

Creatine Deficiency Syndrome via *GATM* Gene Sequencing, Test #241

Brief Description of Clinical Features: Cerebral creatine deficiency syndromes (CCDSs) are inborn errors of creatine metabolism (for review, see Mercimek-Mahmutoglu and Stockler-Ipsiroglu, “Creatine Deficiency Syndromes”, GeneReviews, www.genereviews.org). L-Arginine:glycine amidinotranferase (AGAT) deficiency (OMIM #612718) is an autosomal recessive inborn error of creatine biosynthesis. AGAT enzyme normally catalyzes the first step in creatine synthesis; it transfers the amidino group from arginine to glycine, thus forming ornithine and guanidinoacetate (an immediate precursor of creatine) (Item et al. *Am J Hum Genet* 69: 1127-1133, 2001). Characteristic biochemical findings in affected individuals include low levels of guanidinoacetate in plasma and urine (Verma *Neurology* 75:186-188, 2010). *In vivo* proton magnetic resonance spectroscopy will reveal low brain creatine levels (Verma 2010). Clinical manifestations of AGAT deficiency include developmental delay, mental retardation, severe language impairment, autistic-like behavior, and failure to thrive. Myopathy in adults and hyponatremia in infancy have also been reported. Oral creatine supplementation has been associated with improvement in development as well as muscle weakness (Bianchi et al. *Ann Neurol* 47:511-513, 2000; Johnston et al. 2005 *Am Soc Hum Genet Meeting Abstract*, P. 58, Abstract #205; Edvardson et al. *Mol Genet Metab* 101:228-232, 2010; Verma 2010).

Genetics: L-Arginine:glycine amidinotransferase is encoded by exons 1-9 of the *GATM* gene (OMIM #602360) located on chromosome 15. AGAT deficiency is a rare autosomal recessive disorder, with only four different mutations having been published. All four mutations are severe and lead to premature protein termination. These four pathogenic variants include two nonsense mutations and two frameshifts (including one resulting from a splice donor variant that caused exon 3 skipping) (Johnston et al. 2005).

Description of This Particular Test: Bidirectional sequencing of all nine *GATM* coding exons plus ~50 base pairs of flanking non-coding intronic DNA on either side of each exon is performed using genomic DNA. As indicated, we will also perform sequencing of any single exon (Test #100, \$190) or pair of exons (Test #200, \$340) within the gene for family members of patients with known mutations and to confirm previous research results.

Reference Sequences: Genomic: NC_000015.9 mRNA: NM_001482.2 Protein: NP_001473.1 (CCDS 10122.1)

Indications for Test: Candidates for this test are patients with biochemical findings and/or clinical symptoms consistent with arginine:glycine amidinotranferase (AGAT) deficiency. Testing is also indicated for family members of patients who have known *GATM* mutations.

Sensitivity of Test: At least one *GATM* mutation has been identified in all individuals with enzymatically-confirmed *GATM* deficiency (Item et al. 2001; Johnston et al. 2005). Furthermore, all gene mutations reported to date are detectable using standard polymerase chain reaction and automated sequencing methodologies.

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 2 – 3 weeks.

Specimen Requirements: See page 4 of Requisition Form.

Price: Sequencing of *GATM* \$ 660

CPT Codes							
Test	83890 x1	83891 x1	83898 x9	83904 x9	83894 x1	83912 x1	Total
<i>GATM</i>	\$30	\$40	\$180	\$280	\$40	\$90	\$660

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

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