**CPT2 Gene Analysis in Carnitine Palmitoyltransferase II (CPT2) Deficiency**

**Mendelian Inheritance in Man Numbers:** 255110 – CPT2 Deficiency, Late-Onset; 600649 – CPT2 Deficiency, Infantile; 608836 – CPT2 Deficiency, Lethal Neonatal; 600650 – CPT2 gene

**Clinical features:**
Carnitine Palmitoyltransferase II (CPT2) deficiency is the most common defect of mitochondrial fatty acid oxidation. Three clinical phenotypes have been described. The most common type, described in over 200 cases, is the myopathic (or adult-onset) form characterized by recurrent attacks of myalgia accompanied by myoglobinuria (triggered by exercise, fasting, cold exposure or stress), possible weakness during attacks and usually no signs of myopathy between attacks, with onset between the first and sixth decade.¹ For reasons currently unknown, the majority (~80%) of myopathic form patients are males.²,³ The severe infantile form of CPT2 has been described as liver failure, cardiomyopathy, seizures, hypoketotic hypoglycemia, peripheral myopathy and attacks of abdominal pain and headache with onset in the first year of life.¹ A lethal neonatal form has been identified and is characterized by dysmorphic features (cystic renal dysplasia and neuronal migration defects) along with the symptoms of the infantile form, with death usually occurring within the first month.¹

The clinical features of the neonatal form of carnitine palmitoyltransferase II (CPT2) deficiency may be similar to those of carnitine-acylcarnitine translocase (CACT) deficiency and the two disorders have nearly indistinguishable acylcarnitine profiles. Therefore, it has been suggested that patients who are negative for mutations in the CPT2 gene should have molecular analysis of the SLC25A20 gene.¹¹

**Inheritance pattern:** Autosomal Recessive

**Genetics and biochemical features:**
CPT2 is caused by mutations in the CPT2 gene. The CPT2 protein is located on the inner mitochondrial membrane where it facilitates the transport of long-chain fatty acids into the mitochondrial matrix for β-oxidation by catalyzing the formation of acyl-CoA from acylcarnitine and CoA. In CPT2 deficiency acylcarnitines accumulate and may be transported out of the mitochondria resulting in elevated C12-C18 acylcarnitines detectable via tandem mass spectrometry-based newborn screening. CPT2 enzyme activity and long-chain fatty oxidation are generally lower in the infantile/neonatal forms compared to the myopathic form; however, the range of CPT2 enzyme activity in the infantile and myopathic forms may overlap, which may make enzymatic studies unreliable at predicting disease severity.¹ The CPT2 gene is located on chromosome 1p32 and contains 5 exons. Heterozygous carriers for CPT2 mutations are generally asymptomatic; however, a few symptomatic heterozygotes have been reported.⁴,⁵,⁶

**Reasons for referral:**
1. Confirmation of biochemical diagnosis
2. Carrier testing
3. Genetic counseling
4. Prenatal diagnosis in at risk pregnancies
**Test method:**
Mutation analysis of the CPT2 gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons (1-5), 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.

**Test sensitivity:**
Sequence analysis is expected to identify greater than 95% of CPT2 mutations in affected individuals.1, 3, 7, 8, 9

**Mutation spectrum:**
Approximately 60 CPT2 mutations have been described that are dispersed throughout the 5 exons of the gene and consist mostly of missense mutations although small deletions/duplications, nonsense mutations and splice site mutations have also been described.4 Two missense mutations, S113L and P50H, comprise 60% and 6.5%, respectively, of all mutant alleles in the myopathic form, however most other mutations are not recurrent.2 Genotype-phenotype correlations exist for certain mutations, while for others the clinical presentation is heterogeneous.1,2,4,10

**Specimen Requirements and Shipping/Handling:**
- **Blood:** A single tube with 1-5 mL whole blood in EDTA (1-2mL for infants). Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for one week prior to shipping.
- **Buccal Brushes:** Can be used as an alternative to blood. Can be used as an alternative to blood for CPT2 sequencing only. Gene deletion/duplication testing requires submission of a venous blood sample. When sending a buccal sample, use a GeneDx buccal kit (others not accepted). Submit by mail. Buccal brushes are not accepted on children under 6 months of age.
- **Prenatal Diagnosis:** For prenatal testing for a known mutation in the CPT2 gene, please refer to the specimen requirements table on our website at: http://www.genedx.com/test-catalog/prenatal/. Ship specimen overnight at ambient temperature, using a cool pack in hot weather.

For test codes, prices, CPT codes, and turn-around-times, please refer to the “Carnitine Palmitoyltransferase II (CPT2) Deficiency” page on our website: www.genedx.com

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

**ICD9 codes that might apply to new patients having this diagnostic test:**

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**References:**