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
  - Creatine disorders panel (see table)
- Molecular genetic tests
  - Variants of unknown clinical significance may be identified
  - *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
  - *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
- Diagnostic errors can occur due to rare sequence variations

Reference

Mercimek-Mahmutoglu S, Stöckler-Ipsiroglu S, Salomons GS. Creatine Deficiency Syndromes. 2009 Jan 15 [Updated 2011 Aug 18]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015 (www.ncbi.nlm.nih.gov/books/NBK3794/)

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	*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 ↓creatine	Normal	May be as high as 99%
Guanidinoacetate methyltransferase (GAMT) deficiency	*GAMT*	AR	1/114,000 in Utah		↑ GAA ↓creatine	Normal	May be as high as 99%
Creatine transporter (*SLC6A8)* deficiency	*SLC6A8*	XL	>100 cases		Normal	↑ creatine: creatinine ratio	May be as high as 99%

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