SLC25A20 Gene Analysis in Carnitine-Acylcarnitine Translocase Deficiency

Clinical Features:

Carnitine-acylcarnitine translocase (CACT) deficiency is one of the most severe disorders of fatty acid oxidation associated with a high mortality at the initial presentation or during the first year of life. Onset is typically in the early newborn period with features that include acute metabolic decompensation, cardiomyopathy, arrhythmias, liver dysfunction, and skeletal muscle damage. In a significant proportion of cases, the disorder presents with sudden, unexplained death, presumably due to arrhythmia.[1] A minority of patients have a later onset with a milder clinical phenotype and there are a few reports of long-term survival following an intensive treatment protocol.[1] There is a patient reported who has been treated since birth and is asymptomatic at 4.5 years.[1]

The clinical features of CACT deficiency may be similar to those of the neonatal form of carnitine palmitoyltransferase II (CPT2) deficiency and the two disorders have nearly indistinguishable acylcarnitine profiles. Therefore, it has been suggested that patients who are negative for variants in the *CPT2* gene should have molecular analysis of the *SLC25A20* gene.[4]

Inheritance:

Autosomal Recessive

Genetics:

CACT deficiency is caused by pathogenic variants in the *SLC25A20* gene that encodes the carnitine-acylcarnitine translocase protein that is located in the inner mitochondrial membrane and mediates the transport of acylcarnitine esters into the mitochondrial matrix in exchange for free carnitine. Deficiency of this translocase results in deficient production of energy from mitochondrial fatty acid oxidation, accumulation of long-chain acylcarnitines and deficiency of free carnitine. CACT deficiency can be distinguished from the other fatty acid oxidation defects due to the presence of persistent elevations of plasma long-chain acylcarnitines, little to no fatty acid metabolites in urine and normal ketone response after administration of medium-chain triglycerides.[2] The *SLC25A20* gene is located on chromosome 3p21.31 and has 9 exons.

Test Methods:

Variant analysis of the *SLC25A20* 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 *SLC25A20* 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 two small studies of 6 Caucasian patients and 10 patients of varied ethnic backgrounds diagnosed with CACT deficiency based on reduced carnitine-acylcarnitine translocase activity in fibroblasts, all variants were identified on the *SLC25A20* alleles.[2,3] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:

SLC25A20 variants consist of missense, nonsense, splice site, small insertions/deletions and an exon-level deletion.[1,4] Most variants are private and there appear to be no common variants.[1,3] The c.199-10 T>G variant has most often been described in Asian populations and individuals homozygous for the c.199-10 T>G have been described with neonatal onset [5] Other genotype-phenotype correlations have not been established.[2,3]

References:

1. Korman et al., (2006) Mol Genet Metab 89:332-338 (PMID: 16919490).
2. Iacobazzi et al., (2004) Hum Mutat 24:312-320 (PMID: 15365988).
3. Costa et al., (2003) Mol Genet Metab 78 :68-73 (PMID: 12559850).
4. Wang et al., (2011) Molec Genet and Metab 103 :349-357 (PMID: 21605995).
5. Yan et al. (2017) Medicine (Baltimore) 96 (45):e8549 (PMID: 29137068)