CPT1A Gene Analysis in Carnitine Palmitoyltransferase IA Deficiency

CLINICAL FEATURES

Carnitine palmitoyltransferase IA (CPT1A) deficiency is a very rare disorder of long-chain fatty acid oxidation that typically presents in childhood after a period of fasting or metabolic stress with a Reye-like illness: hypoketotic hypoglycemia, hepatomegaly, sudden onset of liver failure, seizures, and in some instances coma. Between such episodes, individuals appear developmentally normal unless past episodes have resulted in neurological damage. Involvement of cardiac and skeletal muscle is typically not present; however, several cases with slight cardiomegaly or bradycardia have been described.[1] The P479L variant is a common variant in individuals with CPT1A deficiency from the Inuit and Alaska Native populations, and children homozygous for P479L have shown abnormal metabolic response to prolonged fasting and may have an increased risk for infant mortality.[6,7] Acute fatty liver of pregnancy (AFLP) or maternal HELLP syndrome (hypertension, elevated liver enzymes, low platelets) may occur in a pregnant woman carrying a fetus with CPT1A deficiency.[1]

GENETICS

CPT1A deficiency is caused by pathogenic variants in the *CPT1A* gene that encode the carnitine palmitoyltransferase IA (CPT1A) enzyme. CPT1A is expressed in the liver and kidney, and in leukocytes and fibroblasts and is located in the outer mitochondrial membrane where it catalyzes the transfer of the acyl-group from cystolic long-chain acyl-CoA to carnitine, which can then enter the mitochondria. Two additional CPT1 isoforms exist: *CPT1B* expressed in muscle and adipose tissue and *CPT1C* expressed in brain and testes. CPT1B and CPT1C deficiencies have not been described in humans. Deficiency of CPT1A usually results in hypoketotic hypoglycemia and elevated liver enzymes. Total serum carnitine may also be elevated and serum acylcanitine analysis may be normal. CPT1A deficiency is screened for in newborns in many states by detecting an elevated ratio of free carnitine to the sum of C16:0 + C18 acylcarnitines. The *CPT1A* gene is located on chromosome 11q13 and has 19 exons.

INHERITANCE PATTERN

Autosomal Recessive

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the *CPT1A* 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.

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.

T: 1 (844) 241-1233 | **F:** 1 (201) 421-2020 | GeneDx.com
207 Perry Parkway | Gaithersburg, MD 20877

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

The majority of pathogenic variants that have been described in the *CPT1A* gene are missense variants; however, nonsense, splicing, small deletions and insertions, a gross deletion, and frameshift variants have also been reported.

REFERENCES:

1. Bonnefont et al., (2004) Mol Aspects Med 25:495-520. PMID: 15363638
2. Brown et al., (2001) J Lipid Res 42:1134-1142. PMID: 11441142
3. Gobin et al., (2002) Hum Genet 111:179-189. PMID: 12189492
4. Korman et al., (2005) Mol Genet Metab 86:337-343. PMID: 16146704
5. Bennett et al., (2004) Mol Genet Metab 82:59-63. PMID: 15110323
6. Bennett, M. (Updated [Mar. 24, 2009]). Carnitine Palmitoyltransferase 1A Deficiency. In: GeneReviews at Genetests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle, 1197-2009. Available at http://www.genetests.org
7. Gillingham et al., (2011) Mol Genet Metab 104:261-264. PMID: 21763168