Tyrosinemia Type I: FAH Gene Sequencing

**Condition Description**

Tyrosinemia Type I is an autosomal recessive inborn error of tyrosine metabolism [1]. In untreated children, it presents either in young infants with severe liver involvement or later in the first year with liver dysfunction and renal tubular dysfunction associated with growth failure and rickets. Untreated children may have repeated, often unrecognized, neurologic crises that can include changes in mental status, abdominal pain, peripheral neuropathy, and may lead to liver failure, hepatocellular carcinoma and potentially death before the age of ten years. Inclusion of tyrosinemia in the newborn screening panel has improved diagnosis of this condition and initiation of crucial therapy [2]. Combined treatment with nitisinone (orfadine) and a low-tyrosine/phenylalanine diet has resulted in a greater than 90% survival rate, normal growth, improved liver function, prevention of cirrhosis, correction of renal tubular acidosis, and improvement in secondary rickets.

Tyrosinemia Type I results from deficiency of the enzyme fumarylacetoacetate hydrolase (FAH). Typical biochemical findings include increased plasma and urine concentration of succinylacetone, elevated plasma concentrations of tyrosine, methionine, and phenylalanine, and elevated urinary concentration of tyrosine metabolites.

FAH enzyme is encoded by the FAH gene located at 15q23, and mutations to this gene are responsible for tyrosinemia by leading to reduced or absent FAH enzyme activity. The four common FAH mutations (IVS12+5 G>A, IVS6-1 G>T, IVS7-6 T>G, P261L) account for approximately 60% of mutations in tyrosinemia type I in the general US population. The P261L mutation accounts for nearly 100% of mutations responsible for tyrosinemia type I in the Ashkenazi Jewish population [3]. IVS12+5 G>A accounts for 87.9% of mutations in the French Canadian population [4]. However, no genotype/phenotype correlation has been established [5]. Gene sequence analysis is available to test for mutations in the FAH gene. (EU). For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (EV).

**Indications**

This test is indicated for:

- Confirmation of a clinical/biochemical diagnosis of Tyrosinemia Type I.
- Carrier testing in adults with a family history of Tyrosinemia Type I.

**Methodology**

PCR amplification of 14 exons contained in the FAH gene is performed on patient genomic DNA. Direct sequencing of amplification products is performed in both the forward and reverse directions using automated fluorescence deoxy sequencing methods. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements. Large deletions are not detected by this analysis.

Targeted CGH Array: DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region.

**Detection**

The majority (>95%) of patients with clinical and biochemical diagnosis of Tyrosinemia Type I will have an abnormal DNA test.

Clinical Sensitivity: 52/58 mutations identified in 29 patients [6], 47/50 mutations identified in 25 patients [7].

Analytical Sensitivity: ~99%

Results of molecular analysis must be interpreted in the context of the patient’s clinical and/or biochemical phenotype.

**Specimen Requirements**

- **Type: Whole Blood (EDTA)**

  **Specimen Requirements:**
  - EDTA (Purple Top)
  - Infants and Young Children (2 years of age to 10 years old): 3-5 ml
  - Older Children & Adults: 5-10 ml
  - Autopsy: 2-3 ml unclotted cord or cardiac blood

  **Specimen Collection and Shipping:**
  - Ship sample at room temperature for receipt at EGL within 24 hours of collection. Do not refrigerate or freeze.
Type: DNA, Isolated

Specimen Requirements:
- Microtainer
- 8µg
- Isolation using the Perkin Elmer™ Chemagen™ Automated Extraction method or Qiagen™ Puregene kit for DNA extraction is recommended.

Specimen Collection and Shipping:
- Refrigerate until time of shipment in 100 ng/µL in TE buffer. Ship sample at room temperature with overnight delivery.

Type: Saliva

Specimen Requirements:
- Oragene™ Saliva Collection Kit
- Oragene™ Saliva Collection Kit used according to manufacturer instructions. Please contact EGL for a Saliva Collection Kit for patients that cannot provide a blood sample.

Specimen Collection and Shipping:
- Please do not refrigerate or freeze saliva sample. Please store and ship at room temperature.

Special Instructions

Please submit copies of diagnostic biochemical test results with the sample. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of EGL Genetics, please submit a copy of the sequencing report with the test requisition.

Related Tests

- Plasma Amino Acid Analysis (AA) and Urine Organic Acids (OA) including succinylacetone and tyrosine metabolites.
- Custom Diagnostics Known Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.
- Tyrosinemia Type I Deletion/Duplication Assay (EV) is available separately for individuals where mutations are not identified by sequence analysis. Refer to the test requisition or contact the laboratory for more information.
- Prenatal testing is available to couples who are confirmed carriers of mutations. Please contact the laboratory genetic counselor to discuss appropriate testing prior to collecting a prenatal specimen.