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.[1] Symptoms may be confined exclusively to the skin or to the eyes.[1] [1] Eye manifestations usually occur before the skin lesions develop and include photophobia, redness and pain.[1] 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.[1] Lowering plasma tyrosine levels by restricting protein intake leads to resolution of eye and skin symptoms.[2]

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:

1. Charfeddine et al., (2006) Mol Genet Metab 88:184-191.
2. Maydan et al., (2006) J Inherit Metab Dis 29:620-626.
3. Peña-Quintana et al. (2017) Clin. Genet. 92 (3):306-317 (PMID: 28255985)