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Searching for nuclear modifying genes in Leber's hereditary optic neuropathy.

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Introduction. Leber's hereditary optic neuropathy (LHON) is a maternally inherited form of central visual loss affecting young males and related to mitochondrial DNA (mtDNA) point mutations. **Purpose.** To identify nuclear modifying genes which may modulate the variable penetrance in a large Brazilian LHON pedigree (SOA-BR) homoplasmic for the pathogenic mutation at nucleotide 11778/ND4 on an mtDNA haplogroup J. **Methods.** We screened known functional polymorphisms in a set of putative nuclear modifying genes for the pathogenic potential of the 11778/ND4 LHON mutation. These included the following genes: OPA1, APOE, MnSOD, P53, and Aldose reductase. We assessed the allelic combination for the polymorphic variants in the affected patients (n=24), the asymptomatic mutation carriers (n=39) and a control group made up by the off-pedigree individuals (n=66). The asymptomatic carriers were selected older than 35 years of age to minimize the possibility that they may convert to affected individuals. Statistical significance was obtained by the Chi square test. **Results.** Both the APOE and MnSOD polymorphisms were significantly different between affected males vs male asymptomatic mutation carriers (P=0.010 and P=0.148 respectively). The APOE polymorphic variant was also significantly different when all asymptomatic mutation carriers were compared to all affected individuals. **Conclusions.** We identified two functional polymorphisms in the APOE and MnSOD nuclear genes, which may play a modifying role in the expression of LHON in the large SOA-BR family. This is the first indication that LHON may be a genetic disorder with a complex genetic determination. The mtDNA pathogenic mutation is necessary but not sufficient for disease expression, and a complex multifactorial set of determinants, including nuclear modifying genes, may act in synergy.