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 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 and Orotidine, Urine 0092458
- 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

Penetrance – 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%
  - Sequencing – 80%
  - Deletion/duplication analysis – 10% (Shchelochkov, 2009; Yamaguchi, 2006)
- 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

- Lichter-Konecki U, Caldovic L, et al. Ornithine Transcarbamylase Deficiency. 2013 Aug 29 [Updated 2016 Apr 14]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016 (www.ncbi.nlm.nih.gov/books/NBK154378/)
- 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