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.[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 individuals who are negative for variants in the *CPT2* gene should have molecular analysis of the *SLC25A20* gene.[10]

Genetics

CPT2 deficiency 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 ß-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 variants are generally asymptomatic; however, a few symptomatic heterozygotes have been reported.[4,5,6,8]

Inheritance Pattern

Autosomal Recessive

Test Methods

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the CPT2 gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

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The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

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, a gross deletion, 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.2 Genotype-phenotype correlations exist for certain variants, while for others the clinical presentation is heterogeneous. [1,2,4,7,9]

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