Gene Deletion/Duplication

Gene have been gene located at the 21q22 [8]. About 30 mutations in the 2 weeks 81228 x1

JX

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Holocarboxylase Synthetase Deficiency: HLCS Gene Deletion/Duplication

Test Code: JX
Turnaround time: 2 weeks
CPT Codes: 81228 x1

Condition Description

Holocarboxylase Synthetase Deficiency (HLCS) is an autosomal recessive inborn error of biotin metabolism [1]. It is also called early-onset multiple carboxylase deficiency and is clinically and biochemically similar to the disorder late-onset multiple carboxylase deficiency, or biotinidase deficiency, a separate disorder caused by mutations in the biotinidase gene BTD (refer to the Biotinidase Deficiency test for more information) [2].

Biotin is an essential water-soluble vitamin that serves as a coenzyme for four carboxylases in humans (acetyl-CoA carboxylase, pyruvate carboxylase, propionyl-CoA carboxylase, and b-methylcrotonyl-CoA carboxylase) [3]. Its serum level depends on dietary biotin intake and the recycling of endogenous biotin. The normal function of a carboxylase protein requires establishment of a covalent bond with the cofactor biotin. HLCS establishes a covalent bond between a lysine residue in the apocarboxylase molecule and a biotin molecule and is therefore crucial in biotin recycling.

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]. Neonatal screening allows early presymptomatic 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 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).

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 HLCS deficiency

Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes
which cover the entire genomic region. Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient’s phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

### Detection

Detection is limited to duplications and deletions. Array CGH will not detect point mutations or intronic mutations. 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) 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\textsuperscript{TM} 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 sample. 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 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.
- Prenatal testing is available for known familial mutations only. Please call the Laboratory Genetic Counselor before collecting a fetal sample.