T/S/L/Q	A	G	G	G	Yes
	8860	A to G (Thr to Ala)	T/A/A/T	A	G	G	G	Yes
CO3	9540	T to C		T	C	C	C	Yes
	9950	T to C		T	C	C	C	Yes
$tRNA^{Gly}$	10007	T to C	T/C/G/A	T			C	No
ND3	10398	A to G (Thr to Ala)	T/T/T/A	A	G	G	G	Yes
	10400	C to T		C	T	T	T	Yes
ND4	10873	T to C		T	C	C	C	Yes
	11719	G to A		G	A	A	A	Yes
	11969	G to A (Ala to Thr)	A/A/G/A	G	A	A	A	Yes
ND5	12705	C to T		C	T	T	T	Yes
	13074	A to G		A	G	G	G	Yes
	13890	C to T		C		T		No
	13928	G to C		G			C	Yes
ND6	14340	C to T (Val to Met)	V/V/V/G	C	T		T	No
	14569	A to G		A	G			Yes
CytoB	14766	C to T (Thr to Ile)	T/S/I/S	C	T	T	T	Yes
	14783	T to C		T	C	C	C	Yes
	15043	G to A		G	A		A	Yes
	15301	G to A		G	A	A	A	Yes
	15326	A to G (Thr to Ala)	T/M/I/I	A	G	G	G	Yes

[a] Conservation of amino acid for polypeptides in human (H), bovine (B), mouse (M), and *Xenopus* (X).
[b] CRS: Cambridge reference sequence [26].
[c] See the online mitochondrial genome database MITOMAP.

A10398G (T114A) in the ND3 gene, the G11969A (A406T) in the ND4 gene, the C14340T (V112M) in the ND6, and the C14766T (T7I) and A15326G (T194A) in the cyto b gene. Interestingly, these variants in RNAs and polypeptides were further evaluated by phylogenetic analysis of these variants and sequences from other organisms including mouse [29], bovine [30], and *Xenopus laevis* [31]. Of these, the I175V in the CO2, the V112D in the ND6 variants locate at highly conserved residues of corresponding polypeptides, while the A2833G resides at a highly conserved nucleotide of the 16S rRNA. However, none of other variants showed evolutionarily conservation. Despite the presence of several highly evolutionary conservative variants in protein-encoding genes and 16S rRNA gene, the extremely low penetrance of hearing loss with the T1095C mutation implies that the mitochondrial variants may not have a potential modifying role in the phenotypic expression of the T1095C mutation in these Chinese families. However, the history of exposure to aminoglycosides in these three hearing-impaired subjects suggested that the aminoglycosides very likely are the cause of hearing loss.

Acknowledgments

This work was supported by the National Institutes of Health Grants RO1DC04958 from the National Institute on Deafness and Other Communication Disorders and RO1NS44015 from the National Institute of Neurological Disorders and Stroke to M.X.G. and the Chinese National Nature Science Foundation research Grant 30572015 to P.D.

References

[1] M.X. Guan, Prevalence of mitochondrial 12S rRNA mutations associated with aminoglycoside ototoxicity, The Volta Review 105 (2005) 211–237.
[2] N. Fischel-Ghodsian, Genetic factors in aminoglycoside toxicity, Pharmacogenomics 6 (2005) 27–36.
[3] H. Zhao, R. Li, Q. Wang, Q. Yan, J.H. Deng, D. Han, Y. Bai, W.Y. Young, M.X. Guan, Maternally inherited aminoglycoside-induced and nonsyndromic deafness is associated with the novel C1494T mutation in the mitochondrial 12S rRNA gene in a large Chinese family, Am. J. Hum. Genet. 74 (2004) 139–152.
[4] H. Zhao, W.Y. Young, Q. Yan, R. Li, J. Cao, Q. Wang, X. Li, J.L. Peters, D. Han, M.X. Guan, Functional characterization of the mitochondrial 12S rRNA C1494T mutation associated with aminoglycoside-induced and nonsyndromic hearing loss, Nucleic Acid Res. 33 (2005) 1132–1139.
[5] Q. Wang, Q.Z. Li, D. Han, Y. Zhao, L. Zhao, Y. Qian, H. Yuan, R. Li, S. Zhai, W.Y. Young, M.X. Guan, Clinical and molecular analysis of a four-generation Chinese family with aminoglycoside-induced and nonsyndromic hearing loss associated with the mitochondrial 12S rRNA C1494T mutation, Biochem. Biophys. Res. Commun. 340 (2006) 583–588.
[6] T.R. Prezant, J.V. Agapian, M.C. Bohlman, X. Bu, S. Oztas, W.Q. Qiu, K.S. Arnos, G.A. Cortopassi, L. Jaber, J.I. Rotter, M. Shohat, N. Fischel-Ghodsian, Mitochondrial ribosomal RNA mutation associated with both antibiotic-induced and non-syndromic deafness, Nat. Genet. 4 (1993) 289–294.
[7] F.J. del Castillo, M. Rodriguez-Ballesteros, Y. Martin, B. Arellano, J. Gallo-Teran, C. Morales-Angulo, R. Ramirez-Camacho, M. Cruz Tapia, J. Solanellas, A. Martinez-Conde, M. Villamar, M.A. Moreno-Pelayo, F. Moreno, I. del Castillo, Heteroplasmy for the 1555A > G mutation in the mitochondrial 12S rRNA gene in six Spanish families with non-syndromic hearing loss, J. Med. Genet. 40 (2003) 632–636.
[8] X. Estivill, N. Govea, E. Barcelo, C. Badenas, E. Romero, L. Moral, R. Scozzari, L. D'Urbano, M. Zeviani, A. Torroni, Familial progressive sensorineural deafness is mainly due to the mtDNA A1555G mutation and is enhanced by treatment with aminoglycosides, Am. J. Hum. Genet. 62 (1998) 27–35.
[9] G. Matthijs, S. Claes, B. Longo-Bbenza, J.-J. Cassiman, Non-syndromic deafness associated with a mutation and a polymorphism in the mitochondrial 12S ribosomal RNA gene in a large Zairean pedigree, Eur. J. Hum. Genet. 4 (1996) 46–51.
[10] A. Pandya, X. Xia, J. Radnaabazar, J. Batsuuri, B. Dangaansuren, N. Fischel-Ghodsian, W.E. Nance, Mutation in the mitochondrial 12S ribosomal-RNA gene in 2 families from Mongolia with matrilineal aminoglycoside ototoxicity, J. Med. Genet. 34 (1997) 169–172.
[11] H.T. Jacobs, T.P. Hutchin, T. Kappi, G. Gillies, K. Minkkinen, J. Walker, K. Thompson, A.T. Rovio, M. Carella, S. Melchionda, L. Zelante, P. Gasparini, I. Pyykko, Z.H. Shah, M. Zeviani, R.F. Mueller, Mitochondrial DNA mutations in patients with postlingual, nonsyndromic hearing impairment, Eur. J. Hum. Genet. 13 (2005) 26–33.
[12] S.I. Usami, S. Abe, M. Kasai, H. Shinkawa, B. Moeller, J.B. Kenyon, W.J. Kimberling, Genetic and clinical features of sensorineural hearing loss associated with the 1555 mitochondrial mutation, Laryngoscope 107 (1997) 483–490.
[13] R. Li, G. Xing, M. Yan, X. Cao, X.Z. Liu, X. Bu, M.X. Guan, Cosegregation of C-insertion at position 961 with A1555G mutation of mitochondrial 12S rRNA gene in a large Chinese family with maternally inherited hearing loss, Am. J. Med. Genet. 124A (2004) 113–117.
[14] W.Y. Young, L. Zhao, Y. Qian, Q. Wang, N. Li, J.H. Greinwld, M.X. Guan, Extremely low penetrance of hearing loss in four Chinese families with the mitochondrial 12S rRNA A1555G mutation, Biochem. Biophys. Res. Commun. 328 (2005) 1244–1251.
[15] L. Zhao, Q. Wang, Y. Qian, R. Li, J. Cao, L.C. Hart, S. Zhai, D. Han, W.Y. Young, M.X. Guan, Clinical evaluation and mitochondrial genome sequence analysis of two Chinese families with aminoglycoside-induced and nonsyndromic hearing loss, Biochem. Biophys. Res. Commun. 336 (2005) 967–973.
[16] H. Yuan, Y. Qian, Y. Xu, J. Cao, L. Bai, W. Shen, F. Ji, X. Zhang, D. Kang, J.Q. Mo, J.H. Greinwald, D. Han, S. Zhai, W.Y. Young, M.X. Guan, Cosegregation of the G7444A mutation in the mitochondrial COI/tRNA$^{Ser(UCN)}$ genes with the 12S rRNA A1555G mutation in a Chinese family with aminoglycoside-induced and non-syndromic hearing loss, Am. J. Med. Genet. 138A (2005) 133–140.
[17] P. Dai, X. Liu, D. Han, Y. Qian, D. Huang, H. Yuan, W. Li, F. Yu, R. Zhang, H. Lin, Y. He, Y. Yu, Q. Sun, H. Qin, R. Li, X. Zhang, D. Kang, J. Cao, W.Y. Young, M.X. Guan, Extremely low penetrance of deafness associated with the mitochondrial 12S rRNA mutation in 16 Chinese families: implication for early detection and prevention of deafness, Biochem. Biophys. Res. Commun. 340 (2006) 194–199.
[18] R. Li, J.H. Greinwald, L. Yang, D.I. Choo, R.J. Wenstrup, M.X. Guan, Molecular analysis of mitochondrial 12S rRNA and tRNA-$^{Ser(UCN)}$ genes in paediatric subjects with nonsyndromic hearing loss, J. Med. Genet. 41 (2004) 615–620.
[19] Z. Li, R. Li, J. Chen, Z. Liao, Y. Zhu, Y. Qian, S. Xiong, S. Heman-Ackah, J. Wu, D.I. Choo, M.X. Guan, Mutational analysis of the mitochondrial 12S rRNA gene in Chinese pediatric subjects with aminoglycoside induced and non-syndromic hearing loss, Hum. Genet. 117 (2005) 9–15.
[20] D. Thyagarajan, S. Bressman, C. Bruno, S. Przedborski, S. Shanske, T. Lynch, S. Fahn, S. DiMauro, A novel mitochondrial 12SrRNA point mutation in parkinsonism, deafness, and neuropathy, Ann. Neurol. 48 (2002) 30–736.

[21] A. Tessa, A. Giannotti, L. Tieri, L. Vilarinho, G. Marotta, F.M. Santorelli, Maternally inherited deafness associated with a T1095C mutation in the mDNA, Eur. J. Hum. Genet. 9 (2002) 147–149.
[22] Q. Wang, R. Li, H. Zhao, J.L. Peters, Q. Liu, L. Yang, D. Han, J.H. Greinwald, W.Y. Young, M.X. Guan, Clinical and molecular characterization of a Chinese patient with auditory neuropathy associated mitochondrial 12S rRNA T1095C mutation y, Am. J. Med. Genet. 133A (2005) 27–30.
[23] L. Zhao, W.Y. Young, R. Li, Q. Wang, N. Li, Y. Qian, M.X. Guan, Clinical evaluation and sequence analysis of the complete mitochondrial genome of three Chinese patients with hearing impairment associated with the 12S rRNA T1095C mutation, Biochem. Biophys. Res. Commun. 325 (2004) 1503–1508.
[24] J.M. Neefs, Y. Van de Peer, P. De Rijik, A. Goris, R. De Wachter, Compilation of small ribosomal subunit RNA sequences, Nucleic Acids Res. 19 (1991) 1987–2018.
[25] M.J. Rieder, S.L. Taylor, V.O. Tobe, D.A. Nickerson, Automating the identification of DNA variations using quality-based fluorescence re-sequencing: analysis of the human mitochondrial genome, Nucleic Acids Res. 26 (1981) 967–973.
[26] R.M. Andrews, I. Kubacka, P.F. Chinnery, R.N. Lightowlers, D.M. Turnbull, N. Howell, Reanalysis and revision of the Cambridge reference sequence for human mitochondrial DNA, Nat. Genet. 23 (1999) 147.
[27] M. Tanaka, V.M. Cabrera, A.M. Gonzalez, J.M. Larruga, T. Takeyasu, N. Fuku, L.J. Guo, R. Hirose, Y. Fujita, M. Kurata, K. Shinoda, K. Umetsu, Y. Yamada, Y. Oshida, Y. Sato, N. Hattori, Y. Mizuno, Y. Arai, N. Hirose, S. Ohta, O. Ogawa, Y. Tanaka, R. Kawamori, M. Shamoto-Nagai, W. Maruyama, H. Shimokata, R. Suzuki, H. Shimodaira, Mitochondrial genome variation in eastern Asia and the peopling of Japan, Genome Res. 14 (2004) 1832–1850.
[28] M.C. Brandon, M.T. Lott, K.C. Nguyen, S. Spolim, S.B. Navathe, P. Baldi, D.C. Wallace, MITOMAP: a human mitochondrial genome database–2004 update, Nucleic Acids Res. 33 (2005) D611–D613.
[29] M.J. Bibb, R.A. Van Etten, C.T. Wright, M.W. Walberg, D.A. Clayton, Sequence and gene organization of mouse mitochondrial DNA, Cell 26 (1981) 167–180.
[30] G. Gadaleta, G. Pepe, G. De Candia, C. Quagliariello, E. Sbisa, C. Saccone, The complete nucleotide sequence of the *Rattus norvegicus* mitochondrial genome: cryptic signals revealed by comparative analysis between vertebrates, J. Mol. Evol. 28 (1989) 497–516.
[31] A. Roe, D.P. Ma, R.K. Wilson, J.F. Wong, The complete nucleotide sequence of the *Xenopus laevis* mitochondrial genome, J. Biol. Chem. 260 (1985) 9759–9774.