Ornithine Transcarbamylase Deficiency: OTC Gene Deletion/Duplication

**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-/hyperventilation, 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).

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**

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region. Please note that a "backbone" of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

Detection is limited to duplications and deletions. Array CGH will not detect point mutations or intronic mutations. 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) 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 EGL Genetics, 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.
- Prenatal testing is available for known familial mutations only. Please call the Laboratory Genetic Counselor before collecting a fetal sample.