Dear Editor:

It is well known that the majority of Leber’s hereditary optic neuropathy (LHON) cases was caused by 3 mtDNA primary mutations (m.3460G>A, m.11778G>A, and m.14484T>C); other mutations that affected the LHON expression are relatively rare.1 Recently, Liu et al2 reported clinical, genetic, and biochemical characterizations of 6 Chinese families with clinical feature of LHON but lacking the 3 primary mutations. They claimed that mtDNA variant m.12338T>C, together with unknown nuclear modifier genes, account for LHON in these families.2 This conclusion unfortunately received weak support from a phylogenetic analysis of this variant in our previous study.3

First, 5 of 6 families described in their study2 lacked a typical feature of maternally inherited pattern of disease, and 3 families contained single patients. It is very difficult to conclude that these families had typical LHON or other genetic optic diseases.

Second, according to our previous study,3 and current global mtDNA phylogenetic tree,4 m.12338T>C is a characteristic variant of haplogroup F2, which is rather infrequent in east Asians. Haplogroup F2 had a frequency of 0%-25.7% in various general populations across China.4 Furthermore, phylogenetic analysis of F2 mtDNAs suggested that this haplogroup might have occurred in north China around 42,000 years ago.3 We searched 7385 complete mtDNA sequences from published sources and identified 14 occurrences of m.12338T>C (Supplementary material, available at http://aaojournal.org). Among these mtDNAs, 10 belonged to haplogroup F2. To update the phylogenetic relationship of haplogroup F2, we constructed a phylogenetic tree of these 10 mtDNAs, together with 1 mtDNA sequence from our recent study,5 and the 6 mtDNAs in the study by Liu et al.2 As shown in Figure 1 (available at http://aaojournal.org), variant m.12338T>C, together with variants m.1005T>C, m.1824T>C, m.7828A>G, m.10535T>C, m.10586G>A, and m.13708G>A, well define haplogroup F2. This haplogroup can be divided into several sub-haplogroups. As all of the 6 mtDNAs reported by Liu et al2 belonged to haplogroup F2, the occurrence of m.12338T>C in these families is not unexpected. Furthermore, there is no evidence suggesting a high prevalence of LHON in these regions with high frequency of haplogroup F2/m.12338T>C.5 To define the potential association between haplogroup F2 and LHON in Chinese families, the authors should follow the approach described in our recent study for defining mtDNA haplogroup effect on LHON,6 in which we showed an extremely low occurrence of haplogroup F in Chinese patients with m.11778G>A.

Despite that variant m.12338T>C caused a change of methionine in the translational initiation codon of the NADH dehydrogenase subunit 5 gene (MT-ND5) with threonine in F2 lineages, this alteration may not be necessarily pathogenic. The third methionine codon in the MT-ND5 gene may act as a surrogate when the initiation codon was impaired.3 This kind of phenomenon is not rare and can be identified in other mitochondrial DNA genes, both in human and primates.3

In short, the clinical diagnosis of LHON in the 6 families reported by Liu et al2 is quite problematic. These authors also failed to present any functional data to justify the pathogenicity of m.12338T>C in these families. Variant m.12338T>C should still be categorized as a polymorphism rather than a pathogenic mutation, not to mention its role in LHON.

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References

Figure 1. Haplogroup tree of 17 mtDNAs belonging to haplogroup F2, plus the revised Cambridge reference sequence (rCRS). Complete mtDNA sequences WZ411-WZ416,1 AP010683.1, AP010670.1 and AP010706.1,2 AY255168.1 and AY255180.1,3 AP008441.1 and AP008692.1,4 GQ999958.1,5 FJ198215.1,6 FJ48736.1 (sequence available in GenBank) and GC-3 (HQ713445) are shown in this figure. Suffixes C means transversion, “d” indicates a deletion, “+” indicates an insertion; “s” indicates a synonymous variant; “ns” indicates a non-synonymous variant; “r” indicates a variant in the rRNA genes; “t” indicates a variant in the tRNA genes; “nc” indicates a variant in noncoding region; recurrent mutations are underlined; back mutations are underlined and marked “@”. Length polymorphisms of A- and/or C-tract in regions 16180–16193, 303–315 and 514–524 were excluded in the analysis.
Supplemental file

Database search
We searched 7385 complete mtDNA sequences from published sources that were included in the database of the MitoTool (http://www.mitotool.org; the search was performed on 12 January 2011) \(^1\). We identified 14 mtDNAs contained \textit{m.12338T>C} across world. These mtDNAs belonged to haplogroups F2 (n=10) \(^{2-6}\), L3f2b (n=2) \(^7\), D4h3a (n=1) \(^8\), P1d (n=1) \(^9\).

Figure Legend

Figure 1. Haplogroup tree of 17 mtDNAs belonging to haplogroup F2, plus the revised Cambridge reference sequence (rCRS \(^{10}\)). Complete mtDNA sequences WZ411-WZ416 \(^{11}\), AP010683.1, AP010670.1 and AP010706.1 \(^2\), AY255168.1 and AY255180.1 \(^3\), AP008441.1 and AP008692.1 \(^4\), GQ999958.1 \(^5\), FJ198215.1 \(^6\), FJ748736.1 (sequence available in GenBank) and GC-3 (HQ713445) \(^{12}\) are shown in this figure. Suffixes C means transversion, “d” indicates a deletion, “+” indicates an insertion; “s” indicates a synonymous variant; “ns” indicates a non-synonymous variant; “r” indicates a variant in the rRNA genes; “t” indicates a variant in the tRNA genes; “nc” indicates a variant in noncoding region; recurrent mutations are underlined; back mutations are underlined and marked “@”. Length polymorphisms of A- and/or C-tract in regions 16180-16193, 303-315 and 514-524 were excluded in the analysis.
Figure 1
Supplemental References