

## Citrullinemia, Type I via *ASS1* Gene Sequencing (Test #553)

**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 (Citrullinemia Type I; OMIM 215700), argininosuccinate lyase deficiency (OMIM 207900), and arginase deficiency (OMIM 207800). Type I Citrullinemia presents in the neonate following protein intake with massively elevated serum citrulline levels resulting in hyperammonemia. Patients exhibit lethargy, refusal to feed, vomiting, and tachypnea or stroke (Häberle et al. *Mol Genet Metab* 80:302-306, 2003). Untreated, argininosuccinate synthetase deficiency can lead to increased intracranial pressure, increased neuromuscular tone, seizures, loss of consciousness, and death (Thoene, *GeneReviews*, 2008). A milder adult-onset form of the disease has also been described (Häberle et al. *Mol Genet Metab* 80:302-306, 2003). Clinical signs of the milder form I include recurrent lethargy, somnolence, mental retardation, and chronic or recurrent hyperammonemia. Treatment includes a protein restricted diet and sodium benzoate to scavenge ammonia (Thoene, *GeneReviews*, 2008).

**Genetics:** Type I or Classic Citrullinemia is an autosomal recessive disorder. Mutations in the *ASS1* gene cause both the severe neonatal and milder adult onset forms of Citrullinemia Type I (Häberle et al. *Mol Genet Metab* 80:302-306, 2003). The *ASS1* gene encodes argininosuccinate synthetase, a urea cycle enzyme that converts citrulline and aspartate to argininosuccinate. Missense mutations are the predominant type of disease-causing mutations in *ASS1* (Gao et al. *Hum Mut* 22:24-34, 2003). Type II Citrullinemia, a multisystem disorder, is caused by mutations in the *SLC25A13* gene and has clinically and biochemically distinct features.

**Description of This Particular Test:** Argininosuccinate synthetase is coded by exons 3-16 of the *ASS1* gene on chromosome 9q34. 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\_000009.10 mRNA and Protein: CCDS 6933.1

**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). Elevated plasma citrulline and absent argininosuccinate is indicative of absent or reduced argininosuccinate synthetase activity. In the mild form, plasma citrulline levels may be near the upper limit of normal.

**Sensitivity of test:** Test sensitivity should be very high in the newborn with clinical symptoms of ammonium intoxication and a plasma amino acid profile suggestive of argininosuccinate synthetase deficiency. Among 85 families with Type I Citrullinemia, Goa et al. (*Hum Mut* 22:24-34, 2003) found 50 different *ASS1* mutations, and *ASS1* mutations were found in all 21 mild citrullinemia patients studied by Häberle et al. (*Mol Genet Metab* 80:302-306, 2003).

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

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

**Price:** Sequencing of *ASS1* Gene Exons 3-16 \$ 740

**CPT Codes:**

Sample Ascertainment	83890 \$ 30	DNA Isolation	83891 \$ 40
Amplification x14	83898 \$ 210	Sequencing x14	83904 \$ 320
Separation	83894 \$ 60	Interpretation/Report	83912 \$ 80

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

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