Mitochondrial D-loop variation in Leber's hereditary neuropathy patients harboring primary G11778A, G3460A, T14484C mutations: J and W haplogroups as high-risk factors

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Leber's hereditary optic neuropathy (LHON) is a maternally inherited form of retinal ganglion cell degeneration leading to optic atrophy in young adults. It is caused by three primary point mutations including G11778A, G3460A, and T14484C in the mitochondrial genome. These three mutations account for the majority of LHON cases and affect genes that encode different subunits of mitochondrial complex I. Mitochondrial DNA (mtDNA) has a non-coding region at the displacement loop (D-loop) that contains two hypervariable segments (HVS-I and HVS-II) with high polymorphism. To investigate any possible association between LHON primary mutations and mtDNA haplogroups (hg), the nucleotide sequence of the HVS-I region of mtDNA was determined in 30 unrelated Iranian patients with LHON harboring one of the primary mutations and 100 normal controls with the same ethnicity. DNA was extracted from the peripheral blood after having obtained an informed consent. The nucleotide sequence of HVS-I (np 16,024e16,383) was directly determined.

Our analysis revealed a relatively high proportion of haplogroup J in LHON patients (53.3%) compared to normal controls (20%). In addition, a slightly significant increase in normal controls with haplogroup L was confirmed (14% in normal controls vs. 0% in LHON patients at p 5 0.03), whereas other haplogroups did not show contribution to LHON contingency. The analysis presented here provides evidence that there is an association between G11778A and G3460A with haplogroup J (including J1 and J2) and W, respectively. Therefore, we hypothesize that mtDNA haplogroups J (J1 and J2) and W might act as predisposing haplotypes to increase the penetrance of LHON disease.

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