Presence of mutation m.14484T>C in a Chinese family with maternally inherited essential hypertension but no expression of LHON

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ABSTRACT

Essential hypertension (EH, MIM 145500) is the most common cardiovascular disease and affects one-quarter of the world’s adult population. Families with EH in a mode of maternal transmission have been occasionally observed in clinical settings and suggested an involvement of mitochondrial DNA (mtDNA) mutation. We aimed to characterize the role of mtDNA mutation in EH. We reported a large Han Chinese family with a maternally inherited EH and an extraordinarily high percentage of sudden death mainly in affected females. Analysis of the entire mtDNA genome of the proband identified a homoplasmic primary mutation m.14484T>C for Leber’s hereditary optic neuropathy (LHON), along with several variants indicating haplogroup F1 status. Intriguingly, no maternal member in this family had LHON though they all harbored m.14484T>C. The arterial stiffness of the members carrying mutation m.14484T>C was significantly increased than that of non-maternal members without this mutation. No environmental factor (including age, sex, smoking, diabetes, hyperlipidemia) was correlated with the decreased aortic elastic properties observed in affected members. Mitochondrial respiration rate and membrane potential (ΔΨm) were significantly reduced in lymphoblastoid cell lines established from affected members carrying m.14484T>C compared to control cell lines (P<0.05). There was an elevation of reactive oxygen species and a compensatory increase of mitochondrial mass in mutant cell lines. Our results suggest that m.14484T>C causes EH under certain circumstance. This study provides a paradigm for diverse phenotypes of the primary LHON mutation and suggests for the necessity of routine cardiac evaluation in patients with the primary LHON mutation.

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1. Introduction

Essential hypertension (EH, MIM 145500) is one of the most common cardiovascular diseases and acts as a significant risk factor for heart attack, stroke and end-stage renal disease [12]. It causes a heavy global burden and around 7.6 million people die of this disease each year [3]. Though the exact molecular pathogenesis and mode of inheritance of EH have not been fully elucidated, genetic factor was demonstrated to be actively involved in the onset of EH according to family and epidemiologic studies [4,5]. Previous studies showed that about 35–55% of EH cases were associated with mitochondrial dysfunction [6,7]. Clinical observation of many EH cases from families with a maternal transmission of the disease suggested that mitochondrial DNA (mtDNA) mutations might account for the onset of EH [6–8]. There are several reports for identifying pathogenic mtDNA mutations in patients with hypertension [9–13], but the exact mechanism has not been sufficiently elucidated [14].

One clinical feature of mitochondrial disease is the complex symptom caused by the same mtDNA pathogenic mutation. For instance, mutation m.3243A>G could lead to a variety of human disorders such as mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) and diabetes [15,16]. Many factors including mtDNA mutation/background, nuclear genes and environmental factors were actively involved in the development of maternally inherited diseases [17].

In this study, we characterized a large Han Chinese family with maternally inherited EH and mutation m.14484T>C. We found that the maternal members in this family presented no acute or subacute central visual loss but only hypertension. We provided further experimental evidence to show that the onset of hypertension in this family was caused by the LHON mutation m.14484T>C.
2. Materials and methods

A five-generation Han Chinese family (Fig. 1) with maternally inherited EH (family EH10) was diagnosed at the Department of Cardiology in the Calmette Hospital, Kunming Medical University. Among the 36 subjects in this family, 10 individuals died (5 hypertensives and 5 normotensives); living individuals included 10 maternal members (4 hypertensives and 6 normotensives) and 16 non-maternal members (16 normotensives). We divided all the living individuals into case group (maternally-related members) and control group (non-maternal members) for comparison. Physical measurements for each member were conducted following the WHO MONICA Project standards. Individuals with EH were diagnosed according to the Joint National Committee VI criteria [18]. We sequenced the entire mtDNA genome of proband (IV:1) using the method described in our previous study [19] and defined the (potentially) pathogenic mutation in the matriline by a phylogenetic approach [20].

We further quantified the heteroplasmic or homoplasmic status of the identified pathogenic mutation in hair root, saliva and whole blood from the proband, as well as in all maternally-related relatives of the proband and all non-maternal individuals in this pedigree.

We established lymphoblastoid cell lines for three maternally related (affected members III:5 and IV:1 and asymptomatic member V:1) and three unrelated healthy individuals (C1, C2, and C3). We quantified oxygen consumption rates (OCR), intracellular reactive oxygen species (ROS), mitochondrial membrane potential (ΔΨm) and mitochondrial mass in each cell line.

Continuous variables were expressed as mean ± SD, and discrete variables in groups were expressed as frequency. Data were tested for normality using the one-sample Kolmogorov–Smirnov test (2-tailed). Continuous variables between the two groups (maternally-related members and non-maternal members) were analyzed by both non-parametric (Mann–Whitney U test and two-sample Kolmogorov–Smirnov test) and parametric methods (independent samples t-test). Because of the limited sample size for each group (10 versus 16), non-parametric tests were preferred in this study. The parametric tests were also performed as they have more statistical power for the same number of observations under the assumption of normality or the assumption of homogeneity of variance. The Levene’s test was applied to evaluate the equality of variances. Fisher’s exact test (two-tailed) was used to compare the rates of the patient’s gender, smoking and retinal microvascular structural changes (RMSC).

Comprehensively medical examination for all members in this family showed no signs of a hearing problem, muscular diseases and neurological disorders. Examination of electrocardiogram (ECG) and cranial magnetic resonance imaging (MRI) revealed no abnormality. All family members (except for proband IV:1) did not receive any antihypertensive or other cardiovascular drugs before and during their participation in this study. Measurement of aortic PWV and PP (pulse pressure) showed an increased arterial stiffness in the maternally-related offspring (Fig. 2 and Table S1). Nine of 17 maternal members in the pedigree expressed hypertension and the affected male to female ratio was 1:3 (Fig. 1 and Table 1). Among them, five died of sudden death (stroke and acute myocardial infarction) and the percentage of sudden death was 100%. The mean age at onset in this family was 45.5 years (range 20–65).

3. Results

3.1. Clinical features of the family with EH

The proband (IV:1) was a 52-year-old woman and suffered from hypertension at age 47. Her highest blood pressure [systolic blood pressure (SBP)/diastolic blood pressure (DBP)] was 170/110 mm Hg in the past 5 years. The proband visited the Calmette Hospital for further clinical evaluation in 2009 because of intermittent dizziness and headache. After being treated by calcium channel blocker (CCB) and angiotensin-receptor blocker, her blood pressure reduced to a normal range (110–130/70–80 mm Hg). All clinical indexes were normal except for ambulatory arterial stiffness index (AAI, 0.6), symmetric ambulatory arterial stiffness index (S-AAI, 0.4) and pulse wave velocity (PWV, 12.9 m/s), which showed abnormal values and suggested for declined aorta’s compliance (Fig. 2). The echocardiogram showed E/A ratio abnormality, which was one of the most common cardiac abnormalities in hypertension.

The proband had slight myopia at both eyes, and visual acuity was 0.6 in the right eye and 0.9 in the left eye. Ophthalmoscopic examination showed an abnormal pattern of chronic hypertensive retinopathy: the arteriole-to-venule ratio of retinal vessels was reduced to 1:3 and arteriovenous nicking was seen at the upper temporal quadrant, despite that both of her optic disks were normal. Examinations for intraocular pressure, visual field and color vision showed no sign of abnormality. Comprehensive medical examination for all members in this family showed no signs of a hearing problem, muscular diseases and neurological disorders. Examination of electrocardiogram (ECG) and cranial magnetic resonance imaging (MRI) revealed no abnormality. All family members (except for proband IV:1) did not receive any antihypertensive or other cardiovascular drugs before and during their participation in this study. Measurement of aortic PWV and PP (pulse pressure) showed an increased arterial stiffness in the maternally-related offspring (Fig. 2 and Table S1). Nine of 17 maternal members in the pedigree expressed hypertension and the affected male to female ratio was 1:3 (Fig. 1 and Table 1). Among them, five died of sudden death (stroke and acute myocardial infarction) and the percentage of sudden death was 100%. The mean age at onset in this family was 45.5 years (range 20–65).

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Fig. 2. Imaging of MR cine phase-contrast and the velocity–time curves of ascending aorta and the abdominal aorta. The position imaging of ascending aorta (A) and abdominal aorta (B) were measured by MR cine phase-contrast. Non-maternal member IV:8 (48 years old, male) of this family had good compliance and slow PWV (7.2 m/s) (C), whereas the proband (IV:1) had bad compliance and fast PWV (12.9 m/s) (D). Maternal members III:5 and IV:3 of the proband all had bad compliance and fast PWV (E: III:5, 14.5 m/s; F: IV:3, 11.0 m/s). “a”—level of ascending aorta, which is 1.5 cm above the aortic valve; “d”—level of abdominal aorta, which is 1.5 cm above the common iliac bifurcation; “ad” is the distance between the ascending aorta and the abdominal aorta. The beginning points of the time–speed curve of ascending aorta and abdominal aorta are marked by arrows.

Table 1
Clinical information of maternally-related members in family EH10.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Age at test (years)</th>
<th>Age of onset (years)</th>
<th>Age of death (years)</th>
<th>BPT (SBP/DBP) (mm Hg)</th>
<th>HCBPMR (SBP/DBP) (mm Hg)</th>
<th>Cause of death</th>
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<tr>
<td>I:2</td>
<td>F</td>
<td>–</td>
<td>Unknown</td>
<td>65</td>
<td>–</td>
<td>Unknown</td>
<td>Stroke</td>
</tr>
<tr>
<td>I:3</td>
<td>F</td>
<td>–</td>
<td>30</td>
<td>–</td>
<td>180/90</td>
<td>180/100</td>
<td>Accident</td>
</tr>
<tr>
<td>I:4</td>
<td>F</td>
<td>–</td>
<td>76</td>
<td>–</td>
<td>64</td>
<td>160/90</td>
<td>Stroke</td>
</tr>
<tr>
<td>I:5</td>
<td>F</td>
<td>48</td>
<td>69</td>
<td>–</td>
<td>180/90</td>
<td>180/111</td>
<td>AMI</td>
</tr>
<tr>
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<td>M</td>
<td>40</td>
<td>70</td>
<td>–</td>
<td>–</td>
<td>180/100</td>
<td>Stroke</td>
</tr>
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<td>F</td>
<td>73</td>
<td>45</td>
<td>–</td>
<td>160/90</td>
<td>170/90</td>
<td>–</td>
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<tr>
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<td>M</td>
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<td>69</td>
<td>–</td>
<td>105/64</td>
<td>120/70</td>
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<td>M</td>
<td>24</td>
<td>22</td>
<td>–</td>
<td>106/64</td>
<td>–</td>
<td>Drowning</td>
</tr>
<tr>
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<td>F</td>
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<td>47</td>
<td>–</td>
<td>120/80</td>
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<td>F</td>
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<td>F</td>
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<td>–</td>
<td>135/85</td>
<td>156/100</td>
<td>–</td>
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<tr>
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<td>M</td>
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<td>–</td>
<td>106/64</td>
<td>120/68</td>
<td>–</td>
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<td>III:5</td>
<td>M</td>
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<td>–</td>
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<td>24</td>
<td>–</td>
<td>–</td>
<td>100/70</td>
<td>115/75</td>
<td>–</td>
</tr>
</tbody>
</table>

F: female; M: male; SBP: systolic blood pressure; DBP: diastolic blood pressure; AMI: acute myocardial infarction; ND: natural death; HCBPMR: the highest casual blood pressure of medical record; BPT: blood pressure of test.

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We compared the ambulatory blood pressure monitoring (ABPM) parameters, PWV and biochemical test values between the maternal and non-maternal members by using both non-parametric and parametric tests (with adjustment for age, sex and body mass index [BMI]). As shown in Table 2 and Table S2, the maternally-related members had a significantly higher value of 24 h pulse pressure (24hPP) (P<0.05), day pulse pressure (dPP) (P<0.02), night pulse pressure (nPP) (P<0.01), S-AASI (P<0.02), AASI (P<0.02) and PWV (P<0.02) than the non-maternal members. There was statistical difference for SBP of daytime, nighttime and 24-hour (P<0.05) between the two groups when the effects of age, sex, and BMI were taken into consideration. Other factors including age, gender, smoking, BMI, waist hip ratio (WHR), fasting blood sugar, blood lipids, uric acid, and renal function were similar between the two groups (P>0.05). Although the differences of eye vision and rate of retinal microvascular structural changes (RMSC) were not statistically significant, there were trends that the maternally-related members had higher values of PWV and RMSC compared to the non-maternal members.
between the two groups were not statistically different \( (P > 0.05) \), maternally-related subjects had a higher prevalence of retinal microvascular signs (Table 2). All these observations suggested that arterial structural abnormality of mother–offspring units was more severe than that of non-mother–offspring units.

Echocardiographic parameters of all members were shown in Table S3. The maternally-related members displayed a significantly higher level of left ventricular mass index (LVMI) (two-sample Kolmogorov–Smirnov test, \( P = 0.005 \); independent samples t-test, \( P = 0.025 \); adjusted \( P = 0.001 \) (Table 2 and Table S2) compared to non-maternal members. Significant differences for left ventricular diastolic diameter (LVIDd), left atrium diameter (LAD), left ventricular posterior wall thickness (IVSd), left ventricular posterior wall thickness (LVPWd), and E/A were observed between the two groups when effects of age, sex, and BMI were considered \( (P < 0.05) \) (Table S2), suggesting hypertension and arterial stiffness-associated cardiac remodeling.

3.2. Presence of m.14484T>C in the matriline

Analysis of the complete mtDNA sequence of the proband identified a total of 30 homoplasmic variants relative to the revised Cambridge reference sequence (rCRS) [21], in which 23 were haplogroup-characteristic variants and suggested it belongs to haplogroup F1b'd (Fig. 3). Among 7 private variants in this matriline, four \((\text{m.}309\text{insC}, \text{m.}523\text{–}524\text{del}, \text{m.}16183\text{A} > \text{C}, \text{m.}16519\text{T} > \text{C})\) were located in the control region, three were located in the coding region \((\text{m.}2389\text{T} > \text{G} \text{in the } \text{MT-RNR2} \text{ gene, } \text{m.}3398\text{T} > \text{C} \text{in the } \text{MT-ND1} \text{ gene, and } \text{m.}14484\text{T} > \text{C} \text{in the } \text{MT-ND6} \text{ gene})\). All these private variants were previously reported and had no potential pathogenicity except for \(\text{m.}14484\text{T} > \text{C}\), which was one of the well-known primary LHON mutations. Mutation \(\text{m.}14484\text{T} > \text{C}\) was homoplasmic in hair root, saliva and whole blood from the proband (Fig. S1). This mutation was presented in all maternally-related relatives of the proband but was absent in all non-maternal individuals (Figs. S1 and S2). We presented a sequence variation of the proband, together with some related mtDNAs which belonged to the same haplogroup in a tree. Apparently, there was no clear evidence for a synergistic effect between \(\text{m.}14484\text{T} > \text{C}\) and other private variants in this matriline, as this mtDNA did not harbor any private variants on its terminal branch in the tree (Fig. 3). The complete mtDNA sequences of the proband and a healthy control \((\text{C}3)\) belonging to haplogroup F1a1c were deposited in GenBank under accession nos. JN133516–JN133517.

3.3. Alteration of mitochondrial function in mutant cells

To evaluate mitochondrial function of lymphoblastoid cell lines established from three maternally-related members with \(\text{m.}14484\text{T} > \text{C}\) and three unrelated healthy controls, we used a Clark electrode to measure oxygen consumption rate (OCR) in live cells. The mutant cell lines exhibited significantly lower OCR than control cell lines (Fig. 4 and Table S7). We added different respiratory inhibitors to determine which respiratory complex was the pronounced one being affected. We employed ATP-coupled respiration, basal mitochondrial respiration and three unrelated healthy controls, we used a Clark electrode to measure the respiratory capacity respectively on the mitochondrial membrane potential, respectively.

The OCR value of each respective state was normalized to the initial value before adding the inhibitor, which was arbitrarily set to 1. Surprisingly, all three mitochondrial respiration parameters decreased significantly in mutant cell lines \((P < 0.05)\) (Fig. 4B and Table S7). As maximal respiratory capacity reflected the permeability of a mitochondrial outer membrane \(\Delta \Psi_{m}\), we measured mitochondrial potential in cell lines with and without \(\text{m.}14484\text{T} > \text{C}\). Concordant with the OCR result, the mean value of \(\Delta \Psi_{m}\) in mutant cells decreased remarkably \((up to 87.9\%)\) compared to that of control cells \((P < 0.05)\) (Fig. 5A–B and Table S7).

We further tested the alteration of reactive oxygen species (ROS) and mitochondrial mass in cell lines with and without \(\text{m.}14484\text{T} > \text{C}\), which are sensitive to mitochondrial dysfunction. The average ROS level of mutant cells was higher than that of control cells (Fig. 5C–D and Table S7), with an increase of up to 140.6%. Intriguingly, we also observed an elevation of mean value of mitochondrial mass \((up to 37.4\%)\) albeit the difference was not statistically significant) in all mutant cell.
lines (Fig. 5E–G and Table S7), suggesting for a potential compensation for mitochondrial dysfunction in the presence of m.14484T>C. Accordingly, we observed no essential difference for an mtDNA copy number (Fig. S3) and the overall cellular ATP levels (Fig. S4) between mutant and control cell lines.

4. Discussion

Accumulating evidence suggested that mitochondrial damage and dysfunction were actively involved in cardiovascular disease [22,23]. In this study, we performed the clinical, genetic, and molecular characterization of a large family with maternal hereditary hypertension and LHON mutation m.14484T>C. Clinical examination and evaluation showed that the parameters related to vascular aging (including PP, S-AASI, AASI and PWV) of the maternally-related members presented significantly higher values than those of non-maternal members. In particular, four maternally-related members died of hemorrhagic stroke and one died of acute myocardial infarction, indicating problems with vascular remodeling in this family. The aortic stiffness, as one of the main causes of increased blood pressure [24], was evident in affected members (Fig. 3; Tables 2 and S1). Our observation indicated that the primary increase in large artery stiffness caused by mutation m.14484T>C preceded the development of hypertension [25]. However, affected members of this family were not isolated systolic hypertension, indicating that structural abnormality of small arteries may also play a role in EH. More families are required to solidify our speculation.

The striking clinical feature of this family is that all maternally-related members had no apparent sign for LHON but EH, despite that they had...
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m.14484T>C (Fig. S1). Although there are studies reporting that LHON patients expressed cardiac or vascular abnormalities, such as pre-excitation syndrome [26,27], myocardial thickening, left ventricular noncompaction (LVNC), dilated heart [28,29], mild degenerative cardiomyopathy [30], high aortic stiffness indexes [31] and intracranial arteriovenous malformation [32], there is no report for the presence of primary LHON mutation m.14484T>C in a family with EH but without clinical expression of LHON to date. Analyses of demographic data and biochemical test values of all available members in this EH family suggested that no environmental factor, but hereditary factor, accounted for the maternal transmission of the disease. Determination of the entire mtDNA genome showed that no other pathogenic mutation, except for m.14484T>C, would account for hypertension (Fig. 2). Note that this family had a non-syndromic variant m.33987T>C, which was said to be pathogenic in previous studies [33,34]. This variant existed in different populations worldwide and was one of characteristic motifs for haplogroups I2a1 and M65b [35]. By comparing to four near-matched sequences from GenBank and generated in this study, we found that m.33987T>C, together with m.2389 C>T, define a novel subhaplogroup of F1b’d in Chinese. Therefore, variant m.33987T>C should be best categorized as a polymorphism.

Why the primary LHON mutation m.14484T>C did not cause vision loss but hypertension in this family is a riddle. Nikoskela et al. [36] found that only a few LHON mutation carriers with microangiopathy finally developed optic neuropathy, this incomplete penetrance could partially explain why no LHON was observed in this family. It should be mentioned that the maternal lineage of this family belonged to haplogroup F, which was said to be a protective factor for LHON carriers with m.14484T>C [37] and m.11775 G>A [38], and this maternal background may relieve the deleterious effect of pathogenic mtDNA mutation on the eye.

Many mtDNA mutations have been reported to be associated with hypertension or cardiovascular diseases [9–12]. One plausible explanation for the pathogenicity of deleterious mtDNA mutation in hypertension is that it causes a decrease of energy production, overproduction of ROS, metabolic imbalance, and disturbed signal transduction, which finally initiated hypertension, atherosclerosis, apoptosis, and necrosis [39]. Dysfunction of mitochondrial respiratory chain decreased electrochemical potential gradient and impaired ATP synthesis, which further destroyed lysosomal/diastolic functions in vascular smooth muscle cell (VSMC) [40,41]. Elevated ROS induced vascular endothelial cell (VEC) senescence [42,43] and was involved in the development of hypertension and atherosclerosis [22,44]. We were unable to collect VSMC and VEC from the living affected members in this family. However, by using lymphoblastoid cell lines derived from family members and healthy controls, we observed a reduction of respiration rate (including ATP-coupled respiration, maximal respiratory capacity and basal mitochondrial respiration) and ΔΨm, and an increase of ROS level in mutant cell lines. Along with these alterations, there was a substantial increase of mitochondrial mass in mutant cells, which compensated cellular ATP production and mtDNA content in the presence of m.14484T>C. All these lines of evidence supported for mitochondrial defects owing to m.14484T>C. The ROS levels in mutant cells from symptomatic patients (III:5, 47.44% and IV:1, 26.95%) and the asymptomatic patient (V:1, 23.40%) were substantially increased compared to those of control cells (C1, 17.82%; C2, 14.99%; C3, 7.83%). We speculated that an increase of ROS generation and a loss of mitochondrial membrane potential in the presence of m.14484T>C would contribute to endothelial dysfunction, which finally caused impaired elasticity and contractility of the aorta [41,45].

One intriguing observation is that half of the maternally-related members with m.14484T>C presented EH at the time of this study. The incomplete penetrance of EH suggested a potential influence of the nuclear genetic background. Indeed, cells from the asymptomatic member V:1 had increased ROS and decreased mitochondrial membrane potential (Fig. 5 and Table S7), despite the absence of EH and young age (28 years old). Further study, with a proper balance of the different nuclear genetic backgrounds of cases and controls, should be carried out to define the effect of the nuclear background on clinical expression of m.14484T>C. In addition, epigenetic modifications (e.g. gene methylation, acetylation) to genes involved with adverse vessel remodeling, membrane lipid homeostasis and myocardial conduction properties [46,47] should be closely evaluated in future studies, to identify the nuclear genes and other molecular modifications that are actively involved in this process.

In summary, the current report for the presence of m.14484T>C in a Chinese family with maternally inherited EH but without LHON provides a paradigm for diverse phenotypes of the primary LHON mutation. We show several lines of evidence that m.14484T>C caused mitochondrial dysfunction in cells from affected members and this may be the underlying mechanism for hypertension in this family. Given the absence of an overt phenotype in some carriers there is a potential complexity that may also involve mitochondrial genes and other molecular modifications. Patients with the primary LHON mutation should routinely undergo cardiac evaluation of aortic compliance and blood pressure. Our study also provides a new clue for a maternally genetic factor of arterial stiffening and vascular aging. Lifestyle intervention or pharmacotherapy that retards and/or reverses age-related vessel remodeling and stiffness may represent a potential target for treatment and prevention of maternally inherited EH.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary material is available at Journal online. Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.bbadis.2012.06.010.

References


