Failures in Mitochondrial tRNA<sub>Met</sub> and tRNA<sub>Gln</sub> Metabolism Caused by the Novel 4401A>G Mutation Are Involved in Essential Hypertension in a Han Chinese Family

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Abstract—We report here on the clinical, genetic, and molecular characterization of 1 Han Chinese family with maternally transmitted hypertension. Three of 7 matrilineal relatives in this 4-generation family exhibited the variable degree of essential hypertension at the age at onset, ranging from 35 to 60 years old. Sequence analysis of the complete mitochondrial DNA in this pedigree identified the novel homoplasmic 4401A>G mutation localizing at the spacer immediately to the 5′ end of tRNA<sub>Met</sub> and tRNA<sub>Gln</sub> genes and 39 other variants belonging to the Asian haplogroup C. The 4401A>G mutation was absent in 242 Han Chinese controls. Approximately 30% reductions in the steady-state levels of tRNA<sub>Met</sub> and tRNA<sub>Gln</sub> were observed in 2 lymphoblastoid cell lines carrying the 4401A>G mutation compared with 2 control cell lines lacking this mutation. Failures in mitochondrial metabolism are apparently a primary contributor to the reduced rate of mitochondrial translation and reductions in the rate of overall respiratory capacity, malate/glutamate-promoted respiration, succinate/glycerol-3-phosphate-promoted respiration, or NADH/NAD<sup>+</sup>,NADPH/NADP<sup>+</sup>-tetramethyl-p-phenylenediamine/ascorbate-promoted respiration in lymphoblastoid cell lines carrying the 4401A>G mutation. The homoplasmic form, mild biochemical defect, late onset, and incomplete penetrance of hypertension in this family suggest that the 4401A>G mutation itself is insufficient to produce a clinical phenotype. Thus, the other modifier factors, eg, nuclear modifier genes and environmental and personal factors, may also contribute to the development of hypertension in these subjects carrying this mutation. These data suggest that mitochondrial dysfunctions, caused by the 4401A>G mutation, are involved in the development of hypertension in this Chinese pedigree. (Hypertension. 2009;54:00-00.)

Key Words: hypertension ■ mitochondria ■ mutation ■ tRNA metabolism ■ maternal inheritance ■ risk factor ■ Chinese

Cardiovascular disease is the leading cause of death in America and the world. In particular, hypertension affects ≈1 billion individuals worldwide and 130 million in China. The etiology of cardiovascular disease is not well understood because of the multifactorial causes. Cardiovascular disease can be caused by a single gene or multifactorial conditions, resulting from interactions between environment and inherited risk factors. Of hereditary factors, the maternal transmissions of cardiovascular disease have been implicated in some pedigrees, suggesting that the mutation(s) in mitochondrial DNA (mtDNA) is one of the molecular bases for this disorder. Recently, several mtDNA point mutations have been identified to be associated with cardiovascular disease. These mutations included the 1555A>G mutation in the 12S ribosomal RNA (tRNA) gene, the 3260A>G and 3303C>T mutations in the tRNA<sub>Leu(UUR)</sub> gene, the 8348A>G and 8563G>A mutations in the tRNA<sub>Val</sub> gene, and the 4295A>G, 4300A>G, and 4317A>G mutations in the tRNA<sub>Bc</sub> gene. Most recently, the 4291T>C mutation in tRNA<sub>Bc</sub> gene has been associated with a cluster of metabolic defects, including essential hypertension, hypercholesterolemia, and hypomagnesemia in a large family.

With an effort to understand a role of the mitochondrial genome in the pathogenesis of cardiovascular disease in the Chinese population, we have initiated a systematic and extended mutational screening of mtDNA in a large cohort of hypertension subjects in the Geriatric Cardiology Clinic at the Chinese People’s Liberation Army General Hospital. In the present study, we performed the clinical, genetic, and molecular characterizations of another Han Chinese family with maternally transmitted hypertension. Three (2 men/1 woman) of 7 matrilineal relatives in this 4-generation family exhibited the variable severity and age at onset in hypertension. Mutational analysis of the mitochondrial genome has identified the novel 4401A>G mutation in this Chinese family. This novel 4401A>G mutation is localized at the...
systolic blood pressure of $\pm 140$ mm Hg and/or a diastolic blood pressure of $\pm 90$ mm Hg.

**Mutational Analysis of Mitochondrial Genome**

Genomic DNA was isolated from whole blood of participants using Puregene DNA Isolation kits (Gentra Systems). The entire mitochondrial genome of the proband II-1 was PCR amplified in 24 overlapping fragments by use of sets of the light-strand and the heavy-strand oligonucleotide primers, as described elsewhere. Each fragment was purified and subsequently analyzed by direct sequencing in an ABI 3700 automated DNA sequencing using the Big Dye Terminator Cycle sequencing reaction kit. The resultant sequence data were compared with the revised Cambridge reference sequence (GenBank accession No. NC_001807).

For the quantification of the 4401A>G mutation, the first PCR segments (903 bp) were amplified using genomic DNA as a template and oligodeoxynucleotides corresponding with mtDNA at positions 3777 to 4679 to rule out the coamplification of possible nuclear pseudogenes. Then, the second PCR product (225 bp) was amplified using the first PCR fragment as a template, and oligodeoxynucleotides corresponding with mtDNA at positions 4243 to 4467 and subsequently digested with the restriction enzyme BglII as the 4401A>G mutation creates the site for this restriction enzyme. Equal amounts of various digested samples were then analyzed by electrophoresis through 7% polyacrylamide gel. The proportions of digested and undigested PCR products were determined by the Image-Quant program after ethidium bromide staining to determine whether 4401A>G mutation is in the homoplasmy in these subjects. The allele frequency of the 4401A>G variant was determined by PCR amplification using the genomic DNA derived from 242 Han Chinese controls and subsequent restriction enzyme analysis of PCR products, as described above.

**Mitochondrial tRNA Analysis**

Lymphoblastoid cell lines were immortalized by transformation with the Epstein-Barr virus, as described elsewhere. Cell lines derived from 1 proband II-1 and her son III-3 carrying the 4401A>G mutation and 2 Chinese married-in controls (II-2 and III-4) lacking this mutation were grown in RPMI 1640 (Invitrogen), supplemented with 10% FBS. Total mitochondrial RNA were obtained using a TOTALLY RNA kit (Ambion) from mitochondria isolated from lymphoblastoid cell lines (5 x 10^6 to 10^7 cells), as described previously. Two micrograms of total mitochondrial RNA were electrophoresed through a 10% polyacrylamide gel with 7 mol/L urea buffer after heating the sample at 65°C for 10 minutes and then electroblotted onto a positively charged nylon membrane (Roche) for the hybridization analysis with oligodeoxynucleotide probes. For the detection of tRNA^Met^, tRNA^Glu^, tRNA^Lys^, tRNA^Gln^, and tRNA^Ser^ (UCN), the following nonradioactive digoxigenin (DIG)-labeled oligodeoxynucleotides specific for each RNA were used: 5'-TAGTACGGGAAGGGTATAACC-3' (tRNA^Met^); 5'-CTAGGACATGAGAATCCGA-3' (tRNA^Glu^); 5'-TACCTGAGTG-3' (tRNA^Lys^); 5'-TAGTACGGGAAGGGTATAACC-3' (tRNA^Gln^); and 5'-CAACACCCATGGCGCTC-3' (tRNA^Ser^ (UCN)). DIG-labeled oligodeoxynucleotides were generated by using a DIG Oligonucleotide Tailing Kit (Roche). The hybridization was carried out as detailed elsewhere. Quantification of density in each band was made as detailed previously.

**Analysis of Mitochondrial Protein Synthesis**

Pulse labeling of the cell lines for 30 minutes with [35S]methionine-[35S]cysteine in medium-free DMEM in the presence of emetine, a eukaryotic translation product, and quantification of radioactivity in the whole-electrophoretic patterns or in individual well-resolved bands was carried out as detailed previously.

**O2 Consumption Measurements**

Rates of O2 consumption in intact cells were determined with a YSI 5300 oxygraph (Yellow Springs Instruments) on samples of 1 x 10^6 cells in 1.5 mL of special DMEM glucose lacking glucose and supplemented with 10% dialyzed FBS. Polarographic analysis of digitonin-permeabilized cells using different respiratory substrates...
and inhibitors to test the activity of the various respiratory complexes was carried out as detailed previously.33

Results

Clinical Presentation

The proband (II-1) began suffering from hypertension at the age of 60 years. She came to the Geriatric Cardiology Clinic of the Chinese People’s Liberation Army General Hospital for further clinical evaluations at the age of 65 years. Her blood pressure was 180/110 mm Hg. Physical examination, laboratory assessment of cardiovascular disease risk factors, and routine electrocardiography showed no other clinical abnormalities, including diabetes mellitus, vision and hearing impairments, or renal and neurological disorders. Therefore, she exhibited a typical essential hypertension. The family originated from Beijing in northern China, and the majority of family members live in the same area. As shown in Figure 1, this familial history is consistent with a maternal inheritance. None of the offspring of affected fathers had hypertension. Two male matrilineal relatives exhibited hypertension as the sole clinical symptom, whereas other members of this family had normal blood pressure. As shown in Table 1, subject III-3 experienced the hypertension (blood pressure was 140/110 mm Hg) at the age of 36 years, whereas his brother (III-5) had hypertension (blood pressure was 140/95 mm Hg) at the age of 35 years. There is no evidence that any member of this family had any other known cause to account for hypertension. Comprehensive family medical histories of these individuals showed no other clinical abnormalities, including diabetes mellitus, vision and hearing impairments, or renal and neurological disorders.

Mitochondrial DNA Analysis

The maternal transmission of hypertension in this family suggested the mitochondrial involvement and led us to analyze the mitochondrial genome of matrilineal relatives. For this purpose, the DNA fragments spanning the entire mtDNA of the proband II-1 were PCR amplified, and each fragment was purified and subsequently analyzed by direct sequence. As shown in Table 2, the comparison of the resultant sequences with the Cambridge consensus sequence identified a number of nucleoside changes, belonging to the Eastern Asian haplogroup C.34 Of these nucleoside changes,
there were 8 polymorphisms in the D-loop region, 2 variants in the 12S rRNA gene, 1 variant in the 16S rRNA gene, 1 novel 4401A>G mutation in the spacer between tRNA\textsuperscript{Met} and tRNA\textsuperscript{Gln} genes, 20 silent mutations (1 novel and 19 known), and 8 missense mutations in protein-encoding genes.\textsuperscript{35} These missense mutations are 5262G>A (264A>T) in the ND2 gene, 8584G>A (20A>T), 8701A>G (59T>A), and 8860A>G (112T>A) in the ATP6 gene, 10398A>G (114T>A) in the ND3 gene, 11447G>A (230V>M) in the ND4 gene, 14318T>C (119N>S) in the ND6 gene, and 15326A>G (194T>A) in the Cytb gene. These variants in rRNAs and polypeptides were further evaluated by phylogenetic analysis of these variants and sequences from other organisms, including mouse,\textsuperscript{36} bovine,\textsuperscript{37} and Xenopus laevis.\textsuperscript{38} None of variants in the polypeptides and rRNAs were highly evolutionarily conserved and implicated to have significantly functional consequence.

However, the novel A to G transition at the position 4401 (4401A>G) mutation, as shown in Figure 2, lies at the junction of tRNA\textsuperscript{Met} at the H-strand and tRNA\textsuperscript{Gln} at the L-strand.\textsuperscript{19,20} Here the 5' end of the flanking sequence is 4401A/AGTAAAG in the tRNA\textsuperscript{Met} gene, whereas the 5' end of the flanking sequence is 4401T/TCGAG in the tRNA\textsuperscript{Gln} gene.\textsuperscript{39} In fact, the processing of mitochondrial tRNAs requires the precise endonucleolytic cleavage at both 3' and 5' ends catalyzed by RNase P and 3' endonuclease.\textsuperscript{20,40,41} Thus, the 4401A>G mutation may affect the reaction efficiency of the RNase P involved in tRNA\textsuperscript{Met} and tRNA\textsuperscript{Gln} 5' end metabolism. The 4401A>G mutation was further assessed by phylogenetic analysis of this variant and sequences from mouse, bovine, and X laevis, as well as other 13 primates including Gorilla gorilla, Pan paniscus, Pan trossylodes, Pongo pygmaeus, Pongo abelii, Hylobates lar, Macaca mulatta, Macaca sylvanus, Papio hamadryas, Cebus albifrons, Tarsius bancanus, Nycticebus coucang, and Lemur catta (Genbank). In fact, the adenine at the 4401 position is extraordinarily conserved among these species. To determine whether the 4401A>G mutation is present in homoplasy, the fragments spanning the tRNA\textsuperscript{Met} and tRNA\textsuperscript{Gln} genes were PCR amplified and subsequently digested with BfaI, because the 4401A>G mutation creates the site for this restriction enzyme. As shown in Figure 2C, there was no detectable wild-type DNA in 4 matrilineal relatives, indicating that the 4401A>G mutation was present in homoplasy in these matrilineal relatives. In addition, this mutation was absent in 242 Han Chinese controls.

**Mitochondrial tRNA Analysis**

To examine whether the 4401A>G mutation affects the processing of the precursors in the tRNA\textsuperscript{Met} and tRNA\textsuperscript{Gln}, the steady-state levels of the tRNA\textsuperscript{Met} and tRNA\textsuperscript{Gln} were determined by isolating total mitochondrial RNA from cell lines derived from 2 affected individuals (II-1 and III-3) carrying the 4401A>G mutation and 2 married-in controls (II-2 and III-4) lacking this mutation in this Chinese family, separating them by a 10% polyacrylamide/7 M urea gel, electrophobting, and hybridizing with a nonradioactive DIG-labeled oligodeoxynucleotide probe specific for tRNA\textsuperscript{Met} and tRNA\textsuperscript{Gln}. After stripping the blots, the DIG-labeled oligodeoxynucleotide probes,
including tRNAGly, tRNALys, and tRNAGln as representatives of the whole H-strand transcription unit and tRNASer(UCN) derived from the L-strand transcription unit.\(^{19,20}\) These probes specific for the tRNAMet, tRNAGly, tRNALys, tRNAGln, and tRNASer(UCN), respectively, were hybridized with DIG-labeled oligonucleotide probes specific for the tRNAMet. The blots were then stripped and rehybridized with DIG-labeled tRNAGly, tRNALys, tRNAGln, and tRNASer(UCN). The levels of the mitochondrial translation products were determined by scanning the fluorograms for appropriate exposures of the fluorograms and normalization to data obtained for the 143B.TK\(^{+}\) sample. In fact, the overall rates of labeling of the mitochondrial translation products in the cell lines derived from 2 affected individuals (II-1 and III-3) carrying the 4401A>G mutation were decreased 31.7% and 20.8%, with an average of 26.0% relative to the mean value measured in the control cell lines.

**Respiration Defects in the Cell Lines**

The endogenous respiration rates of cell lines derived from 2 affected individuals (II-1 and III-3) carrying the 4401A>G mutation and 2 married-in controls (II-2 and III-4) lacking this mutation in this Chinese family were measured by determining the O\(_2\) consumption rate in intact cells, as described previously.\(^{32}\) As shown in Figure 5A, the rate of total O\(_2\) consumption in the lymphoblastoid cell lines derived from 2 affected individuals (II-1 and III-3) ranged between \(~74.9\%\) and \(80.6\%\), with an average of \(~77.8\%\) relative to the mean value measured in the control cell lines.

To investigate which of the enzyme complexes of the respiratory chain was affected in the mutant cell lines, O\(_2\) consumption measurements were carried out on digitonin-permeabilized cells using different substrates and inhibitors.\(^{33}\) As shown in Figure 5B, in the cell lines derived from 2 affected individuals, the rate of malate/glutamate-driven res-
piration, which depends on the activities of reduced nicotinamide-adenine dinucleotide:ubiquinone oxidoreductase (complex I), ubiquinol-cytochrome c reductase (complex III), and cytochrome c oxidase (complex IV), but usually reflects the rate-limiting activity of complex I, was very significantly decreased, relative to the average rate in the control cell lines, by 77% to 80% (on average). Similarly, the rate of succinate/glycerol-3-phosphate–driven respiration, which depends on the activities of complexes III and IV but usually reflects the rate-limiting activity of complex III, was significantly affected in the mutant cell lines, relative to the average rate in the control cell lines, by 76% to 81% (on average). Furthermore, the rate of \( \text{N}_2\text{N}_2\text{N}_2\text{N}_2\text{-tetramethyl-}p\text{-phenylenediamine/ascorbate-driven} \) respiration, which reflects the activity of complex IV, exhibited a 78% to 82% reduction in complex IV activity (on average) in the mutant cell lines relative to the average rate in the control cell lines.

**Discussion**

In the present study, we performed the clinical, genetic, and molecular characterization of a Han Chinese family with essential hypertension. The hypertension as a sole clinical phenotype was only present in all of the matrilineal relatives of this 4-generation pedigree. Clinical and genetic evaluations revealed the variable severity and age at onset in hypertension among 3 of 7 matrilineal relatives in this Chinese family. In particular, the age at onset in hypertension was 60, 36, and 35 years in 3 affected matrilineal relatives, with an average age of 44 years. The maternal transmission of hypertension in this family suggested that the mtDNA mutation(s) is 1 of the molecular bases for this disorder. Mutational analysis of the mitochondrial genome in this family identified 40 variants belonging to the Eastern Asian haplogroup C. Of these, 39 variants appeared to be polymorphisms, because these variants were not highly evolutionarily conserved and implicated to have significantly functional consequence. However, the homoplasmic A-to-G transition at position 4401 lies in the spacer immediately to the 5' end of the tRNAMet and tRNASer(UCN) genes. Furthermore, the adenine at the 4401 position of the mitochondrial genomes is highly conserved among various primates. This mutation is present only in matrilineal relatives of this family in the homoplasmic form but not in the 242 Han Chinese controls, indicating that this mutation may be involved in the pathogenesis of hypertension.

In fact, 22 human mitochondrial tRNAs are interspersed among the other functional mitochondrial RNAs (2 rRNAs and 11 mRNAs encoding 13 polypeptide subunits of the oxidative phosphorylation complexes) on long precursor transcripts. Of these, 8 tRNAs, including tRNA\(^{\text{Glu}}\) and tRNA\(^{\text{Ser(UCN)}}\), are synthesized from the polycistrionic precursors of the L-strand, whereas the other 14 tRNAs, eg, tRNA\(^{\text{Met}}\), tRNA\(^{\text{Lys}}\), and tRNA\(^{\text{Glu}}\), are transcribed from the precursors of the H-strand transcripts. The processing of
investigated by measuring on activities of the various components of the respiratory chain were various cell lines using different substrates and inhibitors. The analysis of O2 consumption in digitonin-permeabilized cells of the lymphoblastoid cell lines were made on each of lymphoblastoid cell lines. B, Polarographic with error bars representing 2 SEMs. A total of 4 determinations consumption per cell measured in different cell lines are shown, Figure 5.

Respiration assays. A, Average rates of endogenous O2 consumption (glu+mal)O2 consumption (succ+G-3-p)O2 consumption (asc/TIMPD) Total O2 consumption

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<tr>
<td>O2 consumption (asc/TIMPD) (mol/min/cell)</td>
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<td>1.5</td>
<td>2.0</td>
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Figure 5. Respiration assays. A, Average rates of endogenous O2 consumption per cell measured in different cell lines are shown, with error bars representing 2 SEMs. A total of 4 determinations were made on each of lymphoblastoid cell lines. B, Polarographic analysis of O2 consumption in digitonin-permeabilized cells of the various cell lines using different substrates and inhibitors. The activities of the various components of the respiratory chain were investigated by measuring on $-1 \times 10^7$ digitonin-permeabilized cells the respiration dependent on malate/glutamate, on succinate/glycerol-3-phosphate, and on N,N,N',N'-tetramethyl-p-phenylenediamine/ascorbate. A total of 4 determinations were made on each of the lymphoblastoid cell lines. Graph details and symbols are explained in the legend to Figure 3. mal/glutamate indicates malate/glutamate-dependent respiration; succ/G-3-P, succinate/glycerol-3-phosphate-dependent respiration; and asc/TMPD, N,N,N',N'-tetramethyl-p-phenylenediamine/ascorbate-dependent respiration.

Precursors in mitochondrial tRNAs require the precise endonucleolytic cleavage at both 5' and 3' ends. Extra nucleotides at their 5' termini are removed by RNase P, whereas the excision of tRNAs from primary polycistronic mitochondrial transcripts at their 3' end is catalyzed by the 3' endonuclease. Thus, it is anticipated that the A-to-G transition at position 4401 in the H-strand may lead to defective tRNA^{Met} 5' end processing in the H-strand transcripts, and the T-to-C transition at position 4401 may cause the reduced efficiency of the tRNA^{Gln} precursor 5' end cleavage in the L-strand transcripts. There is increasing evidence showing that the 5' and 3' end processing defects arising from pathogenic mitochondrial tRNA mutations could contribute to clinical abnormalities. The deafness-associated 7445T>G mutation in the precursor of the tRNA_{Ser(UCN)}^{Thr} gene and the cardiomyopathies-associated 4269A>G and 4295A>G mutations in the tRNA_{NC}^{Thr} gene altered 3' end processing efficiency of corresponding tRNAs. Similarly, the mitochondrial encephalomyopathy, lactic acidosis, stroke-like symptoms (MELAS)-associated 3243A>G and 3271T>C mutations and mitochondrial myopathy-associated 3302A>G mutation in the tRNA_{Leu(UUR)}^{Leu} led to the tRNA 5' end processing defects. Alternatively, a taurine modification deficiency at the anticodon wobble position of tRNA_{Leu(UUR)}^{Leu} carrying the 3243A>G or 3271T>C mutation is involved in the decreased translation of ND6 with a high content of the UUG codon.

In the current study, compared with a control cell lacking the mutation, a ~30% reduction in the levels of tRNA^{Met} and tRNA^{Gln} were observed in cells carrying the 4401A>G mutation. The lower levels of tRNA^{Met} and tRNA^{Gln} in cells carrying the 4401A>G mutation most probably result from a defect in the 5' end processing of tRNA^{Met} and tRNA^{Gln} precursors. As a result, a shortage of the tRNA^{Met} and tRNA^{Gln} leads to the reduced rate of mitochondrial protein synthesis. These defects appear to be responsible for the reduced activities of the mitochondrial respiration chain. Subsequently, these defects lead to the reduction of ATP production and an increase of reactive oxygen species production. These mitochondrial dysfunctions likely contribute to the development of hypertension. However, the levels of total tRNA^{Met} and tRNA^{Gln} in mutant cells are above a proposed threshold, which is 30% of the control level of tRNA, to support a normal rate of mitochondrial translation. Thus, the homoplasmic form, mild mitochondrial dysfunctions, late onset, and incomplete penetrance of hypertension in this family carrying the 4401A>G mutation indicated that the 4401A>G mutation itself is insufficient to produce a clinical phenotype, as in the cases of hypertension-associated tRNA^{Met} 4435A>G mutation, 18 deafness-associated 12S tRNA 1555A>G mutation, and Leber’s hereditary optic neuropathy-associated ND4 11778G>A mutation. The other modifier factors, eg, nuclear modifier genes, environmental factors, and personal lifestyles, also contribute to the development of hypertension in these subjects carrying the 4401A>G mutation. Therefore, the 4401A>G mutation, acting as an inherited risk factor, is involved in the development of hypertension in this Chinese family.
Perspectives
The genetic and biochemical evidence indicate that the mtDNA 4401A>G mutation is involved in essential hypertension. The tissue specificity of this pathogenic mtDNA mutation is likely attributed to tissue-specific RNA processing or the involvement of nuclear modifier genes. The 4401A>G mutation should be added to the list of inherited risk factors for future molecular diagnosis for hypertension. Thus, our finding will provide new insights into the molecular mechanism, management, and treatment of maternally inherited hypertension. Future research should further explore the emerging link among hypertension, mitochondrial dysfunction, and their causative-effect relationship.

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Disclosures
None.

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