A truncating PET100 variant causing fatal infantile lactic acidosis and isolated cytochrome c oxidase deficiency.

Isolated mitochondrial complex IV (cytochrome c oxidase) deficiency is an important cause of mitochondrial disease in children and adults. It is genetically heterogeneous, given that both mtDNA-encoded and nuclear-encoded gene products contribute to structural components and assembly factors. Pathogenic variants within these proteins are associated with clinical variability ranging from isolated organ involvement to multisystem disease presentations. Defects in more than 10 complex IV assembly factors have been described including a recent Lebanese founder mutation in PET100 in patients presenting with Leigh syndrome. We report the clinical and molecular investigation of a patient with a fatal, neonatal-onset isolated complex IV deficiency associated with multiorgan involvement born to consanguineous, first-cousin British Asian parents. Exome sequencing revealed a homozygous truncating variant (c.142C>T, p.(Gln48*)) in the PET100 gene that results in a complete loss of enzyme activity and assembly of the holocomplex. Our report confirms PET100 mutation as an important cause of isolated complex IV deficiency outside of the Lebanese population, extending the phenotypic spectrum associated with
abnormalities within this gene.