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 in the untreated state. Liver damage and eye or skin findings have not been described. A patient who began treatment after being diagnosed following an abnormal newborn screening result is reported as asymptomatic at 30 months of age. One other individual, fortuitously identified with tyrosinemia type III by metabolic screening in childhood, had no clinical symptoms even though she had never been treated. 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 may exhibit failure to thrive, episodes of tyrosinemia and metabolic acidosis. Symptoms of hawkinsinuria improve within the first year of life. Individuals with either disorder may be detected by newborn screening due to elevated tyrosine. Treatment includes a low phenylalanine and tyrosine diet and mild protein restriction.

Genetics:
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. Prior to genetic testing of the HPD gene, differentiation between tyrosinemia type II and type III required measurement of enzyme activity in liver biopsy. Individuals with the much more rare condition, hawkinsinuria, have been reported with transiently elevated blood tyrosine levels and elevation of hawkinsin (2-amino-3-[[2-(carboxymethyl)-2,5-dihydroxy-1-cyclohex-3-eny]sulfanyl]propanoic acid) in urine that persist. 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 12q24.31 and has 14 exons.

Inheritance Pattern:
Tyrosinemia type III: Autosomal recessive
Hawkinsinuria: Autosomal dominant?

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 or another appropriate method.

Test Sensitivity:
The clinical sensitivity of sequence analysis of the HPD gene cannot be established at this time since there are very few reports of patients with tyrosinemia type III or hawkinsinuria. 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 The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:
HPD variants include missense and nonsense variants in tyrosinemia type III, and missense variants, most commonly the N241S variant, have been reported in patients with hawkinsinuria. HPD variants that affect critical components of the HPD catalytic core (interacting with the coordinating ferric ion or the 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: