Letters to the Editor

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Pathological Significance of the mtDNA COX III Mutation at Nucleotide Pair 9438 in Leber Hereditary Optic Neuropathy

To the Editor:

It has recently been proposed that an mtDNA mutation at nucleotide pair (np) 9438 in the cytochrome c oxidase subunit III (COX III) gene is of primary pathogenic importance in Leber hereditary optic neuropathy (LHON) (Johns and Neufeld 1993). LHON is a form of acute or subacute bilateral central vision loss caused by mtDNA mutations. Primary LHON mutations cause blindness regardless of background mtDNA sequence (haplotype) and are typically not found in controls (Brown and Wallace, in press). The putative LHON G-to-A transition at np 9438 changed the conserved glycine 78 to a serine; eliminated a *Stu*I restriction site at np 9347; was homoplasmic in five LHON probands who were negative for the other known primary mutations, at np 3460, 11778, 14484, and 15257; and was absent in 400 normal and disease controls of unspecified race or ethnic background (Johns and Neufeld 1993). The np 9438 mutation also eliminates a *Hae*III site at np 9438. *Hae*III has commonly been used in surveys of normal mtDNA variation in human populations. In studying African populations, we have observed that this *Hae*III site is absent in 18% (4/22) of eastern Zaire Pygmies and 1.7% (1/60) of Mandinkas. Sequence analysis confirmed that this *Hae*III site loss was due to the G-to-A transition at np 9438. Moreover, this same base change was found in 4.4% (3/69) of normal Cubans, a population of mixed ancestry. Haplotype analysis revealed that all of the African mtDNAs harboring the COX III mutation also had the African-specific *Hpa*I site-gain polymorphism at np 3592, while the Cuban mtDNAs did not. Therefore the np 9438 mutation must have arisen independently in these control populations.

The presence of the np 9438 mutation at significant frequencies in normal African and Cuban populations suggests that it is not pathogenic for most individuals. Considerably more data will be necessary to determine whether this mutation is pathologic when associated with specific mtDNA haplotypes. Until such data become available, caution should be exercised in interpreting the results when screening random LHON patients for the COX III np 9438 mutation.

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References

Brown MD, Wallace DC. The molecular basis of mtDNA disease. J Bioenerg Biomembr (in press)

Johns DR, Neufeld MJ (1993) Cytochrome c oxidase mutations in Leber hereditary optic neuropathy. Biochem Biophys Res Commun 196:810-815

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Reply to Brown et al.

To the Editor:

Brown et al. present data related to the pathogenetic significance of an mtDNA mutation at nucleotide position 9438 in the cytochrome *c* oxidase subunit III (COX III) gene that my colleague and I recently reported in patients with Leber hereditary optic neuropathy (LHON) (Johns