OPA1 mutations induce mitochondrial DNA instability and optic atrophy ‘plus’ phenotypes

Titre	OPA1 mutations induce mitochondrial DNA instability and optic atrophy ‘plus’ phenotypes
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Résumé en anglais	Mutations in OPA1, a dynamin-related GTPase involved in mitochondrial fusion, cristae organization and control of apoptosis, have been linked to non-syndromic optic neuropathy transmitted as an autosomal-dominant trait (DOA). We here report on eight patients from six independent families showing that mutations in the OPA1 gene can also be responsible for a syndromic form of DOA associated with sensorineural deafness, ataxia, axonal sensory-motor polyneuropathy, chronic progressive external ophthalmoplegia and mitochondrial myopathy with cytochrome c oxidase negative and Ragged Red Fibres. Most remarkably, we demonstrate that these patients all harboured multiple deletions of mitochondrial DNA (mtDNA) in their skeletal muscle, thus revealing an unrecognized role of the OPA1 protein in mtDNA stability. The five OPA1 mutations associated with these DOA 'plus' phenotypes were all mis-sense point mutations affecting highly conserved amino acid positions and the nuclear genes previously known to induce mtDNA multiple deletions such as POLG1, PEO1 (Twinkle) and SLC25A4 (ANT1) were ruled out. Our results show that certain OPA1 mutations exert a dominant negative effect responsible for multi-systemic disease, closely related to classical mitochondrial cytopathies, by a mechanism involving mtDNA instability.
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