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] At this time, a single individual homozygous for the P479L variant presented as an adult with recurrent episodes of activity-induced muscle pain with elevated serum creatine kinase.[2] 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:
Autosomal Recessive. CPT1A deficiency is caused by pathogenic variants in the CPT1A gene that encodes the carnitine palmitoyltransferase IA (CPT1A) enzyme. CPTIA 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. The acylcarnitine formed can then enter the mitochondria. Two additional CPTI 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 by newborn screening programs in many states by detecting an elevated ratio of free carnitine to the sum of palmitoylcarnitine (C16) + stearoylcarnitine (C18). The CPT1A gene is located on chromosome 11q13 and has 19 exons.

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 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]

References:

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