Creatine Deficiency Syndromes

Indications for Ordering

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

Test Description

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

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
Creatine Transporter Deficiency (SLC6A8) Sequencing and Deletion/Duplication 2008610
- Preferred molecular test to confirm a diagnosis of creatine transporter deficiency syndrome following clinical and biochemical presentation
Creatine Transporter Deficiency (SLC6A8) Sequencing 2008615
- Molecular test to confirm a diagnosis of creatine transporter deficiency syndrome following clinical and biochemical presentation

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

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

Genes – see table for genes tested and gene-specific information

Test Interpretation

Analytical sensitivity/specificity – 99%

Results
- Biochemical tests
  o Creatine disorders panel (see table)
- Molecular genetic tests
  o Variants of unknown clinical significance may be identified
  o SLC6A8 gene sequencing and deletion/duplication
    ▪ Presence of a pathogenic gene variant in males confirms creatine transporter deficiency
    ▪ Female carriers of a pathogenic gene variant have variable presentation that ranges from asymptomatic to classic disease
    ▪ If no variant is detected, creatine transporter deficiency is less likely but not excluded
  o 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
• **GAMT sequencing**
  - Two pathogenic *GAMT* variants on opposite chromosomes predicts GAMT deficiency
  - One pathogenic *GAMT* variant indicates individual is at least a carrier for GAMT deficiency
  - If no variants are detected, GAMT deficiency is 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

**Reference**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene</th>
<th>Inh.</th>
<th>Incidence</th>
<th>Symptoms</th>
<th>Plasma/serum GAA and creatine</th>
<th>Urine creatine: creatinine ratio</th>
<th>% of variants detected by DNA analysis</th>
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</table>
| Arginine:glycine amidinotransferase (AGAT) deficiency | GATM  | AR   | <15 cases known                  | • Intellectual disability  
• Seizure disorder of variable severity  
• Developmental delay  
• Speech/language delay  
• Movement disorder  
• Behavioral disorder (autism, hyperactivity, self-injury)  
• Onset typically in early childhood  
• ~50% of female carriers of pathogenic SLC6A8 gene variants have symptoms | ↓GAA ↓creatinine               | Normal                           | May be as high as 99%                                                   |
| Guanidinoacetate methyltransferase (GAMT) deficiency | GAMT  | AR   | 1/114,000 in Utah                | ↑ GAA ↓creatinine                                                       | Normal                        | Normal                           | May be as high as 99%                                                   |
| Creatine transporter (SLC6A8) deficiency       | SLC6A8| XL   | >100 cases                       | Normal                                                                   | ↑ creatine: creatinine ratio  | Normal                           | May be as high as 99%                                                   |

Inh. = inheritance; AR = autosomal recessive; XL = X-linked