Ornithine Transcarbamylase Deficiency: OTC Gene Sequencing

Test Code: HU  
Turnaround time: 4 weeks  
CPT Codes: 81405 x1

**Condition Description**

Ornithine Transcarbamylase (OTC) deficiency is the most common inherited urea cycle disorder, and is transmitted in an X-linked pattern [1]. The clinical phenotype in affected males as well as heterozygous females shows a spectrum of severity ranging from neonatal hyperammonemic coma to asymptomatic adults. Clinical presentation is complex because male hemizygotes usually present in infancy, while female heterozygotes may be asymptomatic or develop usually milder disease due to skewed X-inactivation[2].

OTC deficiency results in the accumulation of ammonia and other precursor metabolites during the first few days of life. Because no effective secondary clearance system for ammonia exists, disruption of the urea cycle results in a rapid development of catabolism which may cause cerebral edema, lethargy, anorexia, hyper-/hypoventilation, hypothermia, seizures, neurologic posturing, coma and death, if untreated. Pharmacologic management with sodium benzoate/phenylacetate (Buphenyl) and protein restriction in diet may prevent or alleviate primary complications [3].

OTC deficiency involves an impairment of the reaction that leads to condensation of carbamyl phosphate and ornithine to form citrulline [1]. This impairment leads to reduced ammonia incorporation, which causes symptomatic hyperammonemia and increased urinary excretion of orotic acid. The OTC enzyme is encoded by the OTC gene (Xp21) which is normally expressed in the liver. Heterogeneous mutations have been reported in the OTC gene in individuals with OTC deficiency [4-5]. There is also some evidence for genotype-phenotype correlation [6]. Gene sequence analysis is available to test for mutations in the OTC gene (HU). For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (ET).

**References:**

**Genes**

**OTC**

**Indications**

This test is indicated for:
- Confirmation of a clinical/biochemical diagnosis of OTC deficiency
- Carrier testing in adults with a family history of OTC deficiency

**Methodology**

PCR amplification of 10 exons contained in the OTC gene is performed on patient genomic DNA. Direct sequencing of amplification products is performed in both the forward and reverse directions using automated fluorescence dideoxy sequencing methods. Patient gene sequences are compared to a normal reference sequence. Sequence variations are then classified as mutations, benign variants unrelated to disease, or variations of unknown clinical significance. Variants of unknown clinical significance may require further studies of the patient and/or family members. This assay does not interrogate the promoter region, deep intronic regions, or other regulatory elements. Large deletions are not detected by this analysis.

**Detection**

The majority of patients with clinical and biochemical diagnosis of OTC deficiency will have an abnormal DNA test. Clinical Sensitivity: 26/26 mutations identified in 26 patients [4]; 23/23 mutations identified in 23 patients [5].

Analytical Sensitivity: ~99%

Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

**Specimen Requirements**

Submit only 1 of the following specimen types
Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition.

**Related Tests**

- Plasma Amino Acid (AA) Analysis, Urine Organic Acids (OA) including urine orotic acid (OT), and plasma ammonia levels are used in the diagnosis of a patient with OTC deficiency.
- Custom Diagnostic Mutation Analysis (KM) is available to family members if mutations are identified by sequencing.
- Deletion/Duplication Assay is available separately for individuals where mutations are not identified by sequence analysis. Refer to the test requisition or contact the laboratory for more information.
- Prenatal testing is available for known familial mutations only. Please call the Laboratory Genetic Counselor before collecting a fetal sample.