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

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the *TAT* gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

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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)