LRPPRC mutations cause early-onset multisystem mitochondrial disease outside of the French-Canadian population.

Abstract:
Mitochondrial Complex IV [cytochrome c oxidase (COX)] deficiency is one of the most common respiratory chain defects in humans. The clinical phenotypes associated with COX deficiency include liver disease, cardiomyopathy and Leigh syndrome, a neurodegenerative disorder characterized by bilateral high signal lesions in the brainstem and basal ganglia. COX deficiency can result from mutations affecting many different mitochondrial proteins. The French-Canadian variant of COX-deficient Leigh syndrome is unique to the Saguenay-Lac-Saint-Jean region of Québec and is caused by a founder mutation in the LRPPRC gene. This encodes the leucine-rich pentatricopeptide repeat domain protein (LRPPRC), which is involved in post-transcriptional regulation of mitochondrial gene expression. Here, we present the clinical and molecular characterization of novel, recessive LRPPRC gene mutations, identified using whole exome and candidate
gene sequencing. The 10 patients come from seven unrelated families of UK-Caucasian, UK-Pakistani, UK-Indian, Turkish and Iraqi origin. They resemble the French-Canadian Leigh syndrome patients in having intermittent severe lactic acidosis and early-onset neurodevelopmental problems with episodes of deterioration. In addition, many of our patients have had neonatal cardiomyopathy or congenital malformations, most commonly affecting the heart and the brain. All patients who were tested had isolated COX deficiency in skeletal muscle. Functional characterization of patients' fibroblasts and skeletal muscle homogenates showed decreased levels of mutant LRPPRC protein and impaired Complex IV enzyme activity, associated with abnormal COX assembly and reduced steady-state levels of numerous oxidative phosphorylation subunits. We also identified a Complex I assembly defect in skeletal muscle, indicating different roles for LRPPRC in post-transcriptional regulation of mitochondrial mRNAs between tissues. Patient fibroblasts showed decreased steady-state levels of mitochondrial mRNAs, although the length of poly(A) tails of mitochondrial transcripts were unaffected. Our study identifies LRPPRC as an important disease-causing gene in an early-onset, multisystem and neurological mitochondrial disease, which should be considered as a cause of COX deficiency even in patients originating outside of the French-Canadian population.

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