## Condition Description

Mitochondrial oxidation of fatty acids provides the chief source of energy during prolonged fasting as well as for skeletal muscle during exercise and for cardiac muscle. Carnitine-acylcarnitine translocase is 1 of 10 closely related mitochondrial-membrane carrier proteins that shuttle substrates between cytosol and the intramitochondrial matrix space. Other genetic defects in this pathway can cause LCAD deficiency, MCAD deficiency, SCAD deficiency, CPT I deficiency, and CPT II deficiency. Patients with these defects present with coma after a period of starvation and have low serum ketone concentrations (hypoketotic hypoglycemia). They may also have hyperammonemia, hepatomegaly, cardiomyopathy and muscle weakness.

Carnitine-acylcarnitine translocase deficiency is a rare autosomal recessive disorder of fatty acid oxidation. CACT is the second component of the carnitine shuttle for the import of long-chain fatty acids from the cytosol into the mitochondrion where they undergo $\beta$-oxidation. It is an inner mitochondrial membrane protein which mediates the transport of acylcarnitine esters into the mitochondrial matrix in exchange for free carnitine.

CACT deficiency is, together with infantile carnitine palmitoyltransferase II (CPT2) deficiency, the most severe of the mitochondrial fatty acid oxidation defects. The pathogenesis of the disorder is a combination of the deficient production of energy from mitochondrial fatty acid oxidation and the toxicity of accumulating long-chain acylcarnitines. It usually presents in the early newborn period, with a high mortality at the initial presentation or during the first year of life. The typical features include cardiomyopathy, arrhythmias, hepatic dysfunction, skeletal muscle damage, hyperammonemia, hypoketotic hypoglycemia with dicarboxylic aciduria, elevation of long-chain acylcarnitines, and deficiency of free carnitine. A minority of patients have a later onset with a milder clinical phenotype. In a significant proportion of cases, the presentation is as sudden, unexpected death, presumably due to an arrhythmia.

CACT deficiency is caused by mutations in the **SLC25A20** gene (3p21.31).

For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (HR).


References:

- OMIM #212138: Carnitine-Acylcarnitine Translocase Deficiency

## Genes

**SLC25A20**

## Indications

This test is indicated for:

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

## Methodology

Full Gene Sequencing: PCR amplification of nine exons contained in the **SLC25A20** 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

Clinical Sensitivity: See OMIM 212138. 12/12 abnormal alleles identified in 6 individuals across multiple studies. Mutations in the promoter region, some mutations in the introns and other regulatory element mutations cannot be detected by this analysis. Large deletions will not be detected by this analysis. Results of molecular analysis should be interpreted in the context of the patient's biochemical phenotype.

Analytical Sensitivity: ~99%

## Specimen Requirements

Submit only 1 of the following specimen types

**Type: DNA, Isolated**

**Specimen Requirements:**
Microtainer
8µg
Isolation using the Perkin Elmer™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 24 hours of collection. Do not refrigerate or freeze.

**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.

**Special Instructions**
Submit copies of diagnostic biochemical test results with the sample. Contact the laboratory if further information is needed.

**Related Tests**
- 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 to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.