The human OPA1delTTAG mutation induces premature age-related systemic neurodegeneration in mouse

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Résumé en anglais	Dominant optic atrophy is a rare inherited optic nerve degeneration caused by mutations in the mitochondrial fusion gene OPA1. Recently, the clinical spectrum of dominant optic atrophy has been extended to frequent syndromic forms, exhibiting various degrees of neurological and muscle impairments frequently found in mitochondrial diseases. Although characterized by a specific loss of retinal ganglion cells, the pathophysiology of dominant optic atrophy is still poorly understood. We generated an Opa1 mouse model carrying the recurrent Opa1(delTTAG) mutation, which is found in 30% of all patients with dominant optic atrophy. We show that this mouse displays a multi-systemic poly-degenerative phenotype, with a presentation associating signs of visual failure, deafness, encephalomyopathy, peripheral neuropathy, ataxia and cardiomyopathy. Moreover, we found premature age-related axonal and myelin degenerations, increased autophagy and mitophagy and mitochondrial supercomplex instability preceding degeneration and cell death. Thus, these results support the concept that Opa1 protects against neuronal degeneration and opens new perspectives for the exploration and the treatment of mitochondrial diseases.
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