

## Hyperammonemia via NAGS Gene Sequencing (Test #555)

**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 transcarbamoylase deficiency (OMIM 311250), carbamoyl phosphate synthetase deficiency (OMIM 237300), argininosuccinate synthetase deficiency (OMIM 215700), argininosuccinate lyase deficiency (OMIM 207900), and arginase deficiency (OMIM 207800). A sixth cause of hyperammonemia is N-acetylglutamate synthase (NAGS) deficiency (OMIM 237310; Bachmann et al. *N Eng J Med* 304:543, 1981). N-acetylglutamate is an essential activating cofactor for Carbamoyl Phosphate Synthetase (CPS1) and, therefore, clinical signs of CPS1 and NAGS deficiencies are indistinguishable. Like CPS1 deficiency, two clinical presentations of NAGS deficiency are recognized: an acute neonatal hyperammonemia form and a delayed onset form (Haberle et al. *Hum Mut* 21:593-597, 2003). NAGS deficiency also presents with irritability and hyperammonemia leading to coma and death if untreated. Successful treatment with N-carbamylglutamate has been reported (Bachmann et al. 1981).

**Genetics:** Hyperammonemia due to N-Acetylglutamate Synthase deficiency is an autosomal recessive disorder. NAGS gene mutations are distributed throughout the entire coding region except for the mitochondrial targeting signal encoded by exon 1 (Caldovic et al. *Hum Mut* 28:754-759, 2007). The majority of mutations are missense, however nonsense and splice site mutations are known as well.

**Description of This Particular Test:** N-Acetylglutamate Synthase is coded by exons 1-7 of the NAGS gene on chromosome 17q21. 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\_000017.9 mRNA and Protein: CCDS11473.1

**Indication for Testing:** A plasma ammonia concentration of 150 µmol/L or higher, 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*). Plasma citrulline levels can differentiate between defects in proximal urea cycle enzymes (low citrulline; ornithine transcarbamoylase, carbamoyl phosphate synthetase, N-acetylglutamate synthase) from distal enzymes (high citrulline; argininosuccinate synthetase, argininosuccinate lyase, and arginase).

**Sensitivity of test:** Deficiency of N-Acetylglutamate Synthase is a rare cause of hyperammonemia. Approximately 20 causative mutations have been reported worldwide (Caldovic et al. 2007). Mutations in the NAGS gene should be considered in patients with a high index of suspicion who have normal CPS1 enzyme activity and/or a normal CPS1 gene sequencing result.

**Turn Around Time:** Maximum of 40 days.

**Specimen Requirements:** See page 4 of the Requisition Form.

**Price:** Sequencing of NAGS Exons 1-7 \$430

**CPT Codes:**

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x6	83898	\$ 100	Sequencing x6	83904	\$ 150
Separation	83894	\$ 40	Interpretation/Report	83912	\$ 70

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

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