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HUMAN MITOCHONDRIAL tRNA MUTATIONS IN MATERNALLY INHERITED DEAFNESS

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Abstract

Mutations in mitochondrial tRNA genes have been shown to be associated with maternally inherited syndromic and non-syndromic deafness. Among those, mutations such as $tRNA^{Leu(UUR)}$ 3243A>G associated with syndromic deafness are often present in heteroplasmy, and the non-syndromic deafness-associated tRNA mutations including $tRNA^{Ser(UCN)}$ 7445A>G are often in homoplasmy or in high levels of heteroplasmy. These tRNA mutations are the primary factors underlying the development of hearing loss. However, other tRNA mutations such as $tRNA^{Thr}$ 15927G>A and $tRNA^{Ser(UCN)}$ 7444G>A are insufficient to produce a deafness phenotype, but always act in synergy with the primary mitochondrial DNA mutations, and can modulate their phenotypic manifestation. These tRNA mutations may alter the structure and function of the corresponding mitochondrial tRNAs and cause failures in tRNAs metabolism. Thereby, the impairment of mitochondrial protein synthesis and subsequent defects in respiration caused by these tRNA mutations, results in mitochondrial dysfunctions and eventually leads to the development of hearing loss. Here, we summarized the deafness-associated mitochondrial tRNA mutations and discussed the pathophysiology of these mitochondrial tRNA mutations, and we hope these data will provide a foundation for the early diagnosis, management, and treatment of maternally inherited deafness.

Keywords: deafness; mitochondria tRNA; primary mutation; secondary mutation; maternally inherited

Introduction

Deafness is a very common congenital disorder affecting 1 in every 700-1000 newborns, which can be caused by hereditary and environmental factors including ototoxic drugs such as aminoglycosides[1,2]. Deafness can be classified into syndromic deafness (hearing loss combined with other medical conditions such as diabetes), and non-syndromic deafness (hearing loss as the only obvious medical problem). Mutations in mitochondrial DNA (mtDNA) have been found to be one of the most important causes of maternally inherited syndromic and non-syndromic deafness[3-7]. Among those mutations, the 12S rRNA 1555A>G and 1494C>T mutations have been proved to be associated with aminoglycoside ototoxicity and non-syndromic deafness in many families from different ethnic backgrounds[3-5].On the other hand, mitochondrial tRNA genes are also known as hot spots for mutations associated with both syndromic and non-syndromic hearing loss[6, 7]. In this review, we summarized deafness-associated mitochondrial tRNA mutations and discussed the molecular pathogenetic mechanism of deafness associated tRNA mutations.

Mitochondrial tRNA

In human cells, 22 tRNAs required for the mitochondrial protein synthesis are encoded by mtDNA, which is a double-strand circular molecule with 16,569 base pairs[8, 9]. Among these, 8 tRNAs including $tRNA^{Glu}$, $tRNA^{A1a}$, $tRNA^{Asn}$, $tRNA^{Cys}$, $tRNA^{Tyr}$, $tRNA^{Ser(UCN)}$, $tRNA^{Gln}$ and $tRNA^{Pro}$ reside at the cytosine-rich light (L) strand, the re-

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maining $tRNA^{Phe}$, $tRNA^{Val}$, $tRNA^{Leu(UUR)}$, $tRNA^{Leu(CUN)}$, $tRNA^{Ile}$, $tRNA^{Met}$, $tRNA^{Ser(AGY)}$, $tRNA^{Trp}$, $tRNA^{Asp}$, $tRNA^{Lys}$, $tRNA^{Gly}$, $tRNA^{Arg}$, $tRNA^{His}$ and $tRNA^{Thr}$ are located at the guanine-rich heavy (H) strand[8]. tRNAs often form a highly conserved cloverleaf structure (Figure 1). Unlike canonical tRNAs such as human cytosolic tRNAs, human mitochondrial tRNAs have specific features such as non-classical G-U pairs and mismatches[10, 11]. As illustrated in Figure 1, there are three types of unusual secondary structures in the mitochondrial tRNAs[10, 12]. The $tRNA^{Ser(UCN)}$ has a non-canonical cloverleaf structure with only one base (A9) between the acceptor stem and D stem, a short D loop and an extra loop, and an extended anticodon stem with 6 bp. The $tRNA^{Ser(AGY)}$ lacks the entire D loop. The other 20 tRNAs with the variable sizes and sequence of the D-loops and T-loops, but loss the canonical D-loop/T-loop interaction. Furthermore, mitochondrial tRNAs undergo several important post-transcriptional modifications to ensure they are correctly folded and fully functional[12, 13]. However, comparing with the cytoplasmic tRNAs, there are less numbers of modified nucleotides in mitochondrial tRNAs[12].

Primary Deafness-associated tRNA Mutations

In the mitochondrial tRNA genes have been reported to be responsible for maternally inherited syndromic deafness and non-syndromic deafness[14]. These tRNA mutations, such as 3243A>G and $tRNA^{Ser(UCN)}$ 7445A>G, which referred to as the primary mutations, are the primary factors for the development of deafness[15, 16]. The syndromic deafness-associated tRNA mutations such as $tRNA^{Leu(UUR)}$ 3243A>G are often present in heteroplasmic form, while non-syndromic deafness-associated tRNA mutations including $tRNA^{Ser(UCN)}$ 7445A>G are often in homoplasmy and in high levels of heteroplasmy[3,7].

Primary tRNA mutations associated with syndromic deafness

The heteroplasmic 3243A>G mutation in $tRNA^{Leu(UUR)}$ gene causes mitochondrial encephalomyopathy, lactic acidosis, and stroke-like symptoms (MELAS)[17]. which is also one of the important causes of maternally inherited diabetes and deafness[15, 18]. The primary defect of this mutation is an inefficient aminoacylation of the $tRNA^{Leu(UUR)}$[19, 20] This mutation also affects the processing of the longer RNA precursors[21, 22] and the base post-transcriptional modification of the $tRNA^{Leu(UUR)}$ [23]. In cybrids harboring nearly homoplasmic 3243A>G mutation, the level of aminoacylated $tRNA^{Leu(UUR)}$ was reduced approximately 70% to 75%.20, 22 The deficient aminoacylation of $tRNA^{Leu(UUR)}$ mainly contributes to a shortage of $tRNA^{Leu(UUR)}$,[20, 22] and thereby causing a reduced rate of mitochondrial protein synthesis and respiration defects. Additionally, $tRNA^{Leu(UUR)}$ 3291T>C mutation in this tRNA gene, which cause a decreased mitochondrial translation by wobble modification deficiency, has also been associated with syndromic deafness[24, 25].

Mutations in the $tRNA^{Lys}$ gene, including 8344A>G, 8356T>C, and 8363G>A, are always responsible for myoclonic epilepsy with ragged red fibers (MERRF), compatible with hearing loss[26-31]. Particularly, decrease of the steady-state levels and aminoacylation in the $tRNA^{Lys}$ were observed in cybrid cell lines carrying the 8344A>G mutation[32]. Furthermore, the lack of wobble modification caused by 8344A>G mutation disturbed the condon-anticodon pairing in mutant $tRNA^{Lys}$[23]. Alteration in this tRNA metabolism is apparently responsible for the defect of mitochondrial translation and respiration[23,32].

The $tRNA^{Ser(UCN)}$ 7472insC mutation has been reported in several pedigrees with hearing loss, either in isola-

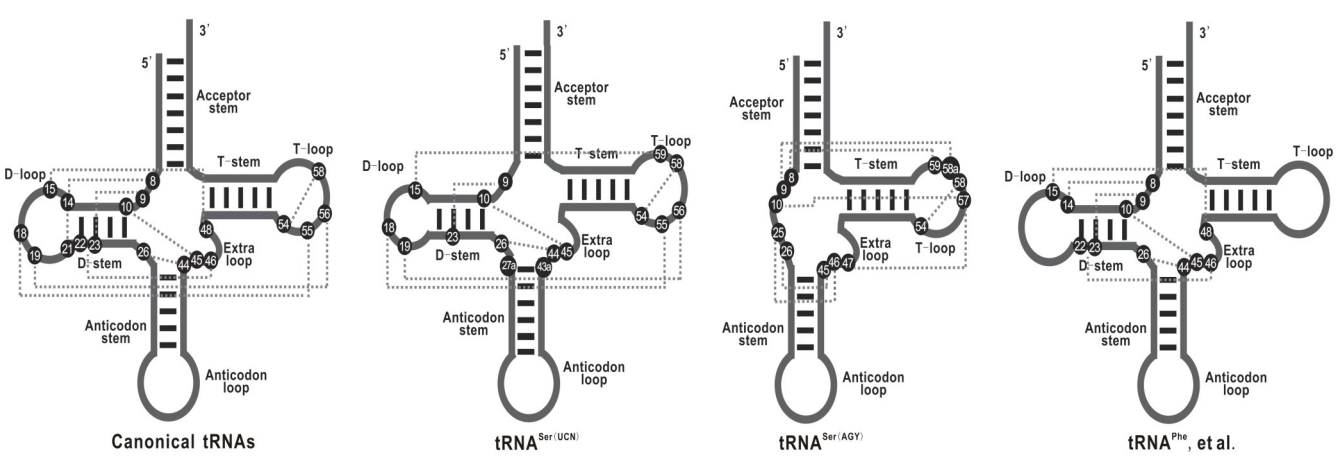

Figure 1 Schematic secondary structure of human mitochondrial tRNAs. Canonical tRNA and three types of mitochondrial tRNAs are shown. Circled numbers represent the nucleotide positions according to the conventional tRNA numbering system.54 Tertiary interactions between nucleobases are indicated by dotted lines.

tion or in combination with ataxia, dysarthria, and, more rarely, focal myoclonus[33, 34]. Cybrid cells harboring homoplasmic 7472insC mutation exhibited a marked decrease (~70%) of $tRNA^{Ser(UCN)}$ abundance by affecting its synthesis rather than the structure stability and also a mild decline (~25%) in steady-state aminoacylation of $tRNA^{Ser(UCN)}$[35].

In two unrelated pedigrees with syndromic hearing loss, the patients were found to harbor the $tRNA^{Glu}$ 14709T>C mutation in heteroplasmy. Only a subtle decrease was found in the steady-state levels of $tRNA^{Glu}$ transcripts by functional analysis in the cybrids with the mutation[36, 37] Therefore, the pathogenecity of $tRNA^{Glu}$ 14709T>C mutation need to be further studied by functional evaluations. Moreover, increasing number of putative syndromic deafness-associated mutations in tRNA genes have been identified in different families during the past several years; however, functional analyses are needed to determine the association between these tRNA mutations and hearing loss[14]

Primary tRNA mutations associated with non-syndromic deafness

The $tRNA^{Ser(UCN)}$ gene is one of the hot spots for mutations associated with non-syndromic deafness.7 These mutations include the 7445A>G, 7511T>C and 7505T>C mutations[16, 38, 39]. The primary defect of $tRNA^{Ser(UCN)}$ mutations appeared to cause a failure in tRNA metabolism, thereby altering mitochondrial translation and respiration[40, 41]. In addition, these mutations often occur in homoplasmy or in high levels of heteroplasmy, indicating a high threshold for pathogenicity[39-41].

The 7445A>G mutation in the precursor of $tRNA^{Ser(UCN)}$ gene has been reported to be associated with deafness in several genetically pedigrees from Scotland, New Zealand, France, Ukraine, Hungary and Japan with or without palmoplantar keratoderma[16, 42-44]. The mutation changed a frameshift signal (AGA) into AGG of the cytochrome oxidase subunit I (COI) on the heavy (H) strand[45]. Meanwhile, it changes L-strand encoded $tRNA^{Ser(UCN)}$ precursor sequence G↓UCU (↓ indicates the in vitro 3'-tRNase processing site) to G↓CCU, which resembles a 3'-tRNase anti-determinant leading to the 3' end endonucleolytic processing defect[40,46].In fact, markedly reduced steady-state levels of $tRNA^{Ser(UCN)}$ and ND6 mRNA belonging to the same precursor of L-strand transcript were observed in cells carrying the 7445A>G mutation[40, 47]. The altered processing of RNA procurers impairs the synthesis rate of ND6 subunit and plays a determinant role in the deafness-associated respiratory phenotype of the mutant cell lines[40, 47].

The 7511T>C mutation has been found in several families with non-syndromic hearing loss from different ethnic groups, including African, French and Japanese[38,48,49]. The 7511T>C mutation converted a highly conserved A-U to a G-U base pairing on the 5' side of the acceptor stem of the $tRNA^{Ser(UCN)}$ [10,41]. Cybrids derived from an affected matrilineal relative carrying the 7511T>C mutation exhibited a ~75% decrease in the steady state level of $tRNA^{Ser(UCN)}$, compared with the control cybrids.41 Thus, the amount of $tRNA^{Ser(UCN)}$ in mutant cells is below the proposed threshold to support a normal rate of mitochondrial protein synthesis. This defect is likely a primary contributor to ~52% reduction in the rate of mitochondrial protein synthesis and mitochondrial dysfunction[41].

The 7505T>C mutation, located at a highly conserved base-pairing (10A-20U) of $tRNA^{Ser(UCN)}$, was identified in a Han Chinese pedigree with maternally transmitted non-syndromic deafness[39]. The abolishment of 10A-20U base-pairing very likely alters the $tRNA^{Ser(UCN)}$ metabolism. Functional significance of this mutation was supported by ~65% reduction in the level of $tRNA^{Ser(UCN)}$ observed in the lymphoblastoid cell lines carrying 7505T>C mutation[39].

Most recently, a heteroplasmic 12201T>C mutation in $tRNA^{His}$ has been identified in a large five-generation Han Chinese pedigree with maternally transmitted late-onset non-syndromic hearing loss[50]. Strikingly, the levels of heteroplasmic 12201T>C mutation in cells correlated with the severity of hearing loss. The 12201T>C mutation destabilizes a highly conservative base-pairing (5A-68U) on the acceptor stem of tRNAHis and may alter the secondary structure, thereby causing a defect in the tRNA metabolism. Functional characterization revealed a ~75% reduction in the steady-state level of tRNAHis in 12201T>C mutant cell lines, compared with the wild-type cell lines. The altered tRNA metabolism results in the impairment of mitochondrial translation and respiration, which leads to the development of deafness.50 Furthermore, other putative mutations, including $tRNA^{Phe}$ 636A>G, $tRNA^{Trp}$ 5568A>G, $tRNA^{Lys}$ 8348A>G and $tRNA^{Ser(AGY)}$ 12236G>A, have been found to be associated with non-syndromic hearing loss. However, further studies are needed for better understanding of their pathogenecity[14].

Secondary deafness-associated tRNA mutations

Variable phenotypes of hearing loss within and among families carrying the same primary mtDNA mutation, such as 1555A>G and 7445A>G mutations, indicated the involvement of modifiers including the secondary mtDNA mutations[44,51]. The secondary mutations are insufficient to produce the deafness phenotype by themselves, but possess a potential modifier role in the phenotypic manifestation of the primary mtDNA mutation. For

instance, the $tRNA^{Thr}$ 15927G>A mutation acts in synergy with the primary 1555A>G mutation, thereby increasing the penetrance and expressivity of hearing loss[52]. On the contrary, there are some tRNA mutations such as $tRNA^{Leu(CUN)}$ 12300G>A mutation, appeared to be suppressor of the primary mutation.

Enhancement of phenotypic expression of the primary mtDNA mutations

The secondary tRNA mutations, such as $tRNA^{Thr}$ 15927G>A, $tRNA^{Ser(UCN)}$/CO1 7444G>A, $tRNA^{Cys}$ 5802T>C, $tRNA^{Arg}$ 10454T>C, $tRNA^{Ser(AGY)}$ 12224C>T, $tRNA^{Cys}$ 5821G>A, $tRNA^{Glu}$ 14693A>G, and $tRNA^{Thr}$ 15908T>C were implicated to enhance the penetrance and expressivity of hearing loss among Chinese families carrying the 12S rRNA 1555A>G mutation[51,53]. These variants are present in homoplasmy, localized at highly conserved nucleotides of tRNAs and may cause potential structural and functional alterations. In particular, the 15927G>A variant locates at the fourth base in the anticodon stem (conventional position 42) of the tRNAThr. A guanine (G42) at this position of $tRNA^{Thr}$ is highly conserved from bacteria to human mitochondria[10,54]. The abolished base-pairing (28C-42G) of this $tRNA^{Thr}$ by the 15927G>A mutation likely altered this tRNA metabolism. Functional significance of this variant was supported by the fact that the lower levels and altered electrophoretic mobility of $tRNA^{Thr}$ were observed in cells carrying 1555A>G and 15927G>A mutations or only 15927G>A variant, but not in these cells carrying only 1555A>G mutation.52 Therefore, these deafness-associated secondary mutations may aggravate mitochondrial dysfunctions caused by the 1555A>G mutation, thereby increasing the penetrance and expressivity of hearing loss in these Chinese pedigrees.

The $tRNA^{Ser(UCN)}$ 7511T>C mutation, in conjunction with the ND1 3308T>C and $tRNA^{Ala}$ 5655T>C mutations, contributed to a higher penetrance of hearing loss in a large African family than these in Japanese and French families[38,41,48,49]. In fact, $tRNA^{Ala}$ 5655T>C mutations caused a significant decrease in the amount of $tRNA^{Ala}$, while the ND1 3308T>C reduced the levels of ND1 mRNA and co-transcribed $tRNA^{Leu(UUR)}$ in mutant cells, respectively[41]. As a consequence, these two mutations aggravated the mitochondrial dysfunction associated with the 7511T>C mutation, thereby accounting for the higher penetrance of deafness in an African family compared with these Japanese and French families carrying the same primary mutation[41,48,49]. Furthermore, the $tRNA^{Ala}$ 5587T>C may also play a role in the penetrance and expressivity of the 7505T>C mutation[39].

Suppression of phenotypic expression of the primary mtDNA mutations

The 12300G>A mutation in the anticodon sequence of the $tRNA^{Leu(CUN)}$ was found in a lung carcinoma cybrid cell line bearing 99% $tRNA^{Leu(UUR)}$ 3243A>G mutant mtDNA[19]. In fact, the wild-type $tRNA^{Leu(UUR)}$ could efficiently decode both the UUA and UUG codons, while the 3243A>G mutant $tRNA^{Leu(UUR)}$ exhibited the absence of taurine modification, resulting in a severe reduction in UUG decoding, which was considered to be the important molecular basis of MELAS syndrome[55]. However, mass spectrometry analysis showed that the suppressor 12300G>A mutation acquired a de novo wobble uridine modification of UAA anticodon, which could potentially decode UUR codons, thereby, rescuing the severe impairment of both mitochondrial translation and respiratory captivity caused by the 3243A>G mutation[56].

The 7472A>C mutation at the $tRNA^{Ser(UCN)}$ gene appeared to be suppressor of the primary 7472insC mutation at the same gene in an Italian family with deafness[57]. Despite harboring the same percentage of 7472insC mutation, the proband developed rapidly progressive encephalopathy with deafness from a low level of heteroplasmic 7472A>C mutation, while his mother had only mild hearing impairment in associated with higher percentage of 7472A>C[57]. Subsequently, Swalwell et al showed that the co-existing of the 7472A>C variation clearly influenced the phenotypic expression associated with the 7472insC mutation by cybrids analysis[58].

Mechanism of Deafness-associated tRNA Mutations

Mitochondrial tRNA mutations have a series of structural and functional effects, including destabilization of tRNA tertiary structure, altered processing of RNA precursors, loss of nucleotide modification, deficient aminoacylation, and reduced fidelity of anticodon-codon recognition. Failures in tRNA metabolism caused by these mutations lead to mitochondrial protein synthesis, and can be worsened by the secondary tRNA mutations. These mitochondrial translational defects result in a decline in ATP production in the cochlear cells. At the meantime, these defects in oxidative phosphorylation would increase the production of reactive oxygen species (ROS), thereby damaging these mitochondrial and cellular proteins, lipids and nuclear acids. The hair cells and cochlear neurons may be preferentially involved since they are exquisitely sensitive to subtle imbalance in cellular redox state or increased level of free radicals. Consequently, the mitochondrial permeability transition pore opens and activates cell apoptosis. This would lead to the dysfunction or death of cochlear and vestibular cells, thereby producing the phenotype of hearing loss.

In summary, mutations in mitochondrial tRNAs represent an important molecular basis for maternally inherited hearing loss with or without additional symptoms. The primary syndromic deafness-associated tRNA mutations, such as $tRNA^{Leu(UUR)}$ 3243A>G mutation involved with MELAS, maternally inherited diabetes mellitus and deafness (MIDD), are present at heteroplasmy with a typical threshold effect. Furthermore, the levels of heteroplasmic of these primary tRNA mutations are considered to be a discriminator of the clinical phenotype and severity of the disorder. However, the non-syndromic-deafness-associated tRNA mutations, including $tRNA^{Ser(UCN)}$ 7445A>G and 7511T>C mutations are often found in homoplasmy or in high levels of heteroplasmy. These tRNA mutations are the primary factors for the development of hearing loss, while environmental factor(s), mtDNA haplotype(s) and nuclear modifier gene(s) may have a modifying role in the penetrance and expressivity of deafness. In particular, secondary tRNA mutations such as $tRNA^{Thr}$ 15927G>A and $tRNA^{Ser(UCN)}$ 7444G>A act in synergy with the primary tRNA mutations, modulating the phenotypic manifestation.

Perspective

The genetic and biochemical evidence shows that the mitochondrial tRNA mutations are one of the most important causes of deafness. However, the pathogenic mechanism of these tRNA mutations need to be further elucidated. Particularly, the tissue-specificity of these pathogenic mtDNA mutations is likely due to tissue-specific RNA processing, posttranscriptional modification or the contribution of nuclear modifier genes, which may also explain the wide range of phenotypic variability observed among these hearing-loss families with the same primary mutation. Furthermore, the establishment of mice model with these mitochondrial tRNA mutations is a critical approach for the further understanding of molecular mechanisms in pathogenesis of tRNA mutations. Therefore, these data will offer valuable information for the development of early diagnosis, management, and treatment approaches of maternally inherited hearing loss.

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