ACAD8 Gene Analysis in Isobutyryl-CoA Dehydrogenase Deficiency

Clinical Features:
Isobutyryl-CoA dehydrogenase (IBD) deficiency is an inborn error of valine metabolism that was first reported in a child with dilated cardiomyopathy, anemia and secondary carnitine deficiency. Very few patients have been reported with IBD deficiency in the literature with the majority of reported patients having been identified after the detection of elevated C4-carnitine by tandem mass spectrometry based newborn screening. Patients first identified by screening have either remained asymptomatic or presented with milder clinical phenotypes including muscle hypotonia, and mild developmental delay.

Genetics:
IBD deficiency is caused by pathogenic variants in the *ACAD8* gene that encodes the isobutyryl-CoA dehydrogenase enzyme which catalyzes the conversion of isobutyryl-CoA to methacrylyl-CoA: the third step in the degradation of valine. An elevated C4-carnitine level may occur in IBD deficiency or short-chain acyl-CoA dehydrogenase (SCAD) deficiency. To discriminate between SCAD deficiency and IBD deficiency, urine organic acid analysis is performed which shows elevated ethylmalonic acid, methylsuccinic acid and n-butyrylglycine in patients with SCAD deficiency and usually shows elevated isobutyrylglycine in IBD deficiency. However, isobutyrylglycine may not always be elevated in patients with IBD deficiency. The *ACAD8* gene is located on chromosome 11q25 and has 11 exons. Based on newborn screening results in the United States, the incidence of IBD deficiency, is at least 1 in 70,000 live births.[1]

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Variant analysis of the *ACAD8* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of the 11 exons, and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *ACAD8* 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 8 patients with elevated C4-carnitine on newborn screening and subsequent diagnosis of IBD deficiency after demonstration of increased levels of isobutyrylcarnitine in fibroblasts,

pathogenic variants were identified on 16/16 *ACAD8* alleles.[1] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:

The majority of pathogenic variants that have been described in the *ACAD8* gene are missense variants; however, nonsense, splicing and a small insertion have also been reported.

References:

1. Oglesbee et al., (2007) Genet Med 9(2):108-116