



Division of Human Genetics

## Creatine Deficiency Syndromes

Genes Tested: *SLC6A8*, *GAMT*, *GATM*

### Molecular Genetics Laboratory

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Additional information and test requisitions are available at:

[www.cincinnatichildrens.org/molecular-genetics](http://www.cincinnatichildrens.org/molecular-genetics)



*Helping you fit the pieces together*

### Shipping Instructions

Please enclose test requisition with sample. All information must be completed before sample can be processed.

Place samples in Styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday

Ship to:

Cytogenetics and Molecular Genetics Laboratories

3333 Burnet Avenue NRB 1042

Cincinnati, OH 45229

513-636-4474

The creatine deficiency syndromes are inborn errors of metabolism which interrupt the biosynthesis or transportation of creatine. Individuals with creatine deficiency syndromes classically present with intellectual disabilities and seizure disorders and may present with pyramidal/extrapyramidal neurologic findings and behavioral problems as well.

Tests which are useful in screening for creatine defects in patients with suspected creatine deficiency syndromes include:

- Proton MRS — absence or reduction of creatine signal in the brains of affected individuals
- Measurement of metabolites—guanidinoacetate (GAA), creatine and creatinine in urine, plasma or cerebrospinal fluid
- Molecular genetic testing
- Enzyme activity levels in fibroblasts (*GAMT*) and lymphoblasts (*GATM*)
- Creatine uptake study in fibroblasts (creatine transporter defects).

**Creatine deficiency syndromes are caused by mutations in three genes:**

- *SLC6A8*
- *GAMT*
- *GATM*

***SLC6A8*:** Mutations in the creatine transporter gene, *SLC6A8*, which result in blockage of the transport of creatine to the brain are the most common cause of creatine deficiency syndrome. Affected individuals may demonstrate cerebral creatine deficiency on MR spectroscopy, normal GAA in urine, and high creatine: creatinine ratio in urine. *SLC6A8* maps to Xq28 and therefore demonstrates an **X-linked** inheritance pattern. Mutations in the *SLC6A8* gene are identified in approximately 1-2% of males with intellectual disabilities and/or severe expressive speech delays, seizures and autistic behaviors. Approximately 50% of females who are heterozygous for a *SLC6A8* mutation have cognitive deficits or behavioral problems as well. Phenotype and age of onset vary widely among affected individuals. Dietary therapy is not effective in the treatment of symptoms in patients with *SLC6A8* mutations.

***GAMT*:** Mutations in the *GAMT* gene are a relatively rare cause of creatine deficiency syndrome. Affected individuals may demonstrate cerebral creatine deficiency on MR spectroscopy and high GAA in urine. Guanidinoacetate methyltransferase deficiency is inherited in an **autosomal recessive** manner and is caused by biallelic mutations in the *GAMT* gene. This gene maps to 19p13.3 and is involved in the biosynthesis of creatine. Individuals with *GAMT* deficiency typically present with severe intellectual disabilities and seizure disorders which may be resistant to drug therapy. Behavioral problems, including autistic behaviors and self-mutilation are common, and pyramidal/extrapyramidal symptoms affect about one-half of patients with *GAMT* deficiency. Dietary management of *GAMT* deficiency via manipulation of critical amino acids may improve clinical outcome.

***GATM (AGAT deficiency)*:** Affected individuals may demonstrate cerebral creatine deficiency on MR spectroscopy and low GAA in urine and plasma. L-arginine:glycine amidinotransferase (*AGAT*) deficiency is inherited as an **autosomal recessive** condition secondary to biallelic mutations in the *AGAT* deficiency (*GATM*) gene. This gene maps to 15q15.3 and is involved in the biosynthesis of creatine. Individuals with *AGAT* deficiency reported to date typically present with mild to moderate intellectual disabilities. Seizure disorders are identified in about 20%. Behavioral problems and pyramidal/extrapyramidal symptoms are not typically seen in patients with *AGAT* deficiency. Dietary management of *AGAT* deficiency via manipulation of critical amino acids may improve clinical outcome.

## INDICATIONS:

- Confirmation of diagnosis in a symptomatic individual
- Carrier/heterozygote detection in individuals with a family history of creatine deficiency syndromes
- Prenatal diagnosis of an at-risk fetus, after confirmation of mutation(s) in the parent(s) (by prior arrangement only).

## METHODOLOGY:

Testing is performed by PCR-based sequencing of the entire coding regions and intron/exon boundaries of the *SLC6A8*, *GAMT* and *GATM* (AGAT deficiency) genes. Testing may be ordered sequentially or in tandem.

## SENSITIVITY:

The sensitivity of DNA sequencing is over 99% for the detection of nucleotide base changes, small deletions, and insertions in the regions analyzed. Large deletions, insertions and genetic recombinational events are not detected by this test. Rare variants at the primer binding sites may lead to erroneous results.

## SPECIMEN:

At least 3 mLs of whole blood in lavender top (EDTA) tube for each test ordered. Label tube with patient's name, birth date, and date of collection.

## TURN-AROUND TIME:

30 days

## COST:

Please call 1-866-450-4198 for pricing or with any billing questions.

## CPT CODES:

<i>SLC6A8</i> :	81479
<i>GAMT</i> :	81479
<i>GATM</i> (AGAT deficiency):	81479
Family specific mutation analysis:	81403

## RESULTS:

Results will be reported to the referring physician or health care provider as specified on the requisition form.