Mutation in NDUFA13/GRIM19 leads to early onset hypotonia, dyskinesia and sensorial deficiencies, and mitochondrial complex I instability

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Résumé en anglais	Mitochondrial complex I (CI) deficiencies are causing debilitating neurological diseases, among which, the Leber Hereditary Optic Neuropathy and Leigh Syndrome are the most frequent. Here, we describe the first germinal pathogenic mutation in the NDUFA13/GRIM19 gene encoding a CI subunit, in two sisters with early onset hypotonia, dyskinesia and sensorial deficiencies, including a severe optic neuropathy. Biochemical analysis revealed a drastic decrease in CI enzymatic activity in patient muscle biopsies, and reduction of CI-driven respiration in fibroblasts, while the activities of complex II, III and IV were hardly affected. Western blots disclosed that the abundances of NDUFA13 protein, CI holoenzyme and super complexes were drastically reduced in mitochondrial fractions, a situation that was reproduced by silencing NDUFA13 in control cells. Thus, we established here a correlation between the first mutation yet identified in the NDUFA13 gene, which induces CI instability and a severe but slowly evolving clinical presentation affecting the central nervous system.
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