Isolated deficiency of long-chain 3-hydroxyl-CoA dehydrogenase (LCHAD) is an autosomal recessive disorder characterized by early-onset cardiomyopathy, hypoglycemia, neuropathy, pigmentary retinopathy, and sudden death. Affected infants with LCHAD deficiency present with hypoketotic hypoglycemia, cardiomyopathy, hypotonia, and hepatomegaly at a median age of 6 months. In childhood, the presentation is myopathic. A minority of patients may present during the neonatal period. Presentation typically appears for the first time after a fast, which usually occurs in the context of intercurrent illness with vomiting. Evaluation for LCHAD deficiency includes acylcarnitine profile, serum free fatty acids, and urine organic acids; however, patients who are asymptomatic at the time of evaluation may not show abnormalities. If high index of suspicion exists on the basis of the history, a skin biopsy could be performed for fatty acid oxidation studies in fibroblasts. The management of affected patients is directed at the avoidance of fasting. Most patients also are provided with uncooked cornstarch and medium chain triglyceride (MCT) oil supplementation to further decrease exposure to fasting. In the majority of cases, the disease is severe and may lead to death during the first few months of life. The disease also may be a cause of sudden infant death, even neonatal. For those infants that are diagnosed and treated, a risk still exists for psychomotor retardation.

LCHAD deficiency results from the inability to metabolize long-chain fatty acids. Thus, the clinical features may result from either toxicity due to long-chain acyl-CoA esters that cause cardiomyopathy and cardiac arrhythmias or from a block in long-chain fatty acid oxidation that leads to an inability to synthesize ketone bodies and/or adenosine triphosphate from long-chain fatty acids. The fatty acid oxidation defect results in adverse effects on a number of organ systems, including the CNS, secondary to the hypoketotic hypoglycemia. Hypotonia and cardiomyopathy reflect the underlying energy deficiency. LCHAD deficiency is caused by mutation in the HADHA gene (2p23) which encodes the alpha subunit of the mitochondrial trifunctional protein. The trifunctional protein complex is an octamer that metabolizes long-chain fatty acids, and the LCHAD activity is specific for compounds of C12-C16 chain length.

Sequencing of the HADHA gene is recommended after a biochemical analysis consistent with LCHAD deficiency, 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 (GN).

**Genes**

HADHA

**Indications**

This test is indicated for:

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

**Methodology**

PCR amplification of 20 exons contained in the HADHA 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: Unknown. 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)
- Urine Organic Acids (OA) Analysis
- Trifunctional Protein Deficiency Gene Sequencing (FZ)
- Custom Diagnostic Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.
- 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.