

## 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, developmental delay, sudden infant death, or later in life with cardiomyopathy (characteristically dilated) or muscle weakness. Variable presentation has 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.<sup>1</sup> Patients respond promptly to carnitine supplementation, with correction of metabolic abnormalities, and improvement in skeletal myopathy and cardiomyopathy reported.<sup>2</sup>

### 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 long chain 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.<sup>3</sup> Approximately 1% of the population carries an abnormal allele for PCD.<sup>3</sup>

### Inheritance Pattern

Autosomal Recessive

### Test Methods

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions, as well as an additional position, c.-149, in the 5' UTR of the SLC22A5 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.

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

Pathogenic SLC22A5 variants reported include missense, nonsense, splice site, small insertions and deletions, exonic deletions and a 5'UTR variant.<sup>5-7</sup> 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.<sup>3</sup> Genotype-phenotype correlations have been reported for some variants.<sup>1,4,8</sup> In one study, the frequency of null SLC22A5 variants was higher in symptomatic individuals compared with asymptomatic adults.<sup>4</sup>

## REFERENCES:

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