HADH Gene Analysis in 3-Hydroxyacyl-CoA Dehydrogenase (HADH) Deficiency

Disorder also known as: 3-alpha-hydroxyacyl-CoA dehydrogenase deficiency, HADH deficiency, familial hyperinsulinemic hypoglycemia

Clinical Features:
3-Hydroxyacyl-CoA dehydrogenase (HADH) deficiency is a rare disorder of mitochondrial fatty acid beta-oxidation. Affected individuals typically present during the first year of life with hypoglycemia, seizures/convulsions, and hyperinsulinism.[1] A single patient has been described who did not have hyperinsulinism however this patient had a very high residual enzyme activity (35% of controls in isolated mitochondria).[2] A Reye-like presentation and fulminant hepatic failure have also been reported.[1,2] Severe developmental disabilities were observed in patients in an affected sibship when treatment was delayed.[1] Most patients have been responsive to diazoxide, which has been reported to be effective in treating severe recurrent hypoglycemia.[1,8]

Genetics:
HADH deficiency is caused by pathogenic variants in the *HADH* gene (formerly referred to as: *HAD, HHF4, HADH1, SCHAD, HADHSC, M/SCHAD, MGC8392*) that encodes the 3-hydroxyacyl-CoA dehydrogenase enzyme that catalyzes the penultimate step of β-oxidation of fatty acids in the mitochondrial matrix. Urine organic acids and acylcarnitine profiles may be normal in affected individuals.[3, 4, 8] However, plasma hydroxybutyrylcarnitine (C4-OH) may be elevated along with elevated urinary medium-chain dicarboxylic and 3-hydroxydicarboxylic metabolites and 3-hydroxyglutarate. Deficient C4-hydroxyacyl-CoA dehydrogenase activity is observed in lymphocytes, fibroblasts, and in other tissues. The HADH protein is also an allosteric inhibitor of pancreatic β-cell glutamate dehydrogenase (GDH) and deficiency of HADH results in a loss of inhibitory regulation of GDH, which leads to hyperinsulinemia.[1, 5] The *HADH* gene is located on chromosome 4q22-q26 and has 8 exons.

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Variant analysis of the *HADH* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *HADH* gene, and if clinically indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for 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 patients with familial hyperinsulinism, variants in the *HADH* gene are expected to account for less than 1% of affected individuals.[6] In one report, variants in the *HADH* gene were identified in 10% (11/115) of patients with diazoxide-responsive hyperinsulinemic hypoglycemia in whom the common genetic causes of hyperinsulinemic hypoglycemia had been excluded (*KCNJ11*, *ABCC8*, *GCK*, *HNF4A* genes).[8] One study that included 6 patients with deficient activity of HADH in liver and muscle failed to identify a *HADH* gene variant in any of the patients.[7] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:

Pathogenic variants in *HADH* consist of missense, nonsense, splice site, small deletions and insertions, and frameshift. A large deletion including exon 1 has also been described.[8] Most reported patients have been homozygotes.[1] Genotype-phenotype correlations have not been established.

References:

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