**TAT Gene Analysis in Tyrosinemia Type II**

**Clinical Features:**
Tyrosinemia type II, also known as oculocutaneous tyrosinemia or Richner-Hanhart syndrome, is an inborn error of the tyrosine catabolic pathway characterized by hypertyrosinemia, keratitis, palmoplantar keratosis and variable intellectual disability. The skin is affected in approximately 80% of reported cases, the eye in approximately 75% and mental retardation is present in over 60% of reported cases. Symptoms may be confined exclusively to the skin or to the eyes. Eye manifestations usually occur before the skin lesions develop and include photophobia, redness and pain. Skin findings usually begin after one year of life but may manifest in individuals as young as one month. These consist of painful, progressive, non-pruritic and hyperkeratotic plaques on the soles and palms, often associated with hyperhidrosis. Neurodevelopmental disability is variable, ranging from severe retardation to a mild decrease in intelligence; there appears to be no relationship between age at diagnosis and degree of intellectual disability. Lowering plasma tyrosine levels by restricting protein intake leads to resolution of eye and skin symptoms.

**Genetics:**
Tyrosinemia type II is caused by pathogenic variants in the *TAT* gene that encodes liver tyrosine aminotransferase (TAT) that catalyzes the conversion of tyrosine to p-hydroxyphenylpyruvate. Deficient TAT enzyme activity results in tyrosinemia, tyrosinuria and increased levels of urinary tyrosine metabolites: p-hydroxyphenylacetate, p-hydroxyphenylpyruvate, p-hydroxyphenyllactate, and N-acetyl tyrosine. The *TAT* gene is located on chromosome 16q22.2 and has 12 exons.

**Inheritance Pattern:**
Autosomal recessive

**Test Methods:**
Variant analysis of the *TAT* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *TAT* 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. Variants found in the first person of a family to be tested are confirmed by repeat analysis or another appropriate method.
Test Sensitivity:
Full sequence analysis of the TAT gene in 14 patients with tyrosinemia type II identified variants on 27/28 (96%) alleles.\(^3\) The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:
TAT variants include missense, nonsense, splicing, small deletions and insertions. Most affected patients have been from consanguineous families and have been homozygous for a single variant.\(^1,2\) Most variants are private, although pathogenic founder variants have been reported.\(^1,2,3\) Genotype-phenotype correlations have not been established as there is considerable phenotypic variability even among individuals sharing the same variant.\(^1,3\)

References: