MLYCD Gene Analysis in Malonyl-CoA Decarboxylase Deficiency

Clinical Features:
Malonyl-CoA decarboxylase (MCD) deficiency is a rare inborn error of metabolism that affects β-oxidation of fatty acids. At this time, over 20 patients with this condition have been reported.[1] Symptoms of MCD deficiency include developmental delay, hypertrophic cardiomyopathy, seizures, acidosis, hypoglycemia and hypotonia as the most common features reported. Patients with no or only mild developmental delay have been described, as has a patient with significant structural brain abnormalities.[2,3] Identification of MCD deficiency may increase as a result of tandem mass spectrometry-based newborn screening.

Inheritance:
Autosomal Recessive

Genetics:
MCD deficiency is caused by variants in the *MLYCD* gene that encodes the malonyl-CoA decarboxylase enzyme, which catalyzes the decarboxylation of malonyl-CoA to acetyl-CoA. Enzyme deficiency results in accumulation of malonyl-CoA, which is an inhibitor of numerous metabolic pathways including succinic acid dehydrogenase and carnitine palmitoyltransferase-I (CPT-I), critical in the TCA cycle and fatty acid oxidation. Inhibition of CPT-I impairs fatty acid oxidation in mitochondria and peroxisomes. MCD deficiency is usually suspected due to the findings of high urinary malonic acid, methylmalonic acid and a mild increase in dicarboxylic acid. High levels of malonylcarnitine and propionylcarnitine can be observed on acylcarnitine analysis by tandem mass spectrometry. Elevated plasma C3-DC is detectable by expanded newborn screening. The diagnosis can be confirmed by molecular genetic studies.[1] Assay of malonyl-CoA decarboxylase activity in cultured fibroblasts and lymphocytes is also confirmatory but is not commercially available. The *MLYCD* gene is located on chromosome 16q24.3 and has 5 exons.

Test Methods:
Variant analysis of the *MLYCD* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of exons 1-5 and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *MLYCD* 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 a single report of 9 patients with MCD deficiency, sequence analysis identified variants on 16/18 *MLYCD* alleles.[4] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant spectrum:
MLYCD variants consist of missense, nonsense, splice site, small insertions/deletions and large deletions including the entire gene and single exons. In one study that combined sequence analysis and deletion/duplication testing, 3/8 patients were found to have a large *MLYCD* deletion that would not be identified by sequence analysis.[2] To date, each family has had its own unique variants and no genotype-phenotype correlation has been identified.[1,2]

References:

1. Malvagia et al., (2007) Ann Hum Genet 71:705-712 (PMID: 17535268).
2. Salomons et al., (2007) J Inherit Metab Dis 30:23-28 (PMID: 17186413).
3. Liu et al. (2016) Am. J. Med. Genet. A 170 (5):1347-51 (PMID: 26858006)
4. Wightman et al., (2003) Hum Mutat 22:288-300 (PMID: 12955715).