Ornithine Transcarbamylase Deficiency

Indications for Ordering

- Confirm diagnosis of ornithine transcarbamylase (OTC) deficiency following clinical and laboratory findings suggestive for OTC deficiency
- Determine carrier status if familial variant has previously been identified
- Early identification of disorder may allow for life-saving therapy and reduce risk of permanent neurological damage

Test Description

- Polymerase chain reaction (PCR) amplification followed by sequencing for all coding regions and intron/exon boundaries of OTC gene
- Multiplex ligation-dependent probe amplification (MLPA) to detect large OTC coding region deletions/duplications

Tests to Consider

Molecular tests
Ornithine Transcarbamylase Deficiency (OTC) Sequencing and Deletion/Duplication 2004896
- Preferred genetic test to confirm OTC deficiency, following suggestive clinical and laboratory findings
Ornithine Transcarbamylase Deficiency (OTC) Sequencing 2004901
- Acceptable initial 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
- Orotic Acid, Urine 3000704
- Ammonia, Plasma 0020043

Disease Overview

Incidence – 1/14,000-77,000 live births (Lichter-Konecki, 2016)

Clinical presentation
OTC deficiency
- Males are typically affected with neonatal onset of symptoms
- Hyperammonemia
- Encephalopathy
- Respiratory alkalosis
- Seizures
- Lethargy
- Vomiting/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

Genetics

Gene – OTC
Inheritance – X-linked
Penetration – dependent on sex of individual and gene variant
- Hemizygous males – 100%
De novo variants – unknown
Variants – most are specific to particular families ("private variants")

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%
  o Sequencing – 80%
  o Deletion/duplication analysis – 10% (Shchelochkov, 2009; Yamaguchi, 2006)
• Analytical sensitivity/specificity – 99%

Results

• Positive
  o Pathogenic variant detected in males
    ▪ Confirms OTC deficiency
  o Pathogenic variant detected in females
    ▪ At least a carrier for OTC deficiency
• Negative – no variant detected
  o OTC deficiency is less likely but not excluded
• Inconclusive – variants of unknown clinical significance may be identified

Limitations

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

References

• Shchelochkov OA, Li FY, et al. High-frequency detection of deletions and variable rearrangements at the ornithine transcarbamylase (OTC) locus by oligonucleotide array CGH. Mol Genet Metab. 2009;96:97-105
• Yamaguchi S, Brailey LL, et al. Mutations and polymorphisms in the human ornithine transcarbamylase (OTC) gene. Hum Mutat. 2006;626-663