The Mitochondrial tRNA<sub>Asp</sub> T7561C, tRNA<sub>His</sub> C12153T, and A12172G Mutations May Be Associated with Essential Hypertension in a Han Chinese Pedigree

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**Keywords**
Hypertension · tRNA<sup>Asp</sup> · tRNA<sup>His</sup> · T7561C · C12153T · A12172G · Chinese family

**Abstract**

**Objectives:** Mutations in mitochondrial tRNA (mt-tRNA) are the important causes for maternally inherited hypertension; however, the pathophysiology of mt-tRNA mutations in clinical expression of hypertension remains poorly understood.

**Material and Methods:** In this study, we report the molecular features of a Han Chinese pedigree with maternally transmitted essential hypertension. The entire mitochondrial genomes are PCR amplified and sequenced. Moreover, phylogenetic analysis, haplogroup analysis, as well as pathogenicity scoring system are used to assess the potential roles for mtDNA mutations.

**Results:** Strikingly, among 10 matrilineal relatives, 3 suffer from variable degree of hypertension at different age at onset. Sequence analysis of the complete mitochondrial genomes suggests the presence of three possible pathogenic mtDNA mutations: tRNA<sup>Asp</sup> T7561C, tRNA<sup>His</sup> C12153T, and A12172G, together with a set of variants belonging to East Asian mitochondrial haplogroup M7a. Interestingly, the T7561C mutation occurs at position 44 in the variable region of tRNA<sup>Asp</sup>, while the C12153T and A12172G mutations are localized at extremely conserved nucleotides in the D-arm and anticodon stem of tRNA<sup>His</sup> gene, respectively, which are critical for tRNA steady-state level and function.

**Conclusions:** Mitochondrial T7561C, C12153T, and A12172G mutations may lead to the failure in tRNAs metabolism and cause mitochondrial dysfunction that is responsible for hypertension. However, the homoplasmy form of mt-tRNA mutations, incomplete penetrance of hypertension suggests that T7561C, C12153T, and A12172G mutations are insufficient to produce the clinical phenotype; hence, other risk factors such as environmental factors, nuclear genes, and epigenetic modifications may contribute to the phenotypic manifestation of maternally inherited hypertension in this Chinese pedigree.

**Introduction**

Hypertension is one of the most frequent causes of death in the world [1]. Essential hypertension (EH, MIM145500) is a complex disease which accounts for 95% of hypertensive cases, and acts as a significant risk
factor for coronary heart disease, stroke, and renal failure [2]. Evidence from randomized control trials has shown that a small drop in blood pressure (BP) may result in a large reduction in the risk of stroke and myocardial infarction [3]. At the same time, chronic high BP could lead to clinical symptoms such as dizziness, headache, chest pain, palpitation, and blurred vision [4]. EH is also called primary hypertension because its etiology is not clear, and there is, so far, no complete understanding thereof [5].

Increasing evidence shows that EH can be caused by single-gene mutations or multi-gene interactions [6]. Familial aggregation of high BP, despite different environmental factors, indicates that genetic factors are involved in the progression of this disorder [7]. In fact, previous studies showed that about 35~55% of EH cases were associated with mitochondrial dysfunction [8, 9]. Notably, the 4 primary cellular functions of mitochondria are to supply energy to the cell in the form of ATP through oxidative phosphorylation (OXPHOS), generate reactive oxygen species (ROS), buffer cytosolic calcium ions, and regulate apoptosis via mitochondrial permeability transition pore [10]. Human mitochondrial DNA (mtDNA) is a double-stranded circular molecule with 16,569 bp encoding 37 genes: 13 for essential subunits of the OXPHOS, two for rRNAs, and 22 for tRNAs required for mitochondrial protein synthesis [11]. Due to the lack of histone protection and a poor DNA repair system, mtDNA has a higher mutation rate than nuclear DNA. Among 22 mt-tRNAs, tRNA$^{\text{Glu}}$, tRNA$^{\text{Ala}}$, tRNA$^{\text{Asn}}$, tRNA$^{\text{Cys}}$, tRNA$^{\text{Tyr}}$, tRNA$^{\text{Ser(UCN)}}$, tRNA$^{\text{Gln}}$, and tRNA$^{\text{Pro}}$ reside at the cytosine-rich light strand; the remaining tRNA$^{\text{Pha}}$, tRNA$^{\text{Ile}}$, tRNA$^{\text{Leu(UGK)}}$, tRNA$^{\text{Leu(CUN)}}$, tRNA$^{\text{Met}}$, tRNA$^{\text{Ser(AGY)}}$, tRNA$^{\text{Trp}}$, tRNA$^{\text{Asp}}$, tRNA$^{\text{Lys}}$, tRNA$^{\text{Gly}}$, tRNA$^{\text{Arg}}$, tRNA$^{\text{His}}$, and tRNA$^{\text{Thr}}$ are located at the guanine-rich heavy strand [12]. Almost every tRNA has a form of cloverleaf structure, including acceptor arm, D-arm, anticodon stem, and TψC loop. As adapter molecules to convert the information stored in amino acid sequences, mt-tRNA plays a central role in protein synthesis [13]. Most recently, several mtDNA mutations had been reported to be associated with EH, such as tRNA$^{\text{Asp}}$ T7561C and T10454C [14], tRNA$^{\text{Met}}$ A4435G [15], tRNA$^{\text{ile}}$ A4295G [16], ND1 T3308C [17], ND6 T14484C [18], and CytB G15059A [19]. However, the pathophysiology of mtDNA mutations remains largely unknown.

In order to understand the pathogenic mechanisms underlying maternally inherited EH, in this study, we performed clinical, genetic and molecular characterization of a three-generation Han Chinese pedigree with EH.

Sequence analysis of the entire mitochondrial genomes revealed the presence of three possible pathogenic mtDNA mutations: tRNA$^{\text{Asp}}$ T7561C, tRNA$^{\text{His}}$ C12153T, and A12172G.

**Materials and Methods**

**Subjects**

As a part of a genetic screening program for maternally transmitted hypertension, one Han Chinese family, as shown in Figure 1, was ascertained at the Second Affiliated Hospital of Zhejiang University School of Medicine. Informed consent, blood samples, and clinical evaluation were obtained from all participants from this pedigree, under the protocols approved by the Ethics Committee of Second Affiliated Hospital of Zhejiang University School of Medicine (No. 2021-1034). Detailed demographics, anthropometrics, vital parameters, and medical history were recorded for each individual from this family. In addition, 255 healthy controls including 125 males and 130 females, aged 33–55 years, with an average of 41 years, were recruited from the Healthy Examination Center of the Second Affiliated Hospital of Zhejiang University School of Medicine.

**Measurement of BP**

To assess BP, a physician measured the systolic and diastolic BP of each participant using a mercury column sphygmomanometer, as described previously [20]. The first and the fifth Korotkoff sounds were taken as indicative of systolic and diastolic BPs, respectively. The average of three such systolic and diastolic BP readings was taken as the examination BP. Hypertension was defined according to the recommendation of the Sixth Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure, and the World Health Organization-International Society of Hypertension, as a systolic BP of ≥140 mm Hg and/or a diastolic BP of ≥90 mm Hg [21].
Screening for mtDNA Mutations

To see whether mtDNA mutations played active roles in EH, we conducted a genetic screening for mtDNA mutations in matrilineal relatives (II-6, II-8, and III-2) of this pedigree. Briefly, the genomic DNA was isolated from whole blood cells of participants using Puregene DNA Isolation Kits (Gentra Systems, Minneapolis, MN, USA). The entire mtDNA genes from the participants were PCR amplified by using 24 primers as described in a previous study [22]. The following thermocycling conditions were used for PCR: 95°C for 5 min; 30 cycles of 94°C for 10 sec, 60°C for 30 sec and 72°C for 1 min, and a final extension at 72°C for 5 min. After confirmation of band of interest, the PCR products were purified using the PureLink Gel Extraction kit (Invitrogen; Thermo Fisher Scientific, Inc.), according to the manufacturer’s recommendations. Subsequently, the PCR products were purified and sequenced using the ABI PRISM™ 3700 machine (Applied Biosystems; Thermo Fisher Scientific, Inc). These sequence results were compared with the updated consensus Cambridge sequence (GenBank accession number: NC_012920.1) and the DNA Star software (DNASTAR Inc. version 7.1.0) was used to identify mutations or variants [23]. All the mismatched nucleotide sequences were carefully noted, compared with 255 healthy controls and searched in the human mitochondrial databases such as MITOMAP (http://www.mitomap.org) and mtDB (http://www.genpat.uu.se/mtDB) for their significance.

Conservation Assessment

We carried out a phylogenetic conservation analysis for the identified mtDNA mutations, as described previously [24]. The conservation index (CI) was then calculated by comparing the human nucleotide variants with the other 14 vertebrates. The CI ≥75% was regarded as having functional potential [25].

Structural Analysis

The published secondary structures for the tRNAs were used to define the stem-and-loop structure [26].

Haplogroup Analysis

The entire mtDNA sequences of the matrilineal relatives (II-6, II-8, and III-2) of this pedigree were assigned to the East Asian mitochondrial haplogroup according to the report by Kong et al. [27].

Determining the Pathogenicity

We further used the pathogenicity scoring system to predict the potential pathogenic role of three tRNA mutations: T7561C, C12153T, and A12172G. According to that standard, a tRNA mutation was regarded as “definitely pathogenic” with a total score of more than 11 points, if the score was between 7–10 points, it belonged to “possibly pathogenic,” whereas a score that was less than 6 points should be classified as “neutral polymorphism” [28].

Results

Clinical Characterization of One Chinese Family with EH

The proband (III-2) was a 41-year-old woman who came from Hangzhou City of Zhejiang Province. She began to suffer from hypertension 1 year ago when she was 40. She went to the Second Affiliated Hospital of Zhejiang University School of Medicine for clinical treatment of hypertension. Physical examination, laboratory assessment of cardiovascular risk factors, and routine electrocardiography showed that she did not have any other clinical abnormalities such as diabetes, vision loss, hearing impairment, or renal and neurological disorders. Therefore, she exhibited a typical EH. In addition, subject II-6, aged 66, was also hypertensive (140/78 mm Hg) and suffered from EH when she was 61, while patient II-8 developed EH (145/95 mm Hg) when she was 60. As shown in Figure 1 and Table 1, the age at onset of hypertension ranged from 40 to 61 years, with an average of 53 years. There was no evidence that any member of this family had any other cause to account for EH. Therefore, the inheritance pattern of this family was consistent with maternal inheritance.

Mutational Analysis of Mitochondrial Genomes

We performed a PCR amplification of fragments spanning their mitochondrial genomes and sequenced the mtDNA genes in 3 matrilineal relatives (II-6, II-8, and III-2). As shown in Table 2, distinct sets of polymorphisms of these subjects belonging to the Eastern Asian haplogroup M7a on their maternal lineages [27]. Among these variants, there were seven variants in the D-loop, two variants in 12S rRNA, and two variants in 16S rRNA, three mutations (T7561C, C12153T and A12172G) in tRNA genes, and the remaining 13 variants were localized...
at OXPHOS-associated genes. Furthermore, six missense variants were identified, including ND2 C5263T (Ala to Val), A8 A8483G (Lys to Glu), and A8507G (Asn to Asp), ND4 G10914A (Cys to Ala), CytB C14766T (Thr to Ile), and A15326G (Thr to Ala). These variants in rRNAs 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]. None of the variants in the polypeptides and rRNAs were highly evolutionary conserved and implicated to have significantly functional consequence.

However, the T7561C in tRNA_Asp, C12153T, and A12172G in tRNA_His were very conserved from various species (Fig. 2–4, Table 3). Moreover, these tRNA mutations were not detected in 255 healthy subjects, indicating that they may have functional potential.

### Table 2. mtDNA mutations in one Han Chinese pedigree with EH

| Gene    | Position | Replacement       | Conservation (H/B/M/X) | CI, % | Previously reported |
|---------|----------|-------------------|------------------------|-------|--------------------|
| D-loop  | 73       | A to G            | NA                     | NA    | Yes                |
|         | 263      | A to G            | NA                     | NA    | Yes                |
|         | 310      | T to CTC          | NA                     | NA    | Yes                |
|         | 489      | T to C            | NA                     | NA    | Yes                |
|         | 16183    | A to C            | NA                     | NA    | Yes                |
|         | 16189    | T to C            | NA                     | NA    | Yes                |
|         | 16240    | A to G            | NA                     | NA    | Yes                |
| 12S rRNA| 750      | A to G            | A/A/A/-               | 96.1  | Yes                |
|         | 1438     | A to G            | A/A/A/G               | 94.2  | Yes                |
| 16S rRNA| 2706     | A to G            | A/G/A/A               | 82.6  | Yes                |
|         | 3107     | Del N             | NA                     | 2.22  | Yes                |
| ND1     | 3316     | G to A            | NA                     | 4.44  | Yes                |
|         | 3970     | C to T            | NA                     | 96.1  | Yes                |
| ND2     | 4769     | A to G            | M/M/M/I               | 53.8  | Yes                |
|         | 5263     | C to T (Ala to Val)| C/C/C/T               | 15.56 | Yes                |
| CO1     | 6392     | T to C            | T/T/T/T               | 100   | Yes                |
|         | 7028     | C to T            | NA                     | 55.7  | Yes                |
| tRNA_Asp| 7561     | T to C            | T/T/T/T               | 100   | Yes                |
| A8      | 8483     | A to G (Lys to Glu)| A/A/A/G               | 71.11 | Yes                |
|         | 8507     | A to G (Asn to Asp)| A/A/A/G               | 28.89 | Yes                |
| tRNA_His| 12153    | C to T            | C/C/C/C               | 100   | Yes                |
|         | 12172    | A to G            | A/A/A/A               | 100   | Yes                |
| ND4     | 10914    | G to A (Cys to Ala)| G/A/G/A               | 6.67  | Yes                |
|         | 11719    | G to A            | NA                     | 9.6   | Yes                |
| ND5     | 12630    | G to A            | NA                     | 97.78 | Yes                |
| CytB    | 14766    | C to T (Thr to Ile)| T/S/T/S               | 69.2  | Yes                |
|         | 15326    | A to G (Thr to Ala)| T/M/I/I               | 71.1  | Yes                |

a Conservation of amino acid for polypeptides or nucleotide for RNAs in human (H), bovine (B), mouse (M), and Xenopus laevis (X). b See the online mitochondrial genome database http://www.mitomap.org. CI, conservation index.

Mitochondrial T7561C, C12153T, and A12172G May Be Pathogenic Mutations Associated with EH

We further assessed the potential pathogenic roles of these mt-tRNA mutations by employing the pathogenicity scoring system [28]. As shown in Table 4, we noticed that the total scores of T7561C, C12153T, and A12172G mutations were 8, 8, and 11 points, suggesting that they may play pathogenic roles in EH.
Fig. 2. Identification of mitochondrial T7561C, C12153T, and A12172G mutations by direct sequencing analysis. Arrows indicate the location of the base changes.

Fig. 3. Sequence alignment of tRNA^{His} gene from various species. Arrows indicate the positions 14 and 37, corresponding to the C12153T and A12172G mutations.

Fig. 4. The secondary structures of tRNA^{Asp} and tRNA^{His} genes. Cloverleaf structures of tRNA^{Asp} and tRNA^{His} are derived from Mitomap database (www.mitomap.org). Arrows indicate the T7561C, C12153T, and A12172G mutations.
Table 3. Molecular features of tRNA^{Asp} T7561C, tRNA^{His} C12153T and A12172G mutations

| tRNA species | Nucleotide alternations | CI, % | Nucleotide at tRNA Location | Homoplasmy/heteroplasmy |
|--------------|-------------------------|------|-----------------------------|-------------------------|
| tRNA^{Asp}   | T7561C                  | 100  | 44                          | Variable region         |
| tRNA^{His}   | C12153T                 | 100  | 14                          | D-arm                   |
|              | A12172G                 | 100  | 37                          | Anticodon stem          |

Table 4. The pathogenicity scoring system for tRNA^{Asp} T7561C, tRNA^{His} C12153T, and A12172G mutations

| Scoring criteria                                             | T7561C mutation | Score/20 | C12153T mutation | Score/20 | A12172G mutation | Score/20 | Classification                                      |
|--------------------------------------------------------------|-----------------|----------|------------------|----------|------------------|----------|----------------------------------------------------|
| More than one independent report                              | Yes             | 2        | Yes              | 2        | Yes              | 2        | ≤6 points: neutral polymorphisms                   |
| Evolutionary conservation of the base pair                    | No changes      | 2        | No changes       | 2        | No changes       | 2        | 7–10 points: possibly pathogenic                   |
| Variant heteroplasmy                                          | No              | 0        | No               | 0        | No               | 0        | 11–13 points (not including evidence from single fiber, steady-state level or trans-mitochondrial cybrid studies): probably pathogenic |
| Segregation of the mutation with disease                      | Yes             | 2        | Yes              | 2        | Yes              | 2        | ≥11 points (including evidence from single fiber, steady-state level or trans-mitochondrial cybrid studies): definitely pathogenic |
| Histochemical evidence of mitochondrial disease                | No evidence     | 0        | No evidence      | 0        | No evidence      | 0        |                                                   |
| Biochemical defect in complex I, III, or IV                   | No              | 0        | No               | 0        | No               | 0        |                                                   |
| Evidence of mutation segregation with biochemical defect from single-fiber studies | No              | 0        | No               | 0        | No               | 0        |                                                   |
| Mutant mt-tRNA steady-state level or evidence of pathogenicity in trans-mitochondrial cybrid studies | Weak evidence   | 2        | Weak evidence    | 2        | Strong evidence  | 5        |                                                   |
| Maximum score                                                | Possibly pathogenic | 8       | Possibly pathogenic | 8       | Definitely pathogenic | 11       |                                                   |
Discussion

Accumulating evidence suggests that mitochondrial damage and dysfunction are actively involved in cardiovascular diseases [32, 33]. In fact, mitochondria provide 95% of the energy needed for cell activities and play an important role in cardiomyocytes and neurons [34]. In a renin-induced rat model of hypertension and impaired cardiac function, mitochondrial degeneration and swelling are accompanied by changes in mitochondrial density and structure [35]. Moreover, in a stress-induced hypertensive rat model, the increase in mitochondrial ROS production by left ventricular cardiomyocytes led to myocardial cell dysfunction and myocardial fibrosis [36], highlighting the direct pathogenic roles for mitochondrial dysfunctions in EH. In the present study, we have performed clinical, genetic, and molecular characterization of a three-generation Han Chinese family with inherited hypertension. The variable severity and age at onset in hypertension are observed in the matrilineal relatives of this pedigree. In particular, the age at onset of hypertension varies from 40 to 61 years, with an average of 53 years. While those of other Chinese families carrying the hypertension-associated A4435G mutation are 50, 52, and 44 years, respectively [37–39]. On the other hand, matrilineal relatives in this family have earlier age onset of hypertension, suggesting that mitochondrial sequence variants may be acted as risk factors for hypertension.

Since mtDNA is in the proximity of ROS generation sites and mitochondria have less sophisticated DNA protection and repair systems, mtDNA is hence vulnerable to a high mutation rate. If all the mtDNAs in a cell are identical, the cell status is referred to as “homoplasmy”; if not, it is called “heteroplasmy.” Neutral polymorphisms are usually homoplasmic, whereas pathogenic mutations are usually heteroplasmic in nature [40]. However, there are pathogenic mtDNA mutations that are homoplasmic and generally involve tRNA genes [41, 42]. These mutations are considered relatively mild and may require additional factors to produce a clinical phenotype [43, 44].

In this study, molecular analysis of the mitochondrial genomes identifies three potential pathogenic mutations: tRNA<sup>asp</sup> T7561C, tRNA<sup>his</sup> C12153T, and A12172G. In fact, the T7561C mutation occurs at position 47 in the variable region of tRNA<sup>asp</sup>, which is very conserved from different species. Notably, nucleotide at that position of mt-tRNAs is often chemically modified, thereby contributing to the structural formation and stabilization of functional tRNAs [45]. Thus, the lack of tRNA<sup>asp</sup> modification caused by the T7561C mutation may lead to the failure of tRNA<sup>asp</sup> metabolism. Furthermore, the homoplasmic C12153T mutation is localized at evolutionary conserved nucleotide of tRNA<sup>his</sup>. Interestingly, the T593C mutation, which occurs at the same position of tRNA<sup>phe</sup> is regarded as a pathogenic mutation for non-syndromic hearing loss and Leber’s hereditary optic neuropathy [46, 47]. Importantly, the T593C mutation causes a markedly decreased in the steady-state level of tRNA<sup>phe</sup>, impairs mitochondrial translation, and reduces the rate of respiratory capacity [46]. Therefore, the C12153T mutation, which is similar to the T593C mutation, may also alter the structure and function of tRNA<sup>his</sup>. While the A12172G mutation affects a highly conserved adenine at position 37, 3’ adjacent to the tRNA’s anticodon, which is important for the fidelity of codon recognition and stabilization [48]. In particular, the hypertension-associated A4435G mutation introduces an m<sup>1</sup>G37 modification of tRNA<sup>met</sup>, decreases efficiency in aminoacylation and steady-state levels of this tRNA, as compared with the control cybrids [49]. Thus, it can be hypothesized that the A12172G mutation, which is similar to the A4435G mutation, changes the conformation of tRNA<sup>his</sup> affects its function, most probably via affecting its modification. In addition, the pathogenicity scoring system indicates that the T7561C, C12135T, and A12172G mutations are “possibly pathogenic” and “definitely pathogenic,” respectively [28]. Nevertheless, the incomplete penetrance of hypertension in this family, the homoplasmic forms of tRNA mutations, suggest that mt-tRNA<sup>asp</sup> T7561C, tRNA<sup>his</sup> C12153T, and A12172G mutations are insufficient to produce the observed clinical phenotypes [50]. Therefore, it is likely that other risk factors, including environmental factors, nuclear genes, and epigenetic modifications, may contribute to the clinical manifestation of hypertension in this pedigree.

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Statement of Ethics

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and approved by an independent Ethic Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (No. 2021-1034). All participants were informed, and their written consent was provided.
Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

X.X. designed the study; H.F. collected the samples and controls; J.S. performed the clinical assessment; H.F. performed PCR-Sanger sequencing and data analysis; X.X. wrote the paper. All authors approved the study.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.
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