Mutations in SDHD lead to autosomal recessive encephalomyopathy and isolated mitochondrial complex II deficiency.

Abstract:
Defects of the mitochondrial respiratory chain complex II (succinate dehydrogenase (SDH) complex) are extremely rare. Of the four nuclear encoded proteins composing complex II, only mutations in the 70 kDa flavoprotein (SDHA) and the recently identified complex II assembly factor (SDHAF1) have been found to be causative for mitochondrial respiratory chain diseases. Mutations in the other three subunits (SDHB, SDHC, SDHD) and the second assembly factor (SDHAF2) have so far only been associated with hereditary paragangliomas and phaeochromocytomas. Recessive germline mutations in SDHB have recently been associated with complex II deficiency and leukodystrophy in one patient. We present the clinical and molecular investigations of the first patient with biochemical evidence of a severe isolated complex II deficiency due to compound heterozygous SDHD gene mutations. The patient presented with early progressive encephalomyopathy due to compound heterozygous p.E69K and p.*164Lext*3 SDHD mutations. Native polyacrylamide gel electrophoresis and western blotting demonstrated an impaired complex II assembly. Complementation of a patient cell line additionally supported the pathogenicity of the novel
This report describes the first case of isolated complex II deficiency due to recessive SDHD germline mutations. We therefore recommend screening for all SDH genes in isolated complex II deficiencies. It further emphasises the importance of appropriate genetic counselling to the family with regard to SDHD mutations and their role in tumorigenesis.