

Tyrosinemia, Type I via *FAH* Gene Sequencing (Test #541)

Brief Description of Clinical Features: Type I tyrosinemia (OMIM #276700) results from deficiency of fumarylacetoacetate hydrolase (FAH), the enzyme that catalyzes the final step in tyrosine catabolism. The precursor metabolite, fumarylacetoacetate, accumulates in hepatocytes in the absence of FAH activity resulting in cellular damage and diversion to succinylacetone, a reactive metabolite known to interfere with hepatic enzymes (Lindblad et al. *Proc Nat Acad Sci* 74:4641-4645, 1977). The first clinical signs usually appear in newborns with severe liver pathology. Biochemical findings include elevated succinylacetone in the blood and urine, elevated plasma concentrations of tyrosine, methionine, and phenylalanine, and elevated tyrosine metabolites in the urine. Some patients present after the newborn period with rickets and failure to thrive secondary to hepatic and renal dysfunction. A significant number of patients have neurological symptoms including peripheral neuropathy characterized by severe pain with extensor hypertonia, muscle weakness, paralysis requiring ventilation, and self-mutilation (Mitchell et al. *N Eng J Med* 322:432-437, 1990). If untreated, death usually occurs before the age of ten years, typically from liver failure, neurologic crisis, or hepatocellular carcinoma (Sniderman-King et al. *GeneReviews* www.genereviews.org). Effective treatment is achieved with nitisinone (NTBC) along with avoidance of dietary phenylalanine and tyrosine. Liver transplantation may be indicated in cases with severe liver damage or hepatocellular carcinoma (Holme et al. *J Inherit Metab Dis* 21:507-517, 1998).

Genetics: Tyrosinemia is an autosomal recessive disorder. Mutations in *FAH* gene (OMIM #276700) are the genetic cause of type I tyrosinemia. Pathogenic mutations are missense, nonsense, splicing and frameshift. Founder mutations have been identified in Ashkenazi Jews (p.Pro261Leu; Elpeleg et al. *Hum Mut* 19:80-81, 2002) and French Canadians (c.1062+5G>A; Grompe et al. *N Eng J Med* 331:353-357, 1994). The birth incidence of type I tyrosinemia in the USA is thought to be ~1:100,000 (Mitchell et al. in Scriver et al. (ed) *The Metabolic and Molecular Basis of Inherited Disease* pp.1777-1806, 2001). Higher incidences in Finland and Norway result from elevated carrier rates for p.Trp262Stop and c.1062+5G>A mutations, respectively.

Description of This Particular Test: This test involves bidirectional DNA sequencing of all 14 coding exons of the *FAH* gene. The entire coding region and ~50 bp of flanking non-coding DNA on either side of each splice site are sequenced.

Reference Sequences: Genomic: NC_000015.8 mRNA: NM_000137.1 protein: NP_000128.1

Indications for Test: Patients suspected of having tyrosinemia based on newborn screening and/or clinical features. We will also sequence the *FAH* gene to determine carrier status.

Sensitivity of Test: Four mutations (c.1062+5G>A, c.456-1G>T, c.554-6T>G, p.Pro261Leu) account for 60% of the *FAH* mutations in the USA. p.Pro261Leu accounts for >99% of the mutations in the Ashkenazi Jewish population (Elpeleg et al. *Hum Mut* 19:80-81, 2002) and the c.1062+5G>A accounts for nearly 90% of mutations in the French Canadian population (Poudrier et al. *Prenat Diagn* 16:59-64, 1996).

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of complete coding regions of *FAH* Gene \$ 690

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x13	83898	\$ 200	Sequencing x13	83904	\$ 290
Separation	83894	\$ 50	Interpretation/Report	83912	\$ 80

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

Contact for info: Thomas L. Winder, PhD, FACMG, www.preventiongenetics.com, tom.winder@preventiongenetics.com