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Maternally inherited aminoglycoside-induced and nonsyndromic hearing loss is associated with the 12S rRNA C1494T mutation in three Han Chinese pedigrees ☆

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Abstract

We report here the clinical, genetic and molecular characterization of three Han Chinese pedigrees with maternally transmitted aminoglycoside-induced and nonsyndromic bilateral hearing loss. Clinical evaluation revealed the wide range of severity, age-at-onset and audiometric configuration of hearing impairment in matrilineal relatives in these families. The penetrances of hearing loss in these pedigrees were 28%, 20%, and 15%, with an average of 21%, when aminoglycoside-induced deafness was included. When the effect of aminoglycosides was excluded, the penetrances of hearing loss in these seven pedigrees were 21%, 13% and 8%, with an average of 14%. Sequence analysis of the complete mitochondrial genomes in these pedigrees showed the presence of the deafness-associated 12S rRNA C1494T mutation, in addition to distinct sets of mtDNA polymorphism belonging to Eastern Asian haplogroups F1a1, F1a1 and D5a2, respectively. This suggested that the C1494T mutation occurred sporadically and multiplied through evolution of the mtDNA. The absence of functionally significant mutations in tRNA and rRNAs or secondary LHON mutations in their mtDNA suggests that these mtDNA haplogroup-specific variants may not play an important role in the phenotypic expression of the C1494T mutation in those Chinese families. In addition, the lack of significant mutation in the *GJB2* gene ruled out the possible involvement of *GJB2* in the phenotypic expression of the C1494T mutation in those affected subjects. However, aminoglycosides and other nuclear modifier genes play a modifying role in the phenotypic manifestation of the C1494T mutation in these Chinese families.

Keywords: Hearing loss; 12S rRNA; Mitochondrial DNA; Penetrance; Mutation; Chinese; Aminoglycoside ototoxicity

Abbreviations: mtDNA, mitochondrial DNA; dB, decibel; LHON, Leber's hereditary optic neuropathy; PCR, Polymerase Chain Reaction.

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1. Introduction

Mutations in mitochondrial DNA (mtDNA), especially in the 12S rRNA gene, are one of the important causes of both aminoglycoside-induced and nonsyndromic hearing loss (Fischel-Ghodsian 2005; Guan 2005). Of these, 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 (Prezant et al., 1993; Matthijs et al., 1996; Pandya et al., 1997; Usami et al., 1997; Estivill et al., 1998; del Castillo et al., 2003; Li et al., 2004a, 2004b, 2005b; Young et al., 2005; Yuan et al., 2005; Zhao et al., 2005b; Jacobs et al., 2005). However, the homoplasmic C1494T mutation in the highly conserved decoding site of this rRNA has been associated with both aminoglycoside-induced and nonsyndromic hearing loss in only three Chinese families and three Spanish pedigrees (Zhao et al., 2004; Wang et al., 2006; Han et al., 2007; Rodriguez-Ballesteros et al., 2006). Matrilineal relatives within and among families carrying the A1555G or C1494T mutation exhibited a wide range of penetrance, severity and age-of-onset in hearing loss (Estivill et al., 1998; del Castillo et al., 2003; Li et al., 2004b; Young et al., 2005; Yuan et al., 2005; Zhao et al., 2004). Functional characterization of cell lines derived from matrilineal relatives of a large Arab-Israeli family or one large Chinese family demonstrated that the A1555G or C1494T mutation led to mild mitochondrial dysfunction and sensitivity to aminoglycosides (Guan et al., 1996, 2000, 2001; Zhao et al., 2004, 2005a). These findings strongly indicated that the A1555G and C1494T mutations by themselves are insufficient to produce the deafness phenotype. Therefore, other modifier factors including aminoglycosides, nuclear modifier genes and mitochondrial variants/haplotypes modulate the expressivity and penetrance of hearing loss associated with the A1555G or C1494T mutation (Bykhovskaya et al., 1998; Estivill et al., 1998; Fischel-Ghodsian 2005; Guan et al., 1996, 2000, 2001, 2006; Young et al., 2006; Zhao et al., 2004).

To further investigate the molecular mechanism of maternally transmitted hearing loss, we have initiated a systematic and extended mutational screening of the 12S rRNA gene in several cohorts of hearing-impaired subjects (Li et al., 2004a, 2005b; Dai et al., 2006; Young et al., 2005; 2006; Zhao et al., 2005b; Tang et al., 2007). In the previous investigation, we showed the highly variable penetrance and expressivity of hearing loss in 36 Han Chinese families carrying the A1555G mutation (Li et al., 2004b, 2005b; Young et al., 2005, 2006; Zhao et al., 2005b; Dai et al., 2006; Yuan et al., 2005; Tang et al., 2007) and three Han Chinese pedigrees carrying the C1494T mutation (Zhao et al., 2004; Wang et al., 2006, Han et al., 2007). Sequence analysis of complete

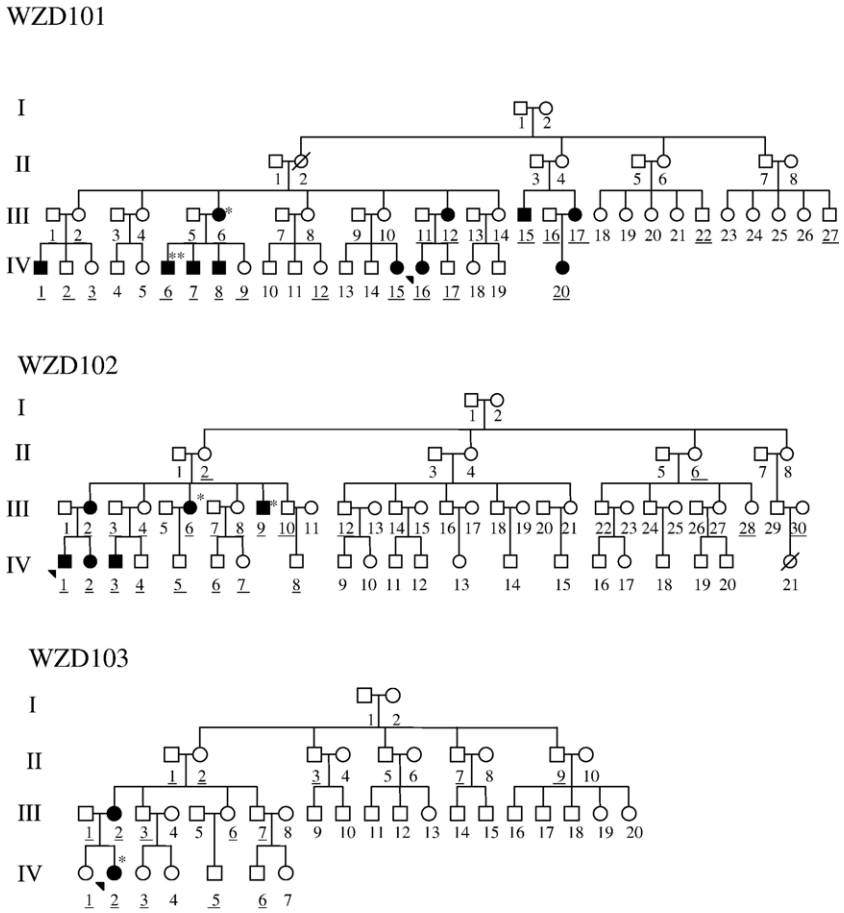

Fig. 1. Three Han Chinese pedigrees with aminoglycoside-induced and nonsyndromic hearing loss. Hearing impaired individuals are indicated by filled symblols. Arrow demotes probands. Asterisks denote individuals who had a history of exposure to aminoglycosides. Subjects used for the genotyping analysis were underlined.