

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

Genetics:

HLCS deficiency has an autosomal recessive inheritance pattern. HLCS deficiency is caused by pathogenic variants in the HLCS gene, which codes for 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 coding exons (4-12), 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 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, restriction fragment analysis, 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 examined 5 U.S. HLCS deficient patients and identified 9/10 mutant alleles.⁴

Variant Spectrum:

Greater than 30 HLCS variants have been described. The vast majority of these are missense variants; however, small deletions/insertions and one splicing defect that appears to be a founder mutation in Scandinavia (IVS10+5 G>A), have been identified. 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 exons 6 and 10. For some variants, genotype information may be helpful in predicting age of onset.¹

References:

1. Suzuki et al. (2005) Hum Mutat 26:285-290
2. Santer et al. (2003) Mol Genet Metab 79:160-166
3. Yang et al (2001) Hum Genet 109:526-534
4. Dupuis et al. (1996) Hum Mol Genet 5:1011-1016