Carnitine Palmitoyltransferase II Deficiency: CPT2 Gene Sequencing

Condition Description

Carnitine palmitoyltransferase II (CPT II) deficiency is a disorder of long-chain fatty-acid oxidation. There are three clinical presentations: a lethal neonatal form, a severe infantile hepatocardiomyocutaneous form, and a myopathic form that is usually mild and can manifest from infancy to adulthood. The former two are severe multisystemic diseases characterized by liver failure with hypoketotic hypoglycemia, cardiomyopathy, seizures, and early death. The myopathic form is characterized by exercise-induced muscle pain and weakness, sometimes associated with myoglobinuria. While the disorder is inherited in an autosomal recessive manner, males are more likely to be affected than females, for currently unknown reasons.

Tandem mass spectrometric measurement of serum/plasma acylcarnitines can be used as an initial screening test. The finding suggestive of a defect in mitochondrial beta-oxidation (and thus suspect for CPT II deficiency) is an elevation of C12 to C18 acylcarnitines, notably of C16 and C18:1. Diagnosis can be made by detection of reduced CPT enzyme activity, however, measured enzyme activity is dependent on assay conditions, which have not been standardized, making comparisons of published data from different laboratories difficult. Molecular genetic testing of CPT2 (1p32), the only gene known to be associated with CPT II deficiency, provides additional means for noninvasive, rapid, and specific diagnosis. Carriers can be detected by measuring enzyme activity in muscle homogenates; no data regarding the use of MS/MS for carrier detection are available. When causative mutations are known, carrier testing should rely on molecular genetic methods.

Sequencing of the CPT2 gene is recommended after a biochemical analysis consistent with CPT II, and provides a complementary method to confirm the presence of mutations in a proband, identify carriers among the proband's relatives, and provide prenatal diagnosis in families with known mutations.

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

References:
- GeneReviews Clinical Summary

Genes

CPT2

Indications

This test is indicated for:
- Confirmation of a clinical/biochemical diagnosis of CPT II.
- Carrier testing in adults with a family history of CPT II.

Methodology

PCR amplification of 5 exons contained in the CPT2 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: It is estimated that sequencing will detect >95% of mutations in the CPT2 gene. 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

* Preferred specimen type: Whole Blood

Type: Whole Blood

Specimen Requirements:

In EDTA (purple top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml
Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

### Special Instructions

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

- Acylcarnitine profile (AR).
- 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.