

## *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:**

Variant analysis of the *FAH* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of exons 1-14, and the corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *FAH* 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. Variant 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:

In 25 patients from various ethnic backgrounds diagnosed with tyrosinemia type I based on undetectable fumarylacetoacetase activity in fibroblasts, pathogenic variants were identified on 46/50 *FAH* alleles.<sup>4</sup> The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

## Variation 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:

1. Arranz et al., (2002) Hum Mutat 20:180-188.
2. St-Louis, M. and Tanguay R.M. (1997) Hum Mutat 9 :291-299.
3. Grompe et al., (1994) N Engl J Med 11(6):353-7.
4. Bergman et al., (1998) Hum Mutat 12 :19-26.
5. Rootwelt et al., (1994) Am J Hum Genet 55 :1122-1127.