Mitochondrial DNA mutations associated with deafness.

Min-Xin Guan, Ph.D., Professor of Genetics and Medicine
Zhejiang University School of Medicine, Hangzhou, Zhejiang 310058, China
gminin88@zju.edu.cn

Mitochondrial DNA mutations are one of the important causes of both syndromic and non-syndromic deafness. The mitochondrial 12S rRNA is a hot spot for mutations associated with both aminoglycoside-induced and nonsyndromic hearing loss. Of those, the homoplasmic 1555A>G and 1494C>T mutations at the highly conserved decoding region of the 12S rRNA have been associated with hearing loss worldwide. In particular, these two mutations account for a significant number of cases of aminoglycoside ototoxicity. The 1555A>G or 1494C>T mutation is expected to form a novel 1494C-G1555 or 1494U-A1555 base-pair at the highly conserved A-site of 12S rRNA. These transitions make the human mitochondrial ribosomes more bacteria-like and alter binding sites for aminoglycosides. As a result, the exposure to aminoglycosides can induce or worsen hearing loss in individuals carrying one of these mutations. Nuclear modifier genes, TRMU, GTPBP3, MTO1 and YARS2 have been shown to modulate the phenotypic manifestation of the 12S rRNA 1555A>G and 1494C>T mutations. Of tRNA muations, syndromic deafness-associated tRNA mutations such as tRNA(Leu(UUR)) 3243A>G are often present in heteroplasmy, while non-syndromic deafness-associated tRNA mutations including $tRNA^{Ser(UCN)}$ 7445A>G, $tRNA^{His}$ 12201T>C, $tRNA^{Glu}$ 14692A>G, $tRNA^{Asp}$ 7551A>G often occur in homplasmy or in high levels of heteroplasmy. Theses tRNA mutations cause structural and functional alteration. Functional alteration of tRNAs included structural stability of tRNA, processing of tRNA precursors, aminoacrylation and codon recognition. A failure in tRNA metabolism caused by these tRNA mutations impaired mitochondrial translation and respiration, thereby causing mitochondrial dysfunctions responsible for deafness. These data offer valuable information for the early diagnosis, management and treatment of maternally inherited deafness.