ACAT1 Gene Analysis in β-Ketothiolase Deficiency
(Alpha-Methylacetoacetic Aciduria, Mitochondrial Acetoacetyl-CoA Thiolase Deficiency, or T2 Deficiency)

Clinical Features:
Mitochondrial acetoacetyl-CoA thiolase deficiency, commonly known as β-ketothiolase deficiency, is an inborn error of isoleucine and ketone-body metabolism. This disorder is characterized by acute episodes of ketoacidosis and by the excretion of specific organic acids in urine. The attacks may be induced by infections or a high intake of protein. Patients can develop severe life-threatening episodes associated with coma, confusion, or lethargy that can lead to developmental delay. The onset is usually in late infancy or childhood and severity of symptoms is variable. A number of patients have been reported with mental retardation or speech problems; however, affected asymptomatic siblings have also been diagnosed. Given the heterogeneity of severity at presentation, individual treatment programs are necessary; however, many patients have had a favorable outcome after diagnosis with treatment.

Genetics:
β-Ketothiolase deficiency is caused by variants in the ACAT1 gene that encodes mitochondrial acetoacetyl-CoA thiolase, which is responsible for the cleavage of 2-methylacetoacetyl-CoA in isoleucine metabolism. Urine organic acid profiles of patients with β-ketothiolase deficiency are typically characterized by massive excretion of tiglylglycine, 2-methyl-2-hydroxybutyrate and 2-methylacetoacetate in both ketoacidotic and stable conditions; however, patients have been described who do not excrete tiglylglycine even during a ketoacidotic episode.1 β-Ketothiolase deficiency is the most likely organic acidemia to be missed by organic acid analysis. The ACAT1 gene is located on chromosome 11q22.3-q23.1 and has 12 exons.

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Variant analysis of the ACAT1 gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of exons 1-12, and the corresponding intron/exon boundaries. If sequencing identifies a varaint on only one allele of the ACAT1 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 two studies of patients with β-ketothiolase deficiency, variants were identified on 46/46 and 10/10 ACAT1 alleles respectively.\(^1,2\) In a third study, two variants were identified in 12/13 patients.\(^3\)

Variant Spectrum:
The majority of pathogenic variants reported are missense, splicing, and frameshift variants; however, nonsense, small deletion and insertions, and gross deletions and insertions have been reported.

References: