HPD Gene Analysis in Tyrosinemia Type III and Hawkinsinuri

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. [1,2,4,5] Liver damage and eye or skin findings have not been described.[1,2] 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.4 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.[2, 3] 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.[1] 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-enyl]sulfanyl]propanoic acid) in urine that persist. [2] 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

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the *HPD* gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations.

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Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

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]

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