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 individuals 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 individuals with HLCS deficiency respond to biotin administration, however individuals may differ in the level of responsiveness to biotin.[1,2]

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.[1,3]

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the HLCS gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

VARIANT SPECTRUM

Greater than 30 HLCS variants have been described. The vast majority of these are missense variants. 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.[4] 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.[5] For some variants, genotype information may be helpful in predicting age of onset.[5]

REFERENCES:

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