**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. Features of MCD deficiency most often include developmental delay, hypertrophic cardiomyopathy, seizures, acidosis, microcephaly, hypoglycemia and hypotonia. In addition, several individuals have been described with abnormal brain MRI including T2 hyperintensities in periventricular white matter and basal ganglia. An individual with significant structural brain abnormalities has also been reported.²⁻⁴

**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 and results in the accumulation of malonyl-CoA. Malonyl-CoA 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. 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. The diagnosis can be confirmed by molecular genetic studies.¹ Assay of malonyl-CoA decarboxylase activity in cultured fibroblasts and lymphocytes is confirmatory but is not commercially available. The **MLYCD** gene is located on chromosome 16q24.3 and has 5 exons.

**Test Methods:**
Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the **MYLCD** 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:**

*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 affected individuals were found to have a large *MLYCD* deletion that would not be identified by sequence analysis. The majority of reported variants are private and no genotype-phenotype correlation has been identified.

**References:**