ETFA, *ETFB*, and *ETFDH* Gene Analysis in Glutaric Aciduria II (GAII) or Multiple Acyl-CoA Dehydrogenase Deficiency (MADD)

Clinical Features:

Multiple Acyl-CoA Dehydrogenase Deficiency (MADD) or Glutaric Aciduria II (GAII) is a rare disorder that can result from deficiency of the alpha or beta subunits of electron transfer flavoprotein or its dehydrogenase ETF:ubiqinone oxidoreductase (ETF-DH or ETF:QO). Defects in any of these genes may lead to a range of clinical phenotypes from mild to severe, depending upon the pathogenic variant. Three clinical phenotypes for GAII have been described. Type I presents as a life-threatening disorder during the neonatal period with tachypnea, dyspnea, profound acidosis, severe hypotonia, and convulsions. Hepatomegaly, hypoketotic hypoglycemia, hyperammonemia, sweaty-sock like odor, and congenital anomalies including renal cystic dysplasia, heart abnormalities, central nervous system malformations, facial dysmorphism, rocker bottom feet, and abnormalities of the external genitalia may also be present. Type II presentation is similar to Type I without congenital anomalies, while a Type III presentation occurs later with intermittent episodes of vomiting, hypoglycemia, and metabolic acidosis during infancy or episodic muscular weakness and pain during adulthood along with progressive myopathy; this type may be underdiagnosed.[9] Recurrent pancreatitis has also been reported with abdominal symptoms.[1,2]

Genetics:

The electron transfer flavoprotein (ETF) is located in the mitochondrial matrix as a heterodimer of alpha and beta subunits and electron transfer flavoprotein dehydrogenase (ETF-DH) is located in the inner mitochondrial membrane. ETF is an electron acceptor for the acyl-CoA dehydrogenases involved in fatty acid oxidation as well as for several dehydrogenases involved in amino acid and choline metabolism. These electrons are subsequently transferred via ETF-DH to ubiquinone in the respiratory chain. During episodes of metabolic crisis, urinary organic acid profiles show dicarboxylic aciduria and a characteristic accumulation of marker metabolites of the blocked dehydrogenases. Plasma acylcarnitine analysis shows an increase of all chain length acylcarnitines. Patients with GAII may have normal organic acid profiles between periods of catabolic stress. The two ETF subunits are encoded by the *ETFA* (12 exons) and *ETFB* (6 exons) genes located on chromosomes 15q23-25 and 19q13.3, respectively. ETF-DH is encoded by the *ETFDH* gene (13 exons) on chromosome 4q32-qter. As not all patients with GAII have pathogenic variants in the *ETFA*, *ETFB* or *ETFDH* genes, pathogenic variants in other genes are predicted to also cause GAII.[1,3,4,5] Recently, defects in genes encoding riboflavin transporters have been identified that can result in similar biochemical and clinical abnormalities.[9] Of patients with variants identified in *ETFA, ETFB* or *ETFDH,* ~11-27% of patients had *ETFA* variants, ~27-33% had *ETFB* variants, and ~47-56% had *ETFDH* variants.[3, 6] Of 350 patients with the Type III presentation, 93% had variants in the *ETFDH* gene, while variants in *ETFA* (5%) and *ETFB* (2%) were rare.[9] Most patients with riboflavin-responsive GAII have been reported to have pathogenic variants in the *ETFDH* gene.[7, 8] Of

patients with the Type III presentation, 98.4% were riboflavin-responsive.[9]

Inheritance Pattern:

Autosomal Recessive

Test Methods:

Variant analysis of the *ETFDH*, *ETFB* and *ETFA* genes is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of the coding exons and the corresponding intron/exon boundaries. If clinically indicated, for patients who have a single variant identified after full sequencing of all three genes, or when otherwise appropriate, GeneDx will perform reflex deletion/duplication testing (ExonArrayDx) at no additional charge. 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. Testing for the *ETFDH*, *ETFB,* and *ETFA* genes can be ordered sequentially, if specifically requested, or all 3 genes can be analyzed simultaneously if a more rapid turnaround time is needed. If other studies have determined which subunit of the genes is defective, sequencing of the appropriate gene should be ordered.

Test Sensitivity:

In patients with GAII confirmed by ETF enzyme assay or fatty acid oxidation studies, sequence analysis has identified 2 variants in approximately 75-87% of patients.[1,3 6] In another study of 19 patients with GAII with reduced or absent ETF:QO protein, two pathogenic variants were identified in 89% of patients.[5] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:

Variants in the three genes include missense, nonsense, frameshift, gross deletions, small insertions and deletions, frameshift, and splice site changes.[3]

References:

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