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

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the ACAD8gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

T: 1 (844) 241-1233 | **F:** 1 (201) 421-2020 | GeneDx.com
207 Perry Parkway | Gaithersburg, MD 20877

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):108-16 (PMID: 1730402)