

## FAH Gene Analysis in Tyrosinemia Type I

### Clinical Features

Tyrosinemia type I, also known as hepatorenal tyrosinemia, is a rare inborn error of tyrosine metabolism. Clinical symptoms are highly variable even among members of the same family and affected individuals can present at any time from the neonatal period to adulthood. The disorder has been classified based on the age of onset, which broadly correlates with disease severity. The acute form typically presents prior to 6 months of age with acute liver failure. A sub-acute form manifests between 6 months and 1 year of age with liver disease, hypoglycemia, failure to thrive, coagulopathy, hepatosplenomegaly, renal Fanconi syndrome that may lead to rickets, and hypotonia. The chronic form presents after the first year of life with chronic liver disease, renal disease, rickets, cardiomyopathy and/or neurologic crises similar to porphyria. Patients with all forms have a high risk of developing hepatocarcinoma, even at a very young age. The incidence of tyrosinemia type I is estimated at approximately 1/100,000; however, in the Saguenay-Lac-St.-Jean region of Quebec the incidence is 1 in 1,846 newborns.<sup>1,2</sup>

### Genetics

Tyrosinemia type I is caused by pathogenic variants in the *FAH* gene that encodes fumarylacetoacetase, an enzyme that catalyzes the hydrolysis of fumarylacetoacetate into fumarate and acetoacetate; the last step in the degradation pathway of tyrosine. Patients present with elevated succinylacetone in urine and serum and very high AFP levels. Deficiency of the fumarylacetoacetase enzyme causes the accumulation of succinylacetone, maleylacetoacetate and fumarylacetoacetate. The *FAH* gene is located on chromosome 15q23-q25 and has 14 exons.

### Inheritance Pattern

Autosomal Recessive

### Test Methods

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the *FAH* 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. 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

Variants reported in the *FAH* gene include missense, nonsense, splice site, small deletions/insertions and a large deletion. Several common variants have been described in various populations including a IVS12+5 G>A splice

site variant which has been found in approximately 86% of patients from the province of Quebec, Canada and is homozygous in approximately 80% of patients from the Saguenay-Lac-Sainte-Jean region of Quebec.<sup>2,3</sup> This variant is also observed at increased frequency in individuals from northwestern Europe. The IVS6-1 G>T variant is common in the Mediterranean area and the W262X variant is prevalent in the Finnish population. The R341W (c.1021 C>T) variant is associated with pseudodeficiency of fumarylacetoacetase. Homozygosity for R341W or compound heterozygosity for R341W and a pathogenic variant results in low enzyme activity but no clinical symptoms.<sup>5</sup> Other genotype-phenotype correlations have not been established.<sup>1,4</sup>

## REFERENCES:

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