

Argininemia via *ARG1* Gene Sequencing (Test #552)

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 (Argininemia; OMIM 207800). Untreated patients with arginase deficiency develop spastic paraplegia, epileptic seizures, and severe mental retardation (Cederbaum et al. *Pediat* 90:569-573, 1977). Hyperammonemia due to arginase deficiency is usually less severe than that arising from defects in the proximal urea cycle enzymes. Early growth and development are generally normal until ages 1 to 3 years when symptoms begin to be evident (Cederbaum and Crombez, *GeneReviews*, 2007). An arginine restricted diet along with sodium benzoate to scavenge ammonia has been found to be effective treatment (Bernar et al. *Pediat* 108:432-435, 1986).

Genetics: Argininemia is an autosomal recessive disorder. *ARG1* mutations are the only known cause of argininemia. *ARG1* encodes arginase, a liver-specific enzyme that generates urea and ornithine from arginine in the last step of the urea cycle. The *ARG1* gene product is also active in red blood cells. Missense and nonsense mutations are the predominant types of disease-causing mutations in the *ARG1* gene.

Description of This Particular Test: Arginase is coded by exons 1-8 of the *ARG1* gene on chromosome 6q23. 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_000006.10 **mRNA and Protein:** CCDS 5145.1

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*, 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). Individuals with elevated serum arginine levels or reduced arginase activity in red cells are candidates for *ARG1* testing.

Sensitivity of test: In patients previously diagnosed with elevated serum arginine and decreased enzyme activity, test sensitivity should be very high. For example, in eleven argininemia patients Uchino et al. (*Hum Genet* 96:255-260, 1995) detected 21 of 22 possible mutant alleles.

Turn Around Time: Maximum of 40 days.

Specimen Requirements: See page 4 of Requisition Form.

Price: *ARG1* Gene Sequencing \$ 490

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x8	83898	\$ 130	Sequencing x8	83904	\$ 190
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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