Optic neuropathy, cardiomyopathy, cognitive disability in patients with a homozygous mutation in the nuclear MTO1 and a mitochondrial MT-TF variant

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Résumé en anglais	We report on clinical, genetic and metabolic investigations in a family with optic neuropathy, non-progressive cardiomyopathy and cognitive disability. Ophthalmic investigations (slit lamp examination, funduscopy, OCT scan of the optic nerve, ERG and VEP) disclosed mild or no decreased visual acuity, but pale optic disc, loss of temporal optic fibers and decreased VEPs. Mitochondrial DNA and exome sequencing revealed a novel homozygous mutation in the nuclear MTO1 gene and the homoplasmic m.593T>G mutation in the mitochondrial MT-TF gene. Muscle biopsy analyses revealed decreased oxygraphic Vmax values for complexes I+III+IV, and severely decreased activities of the respiratory chain complexes (RCC) I, III and IV, while muscle histopathology was normal. Fibroblast analysis revealed decreased complex I and IV activity and assembly, while cybrid analysis revealed a partial complex I deficiency with normal assembly of the RCC. Thus, in patients with a moderate clinical presentation due to MTO1 mutations, the presence of an optic atrophy should be considered. The association with the mitochondrial mutation m.593T>G could act synergistically to worsen the complex I deficiency and modulate the MTO1-related disease.

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