Leber's Hereditary Optic Neuropathy

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 al[2] 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] Moreover, the authors apparently neglected the following important issues during their analyses.

First, 5 of 6 families described in their study[2] 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 phylogenic 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.[3] 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 al[2] 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*.[3] 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 al[2] 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[3] rather than a pathogenic mutation, not to mention its role in LHON.

Rui Bi, BS
A-Mei Zhang, PhD
Yong-Gang Yao, PhD
Kunming, China

References

1. Zou Y, Jia X, Zhang A-M, et al. The MT-ND1 and MT-ND5 genes are mutational hotspots for Chinese families with clinical features of LHON but lacking the three primary mutations. Biochem Biophys Res Commun 2010;399:179–85.
2. Liu X-L, Zhou X, Zhou J, et al. Leber's hereditary optic neuropathy is associated with the T12338C mutation in mitochondrial ND5 gene in six Han Chinese families. Ophthalmology 2011;118:978–85.
3. Kong Q-P, Yao Y-G, Sun C, et al. Phylogeographic analysis of mitochondrial DNA haplogroup F2 in China reveals T12338C in the initiation codon of the ND5 gene not to be pathogenic. J Hum Genet 2004;49:414–23.
4. van Oven M, Kayser M. Updated comprehensive phylogenetic tree of global human mitochondrial DNA variation. Hum Mutat 2009;30:E386–94.
5. Bi R, Li W-L, Chen M-Q, et al. Rapid identification of mtDNA somatic mutations in gastric cancer tissues based on the mtDNA phylogeny. Mutat Res 2011;709–710:15–20.
6. Ji Y, Zhang A-M, Jia X, et al. Mitochondrial DNA haplogroups M7b1'2 and M8a affect clinical expression of leber hereditary optic neuropathy in Chinese families with the m.11778G→A mutation. Am J Hum Genet 2008;83:760–8.

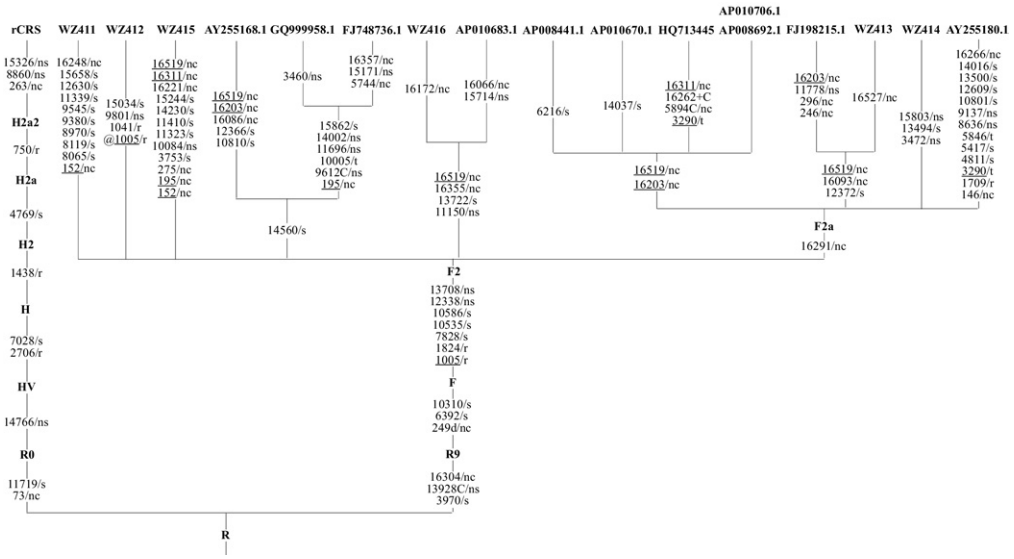

Figure 1. Haplogroup tree of 17 mtDNAs belonging to haplogroup F2, plus the revised Cambridge reference sequence (rCRS).[10] Complete mtDNA sequences WZ411-WZ416,[11] AP010683.1, AP010670.1 and AP010706.1,[2] AY255168.1 and AY255180.1,[3] AP008441.1 and AP008692.1,[4] GQ999958.1,[5] FJ198215.1,[6] FJ748736.1 (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.

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 *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.

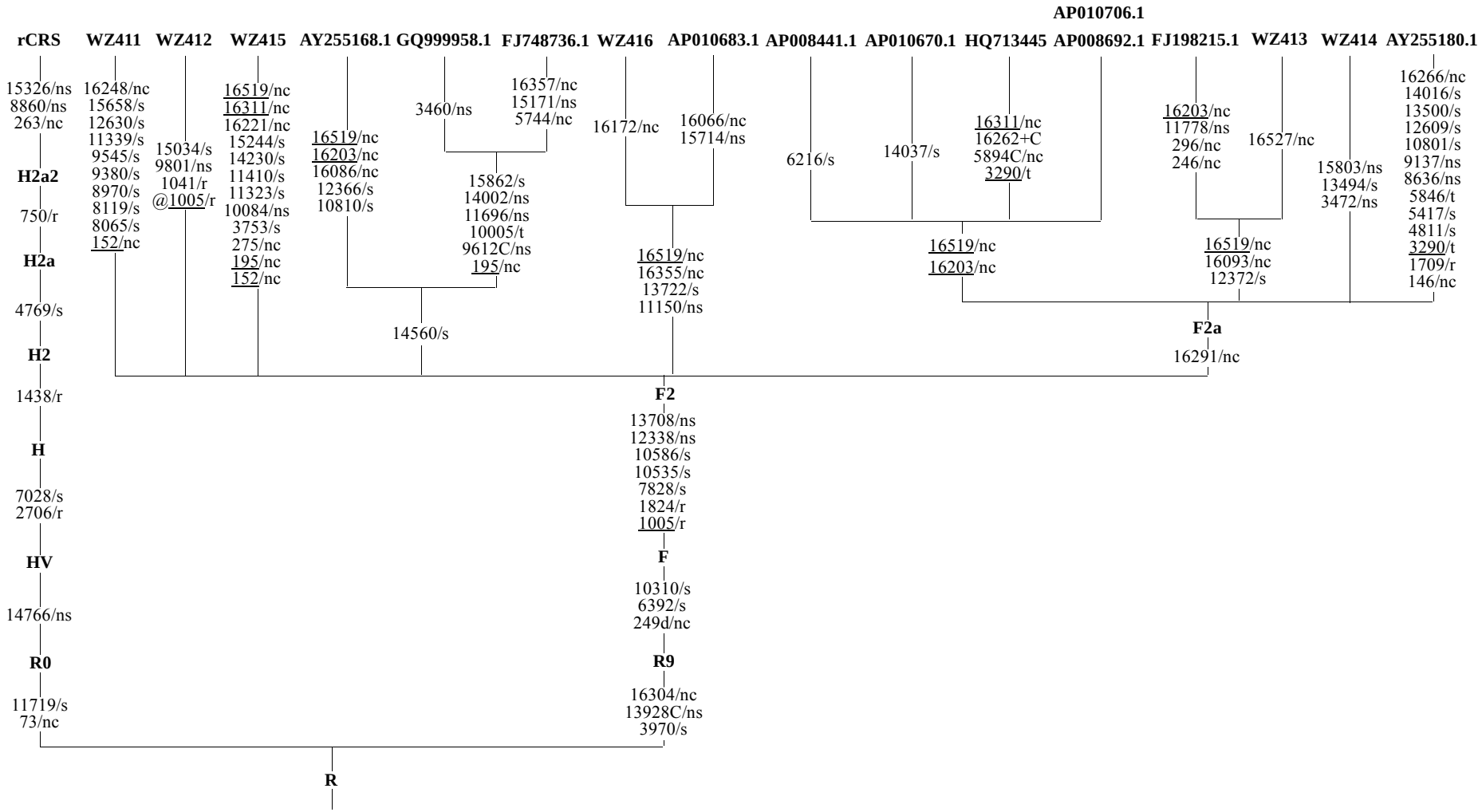
rCRS
WZ411
WZ412
WZ415
AY255168.1
GQ999958.1
FJ748736.1
WZ416
AP010683.1
AP008441.1
AP010670.1
HQ713445
AP010706.1
AP008692.1
FJ198215.1
WZ413
WZ414
AY255180.1
15326/ns
8860/ns
263/nc
H2a2
750/r
H2a
4769/s
H2
1438/r
H
7028/s
2706/r
HV
14766/ns
R0
11719/s
73/nc
16248/nc
15658/s
12630/s
11339/s
9545/s
9380/s
8970/s
8119/s
8065/s
152/nc
15034/s
9801/ns
1041/r
@1005/r
16519/nc
16311/nc
16221/nc
15244/s
14230/s
11410/s
11323/s
10084/ns
3753/s
275/nc
195/nc
152/nc
16519/nc
16203/nc
16086/nc
12366/s
10810/s
14560/s
3460/ns
15862/s
14002/ns
11696/ns
10005/t
9612C/ns
195/nc
16357/nc
15171/ns
5744/nc
16172/nc
16066/nc
15714/ns
16519/nc
16355/nc
13722/s
11150/ns
F2
13708/ns
12338/ns
10586/s
10535/s
7828/s
1824/r
1005/r
F
10310/s
6392/s
249d/nc
R9
16304/nc
13928C/ns
3970/s
R
6216/s
14037/s
16311/nc
16262+C
5894C/nc
3290/t
16519/nc
16203/nc
16203/nc
11778/ns
296/nc
246/nc
16527/nc
16519/nc
16093/nc
12372/s
F2a
16291/nc
15803/ns
13494/s
3472/ns
16266/nc
14016/s
13500/s
12609/s
10801/s
9137/ns
8636/ns
5846/t
5417/s
4811/s
3290/t
1709/r
146/nc

Figure 1

Supplemental References

1. Fan L, Yao Y-G. MitoTool: a web server for the analysis and retrieval of human mitochondrial DNA sequence variations. Mitochondrion 2011;11:351-6.
2. Bilal E, Rabadan R, Alexe G, et al. Mitochondrial DNA haplogroup D4a is a marker for extreme longevity in Japan. PLoS ONE 2008;3:e2421.
3. Kong Q-P, Yao Y-G, Sun C, et al. Phylogeny of east Asian mitochondrial DNA lineages inferred from complete sequences. Am J Hum Genet 2003;73:671-6.
4. Tanaka M, Cabrera VM, González AM, et al. Mitochondrial genome variation in Eastern Asia and the peopling of Japan. Genome Research 2004;14:1832-50.
5. Yu D, Jia X, Zhang A-M, et al. Molecular characterization of six Chinese families with m.3460G>A and Leber hereditary optic neuropathy. Neurogenetics 2010;11:349-56.
6. Ji Y, Zhang A-M, Jia X, et al. Mitochondrial DNA haplogroups M7b1'2 and M8a affect clinical expression of leber hereditary optic neuropathy in Chinese families with the m.11778G→A mutation. Am J Hum Genet 2008;83:760-8.
7. Behar DM, Villems R, Soodyall H, et al. The dawn of human matrilineal diversity. Am J Hum Genet 2008;82:1130-40.
8. Perego UA, Achilli A, Angerhofer N, et al. Distinctive Paleo-Indian migration routes from Beringia marked by two rare mtDNA haplogroups. Curr Biol 2009;19:1-8.
9. Ingman M, Gyllensten U. Mitochondrial genome variation and evolutionary history of Australian and New Guinean aborigines. Genome Res 2003;13:1600-6.
10. Andrews RM, Kubacka I, Chinnery PF, et al. Reanalysis and revision of the Cambridge reference sequence for human mitochondrial DNA. Nat Genet 1999;23:147.
11. Liu X-L, Zhou X, Zhou J, et al. Leber's Hereditary Optic Neuropathy Is Associated with the T12338C Mutation in Mitochondrial ND5 Gene in Six Han Chinese Families. Ophthalmology 2011;118:978-85.
12. Bi R, Li W-L, Chen M-Q, et al. Rapid identification of mtDNA somatic mutations in gastric cancer tissues based on the mtDNA phylogeny. Mutat Res 2011;709-710:15-20.