ACADSB Gene Analysis in Short/Branched Chain Acyl-CoA Dehydrogenase Deficiency

CLINICAL FEATURES

Short/branched chain acyl-CoA dehydrogenase (SBCAD) deficiency also known as 2-methylbutyryl-CoA dehydrogenase deficiency is a rare disorder of isoleucine metabolism. The clinical spectrum of this disorder has not been clearly defined as few patients with SBCAD deficiency have been described. Very few symptomatic patients have been reported. Several symptomatic patients presented with acute crisis in the newborn period including lethargy, poor feeding, apnea, hypothermia, hypoglycemia, EEG and MRI abnormalities, convulsions, lactic acidosis, respiratory distress, seizures, sepsis, disseminated intravascular coagulation and cerebral hemorrhage. Another group of symptomatic patients presented after the neonatal period with symptoms that include hypotonia, motor delay, strabismus, apnea, infantile spasms, developmental delay, attention deficit hyperactivity disorder, recurrent vomiting and failure to thrive. A mother of one of the affected patients was also diagnosed with SBCAD deficiency but is healthy. Most patients have been diagnosed following positive newborn screening result for C5 elevation or were identified after the diagnosis of SBCAD in a sibling. These individuals have remained healthy, most with little or no treatment.[1,2]

INHERITANCE PATTERN

Autosomal Recessive

GENETICS

SBCAD deficiency is caused by variants in the *ACADSB* gene that encodes the 2-methylbutyryl-CoA dehydrogenase enzyme that catalyzes the third step in the metabolism of isoleucine. Enzyme deficiency results in an increase in urinary excretion of 2-methylbutyrylglycine. Tandem MS analysis of acylcarnitines in SBCAD deficient patients may reveal elevated C5 (representing 2-methylbutyrylcarnitine); however, this cannot be distinguished from the isolated elevation of its C5 isomer, isovalerylcarnitine, that is elevated in isovaleric acidemia. The *ACADSB* gene is located on chromosome 10q25-26 and has 11 exons.

TEST METHODS

Variant analysis of the *ACADSB* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and 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.

TEST SENSITIVITY

There have been only a few small studies of patients with SBCAD deficiency. In 6 of these studies (total of 18 patients), sequencing genomic DNA identified *ACADSB* variants on 33/36 alleles (92%).[2-7] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

VARIANT SPECTRUM

At this time, less than 20 variants in the *ACADSB* gene have been reported and include missense and splice site variants. Most variants are private, with the exception of IVS3+3 A>G found in two unrelated families of African origin and M389V (aka M356V) found in patients of Hmong descent who were identified by expanded newborn screening.[1]

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