

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

### **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.<sup>1</sup> For reasons currently unknown, the majority (~80%) of myopathic form patients are males.<sup>2,3</sup> 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.<sup>1</sup> 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.<sup>1</sup>

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 variants in the *CPT2* gene should have molecular analysis of the *SLC25A20* gene.<sup>11</sup>

### **Inheritance Pattern:**

Autosomal Recessive

### **Genetics:**

*CPT2* is caused by pathogenic variants 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  $\beta$ -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 acid 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.<sup>1</sup> The *CPT2* gene is located on chromosome 1p32 and contains 5 exons. Heterozygous carriers for *CPT2* variants are generally asymptomatic; however, a few symptomatic heterozygotes have been reported.<sup>4,5,6</sup>

## Test Methods:

Variant 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. 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.

## Test Sensitivity:

Sequence analysis is expected to identify greater than 95% of *CPT2* pathogenic variants in affected individuals.<sup>1, 3, 7, 8, 9</sup> The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

## Variant Spectrum:

Over 100 *CPT2* pathogenic variants have been described that are dispersed throughout the 5 exons of the gene and consist mostly of missense variants although small deletions/duplications, nonsense, splicing, and frameshift variants have also been described. Two missense variants, S113L and P50H, comprise 60% and 6.5%, respectively, of all mutant alleles in the myopathic form, however most other variants are not recurrent.<sup>2</sup> Genotype-phenotype correlations exist for certain variants, while for others the clinical presentation is heterogeneous.<sup>1,2,4,10</sup>

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