**ACSF3 Gene Analysis in Combined Malonic and Methylmalonic Aciduria (CMAMMA)**

**Clinical Features:**
Combined malonic and methylmalonic aciduria (CMAMMA) is an inborn error of metabolism characterized by elevations of urinary malonic acid (MA) and methylmalonic acid (MMA).\(^1,2\) In the classic form, MA elevations are typically higher than MMA, and affected individuals have normal malonyl-CoA decarboxylase enzyme activity.\(^1,2,3\) CMAMMA has a broad phenotypic spectrum, presenting in childhood and in adults. Most affected individuals have metabolic acidosis, developmental delay, seizures, and cardiomyopathy. Other findings reported include: coma, hypoglycemia, failure to thrive, immunodeficiency, microcephaly, dystonia reported in children, whereas adults have also presented with psychiatric disease, memory problems, and cognitive decline.\(^1,2\) The incidence of CMAMMA has been estimated at approximately 1 in 30,000.\(^2\) However, some affected individuals exhibit no clinical symptoms and the disorder is believed to be under-diagnosed.\(^1,3\)

**Genetics:**
CMAMMA is caused by variants in the *ACSF3* gene that encodes a putative mitochondrial methylmalonyl-CoA and malonyl-CoA synthetase. Acyl-CoA synthases activate the thioester linkage between fatty acids and coenzyme A that is required to move the fatty acid into the mitochondria for β-oxidation.\(^2\) Patients with CMAMMA typically have urinary MA elevations greater than MMA, elevated serum MMA, and normal serum B\(_{12}\), acylcarnitines, total homocysteine, and malonyl-CoA decarboxylase activity.\(^2\) The *ACSF3* gene is located on chromosome 16q24.3 and has 9 coding exons.

**Inheritance Pattern:**
Autosomal Recessive

**Test Methods:**
Variant analysis of the *ACSF3* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *ACSF3* 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:
There have been very few reports of patients with CMAMMA. In one report of 9 individuals diagnosed with CMAMMA, variant analysis identified variants on 16/18 (89%) ACSF3 alleles.\(^2\) In one study of 131 patients with methylmalonic aciduria and no clinical diagnosis following functional studies of vitamin B\(_{12}\) metabolism, five patients were found to harbor biallelic variants in the ACSF3 gene.\(^3\) The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:
ACSF3 variants include missense, nonsense, splice-site, a small deletion, and a gross deletion.\(^1,2,3\) Approximately 50% of patients reported thus far have been apparently homozygous for an ACSF3 variant.\(^1,2\)

References:
2. Sloan et al. (2011) Nature Genetics 43 (9):883-6 (PMID: 21841779)