MMACHC Gene Analysis in Methylmalonic Aciduria and Homocystinuria, cobalamin C (cblC) Type

Clinical Features:
Methylmalonic aciduria and homocystinuria, cblC type, is a defect in B_{12} metabolism. Patients may present with severe early-onset disease that includes megaloblastic and macrocytic anemia, failure to thrive, microcephaly, lethargy, and feeding difficulties. Neurologic symptoms may include seizures, hypotonia, intellectual disability, developmental delay, ataxia, optic atrophy, retinal degeneration, and pigmentary retinopathy. Late-onset cases may present with megaloblastic anemia and/or psychiatric disturbance, anorexia, irritability, fatigue, myelopathy, nephropathy, thromboembolic events, or dementia.[1,3]

Genetics:
Methylmalonic aciduria and homocystinuria, cblC type, is due to pathogenic variants in the *MMACHC* gene, which cause decreases in adenosylcobalamin and methylcoblamin and deficient activity of both methylmalonyl-CoA mutase and methionine synthase/methyltetrahydrofolate: homocysteine methyltransferase. *MMACHC* pathogenic variants cause increases in homocystine and methylmalonate; the methylmalonate concentration is usually less than that in methylmalonyl-CoA mutase deficiency. Other more rare forms of methylmalonic aciduria and homocystinuria have been identified by complementation studies, including cblD (*MMADHC*), cblF (*LMBRD1*), and cblJ (*ABCD4*) deficiency.[6-9] *MMACHC* is located on chromosome 1p34.1.

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Variant analysis of the *MMACHC* gene is performed on genomic DNA from the submitted specimen. The entire coding sequence and intron/exon boundaries of the MMACHC gene are analyzed by bi-directional sequencing. If sequencing identifies a variant on only one allele of the *MMACHC* 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 large study, sequencing of the *MMACHC* gene identified variants in both alleles in 95% of patients with methylmalonic aciduria and homocystinuria, cblC type. In approximately 2.5% of patients with cblC deficiency confirmed by complementation studies, only a single *MMACHC* variant was identified and in the remaining 2.5% no variant was identified on either allele.[4] For individuals with no *MMACHC* gene variants identified, evaluation of other genes in the clbC complementation group (*PRDX1*, *HCFC1*, *THAP11*, and *ZNF143*) may be warranted.[6] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:

Missense, nonsense, and splice-site variants, small deletions/duplications, gross deletions, and variants affecting the start codon have been reported.[5] One variant, c.271dupA, was observed in 40% of alleles of patients with methylmalonic acidemia and homocystinuria, cblC and found in the homozygous state in approximately 22% of patients.[2] This variant was found in several different ethnic groups.

References:

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