

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 cytosolic long-chain acyl-CoA to carnitine. The acylcarnitine formed 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 acylcarnitine 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 palmitoylcarnitine (C16) + stearyl carnitine (C18). The *CPT1A* gene is located on chromosome 11q13 and has 19 exons.

Inheritance Pattern:

Autosomal Recessive

Test Methods:

Variant analysis of the *CPT1A* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons (2-19) and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *CPT1A* gene, and if clinically indicated, reflex *CPT1A* deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons

of this gene. 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:

In four small studies of 16 patients diagnosed with CPT1A deficiency based on reduced CPT1A enzyme activity, pathogenic variants were identified on over 95% (31/32) of alleles.^{2,3,4,5} The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

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:

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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