Mutation screening of 75 candidate genes in 152 complex I deficiency cases identifies pathogenic variants in 16 genes including NDUFB9.

Abstract:
Mitochondrial complex I deficiency is the most common cause of mitochondrial disease in childhood. Identification of the molecular basis is difficult given the clinical and genetic heterogeneity. Most patients lack a molecular definition in routine diagnostics. A large-scale mutation screen of 75 candidate genes in 152 patients with complex I deficiency was performed by high-resolution melting curve analysis and Sanger sequencing. The causal role of a new disease allele was confirmed by functional complementation assays. The clinical phenotype of patients carrying mutations was documented using a standardised questionnaire. Causative mutations were detected in 16 genes, 15 of which had previously been associated with complex I deficiency: three mitochondrial DNA genes encoding complex I subunits, two mitochondrial tRNA genes and nuclear DNA genes encoding six complex I subunits and four assembly factors. For the first time, a causal mutation is described in NDUFB9, coding for a complex I subunit, resulting in reduction in NDUFB9 protein and both amount and activity of complex I. These features were rescued by expression of
wild-type NDUFB9 in patient-derived fibroblasts. Mutant NDUFB9 is a new cause of complex I deficiency. A molecular diagnosis related to complex I deficiency was established in 18% of patients. However, most patients are likely to carry mutations in genes so far not associated with complex I function. The authors conclude that the high degree of genetic heterogeneity in complex I disorders warrants the implementation of unbiased genome-wide strategies for the complete molecular dissection of mitochondrial complex I deficiency.