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

*Mendelian Inheritance in Man Numbers: 252011 Mitochondrial complex II deficiency 600857 SDHA*

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

**Inheritance pattern:**
Autosomal recessive for Leigh Syndrome (LS) due to mitochondrial complex II deficiency; Autosomal recessive for mitochondrial complex II deficiency and familial neonatal cardiomyopathy.

**Genetics:**
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 mutations 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 mutations in *SDHA* cause Leigh encephalopathy and mitochondrial complex II deficiency.

**Reasons for referral:**
- Confirmation of a clinical diagnosis
- Carrier testing
- Genetic counseling
- Prenatal diagnosis in at risk pregnancies

**Test method:**
Mutation 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. Mutations 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 exon-level resolution (ExonArrayDx) is not available for the *SDHA* gene due to the presence of non-processed pseudogenes.

**Mutation spectrum**
To date, very few mutations have been reported in the *SDHA* gene and all are missense or nonsense mutations [1-7]. Deletions and duplications have not been reported.

**Test sensitivity**
At this time, three patients with autosomal recessive Leigh syndrome due to complex II deficiency have been reported each with two mutations in *SDHA*. In one of these reports, two mutations in the *SDHA* gene were detected in a patient with Leigh syndrome and isolated mitochondrial complex II deficiency, but in six additional patients mutations in *SDHA* were not detected [2]. To our knowledge, a large study of the frequency of *SDHA* mutations in patients recognized as having Leigh syndrome due to mitochondrial complex II deficiency has not been published.
In addition, a single missense mutation 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.

**Specimen Requirements and Shipping/Handling:**
- **Blood:** A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for 7 days prior to shipping.
- **Buccal Brushes:** NOT ACCEPTED FOR THIS TEST
- **Prenatal Diagnosis:** For prenatal testing for a known mutation in the SDHA gene, please refer to the specimen requirements table on our website at: [http://www.genedx.com/test-catalog/prenatal/](http://www.genedx.com/test-catalog/prenatal/). Ship specimen overnight at ambient temperature, using a cool pack in hot weather.

**Required Forms:**
- Sample Submission (Requisition) Form – complete all pages
- Payment Options Form or Institutional Billing Instructions

**CPT Codes and Turn-Around-Times – Please contact us for prices:**
- Test# 582  Mutation detection in a new patient
- Test# 901 Testing of a relative for one (two) specific known mutations
- Test# 902  Prenatal diagnosis for a specific known mutation (including maternal cell contamination studies)

Approx. 6 weeks
Approx. 2-3 weeks
Approx. 2 weeks

**CPT codes for mutation detection in a new patient - All codes and units apply:**
- 81479

**ICD9 codes that might apply to new patients having this diagnostic test -**
- Disorder of mitochondrial metabolism 277.87
- Lactic acidosis 276.2
- Leigh syndrome 330.8

**References cited:**