SDHA Gene Analysis in Mitochondrial Complex II deficiency (MT-C2D)

DISORDER ALSO KNOWN AS
Leigh syndrome; Kearns-Sayre syndrome

CLINICAL FEATURES
Mitochondrial complex II deficiency is a disorder of the mitochondrial respiratory chain with heterogeneous clinical manifestations. Clinical features may include psychomotor regression in infants, poor growth with lack of speech development, severe spastic quadriplegia, dystonia, progressive leukoencephalopathy, muscle weakness, exercise intolerance, and cardiomyopathy. Some patients manifest Leigh syndrome or Kearns-Sayre syndrome.

Recently variants in the SDHA gene have been reported to cause familial neonatal isolated cardiomyopathy.[6]

INHERITANCE PATTERN/GENETICS
Autosomal recessive for Leigh Syndrome (LS) due to mitochondrial complex II deficiency. Autosomal recessive for mitochondrial complex II deficiency and familial neonatal cardiomyopathy.

The succinate dehydrogenase (succinate: ubiquinone oxidoreductase) enzyme is a component of both the Krebs cycle and complex II of the mitochondrial respiratory chain and is composed of four subunits: SDHA, SDHB, SDHC and SDHD, which are encoded by the SDHA, SDHB, SDHC and SDHD genes respectively. SDHA, a flavoprotein and SDHB, an iron-sulfur protein, together constitute the catalytic domain, while SDHC and SDHD encode membrane anchors that allow the complex to participate in the respiratory chain as complex II. Heterozygous germline variants in SDHB, SDHC, SDHD have been associated with hereditary paragangliomas and pheochromocytoma syndrome (please see separate information sheet for information on SDHB, SDHC, SDHD testing), while bi-allelic variants in SDHA cause Leigh encephalopathy and mitochondrial complex II deficiency.

TEST METHODS
Variant analysis of the SDHA gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of the coding exons and corresponding intron/exon boundaries. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis or another appropriate method. Deletion/duplication analysis by targeted array CGH analysis with exonlevel resolution (ExonArrayDx) is not available for the SDHA gene due to the presence of nonprocessed pseudogenes.

TEST SENSITIVITY
At this time, three patients with autosomal recessive Leigh syndrome due to complex II deficiency have been reported each with two variants in SDHA. In one of these reports, two variants in the SDHA gene were detected in a patient with Leigh syndrome and isolated mitochondrial complex II deficiency, but in six additional patients variants in SDHA were not detected.[2] To our knowledge, a large study of the frequency of SDHA variants in patients recognized as having Leigh syndrome due to mitochondrial complex II deficiency has not been published. In addition, a single missense variant in the SDHA gene has been reported in one family suggestive of autosomal dominant inheritance based on a mitochondrial disorder (late onset optic atrophy, ataxia and myopathy) in two affected siblings with reduced complex II and succinate dehydrogenase (SDH) activities.[4]

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