OTC Gene Analysis in Ornithine Transcarbamylase (OTC) Deficiency

Clinical Features:
Ornithine Transcarbamylase (OTC) deficiency is the most common disorder of the urea cycle. This disorder is X-linked and males usually present in the neonatal period with massively elevated ammonia levels and hyperammonemic coma, encephalopathy, respiratory alkalosis, and high mortality. However, the clinical features of OTC deficiency are variable and individuals may present at any age with hyperammonemia as a result of environmental stressors. Approximately 20% of females who are heterozygous for variants in the *OTC* gene are clinically symptomatic with disease severity similar to males with partial deficiency.[1,2] Heterozygous females and partially deficient males may present with late onset of symptoms, even into adulthood, with recurrent vomiting, history of protein avoidance, Reye-like syndrome, major neurologic impairment, neurobehavioral changes or seizures associated with hyperammonemia.

Genetics:
OTC deficiency is caused by pathogenic variants in the *OTC* gene that encodes the enzyme ornithine transcarbamylase, a homotrimeric mitochondrial matrix enzyme catalyzing the synthesis of citrulline from carbamyl phosphate and ornithine in the urea cycle. Enzyme deficiency leads to elevated ammonia with subsequently elevated plasma glutamine, alanine and asparagine. Plasma citrulline and arginine levels are low and urinary orotic acid is elevated. The severity of the disease is related to the degree of enzyme deficiency measured from a liver biopsy specimen. Newborn screening for OTC deficiency is not currently available. The *OTC* gene is located on chromosome Xp21.1 and has 10 exons. OTC deficiency is the most common defect of the urea cycle with an estimated incidence of 1 in 14,000.[1]

Inheritance Pattern:
X-linked, 20% of heterozygous females are symptomatic

Test Methods:
Variant analysis of the *OTC* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of exons 1-10, and corresponding intron/exon boundaries. In females, where sequencing cannot detect deletions of entire exons, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is included to evaluate for a deletion or 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 using sequencing, restriction fragment analysis, or another appropriate method.

Test Sensitivity:

Variants are found in about 80% of patients with enzymatically confirmed OTC deficiency. The remaining patients may have variants in either the regulatory regions or deep within the introns of the *OTC* gene that would not be identified by this analysis.[5,6] Large deletions, that would not be detectable by sequence analysis in females, have been found in 8-15.7% of patients.[4,7] Gene copy number analysis by ExonArrayDx enables detection of both complete and partial *OTC* gene deletions. The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

Variant Spectrum:

OTC variants occur throughout the gene and include missense, nonsense, splice-site, regulatory, small insertions/deletions, and large duplications/deletions.[8] Approximately 13% of variants involve consensus splice-sites or last nucleotide of exons and almost all of these variants are associated with the neonatal phenotype.[2] Large deletions have been found in 8-15.7% of patients.[4,7] There are over 500 *OTC* variants described, the majority of which are private and occur de novo in the sperm.[1] Gonadal mosaicism, while rare, has been reported.[3] Genotype-phenotype correlations have been identified; however, phenotypic heterogeneity exists even within members of the same family.[1,2]

References:

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