

Carnitine Deficiency, Primary (Carnitine Uptake Defect): *SLC22A5* Gene Sequencing

Test Code: KC

Turnaround time: 4 weeks

CPT Codes: 81405 x1

Condition Description

Carnitine deficiency is an autosomal recessive disorder of fatty acid oxidation [1]. Deficiency of the sodium ion-dependent carnitine transporter, called OCTN2, increases urinary carnitine losses and produces carnitine deficiency in affected tissues. Since carnitine is required for the entry of long-chain fatty acids into mitochondria, carnitine deficiency impairs mitochondrial fatty acid beta-oxidation and subsequent energy production, especially during fasting or illness.

Carnitine deficiency can be identified in infants by expanded newborn screening using tandem mass spectrometry which may detect low levels of free carnitine (C0) [2-3]. If untreated, affected patients typically present in childhood with hypoketotic hypoglycemia, hepatic encephalopathy, hypotonia, cardiomyopathy or sudden death. Treatment with oral carnitine at pharmacologic levels is quite effective in treating cardiomyopathy and muscle weakness in these children. In some cases, neonatal screen results of low C0 are due to primary carnitine deficiency in their affected mothers [4]. Primary or systemic carnitine deficiency is distinct from secondary carnitine deficiency, which may be a symptom of other mitochondrial beta-oxidation disorders.

Carnitine deficiency is caused by mutations in the *SLC22A5* (5q31) gene encoding the sodium ion-dependent carnitine transporter (OCTN2) [5-6]. There is some evidence for genotype and phenotype variation [8] but well established associations are limited [9-10]. Diagnosis is based on the identification of very low C0 levels in plasma and is confirmed by the measurement of diminished OCTN2 activity in skin fibroblasts or mutational analysis of the *SLC22A5* gene [7]. Gene sequence analysis is available to test for mutations in the *SLC22A5* gene (test code KC). For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (test code KE).

References:

1. Stanley C.A. Carnitine deficiency disorders in children. *Ann NY Acad Sci* 2004, 1033:42-51.
2. Wilcken et al. Screening newborns for inborn errors of metabolism by tandem mass spectrometry. *N Engl J Med* 2003, 348:2304-2312.
3. Wilcken et al. Carnitine transporter defect diagnosed by newborn screening with electrospray tandem mass spectrometry. *J Pediatr* 2001, 138:581-584.
4. Schimmenti et al. Expanded newborn screening identifies maternal primary carnitine deficiency. *Mol Genet Metab* 2007, 90:441-445
5. Nezu et al. Primary systemic carnitine deficiency is caused by mutations in a gene encoding sodium ion-dependent carnitine transporter. *Nat Genet* 1999, 21:91-94.
- > 6. Wang et al. Mutations in the organic cation/carnitine transporter OCTN2 in primary carnitine deficiency. *Proc Natl Acad Sci USA* 1999, 96:2356-2360.
7. Amat et al. Pharmacological rescue of carnitine transport in primary carnitine deficiency. *Hum Mutat* 2006, 27:513-523.
8. Wang et al. Phenotype and genotype variation in primary carnitine deficiency. *Genet Med* 2001, 3:387-392.
9. Lamhonwah et al. Novel *OCTN2* mutations: no genotype-phenotype correlations: early carnitine therapy prevents cardiomyopathy. *Am J Med Genet* 2002, 111:271-284.
10. Wang et al. Functional analysis of mutations in the *OCTN2* transporter causing primary carnitine deficiency: lack of genotype-phenotype correlation. *Hum Mutat* 2000, 16(5):401-7.
11. Vijay et al. Carnitine transporter defect: diagnosis in asymptomatic adult women following analysis of acylcarnitines in their newborn infants. *J Inherit Metab Dis* 2006, 29:627-630.

Genes

[SLC22A5](#)

Indications

This test is indicated for:

- Confirmation of a clinical/biochemical of carnitine deficiency
- Carrier testing in adults with a family history of carnitine deficiency

Methodology

PCR amplification of 10 exons contained in the *SLC22A5* gene is performed on patient genomic DNA. Direct sequencing of amplification products is performed in both the forward and reverse directions using automated fluorescence dideoxy sequencing methods. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then classified as mutations, benign variants unrelated to disease or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions or other regulatory elements. Large deletions are not detected by this analysis.

Detection

The majority of patients with clinical and biochemical diagnosis of carnitine deficiency will have an abnormal DNA test.

Clinical Sensitivity: 22/22 mutations identified in 11 patients [9]; 8/8 mutations identified in 4 patients [10].

Analytical Sensitivity: ~99%

Specimen Requirements

Submit only 1 of the following specimen types

Type: Saliva

Specimen Requirements:

Oragene™ Saliva Collection Kit

Orangene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:

Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Type: DNA, Isolated

Specimen Requirements:

Microtainer

8µg

Isolation using the Perkin Elmer™ Chemagen™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:

Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Whole Blood (EDTA)

Specimen Requirements:

EDTA (Purple Top)

Infants and Young Children (2 years of age to 10 years old: 3-5 ml

Older Children & Adults: 5-10 ml

Autopsy: 2-3 ml unclotted cord or cardiac blood

Specimen Collection and Shipping:

Ship sample at room temperature for receipt at EGL within 72 hours of collection. Do not freeze.

Special Instructions

Submit copies of diagnostic biochemical test results with the sample. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

Related Tests

- Urine organic acids (OA), and plasma acylcarnitine profile (AR) are used in the diagnosis of a patient with CUD.
- [Custom diagnostic mutation analysis \(KM\)](#) is available to family members if mutations are identified by sequencing.
- A deletion/duplication assay is available separately for individuals where mutations are not identified by sequence analysis. Refer to the test requisition or contact the laboratory for more information.
- Prenatal testing is available for known familial mutations only. Please call the Laboratory Genetic Counselor before collecting a fetal sample.