Tyrosinemia Type I: \textit{FAH} Gene Deletion/Duplication

\textbf{Test Code:} EV  
\textbf{Turnaround time:} 2 weeks  
\textbf{CPT Codes:} 81228 x1

\section*{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

This 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 (\textit{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.

The \textit{FAH} enzyme is encoded by the \textit{FAH} gene located at 15q23, and mutations to this gene are responsible for tyrosinemia by leading to reduced or absent \textit{FAH} enzyme activity. The four common \textit{FAH} mutations (\textit{IVS12+5 G&A}, \textit{IVS6-1 G&T}, \textit{IVS7-6 T&G}, and \textit{P261L}) account for approximately 60\% of mutations in tyrosinemia type I in the general US population. The \textit{P261L} mutation accounts for nearly 100\% of mutations responsible for tyrosinemia type I in the Ashkenazi Jewish population [3]. \textit{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 \textit{FAH} gene.

\section*{Genes}

\textit{FAH}

\section*{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.

\section*{Methodology}

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.

Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient’s phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

\section*{Detection}

Detection is limited to duplications and deletions. The CGH array will not detect point or intronic mutations.

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

\section*{Specimen Requirements}

Submit only 1 of the following specimen types
* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

### Special Instructions

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

### Related Tests

- **Amino Acid Analysis - Plasma (AA)** and **Organic Acids - Urine (OA)** including succinylacetone and tyrosine metabolites.
- Sequence analysis of the **FAH** gene is available and is required before deletion/duplication analysis.
- 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.