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Mitochondrial DNA haplotype analysis as a tool for reconstruction of large Leber's hereditary optic neuropathy pedigrees.

Luana Mendieta1, Solange Salomao1, Valerio Carelli2 1 Dept. of Ophthalmology, Federal University of Sao Paulo, Sao Paulo, Brazil, 2Dipartimento di Scienze Neurologiche, Universitá di Bologna, Italy.

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 reconnect a recently reported large Brazilian family (SOA-BR) of Italian maternal ancestry with the pedigree branch still living in Italy.

Methods. We used a combination of restriction fragment length polymorphisms analysis and direct sequence of the control region to define high-resolution mtDNA haplotypes in the SOA-BR family and 89 unrelated index cases with LHON consecutively diagnosed in Italy. LHON diagnosis was defined by the presence of an established mtDNA pathogenic mutation.

Results. We identified identical haplotypes in the SOA-BR family and two Italian families strongly suggesting a common founder. Re-investigation of these maternal lineages allowed us to reconnect the SOA-BR family with their Italian relatives. In the SOA-BR pedigree two heteroplasmic polymorphisms in the D-loop region reached, over the generations, both fixation or reversion to the original sequence.

Conclusions. We have applied, as a tool, high-resolution mtDNA haplotype analysis to reconnect apparently unrelated LHON pedigrees into single large maternal lineages descending from the same founder. Reconstruction of large pedigrees is useful for studies aimed to study penetrance, segregation of heteroplasmic nucleotide changes and to locate nuclear modifier genes in LHON.