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

Clinical Features:
Mitochondrial acetoacetyl-CoA thiolase deficiency, commonly known as ß-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:
ß-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 ß-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] ß-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 varainton 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 ß-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:

1. Zhang et al., (2004) Pediatr Res 56(1) :60-4
2. Fukao et al., (2001) Mol Genet Metab 72 :109-114
3. Fukao et al., (1995) Hum Mutat 5:113-120
4. Fukao et al., (2007) Mol Genet Metab 92:375-378
5. Merinero, et al., (1987) J Inher Metab Dis 10 (Suppl 2):2769