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:

1. Alfares et al. (2011) J. Med. Genet. 48 (9):602-5 (PMID: 21785126)
2. Sloan et al. (2011) Nature Genetics 43 (9):883-6 (PMID: 21841779)
3. Pupavac et al. (2016) Mol. Genet. Metab. : (PMID: 26827111)