Executive summary

Leber hereditary optic neuropathy (LHON) is a mitochondrial genetic disease that commonly causes blindness in young adult males. Three primary mitochondrial DNA mutations are found in more than 95% of LHON cases worldwide. The marked incomplete penetrance and gender bias of this disease indicates that additional genetic and/or environmental factors are required for the phenotypic expression of the pathogenic mtDNA mutations in LHON. Numerous efforts have been done to have a better understanding on the pathogenesis of LHON, covering from the single gene study to global gene expression profile, especially to hunt for nuclear modifier, if any present. The oligonucleotide microarrays of LHON using cybrids and lymphoblastoid cell line and global gene expression profile (transcriptomic profiles) in LHON lymphocytes have been studied but yielded limited results. In the present study, we explored the differential mitochondrial proteomic profiles of affected LHON (n=7), unaffected LHON (n=3) and the control (n=5) fibroblasts using 2 Dimensional polyacrylamide gel electrophoresis (2-DE) and mass spectrometry. Out of 29 proteins identified by 2-DE proteomics, 20 different proteins were significantly different between the affected and the control groups while 23 proteins were different between the unaffected and the controls. Comparison between the affected and the unaffected groups revealed 7 different proteins which were significantly different. Most of the proteins identified in the study were from the mitochondrial proteins and they were down regulated in 11778G>A mutant fibroblasts. These proteins were from the subunits of OXPHOS, intermediary metabolism, nucleoid related proteins, chaperones, cristae remodeling and an anti-oxidant enzyme. Protein-protein interaction analysis of identified proteins showed two broad categories: those related with bioenergetic pathway and those related with protein folding. This result is further supported by functional annotation and clustering analysis. The important findings of the present proteomic study are that the proteomic changes in the cells with LHON mutation were mostly down regulation, and that the aerobic respiration and the protein quality control system of the mitochondria are critically affected, the conditions that would be incompatible with the higher energy demanding cells such as the retinal ganglion cells.