Gene Sequencing

Gene located at the 21q22 [8]. About 30 mutations in the gene have been identified. Gene sequence analysis is available to test for mutations in the gene (JW). For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (JX).

The age of onset is one of the distinguishing factors with HLCS typically presenting between birth and 3 months of age and biotinidase deficiency typically presenting after 3 months. The symptoms in these disorders are similar and clinical differentiation is often difficult. In untreated states, both are usually characterized by seizures, hypotonia, ataxia, developmental delay, vision problems, hearing loss, and cutaneous changes such as alopecia, skin rash, and candidiasis. With age, motor limb weakness, spastic paresis, and decreased visual acuity occur. Both HLCS and biotinidase deficiency are biotin-responsive and early recognition and biotin supplementation result in rapid clinical improvement [4-5]. Newborn screening allows early symptomatic treatment that can prevent neurological deterioration [6].

Organic acid abnormalities are similar in HLCS and biotinidase deficiency and may be reported as consistent with multiple carboxylase deficiency on tandem mass spectrometry utilized in neonatal screening. Definitive enzyme determinations are required to distinguish between the two disorders [7].

Biotinidase activity is normal in serum of individuals with holocarboxylase synthetase deficiency; therefore, the enzymatic assay of biotinidase activity used in newborn screening is specific for biotinidase deficiency and does not identify children with holocarboxylase synthetase deficiency. Both biotinidase deficiency and holocarboxylase synthetase deficiency are characterized by deficient activities of the three mitochondrial carboxylases in peripheral blood leukocytes prior to biotin treatment. In both disorders, these activities increase to near-normal or normal after biotin treatment.

HLCS enzyme deficiency is caused by mutations in the HLCS gene located at the 21q22 [8]. About 30 mutations in the HLCS gene have been reported and a majority of them are missense and nonsense mutations with 5 polymorphisms described as well [9]. There is some evidence for genotype-phenotype correlation, e.g. the missense mutations L237P and L470S and the null mutations 780delG, 6556insA, and R665X were reported and a majority of them are missense and nonsense mutations with 5 polymorphisms described as well [9]. There is some evidence for genotype-phenotype correlation, e.g. the missense mutations L237P and L470S and the null mutations 780delG, 6556insA, and R665X were associated with reduced enzyme activity and earlier onset of the disease [9]. Gene sequence analysis is available to test for mutations in the HLCS gene (JW). For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (JX).

References:

Genes

HLCS

Indications

This test is indicated for:
- Confirmation of a clinical/biochemical diagnosis of HLCS deficiency
- Carrier testing in adults with a family history of HLS deficiency

Methodology

PCR amplification of 14 exons contained in the HLCS 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

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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 HLCS deficiency will have an abnormal DNA test.

Clinical Sensitivity: 18/18 mutations identified in 9 patients [8]; 6/8 mutations identified in 4 patients [10]; 18/18 mutations identified in 9 patients [11].

Analytical Sensitivity: ~99%.

Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types

* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow 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**

Laboratory, please submit a copy of the sequencing report with the 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 Emory Genetics test requisition.

**Related Tests**

- Urine Organic Acids (OA), and Plasma Acylcarnitine Profile (AR) are used in the diagnoses of a patient with HLCS deficiency
- Biotinidase Assay (BX) may also be used in some instances to aid in diagnosis of HLCS deficiency
- 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.