

Ornithine Transcarbamylase Deficiency

Ornithine transcarbamylase (OTC) deficiency is a urea cycle disorder caused by variants in the *OTC* gene that encodes for the OTC enzyme. The urea cycle is a sequence of reactions occurring in the liver that processes excess nitrogen produced by protein metabolism. When the OTC enzyme is damaged or missing, nitrogen accumulates in the bloodstream in the form of ammonia, which negatively affects the nervous system, causing neurological symptoms and liver damage. Symptoms of OTC can manifest as part of a severe neonatal-onset phenotype in newborn males (rarely in females) with OTC deficiency; however, symptoms can also occur in the postnatal, childhood, adolescent, and adult periods in affected males and carrier females who have partial OTC deficiency.

Infants with severe neonatal-onset OTC deficiency often present with lethargy, hypotonia, unwillingness to eat, poor breath and body temperature control, hyperventilation, encephalopathy, seizures, coma, and death. For infants with severe OTC deficiency who survive the neonatal period, complications may include developmental delay, intellectual disability, and progressive liver damage; they typically require a liver transplant by six months of age. Postneonatal-onset OTC deficiency occurs in both males and females. Symptoms may include encephalopathic or psychotic episodes (eg, delirium, erratic behavior, and reduced consciousness), migraine headaches, recurrent vomiting, Reye-like syndrome, aversion to protein-rich foods, and seizures due to hyperammonemic crises. Individuals with partial OTC deficiency may also have developmental delay, learning and intellectual disability, attention deficit hyperactivity disorder (ADHD), and executive function deficits.

Disease Overview

Incidence

1/14,000-77,000 live births¹

Clinical Presentation

OTC Deficiency

- Neonatal onset typically affects males; rare in females
- Hyperammonemia
- Encephalopathy
- Respiratory alkalosis
- Seizures
- Lethargy
- Vomiting and feeding difficulties
- Coma/death

Partial OTC Deficiency

- Hemizygous males with mild variants and heterozygous females may develop symptoms in infancy, childhood, adolescence, or adulthood
 - Heterozygous females with a pathogenic variant have variable presentations that range from asymptomatic to classic, life-threatening disease due to skewed X-chromosome inactivation
- Recurrent vomiting with clinical picture resembling Reye-like syndrome
- Neurobehavioral changes or seizures associated with hyperammonemia

Tests to Consider

Molecular Test

[Ornithine Transcarbamylase Deficiency \(OTC\) Sequencing and Deletion/Duplication 2004896](#)

Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Preferred genetic test to confirm OTC deficiency, following suggestive clinical and laboratory findings

Biochemical Tests

Initial laboratory screening tests for suspected urea cycle disorders

[Amino Acids Quantitative by LC-MS/MS, Plasma 2009389](#)

Method: Quantitative Liquid Chromatography/Tandem Mass Spectrometry

[Orotic Acid, Urine 3000704](#)

Method: Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

[Ammonia, Plasma 0020043](#)

Method: Enzymatic

Related Tests

[Familial Mutation, Targeted Sequencing 2001961](#)

Method: Polymerase Chain Reaction/Sequencing

Useful for confirming a diagnosis or assessing carrier status when a pathogenic sequence variant has been identified in a family member

[Deletion/Duplication Analysis by MLPA 3003144](#)

Method: Multiplex Ligation-dependent Probe Amplification

Useful for confirming a diagnosis or assessing carrier status when a deletion or duplication has been identified in a family member

Genetics

Gene

OTC

Inheritance

X-linked

Penetrance

Dependent on sex of individual and gene variant

- Hemizygous males: 100%

Variants

Most are specific to particular families; rate of de novo variant occurrence is 26% for males and 67% for females²

Test Interpretation

Biochemical Testing

- Plasma ammonia: elevated
- Plasma glutamine and alanine: elevated
- Plasma citrulline and arginine: low
- Urine orotic acid excretion: elevated

Molecular Testing: *OTC*

Sensitivity/Specificity

- Clinical sensitivity: ~90%
 - Sequencing: 80%
 - Deletion/duplication analysis: 10%^{3,4}
- Analytical sensitivity/specificity: 99%

Results

- Positive
 - Pathogenic variant detected in males
 - Confirms OTC deficiency
 - Pathogenic variant detected in females
 - At least a carrier for OTC deficiency
- Negative
 - No variant detected
 - OTC deficiency is less likely but not excluded
- Inconclusive: variants of unknown clinical significance may be identified

Limitations

- Not determined or evaluated:
 - Regulatory region and deep intronic variants
 - Breakpoints of large deletions/duplications
 - Variants in genes other than *OTC*
- Diagnostic errors can occur due to rare sequence variations

References

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3. Shchelochkov OA, Li FY, Geraghty MT, et al. [High-frequency detection of deletions and variable rearrangements at the ornithine transcarbamylase \(OTC\) locus by oligonucleotide array CGH](#). Mol Genet Metab. 2009;96(3):97-105. PubMed
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