

Ornithine Transcarbamylase Deficiency (OTC) Sequencing and Deletion/Duplication

DNA TESTING TO DIAGNOSE OTC DEFICIENCY

Disease Overview

- Ornithine transcarbamylase (OTC) deficiency is the most common of the urea-cycle disorders. The urea cycle is the body's primary system for removing waste nitrogen produced from the metabolism of protein and other nitrogen-containing molecules. Defects in the urea cycle can lead to life-threatening accumulations of ammonia.
- Waste nitrogen is converted to ammonia and then transferred to the liver for processing via the urea cycle. OTC is one of the proximal enzymes in the urea cycle and converts carbamylphosphate and ornithine to citrulline. The more distal enzymes in the urea cycle use citrulline as a substrate to produce urea, which is then excreted.
- Classic OTC deficiency is characterized by hyperammonemia, cyclical vomiting, seizures, lethargy, coma, and neonatal death if not treated.
- Males with OTC deficiency are typically severely affected, with onset of symptoms occurring in the first few days of life. Some males with OTC deficiency may show only mild symptoms with adult onset of disease.
- Females can have variable clinical presentations ranging from completely asymptomatic to classic, life-threatening neonatal disease. Approximately 15 percent of female carriers of OTC deficiency develop hyperammonemia at some point in their lives due to skewed X-inactivation.
- A diagnosis of OTC deficiency is suspected in symptomatic individuals with elevated plasma ammonia levels, low plasma citrulline and arginine concentration, and elevated urine orotic acid levels.
- Treatment of OTC deficiency includes reducing plasma ammonia concentration with dialysis, administering nitrogen scavengers to allow excretion of excess nitrogen via alternative pathways, reducing protein in the diet, providing calories through carbohydrates and fat to reduce catabolism, and reducing the risk of neurological damage during stabilization with administration of IV fluids. In severe cases, liver transplantation may be considered.

Epidemiology

Incidence is approximately one in 14,000 births in the United States.

Genetics

- X-linked inheritance.
- *OTC* is the only gene associated with OTC deficiency.
- De novo mutation rate is unknown but may vary by gender. Females with a mutation may be more likely than males to have a sporadic mutation.

Indications for Ordering

- Diagnostic testing for individuals with clinical and/or biochemical evidence of OTC deficiency.
- Carrier testing for female relatives of an individual with OTC deficiency.

Contraindication for Ordering

Prenatal testing.

Additional Ordering Notes

If there is a family history of OTC deficiency and the specific familial mutation has already been identified, testing can be performed on at-risk family members by contacting ARUP's genetic counselor and requesting targeted sequencing for the familial mutation.

Interpretation

- One copy of a pathogenic *OTC* mutation in males predicts OTC deficiency.
- Females with one copy of a pathogenic mutation have variable presentations that range from asymptomatic to classic, life-threatening disease.
- When no pathogenic mutations are detected by sequencing and deletion/duplication analysis, the possibility that the individual is a carrier of or affected with OTC deficiency is reduced. Medical management should rely on clinical findings.
- *OTC* mutations of unknown clinical significance may be detected by this assay.

Methodology and Limitations

- PCR followed by bidirectional sequencing of the entire coding region and intron-exon boundaries of the *OTC* gene.
- Multiplex ligation-dependent probe amplification (MLPA) to identify large exonic deletions/duplications in the *OTC* gene.
- Combined clinical sensitivity for sequencing and deletion/duplication analysis up to 90 percent. Approximately 80 percent of detectable mutations are sequence variants, while up to 10 percent of causative mutations are large deletions.
- Analytical sensitivity and specificity are 99 percent.
- Rare diagnostic errors may occur due to primer- or probe-site mutations.
- Regulatory region mutations and deep intronic mutations will not be detected. Breakpoints of large deletions/duplications will not be determined.

- Genes associated with urea cycle disorders, other than *OTC*, will not be evaluated.

Related Tests

- Amino Acids Quantitative, Plasma (0080710)
- Orotic Acid, Urine (0092458)

References

1. GeneTests: Urea Cycle Disorders Overview. www.genetests.org (accessed on November 29, 2010).

2. Summar ML. Urea cycle disorders. In *Pediatric endocrinology and inborn errors of metabolism*. K Sarafoglou, GF Hoffman, KS Roth, eds. 2009; New York: McGraw-Hill.
3. Brusilow SW and Horwich AL. Urea Cycle Enzymes. in *The metabolic and molecular bases of inherited disease*, 8th ed. CR Scriver, et al, eds. 2001; New York: McGraw-Hill: 1916–25.
4. Tuchman M, et al. Mutations and polymorphisms in the human ornithine transcarbamylase gene. *Hum Mutat* 2002 19(2):93–107.

Test Information

2004896	Ornithine Transcarbamylase Deficiency (OTC) Sequencing and Deletion/Duplication
2004901	Ornithine Transcarbamylase Deficiency (OTC) Sequencing
2004892	Ornithine Transcarbamylase Deficiency (OTC) Deletion/Duplication

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.