

# Creatine Deficiency Syndromes

## Indications for Ordering

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Confirm diagnosis following clinical and/or biochemical evidence for creatine deficiency syndromes

## Test Description

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### Biochemical tests

Creatine disorder panels (plasma/serum and urine)

- Liquid chromatography followed by tandem mass spectrometry to measure creatine, guanidinoacetate (GAA), and ratio of creatine:creatinine

### Molecular tests

- Polymerase chain reaction amplification followed by sequencing for all coding regions and intron/exon boundaries
- Multiplex ligation-dependent probe amplification

## Tests to Consider

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### Typical testing strategy

- Creatine content in the brain (by magnetic resonance [MR] spectroscopy)
- Creatine and GAA evaluation (plasma/serum and urine)
- Creatine:creatinine ratio evaluation (urine)
- DNA studies

### Biochemical tests

[Creatine Disorders Panel, Urine 2002333](#) and [Creatine Disorders Panel, Serum or Plasma 2002328](#)

- Initial tests to diagnose or rule out creatine deficiency syndromes following clinical presentation
- Typically ordered simultaneously

### Molecular tests

[Arginine:Glycine Amidinotransferase \(GATM\) Deficiency Sequencing 2011144](#)

- Preferred molecular test following biochemical testing suggestive of arginine:glycine amidinotransferase (AGAT) deficiency

[Guanidinoacetate Methyltransferase \(GAMT\) Deficiency Sequencing 2011140](#)

- Preferred molecular test following biochemical testing suggestive of guanidinoacetate methyltransferase (GAMT) deficiency

## Disease Overview

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See table for disease information

**Incidence:** unknown

- Up to 1% of males with intellectual disability of unknown etiology may have a creatine deficiency syndrome

## Genetics

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**Genes:** See table for genes tested and gene-specific information

## Test Interpretation

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**Analytical sensitivity/specificity:** 99%

### Results

- Biochemical tests
  - Creatine disorders panel (see table)
- Molecular genetic tests
  - Variants of unknown clinical significance may be identified
  - *GATM* sequencing
    - Two pathogenic *GATM* variants on opposite chromosomes predicts AGAT deficiency
    - One pathogenic *GATM* variant indicates individual is at least a carrier for AGAT deficiency
    - If no variants are detected, AGAT deficiency less likely but not excluded

### Limitations

- Not determined or evaluated
  - Variants in genes not analyzed
  - Deep intronic and regulatory region variants
  - Breakpoints for large deletions/duplications
  - Deletions/duplications in exons, 2, 3, 5, 7, 13
- Diagnostic errors can occur due to rare sequence variations

## Reference

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Mercimek-Andrews S, Salomons GS. [Creatine deficiency syndromes](#). In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. University of Washington, Seattle; 1993-2020. (Last update: Dec 2015; Accessed: Oct 2020)

Disorder	Gene	Inh.	Incidence	Symptoms	Plasma/serum GAA and creatine	Urine creatine: creatinine ratio	% of variants detected by DNA analysis
Arginine:glycine amidinotransferase (AGAT) deficiency	<i>GATM</i>	AR	<15 cases known	<ul style="list-style-type: none"> <li>• Intellectual disability</li> <li>• Seizure disorder of variable severity</li> <li>• Developmental delay</li> <li>• Speech/language delay</li> <li>• Movement disorder</li> <li>• Behavioral disorder (autism, hyperactivity, self-injury)</li> <li>• Onset typically in early childhood</li> <li>• ~50% of female carriers of pathogenic <i>SLC6A8</i> gene variants have symptoms</li> </ul>	↓GAA ↓creatinine	Normal	May be as high as 99%
Guanidinoacetate methyltransferase (GAMT) deficiency	<i>GAMT</i>	AR	1/114,000 in Utah		↑ GAA ↓creatinine	Normal	May be as high as 99%
Creatine transporter ( <i>SLC6A8</i> ) deficiency <sup>a</sup>	<i>SLC6A8</i>	XL	>100 cases		Normal	↑ creatine: creatinine ratio	May be as high as 99%
<sup>a</sup> <i>SLC6A8</i> is not currently tested at ARUP Inh. = inheritance; AR = autosomal recessive; XL = X-linked;							