DE NOVO MITOCHONDRIAL DNA ALTERATION IN CHILD WITH COMPLEX NEUROLOGICAL COMPROMISSION

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Background: A wide spectrum of neurological and neuromuscular human diseases have been associated with mitochondrial DNA (mtDNA) variations, causing defects of oxidative phosphorylation. These dysfunctions affect preferentially tissues with high energy demands and give arise to several degenerative disorders such as optic neuropathy, cerebellar ataxia, movement disorders, dementia, muscle weakness and deafness. The extremely heterogeneous clinical phenotype is due to the involved tissue, to specific mtDNA mutations and their heteroplasmic level, but also to nuclear DNA alterations, environmental and epigenetic factors. In this study we investigated a child affected by a complex neurological disease whose clinical features were suggestive of a mitochondrial involvement. Methods: mtDNA from proband, her healthy relatives (grandmother, mother and two sisters) and 80 controls were collected and studied by sequencing. The enzymatic activity of specific respiratory chain complex was tested on lymphocytes by spectrophotometric assay. Bioinformatic analysis was performed to predict the pathogenicity of the detected variants. Results: In all subjects we detected 11 known polymorphisms, whereas 1 novel heteroplasmic variant in complex I [ND5:12514G>A (E60K)] was present only in the proband and in her grandmother and absent in controls. The bioinformatics predicted the novel variant to be deleterious. Further, spectrophotometric assay of complex I activity was lower both in the proband and in her relatives than in the controls. Conclusions: We report a novel mtDNA variant detected in a patient affected by a complex neurological disease. The reduction of complex I respiratory chain activity associated to this variant suggests it could exert a pathogenic role in the disease.