AUH Gene Analysis in 3-Methylglutaconic Aciduria Type I

Clinical Features:
3-Methylglutaconic aciduria type I (MGA1) is a rare disorder of leucine catabolism. Very few patients with this condition have been described in the literature. The clinical picture ranges from asymptomatic patients to patients with speech delay or mild developmental delay and gastroesophageal reflux to those with severe encephalopathy with basal ganglia involvement, seizures, and severe psychomotor retardation with progressive neurological deterioration.

Genetics:
MGA1 deficiency is caused by pathogenic variants in the *AUH* gene that encodes the 3-methylglutaconyl-CoA hydratase enzyme that catalyzes the fifth step in leucine catabolism: the conversion of 3-methylglutaconyl-CoA to 3-hydroxy-3-methylglutaryl-CoA. Enzyme deficiency results in increased urinary excretion of 3-methylglutaconic acid, 3-methylglutaric acid, and 3-hydroxyisovaleric acid. Patients with other distinct genetic syndromes, notably Barth syndrome and Costeff syndrome, may also excrete 3-methylglutaconic and 3-methylglutaric acids, but at much lower levels than that seen in patients with MGA1 deficiency. The excretion of 3-hydroxyisovaleric acid is not present in Barth or Costeff syndromes but is not specific for MGA1, as it is present in biotinidase and holocarboxylase synthase deficiencies. In addition, a patient with MGA1 deficiency has been reported who did not excrete 3-hydroxyisovaleric acid.[1] The *AUH* gene is located on chromosome 9 and has 10 exons.

Inheritance Pattern:
Autosomal Recessive

Test Methods:
Variant analysis of the *AUH* 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 *AUH* 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:
There have been only a few small studies of patients with MGA1 deficiency. In 3 of these studies, two *AUH* variants were identified in all of the patients (total of 6 patients or 12/12 *AUH* alleles characterized).[1, 2, 3] In 227 patients with elevated urinary excretion of 3-

methylglutaconic acid, 3 individuals were identified as having MGA1 deficiency.[5] Most of the remaining patients in this group were diagnosed with another classic metabolic disorder/inborn error of metabolism (n=84) or with a mitochondrial disorder (n=100).[5] The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant spectrum:

The pathogenic variants that have been described in the *AUH* gene include missense, nonsense, splice site, small deletions/insertions, frameshift, and a large deletion. Geneotype-phenotype correlations have not been reported.[4]

References:

1. Ly et al., (2003) Hum Mutat 21:401-407.
2. Illsinger et al., (2004) Pediatr Neurol 30:213-215.
3. Matsumori et al., (2005) Pediatr Int 47:684-686.
4. Wortmann et al., (2010) Neurology 75:1079-1083.
5. Wortmann et al., J Inher Metab Dis (2013) 36:913-921.