

Hyperammonemia via *OTC* Gene Sequencing (Test #551)

Brief Description of Clinical Features: Urea cycle defects are characterized by (1) hyperammonemia, (2) encephalopathy, and (3) respiratory alkalosis. Five clinical disorders have been described involving defective urea cycle enzymes: ornithine transcarbamylase deficiency (OMIM 311250), carbamoyl phosphate synthetase deficiency (OMIM 237300), argininosuccinate synthetase deficiency (OMIM 215700), argininosuccinate lyase deficiency (OMIM 207900), and arginase deficiency (OMIM 207800). Ornithine transcarbamylase (*OTC*) functions in the liver to generate citrulline from ornithine and carbamoyl phosphate, thus recycling free ammonia. Deficiency of this enzyme leads to elevated ammonia and subsequent ammonia intoxication. Clinical symptoms of hyperammonemia due to *OTC* deficiency (OMIM 311250) can appear in the neonatal period in patients with significant enzyme deficiency, or as late as adulthood in individuals with partial enzyme deficiency (Finkelstein et al. *J Pediat* 117: 897-902, 1990; Drogari et al. *Arch Dis Child* 63:1363-1367, 1988). Untreated infants develop cerebral edema leading to lethargy, diminished appetite, seizures and coma. Patients presenting after the neonatal period may demonstrate irritability, vomiting, lethargy, and coma especially after a high protein meal, or while fasting or during an infection (Oizumi et al. *Clin Genet* 25:538-542, 1984).

Genetics: Hyperammonemia due to *OTC* deficiency is an X linked recessive disorder. Although most patients are males, carrier females can experience serious symptoms early in life (Rowe et al. *New Eng J Med* 314:541-547, 1986) or in adulthood (Gilchrist and Coleman *Ann Intern Med.* 106:556-558, 1987). Approximately 15% of carrier females develop hyperammonemia (Brusilow *Prog Liver Dis* 13:293-309, 1995). Over 300 *OTC* mutations have been reported (Yamaguchi et al. *Hum Mut* 27:626-632, 2006). The majority are missense, however many nonsense and splice site mutations are known as well. Tuchman (*Hum Mut* 2:174-178, 1993) reported that approximately 10 to 15% of all mutations associated with *OTC* deficiency were large deletions involving all or part of the *OTC* gene. By array CGH, Shchelochkov et al. (*Mol Genet and Metab* 96:97-105, 2009) found deletions in half of their patients with normal *OTC* gene sequencing results.

Description of This Particular Test: Ornithine transcarbamylase is coded by exons 1-10 of the *OTC* gene on chromosome Xp11. Testing is accomplished by amplifying each coding exon and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

Reference Sequences: Genomic: NC_000023.9 mRNA: NM_000531.4 Protein: NP_000522.3

Indication for Testing: A plasma ammonia concentration of ≥ 150 $\mu\text{mol/L}$, associated with a normal anion gap and a normal serum glucose concentration is a strong indication for the presence of a urea cycle defect (Summar *GeneReviews.org* 2005). Plasma citrulline levels can differentiate between defects in proximal urea cycle enzymes (low citrulline; *OTC* and carbamoyl phosphate synthetase) from distal enzymes (high citrulline; argininosuccinate synthetase, argininosuccinate lyase, and arginase).

Sensitivity of test: Yamaguchi et al. (*Hum Mut* 27:626-632, 2006) reported that mutations could be found in approximately 80% of patients. In a study of 341 *OTC* mutations, the same authors found that 43% were associated with neonatal onset, 20% with later onset in males and 35% with manifesting females. Array CGH should be considered in all patients with normal sequencing results to rule out a deletion.

Turn Around Time: Maximum of 40 days, although many tests are completed in 2-3 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of *OTC* Exons 1-10 \$ 540

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x9	83898	\$ 150	Sequencing x9	83904	\$ 220
Separation	83894	\$ 40	Interpretation/Report	83912	\$ 60

Accreditation Info. CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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