

Tyrosinemia Types I, II and III Panel

Panel Gene List: *FAH*, *HPD* and *TAT*

Clinical and Features:

Tyrosinemia types I, II and III are all inborn errors of tyrosine metabolism. Tyrosinemia type I, II and III are caused by pathogenic variants in the *FAH*, *TAT* and *HPD* genes respectively. The *FAH* gene encodes fumarylacetoacetase that catalyzes the hydrolysis of fumarylacetoacetate into fumarate and acetoacetate, the final step in the tyrosine degradation pathway. The *TAT* gene encodes tyrosine aminotransferase that catalyzes the conversion of tyrosine to *p*-hydroxyphenylpyruvate, and the *HPD* gene encodes 4-hydroxyphenylpyruvic acid dioxygenase that catalyzes the second step of the tyrosine degradation pathway: the conversion of 4-hydroxyphenylpyruvic acid to homogentisate. All three disorders can present with elevated blood tyrosine levels which may be detected on newborn screening and elevated tyrosine derivatives in urine. Elevated succinylacetone in urine or blood is a pathognomonic marker for tyrosinemia type I.

Tyrosinemia type I (*FAH* gene) is the most well described of the three disorders with untreated patients presenting in infancy with severe liver involvement or presenting in the first year with liver dysfunction and renal tubular dysfunction associated with growth failure and rickets. Neurological crisis that can include change in mental status, abdominal pain, peripheral neuropathy and/or respiratory failure may also occur. Patients have a high risk of developing hepatocarcinoma, even at a very young age.¹ Tyrosinemia type II (*TAT* gene) is characterized by keratitis, palmoplantar keratosis, ophthalmologic involvement and intellectual disability. The skin is affected in approximately 80% of reported cases, the eye in approximately 75% and mental retardation is present in over 60% of reported cases.² Eye manifestations usually occur before the skin lesions develop and include photophobia, redness and pain.² Neurodevelopmental disability is variable, ranging from severe retardation to a mild decrease in intelligence.² Tyrosinemia type III (*HPD* gene) is the rarest of the three disorders with few individuals described. Like type II, there is no liver involvement but skin and ocular changes have been described. Affected patients also have neurologic findings including neurodevelopmental delay and/or intermittent ataxia.^{3,4} 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 exhibit failure to thrive, episodes of tyrosinemia and metabolic acidosis that respond to protein restriction. Symptoms improve within the first year of life.^{4,5} Patients with hawkinsinuria may also be detected by newborn screening.

Inheritance Pattern/Genetics:

Autosomal recessive

Test Methods:

Using genomic DNA from the submitted specimen, analysis of the *FAH*, *HPD* and *TAT* genes is performed using bi-directional sequence analysis of the coding exons and the corresponding intron/exon boundaries. In addition, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed concurrently to evaluate for a deletion or duplication of one or more exons of these genes. 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.

Clinical Sensitivity:

Based on the sensitivity of variant analysis for the individual genes, it is estimated that this panel would detect a pathogenic variant in 88% to greater than 95% of patients with tyrosinemia due to pathogenic variants in one of the 3 genes.^{1, 3-8}

References:

1. Bergman et al., (1998) *Hum Mutat* 12 :19-26.
2. Charfeddine et al., (2006) *Mol Genet Metab* 88:184-191.
3. Ruetschi et al., (2000) *Hum Genet* 106:654-662.
4. Tomoeda et al., (2000) *Mol Genet Metab* 71:506-510.
5. Item et al., (2007) *Mol Genet Metab* 91:379-383.
6. Szymanska et al. (2015) *Mol Genet Metab Rep* 5 :48-50 (PMID: 28649543)
7. Heylen et al. (2012) *Mol. Genet. Metab.* 107 (3):605-7 (PMID: 23036342)
8. Peña-Quintana et al. (2017) *Clin. Genet.* 92 (3):306-317 (PMID: 28255985)