

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 can 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, neurological signs, unexplained hepatic dysfunction, or other features of the disorder.^{7,8}

Approximately 20% of females with pathogenic *OTC* variants are clinically symptomatic with disease severity similar to males with partial deficiency.^{1,2} This can be due to skewed X-chromosome inactivation in females, the severity of the specific mutation, and/or differences in environmental stressors. Heterozygous females and partially deficient males may present with later onset of symptoms even into adulthood, often precipitated by stress, with symptoms that include recurrent vomiting, history of protein avoidance, Reye-like syndrome, major neurologic impairment, migraine headaches, neurobehavioral changes, or seizures usually associated with hyperammonemia.⁸

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 *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, approximately 20% of heterozygous females are symptomatic with partial OTC deficiency, but females and males may have mild symptoms and may not be diagnosed until adolescence or in adulthood.

TEST METHODS

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the *OTC* 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.

VARIANT SPECTRUM

OTC variants occur throughout the gene and include missense, nonsense, splice-site, regulatory, small insertions/deletions, and large duplications/deletions.⁶ 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.^{4,5} There are over 500 *OTC* variants described, the majority of which are private.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}

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