HLCS Gene Analysis in Holocarboxylase Synthetase Deficiency / Multiple Carboxylase Deficiency

Clinical Features:
Holocarboxylase Synthetase (HLCS) Deficiency (or Multiple Carboxylase Deficiency) is a rare disorder of biotin metabolism. Most patients with HLCS deficiency present with symptoms in the newborn to early infantile period that include metabolic acidosis and organic aciduria, irritability, lethargy, hypotonia, seizures, coma, developmental delay, and dermatitis. Nearly all patients with HLCS deficiency respond to biotin administration, however patients may differ in the level of responsiveness to biotin.[4]

Inheritance:
Autosomal Recessive

Genetics:
HLCS deficiency is caused by pathogenic variants in the *HLCS* gene, which encodes the holocarboxylase synthetase enzyme. Holocarboxylase synthetase is responsible for attaching the required coenzyme, biotin, to four carboxylase enzymes (pyruvate carboxylase, propionyl-CoA carboxylase, 3-methylcrotonyl-CoA carboxylase and acetyl-CoA carboxylase). HLCS deficiency results in a decrease in the activity of the carboxylases and results in impairment of gluconeogenesis, fatty acid metabolism, and amino acid catabolism. Characteristic laboratory findings include metabolic acidosis and organic aciduria due to the accumulation of 3-hydroxyisovalerate, 3-methylcrotonylglycine, 3-hydroxypropionate, methylcitrate, and lactate. The *HLCS* gene is located on chromosome 21q22.1 and has 9 coding exons.[3,4]

Test Methods:
Variant analysis of the *HLCS* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of the 9 coding exons (exons 4-12; reference sequence NM_000411), and corresponding intron/exon boundaries. In the literature these coding exons are denoted as exons 6-14.[1,3] If sequencing identifies a variant on only one allele of the *HLCS* gene and if clinically indicated, reflex exon-level deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing or another appropriate method.

Test Sensitivity:
In one study of 9 HLCS deficiency patients worldwide, two variants were identified in all patients.[3] A second study analyzed more than 95% of the *HLCS* coding sequence of 5 U.S.

HLCS deficient patients and identified 9/10 mutant alleles.[4] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:

Greater than 30 *HLCS* variants have been described. The vast majority of these are missense variants; however, small deletions/insertions, a large deletion, and one splicing defect that appears to be a founder mutation in Scandinavia (IVS10+5 G>A), have been identified. A paracentric inversion of chromosome 21 that disrupts the *HLCS* gene has also been reported.[5] The p.L237P and c.780delG variants appear to be predominant in the Japanese population. Otherwise, variants occur throughout the coding region of the *HLCS* gene with the exception of exon 6 and 10.[1] For some variants, genotype information may be helpful in predicting age of onset.[1]

References:

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2. Santer et al. (2003) Mol Genet Metab 79:160-166 PMID: 12855220
3. Yang et al (2001) Hum Genet 109:526-534 PMID: 11735028
4. Dupuis et al. (1996) Hum Mol Genet 5:1011-1016 PMID: 8817339
5. Quinonez et al. (2017) JIMD Rep 34 :55-61 PMID: 27518780