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 which may be induced by infections or a high intake of protein. Severe life-threatening epis odes may occur 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 intellectual disability or speech problems; however, affected asymptomatic siblings have also been diagnosed. Given the heterogeneous severity at presentation, individual treatment programs are necessary; however, many patients have had a favorable outcome after diagnosis with treatment.[1, 2, 3]

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 as those who do not excrete tiglylglycine even during a ketoacidotic episode.[1] 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. 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.

The methods used by GeneDx are expected to be greater than 99% sensitive in detecting variants identifiable by sequencing.

VARIANT SPECTRUM

The majority of pathogenic variants reported are missens e, splicing, and frameshift variants; however, nons ense, small deletion and insertions, and gross deletions and insertions have been reported.

REFERENCES:

1. Zhang et al. (2004) Pediatric Research 56 (1):60-4 (PMID: 15128923)
2.Fukao et al. (2001) Molecular Genetics And Metabolism 72 (2):109-14 (PMID: 11161836)
3.Fukao et al. (1995) Human Mutation 5 (2):113-20 (PMID: 7749408)

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