HPD Gene Analysis in Tyrosinemia Type III and Hawkinsinuria

Clinical Features:
Tyrosinemia type III is a rare autosomal recessive disorder of tyrosine catabolism caused by a deficiency of 4-hydroxyphenylpyruvate dioxygenase. This disorder is characterized by neurologic findings including neurodevelopmental delay and/or intermittent ataxia. Liver damage, eye or skin findings have not been described. Another rare disorder of tyrosine metabolism has also been attributed to pathogenic variants in the HPD gene, hawkinsinuria. Individuals with hawkinsinuria may be asymptomatic or exhibit failure to thrive, episodes of tyrosinemia and metabolic acidosis that respond to protein restriction. Symptoms improve within the first year of life. Patients with either disorder may be detected by newborn screening.

Genetics:
Tyrosinemia type III has an autosomal recessive inheritance pattern, while Hawkinsinuria has an autosomal dominant inheritance pattern. Tyrosinemia type III is caused by pathogenic variants in the HPD gene that encodes the 4-hydroxyphenylpyruvic acid dioxygenase (HPD) enzyme. HPD catalyzes the second step of the tyrosine degradation pathway: the conversion of 4-hydroxyphenylpyruvic acid to homogentisate. In tyrosinemia type III, deficiency of HPD results in elevated blood tyrosine levels and excretion of tyrosine derivatives in urine. Elevated tyrosine can be detected by newborn screening. Prior to genetic testing of the HPD gene, differentiation between tyrosinemia type II and type III required measurement of enzyme activity in liver biopsy. Several individuals have been described with hawkinsinuria. These individuals have transiently elevated blood tyrosine levels and excrete hawkinsin (2-amino-3-[2-(carboxymethyl)-2,5-dihydroxy-1-cyclohex-3-enylsulfanyl]propanoic acid) throughout their life even after clinical symptoms improve. The first two individuals described with hawkinsinuria, had a single missense change (A33T) that is now known to be a common polymorphism. The HPD gene is located on chromosome 12q24→qter and has 14 exons.

Test Methods:
Variant analysis of the HPD 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 HPD 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 are very few reports of patients with tyrosinemia type III or hawkinsinuria; therefore, the sensitivity of variant analysis of the HPD gene cannot be established at this time. One study examined 3 families with tyrosinemia type III with deficient HPD enzyme activity in liver and identified variants on both HPD alleles in affected individuals from each family.\(^1\) A second report found a homozygous variant in a patient diagnosed with tyrosinemia type III.\(^2\) A third study reported a patient with hawkinsinuria who is compound heterozygous for a known tyrosinemia type III variant and a novel variant associated with hawkinsinuria inherited from his affected mother.\(^3\)

Variant Spectrum:
HPD variants include missense and nonsense variants in tyrosinemia type III, and missense variants have been reported in patients with hawkinsinuria. HPD variants that affect critical components of the HPD catalytic pocket (residues coordinating the ferric ion and the substrate’s phenol ring) are highly evolutionarily conserved. Disrupting these sites is predicted to destroy the enzyme function and be associated with tyrosinemia type III.\(^3\) It has been proposed that variants in residues more distant from the catalytic core may affect the HPD protein structure and be associated with hawkinsinuria.\(^3\)

References: