SLC22A5 Gene Analysis in Primary/Systemic Carnitine Deficiency

Clinical Features:
Primary/systemic carnitine deficiency (PCD) is a disorder of fatty acid oxidation caused by defective carnitine transport. Patients may present as infants with nonketotic hypoglycemia, hypotonia, Reye syndrome, sudden infant death, or later in life with cardiomyopathy (characteristically dilated) or muscle weakness. Variable presentation have been observed within an individual family and diet may contribute to the pathogenesis of this disorder. Delayed diagnosis has been reported as common. PCD can be identified by MS/MS based newborn screening and positive newborn screening results have also occurred in infants of mothers affected with PCD even though the mother has had mild or no symptoms.[1] Patients respond promptly to carnitine supplementation, with correction of metabolic abnormalities, and improvement in skeletal myopathy and cardiomyopathy reported.[7-9] However, developmental delay due to hypoglycemia that occurred prior to treatment usually persists.

Inheritance Pattern:
Autosomal Recessive

Genetics:
PCD is caused by pathogenic variants in the *SLC22A5* gene that encodes the OCTN2 carnitine transporter. Deficiency of carnitine transport causes failure of carnitine uptake from blood into tissues resulting in urinary carnitine wasting, low serum carnitine levels, and decreased intracellular carnitine accumulation. Newborn screen shows decreased free carnitine. Urine organic acids are usually normal. Carnitine is essential for the transfer of longchain fatty acids from the cytosol to mitochondria for beta-oxidation. Lack of carnitine impairs the ability to use fat as fuel during periods of fasting or stress. The *SLC22A5* gene is located on chromosome 5q31 and has 10 exons. PCD has a frequency of approximately 1 in 40,000 and is the second most frequent disorder of fatty acid oxidation after medium chain acyl-CoA dehydrogenase deficiency.[2] Approximately 1% of the population carries an abnormal allele for PCD.[2]

Test Methods:
Variant analysis of the *SLC22A5* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *SLC22A5* 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 or another appropriate method.

Test Sensitivity:

In five separate studies each including between 4 and 9 patients with PCD diagnosed based on reduced carnitine transport in fibroblasts, all variants were identified on the *SLC22A5* alleles.[1-5] In a study of 95 patients with carnitine transport less than 20% of controls in fibroblasts, molecular analysis identified causative variants in 84% of alleles.[6] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant spectrum:

SLC22A5 variants consist of missense, nonsense, splice site and small insertions and deletions. A single large deletion of 1,395 bp has also been reported. Most variants are private and are located around the intracellular loop of the transmembrane domains 10 and 11 of the OCTN2 protein encoded by exon 8.[2] Genotype-phenotype correlations have been reported for some variants. In one study, the frequency of null *SLC22A5* variants was higher in patients presenting with symptoms of PCD compared to asymptomatic adult women, with no asymptomatic adults being homozygous or compound heterozygous for two null alleles.[11] The p.Pro46Ser variant has rarely been identified in symptomatic individuals.[1, 11]

References:

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