

Chapter 2

Creatine Deficiency Syndromes - GeneReviews - NCBI Bookshelf

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*GeneReviews at GeneTests: Medical Genetics Information Resource Available at
<http://www.genetests.org>, January 2009 (update August 2011)*

Creatine Deficiency Syndromes

Synonym: Cerebral Creatine Deficiency Syndromes. Includes: Guanidinoacetate Methyltransferase Deficiency, L-Arginine:Glycine Amidinotransferase Deficiency, SLC6A8-Related Creatine Transporter Deficiency

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Initial Posting: January 15, 2009; Last Update: August 18, 2011.

Summary

Disease characteristics. The cerebral creatine deficiency syndromes (CCDS), inborn errors of creatine metabolism, include the two creatine biosynthesis disorders, guanidinoacetate methyltransferase (GAMT) deficiency and L-arginine:glycine amidinotransferase (AGAT or GATM) deficiency, and the creatine transporter (SLC6A8) deficiency. Intellectual disability and seizures are common to all three CCDS. The majority of individuals with GAMT deficiency have a behavior disorder that can include autistic behaviors and self-mutilation; a significant proportion have pyramidal/extrapyraxidal findings. Onset is between ages three months and three years. Only seven individuals with AGAT deficiency have been reported. The phenotype of SLC6A8 deficiency in affected males ranges from mild intellectual disability and speech delay to severe intellectual disability, seizures, and behavior disorder; age at diagnosis ranges from two to 66 years. Females heterozygous for SLC6A8 deficiency may have learning and behavior problems.

Diagnosis/testing. Cerebral creatine deficiency in cranial MR spectroscopy (MRS) is the characteristic hallmark of all CCDS. Diagnosis of CCDS relies on: measurement of guanidinoacetate (GAA), creatine, and creatinine in urine and plasma; and molecular genetic testing of the three genes involved, *GAMT*, *GATM*, or *SLC6A8*. If molecular genetic test results are inconclusive, GAMT enzyme activity (in cultured fibroblast or lymphoblasts), GATM enzyme activity (in lymphoblasts), or creatine uptake in cultured fibroblasts can be assessed.

Management. *Treatment of manifestations:* GAMT deficiency and AGAT deficiency are treated with oral creatine monohydrate to increase cerebral creatine levels. Treatment of GAMT deficiency may also require supplementation of ornithine and dietary restriction of arginine. In males with SLC6A8 deficiency creatine supplementation alone does not improve clinical outcome and does not result in increased cerebral creatine levels; likewise, high-dose L-arginine and L-glycine supplementation did not improve clinical or biochemical outcome. One female with intractable epilepsy responded to high-dose L-arginine and L-glycine supplementation with cessation of seizures.

Prevention of primary manifestations: Whether early treatment prevents disease manifestations is unknown; however, newborn sibs of individuals with AGAT or GAMT deficiency seem to benefit from early treatment.

Surveillance: In those treated with creatine monohydrate, routine measurement of renal function to detect possible creatine-associated nephropathy is warranted.

Testing of relatives at risk: Early diagnosis of neonates at risk for GAMT deficiency, AGAT deficiency, and SLC6A8 deficiency by biochemical or molecular genetic testing allows for early diagnosis and treatment of the defects in creatine metabolism.

Genetic counseling. GAMT deficiency and AGAT deficiency are inherited in an autosomal recessive manner. At conception, each sib of an individual with GAMT deficiency or AGAT deficiency has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. SLC6A8 deficiency is inherited in an X-linked manner. Mothers who are carriers have a 50% chance of transmitting the mutation in each pregnancy: sons who inherit the mutation will be affected; daughters who inherit the mutation will be carriers and may have learning and behavioral problems. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible for all three defects in creatine metabolism if the disease-causing mutation(s) in the family are known.

Diagnosis

Clinical Diagnosis

The cerebral creatine deficiency syndromes (CCDS) are inborn errors of creatine metabolism that include [Stöckler-Ipsiroglu & Salomons 2006]:

- **Two creatine biosynthesis defects**
 - Guanidinoacetate methyltransferase (GAMT) deficiency
 - L-Arginine:glycine amidinotransferase (AGAT or GATM) deficiency
- **One creatine transporter defect.** Creatine transporter (SLC6A8) deficiency

A CCDS is suspected in a young child with global developmental delay and an older child with intellectual disability, epilepsy, pyramidal / extrapyramidal neurologic findings, and behavior problems (Table 1).

Table 1. Clinical Features of GAMT, AGAT, and SLC6A8 Deficiency

Deficiency	Number of Individuals	Intellectual Disability	Epilepsy		Pyramidal / Extrapyramidal Findings	Behavioral Problems
			Frequency	Drug Resistance		
GAMT	52	Mild to severe	48/52 (93%) ¹	30% ¹	None to severe ²	Hyperactive, autistic, autoaggressive ³
AGAT	7	Mild to moderate	2/7 (28.5%)	None	None	None
SLC6A8	>150 ⁴	Mild to severe	16/24 males ⁵	One patient ⁶	None to moderate ⁷	Autistic-like

1. Based on the 27 patients reported by Mercimek-Mahmutoglu et al [2006]

2. Complex extrapyramidal and pyramidal movement disorder

3. Self-mutilation (biting of fingers and lips)

4. The authors are aware of more than 150 patients; however, the clinical characteristics have only been described for ~35 families. The most recent papers that reviewed these data are Kleefstra et al [2005] (17 patients) and Almeida et al [2006] (24 patients).

5. Sixteen out of 24 males reported had epilepsy [Almeida et al 2006]. In the literature 25 out of 38 males with creatine transporter deficiency had seizures and/or febrile seizures. Six of the seven persons reported by Fons et al [2009] had non-febrile seizures.

6. Mancardi et al [2007]

7. Extrapyramidal movement disorder

Testing

Screening Tests

Levels of guanidinoacetate (GAA), creatine, and creatinine are measured in urine (Table 2), plasma (Table 3), and cerebrospinal fluid (CSF) (Table 4) [Almeida et al 2004, Cognat et al 2004].

Table 2. Urinary Metabolites by CCDS Disorder

Deficiency		GAA ¹ Concentration	Creatine Concentration	24-Hour Creatinine Excretion ²	Creatine / Creatinine Ratio
GAMT		High ³	Low ⁴	Low to normal	Normal
AGAT		In or below the low normal range ⁵	Low ⁴	Low	Normal
SLC6A8	Males	Normal to slightly increased ⁶	High normal to high	Low	High ⁷
	Females	Normal	Normal to mildly elevated	Unknown	Normal to mildly elevated

1. Guanidinoacetate

2. Urinary creatinine excretion is directly related to the intracellular creatine pool, which is diminished in disorders of creatine synthesis and creatine transport. Although assessment of the creatinine excretion in 24-hour urine samples may be helpful in the diagnosis of CCDS, this test reflects a nonspecific reduction of the body creatine pool and, thus, may not be reliable in individuals with reduced muscle mass (e.g., newborns; very young infants; and persons with muscle disease).

3. Pathognomonic finding

4. Battini et al [2002], Stöckler-Ipsiroglu et al [2005]

5. Almeida et al [2004] Cognat et al [2004]

6. If GAA is presented as guanidinoacetate mmol/mol creatinine, the values may appear slightly increased because of the generally lower creatinine values in males with SLC6A8 deficiency.

7. Diagnostic finding

Table 3. Plasma Concentration of Metabolites by CCDS Disorder

Deficiency		GAA ¹	Creatine	Creatinine
GAMT		20-30x normal ²	Low	Low to normal ⁶
AGAT		Less than age-related lowest level ^{3, 4}	No data ⁵	
SLC6A8	Males	Normal	Normal to high ³	
	Females		Unknown	
Normal		See age-related reference range ³	Normal	Normal

1. Guanidinoacetate

2. Mercimek-Mahmutoglu et al [2006]

3. Almeida et al [2004]

4. Cognat et al [2004]

5. In the individuals reported with AGAT deficiency, creatine concentrations were normal in plasma [Stöckler-Ipsiroglu & Salomons 2006].

6. Determination of plasma creatinine concentration alone cannot identify a CCDS.

Table 4. CSF Concentration of Metabolites by CCDS Disorder

Deficiency	GAA ¹	Creatine	Creatinine
GAMT	100-300x normal ²	Low	
AGAT	No data	Normal ³	
SLC6A8	Males	Normal	Reduced
	Females	Unknown	
Normal	See age-related reference range ⁴	Normal	Normal

1. Guanidinoacetate

2. Mercimek-Mahmutoglu et al [2006]

3. Stöckler-Ipsiroglu & Salomons [2006]

4. Almeida et al [2004], Cognat et al [2004]

In vivo assessment of brain creatine levels. Proton magnetic resonance spectroscopy (MRS) reveals almost complete depletion of the cerebral creatine pool in all individuals with GAMT deficiency and AGAT deficiency and in males with SLC6A8 deficiency; partial depletion or even normal levels of the cerebral creatine pool are observed in females with SLC6A8 deficiency [van de Kamp et al 2011a].

Note: Complete lack of creatine in the presence of a normal choline and N-acetyl aspartate (NAA) levels in MRS is unique to CCDS [Stöckler et al 1996].

Confirmatory Tests

Assay of enzyme catalytic activity. Enzyme assays are performed in cultured skin fibroblasts (GAMT) and EBV-transformed lymphoblasts (GAMT and AGAT) [Item et al 2001, Verhoeven et al 2003, Verhoeven et al 2004].

- **GAMT enzyme activity** was less than 0.1 nmol/hr/mg protein in affected individuals (controls 0.61-0.84). For laboratories offering assay of GAMT enzyme activity, see [Testing](#).
- **AGAT enzyme activity** was less than 0.3 nmol/hr/mg protein in affected individuals (controls 12.6-23.4). For laboratories offering assay of AGAT (GATM) enzyme activity, see [Testing](#).

Creatine uptake studies. In the presence of a strong suspicion of SLC6A8 deficiency in a male (e.g., elevated urine creatine-to-creatinine ratio or creatine deficiency in the cranial MR-spectroscopy) with no detected pathogenic mutation or with a novel mutation of uncertain pathogenicity, creatine uptake studies in cultured fibroblasts are important in the assessment of SLC6A8 deficiency. In males the creatine uptake is less than 10% of normal control fibroblasts (incubated with 25 µmol creatine) [Salomons et al 2001, Rosenberg et al 2007].

This testing may also be essential in a symptomatic heterozygous female with a novel mutation of uncertain pathogenicity.

For laboratories offering assay of creatine uptake studies, see [Testing](#).

Molecular Genetic Testing

Genes. The three genes in which mutations give rise to CCDS are:

- Two autosomal genes, *GAMT* (encoding guanidinoacetate N-methyltransferase) and *GATM* (encoding L-arginine:glycine amidinotransferase) (see Table 5)
- One X-linked gene, *SLC6A8* (encoding the sodium-and chloride-dependent creatine transporter 1 protein) (see Table 6.)

GAMT. Homozygous or compound heterozygous mutations have been identified by sequence analysis in *GAMT* in all individuals with enzymatically confirmed GAMT deficiency [Mercimek-Mahmutoglu et al 2006, Dhar et al 2009, Sempere et al 2009].

GATM. Homozygous or compound heterozygous mutations have been identified by sequence analysis in *GATM* in all individuals with enzymatically confirmed AGAT (*GATM*) deficiency [Item et al 2001, Battini et al 2002, Johnston et al 2005, Edvardson et al 2010].

Table 5. Summary of Molecular Genetic Testing Used in Autosomal Recessive CCDS

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Gene ^{1, 2}	Test Availability
<i>GATM</i>	Sequence analysis	Sequence variants ^{3, 4}	100%	Clinical Testing
<i>GATM</i>	Sequence analysis	Sequence variants ^{4,5}	100%	Clinical Testing

Test Availability refers to availability in the GeneTests Laboratory Directory. *GeneReviews* designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.

1. The ability of the test method used to detect a mutation that is present in the indicated gene
2. In individuals with biochemical and/or enzymatic diagnosis of a specific CCDS
3. The most common *GATM* pathologic variant is c.59G>C (35%); another common variant is c.327G>A (18%) [Mercimek-Mahmutoglu et al 2006] (see Table 7).
4. Examples of mutations detected by sequence analysis may include small intragenic deletions/insertions, missense, nonsense, and splice site mutations.
5. The *GATM* mutation c.9297G>A was observed in one family [Item et al 2001] (see Table 8). The c.1111_1112insA variant, producing a frameshift at Met-371 and premature termination at codon 376 was observed in one family [Edvardson et al 2010] (see Table 8).

SLC6A8. A hemizygous mutation has been identified in *SLC6A8* by sequence analysis in all males with *SLC6A8* deficiency confirmed by either creatine uptake studies in cultured fibroblasts or by metabolic workup (i.e., cranial MRS and/or urinary creatine-to-creatinine ratio).

The prevalence of deletions that comprise single exons or multiple exons or that extend into the coding region of contiguous gene(s) is unknown. So far, deletions have been identified in only two persons by using multiplex ligation dependent probe amplification (MLPA): in one the deletion comprised exons 8-13; in the other it comprised the complete coding region of the gene [Anselm et al 2006].

Table 6. Summary of Molecular Genetic Testing Used in X-Linked CCDS

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Rate by Test Method ¹		Test Availability
			Affected Males	Carrier Females	
<i>SLC6A8</i>	Sequence analysis	Sequence variants ²	100% ^{3, 4}	100% ^{4, 5}	Clinical
	Deletion / duplication analysis ⁶	Partial and whole-gene deletions	Unknown	Unknown	Testing

Test Availability refers to availability in the GeneTests™ Laboratory Directory. *GeneReviews* designates a molecular genetic test as clinically available only if the test is listed in the GeneTests™ Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.

1. The ability of the test method used to detect a mutation that is present in the indicated gene
2. The most common type of mutations detected are missense variants and one amino acid deletion, but also splice errors, frame shifts, nonsense mutations and deletions comprising several exons have been detected [Salomons et al 2001, Rosenberg et al 2004, Betsalel et al 2011].
3. Lack of amplification by polymerase chain reaction (PCR) prior to sequence analysis can suggest a putative exonic or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by deletion/duplication analysis (see Table 9).
4. Sequence analysis of *SLC6A8* may miss somatic (and germline) mosaicism [Betsalel et al 2008].
5. Sequence analysis of genomic DNA cannot detect deletion of an exon(s) or whole-gene deletion on the X chromosome in carrier females.
6. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; a variety of methods including quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), or targeted chromosomal microarray analysis (gene/segment-specific) may be used. A full chromosomal microarray analysis that detects deletions/duplications across the genome may also include this gene/segment. See [array GH](#).

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click [here](#).

Testing Strategy

Confirming/establishing the diagnosis in a proband. The diagnostic testing algorithm for an individual with the listed clinical features and/or reduced creatine levels on cranial MRS (see [Figure 1](#)) is:

- Measurement of guanidinoacetate (GAA), creatine, and creatinine in urine ([Table 2](#)) and plasma ([Table 3](#)).
 - If GAA concentration in urine is high, molecular genetic testing of *GAMT*
 - If GAA concentration in urine is low and plasma concentration of GAA is low, molecular genetic testing of *GATM*
- If creatine/creatinine ratio in urine is high and GAA concentration in the urine is normal or slightly increased, molecular genetic testing of *SLC6A8*. Note: Diagnosis of heterozygous female probands requires molecular genetic testing of *SLC6A8* because they may have a normal creatine-to-creatinine ratio in urine and normal creatine content on cranial MRS [van de Kamp et al 2011a].
- If molecular genetic test results are inconclusive (i.e., if sequence variants of unknown significance are identified), *GAMT* enzyme activity (in cultured fibroblast or lymphoblasts), *AGAT* enzyme activity (in lymphoblasts), or creatine uptake in cultured fibroblasts can be assessed.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutation(s) in the family.

Note: (1) Carriers for the autosomal recessive disorders *GAMT* deficiency and *AGAT* deficiency are not at risk of developing the disorder. (2) Carriers for the X-linked disorder *SLC6A8* deficiency may develop clinical findings related to the disorder. Identification of female carriers requires either (a) prior identification of the disease-causing mutation in the family or, (b) if an affected male is not available for testing, molecular genetic testing first by sequence analysis and then by deletion/duplication analysis.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation(s) in the family.

Note: It is the policy of *GeneReviews* to include in *GeneReviews*[™] chapters any clinical uses of testing available from laboratories listed in the *GeneTests*[™] Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *GAMT*, *GATM*, and *SLC6A8*.

Clinical Description

Natural History

Intellectual disability and seizures are common to all three creatine deficiency syndromes. Intellectual disability is associated with expressive speech delay and behavioral disorder [Stöckler-Ipsiroglu & Salomons 2006].

GAMT Deficiency

To date, approximately 52 affected individuals have been published either as single case reports or small groups of cases [Mercimek-Mahmutoglu et al 2006, Verbruggen et al 2007a, Vodopiutz et al 2007, Dhar et al 2009, Engelke et al 2009, O'Rourke et al 2009, Sempere et al 2009, Mercimek-Mahmutoglu et al 2010b].

A review of 27 individuals with GAMT deficiency revealed that intellectual disability and epilepsy are the most consistent clinical features [Mercimek-Mahmutoglu et al 2006]. About 45% of individuals with GAMT deficiency have a severe phenotype characterized by severe intellectual disability, intractable epilepsy, and severe pyramidal/ extrapyramidal findings [Mercimek-Mahmutoglu et al 2006].

Onset of the first clinical manifestations ranges from early infancy (age 3-6 months) to age three years.

Intellectual disability, the most consistent clinical manifestation, is present in all affected individuals. The severity of intellectual disability ranges from mild to severe. Mercimek-Mahmutoglu et al [2006] reported that about 80% of individuals with GAMT deficiency have severe intellectual disability with IQ estimated between 20 and 34.

Irrespective of age and degree of intellectual disability, almost all affected individuals have a vocabulary of fewer than ten words [Mercimek-Mahmutoglu et al 2006]. Variable expressive language deficits were reported in two siblings with GAMT deficiency: the index case spoke fewer than ten words whereas her younger sister spoke in short sentences at age 13 years [O'Rourke et al 2009].

Seizures, the second most consistent manifestation in GAMT deficiency, are observed in 92.5% of affected individuals. Seizure types include myoclonic, generalized tonic-clonic, sporadic partial complex seizures, head nodding, and drop attacks. Seizure severity ranges from occasional seizures to seizures which are non-responsive to various antiepileptic drugs [Mercimek-Mahmutoglu et al 2006].

A movement disorder, observed in 48% of individuals, is mainly extrapyramidal and includes chorea, athetosis, and ataxia. Pathologic signal intensities in the basal ganglia in brain MRI are observed in individuals with the most severe movement disorder. The onset is usually before age 12 years; however, recently a young woman with GAMT deficiency was reported to have onset movement disorder including ballistic and dystonic movements at age 17 years [O'Rourke et al 2009].

A behavior disorder, such as hyperactivity, autism, or self-injurious behavior, is reported in 78% of affected individuals [Mercimek-Mahmutoglu et al 2006].

AGAT (GATM) Deficiency

To date seven individuals from three families have been diagnosed with AGAT deficiency [Item et al 2001, Battini et al 2002, Battini et al 2006, Johnston et al 2005, Edvardson et al 2010].

In one extended Italian family, two sisters had global developmental delay; one had occasional fever-induced seizures [Item et al 2001]. Their younger sib, diagnosed at age three weeks and treated with creatine supplementation starting at age four months, was reported to have normal development at age 18 months [Battini et al 2006]. A second cousin of the three sibs who presented with global developmental delay was also affected [Battini et al 2002].

In the second family, a 14-month old American girl of Chinese descent presented with psychomotor delay, severe language impairment, failure to thrive, and autistic behavior [Johnston et al 2005].

In the third family, two siblings, age 21 years and 14 years, presented with mild intellectual disability, muscle weakness, and failure to thrive at age two years. Both had the novel features of proximal muscle weakness and fatigability [Edvardson et al 2010].

SLC6A8 Deficiency

Affected males. Since the first description of SLC6A8 deficiency by Salomons et al [2001], 45 families comprising a total of 94 individuals with an *SLC6A8* mutation have been reported [Betsalel et al 2011]. However, clinical characteristics have been reported in only 36 families; thus, information on the phenotype is not complete. The phenotype ranges from mild intellectual disability and speech delay to severe intellectual disability, seizures, and behavioral disorder that may become more marked during the course of the disease.

The age at diagnosis ranges from two to 66 years indicating that life expectancy can be normal. Now that the disorder is reasonably well described and diagnostic testing is more widely available, it is anticipated that diagnosis will mainly occur within the first five years of life.

Various types of epilepsy affect a large proportion of males with SLC6A8 deficiency [Almeida et al 2006, Fons et al 2009]. Usually the epilepsy is well controlled with antiepileptic drugs (AEDs). Global developmental delay, hyperactivity, and language delay were evident by age two years in a male who had his first febrile seizure at age four years nine months, followed by frequent generalized tonic-clonic seizures two weeks later. Seizures were not controlled with four antiepileptic drugs as monotherapy, but did respond to combination therapy. He was diagnosed with SLC6A8 deficiency at age five years [Mancardi et al 2007].

A neuropsychological profile in four affected boys from two unrelated families from the Netherlands revealed hyperactive impulsive attention deficit and a semantic-pragmatic language disorder (difficulty in understanding the meaning of words) with oral dyspraxia [Mancini et al 2005].

Individuals with SLC6A8 deficiency may also have growth retardation, mild generalized muscular hypotrophy, dysmorphic facial features (such as broad forehead and flat mid-face), microcephaly, and brain atrophy identified in cranial MRI [Mancini et al 2005, Poo-Arguelles et al 2006].

Kleefstra et al [2005] reported two adult males who had progressive intestinal, neurologic, and psychiatric problems.

One boy with SLC6A8 deficiency developed multiple premature ventricular contractions in his second year [Anselm et al 2008].

Heterozygous females. Some females heterozygous for their family-specific *SLC6A8* mutation had learning problems/mild intellectual disabilities [van de Kamp et al 2011a]. The expected extreme ends of the phenotypic spectrum in females (i.e., asymptomatic at the mild end and findings similar to affected males at the severe end) are presumed to result from skewing of X-chromosome inactivation in the brain.

For example, a female with SLC6A8 deficiency with global developmental delay, behavioral problems, and intractable epilepsy starting at age three years had the most severe clinical phenotype observed in affected females [Mercimek-Mahmutoglu et al 2010a]. Although she did not have evidence of skewed X-chromosome inactivation in peripheral blood cells, tissue-specific skewed X-chromosome inactivation in the brain could explain her severe neurologic findings.

Genotype-Phenotype Correlations

No genotype-phenotype correlations are known for any of the CCDS.

Of note, the phenotypes of individuals homozygous for the two most common *GAMT* mutations (c.59G>C and c.327G>A) range from mild to severe.

Prevalence

GAMT deficiency. Approximately 52 individuals with GAMT deficiency have been diagnosed worldwide. Caldeira Araújo et al [2005] screened plasma and urinary uric acid and creatinine levels in 180 institutionalized individuals with severe intellectual disability. Urinary GAA was measured in individuals with high urinary uric acid to creatinine ratio and/or low plasma creatinine levels. The prevalence of GAMT deficiency was 1.1% (2/180) in this study. Of note, the high prevalence in this small Portuguese population in Madeira is likely the result of its relative isolation over a long period.

Eight carriers for the c.59G>C founder mutation were identified in 1002 newborn screening samples from a Portuguese population, suggesting a carrier rate of 0.8% [Almeida et al 2007].

AGAT deficiency. No prevalence studies have been performed to date. Seven individuals with AGAT deficiency have been reported worldwide: four from one Italian family [Item et al 2001, Battini et al 2002, Battini et al 2006]; one from the US [Johnston et al 2005]; and two sibs of Yemenite Jewish descent [Edvardson et al 2010].

SLC6A8 deficiency. SLC6A8 deficiency, studied in many cohorts ranging from 37 to 478 individuals with familial or non-familial intellectual disability, was found in:

- 2.1% of males with nonsyndromic X-linked intellectual disability [Rosenberg et al 2004, Mercimek-Mahmutoglu et al 2009];
- 2.2% of males with global developmental delay (defined as IQ<70) [Newmeyer et al 2005];
- 0.8% of males with intellectual disability of unknown cause who had normal testing for fragile X syndrome [Clark et al 2006];
- 5.4% of males with familial intellectual disability of unknown cause who had normal testing for fragile X syndrome;
- 3.5% of males with non-familial intellectual disability of unknown cause [Lion-François et al 2006];
- 66 individuals newly added to the European X-linked intellectual disability (EURO-MRX) consortium (prevalence of 1.5%) [Betsalel et al 2008];
- 2.3% of 157 males with global developmental delay, intellectual disability, and epilepsy [Mercimek-Mahmutoglu et al 2009];
- 2% of the X-linked intellectual disability in the Estonian population [Puusepp et al 2009].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Secondary (cerebral) creatine deficiencies have been observed in argininosuccinic aciduria (caused by argininosuccinate lyase deficiency), citrullinemia type 1 (caused by argininosuccinate synthetase enzyme deficiency) [van Spronsen et al 2006], and gyrate atrophy of the choroid and retina (caused by ornithine aminotransferase enzyme deficiency) [Nanto-Salonen et al 1999].

These disorders should be considered in individuals with partial cerebral creatine deficiency in the brain detected by MRS who have normal concentrations of guanidinoacetate (GAA) in the urine, plasma, and CSF and a normal creatine-to-creatinine ratio in urine.

Note to clinicians: For a patient-specific ‘simultaneous consult’ related to this disorder, go to [SimulConsult®](#), an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

- GAMT deficiency
- AGAT deficiency
- SLC6A8 deficiency

Management

Evaluations Following Initial Diagnosis

To assess the extent of disease and needs of an individual diagnosed with CCDS the following investigations should be performed:

- Detailed neurologic clinical evaluation. For individuals with GAMT deficiency use of a scoring system for cognitive ability, epilepsy, and movement disorder is recommended [Mercimek-Mahmutoglu et al 2006].
- Neuropsychological assessment of behavior and speech
- Video documentation of movement disorder
- EEG

- ECG and cardiac ECHO for cardiac involvement
- Prior to initiation of creatine monohydrate supplementation, glomerular filtration rate (GFR) for baseline assessment of kidney function
- Baseline determination of cerebral creatine level by in vivo MRS to document creatine deficiency [Stöckler et al 1996, Schulze et al 2001].

Treatment of Manifestations

GAMT deficiency. Treatment of GAMT deficiency aims to increase cerebral creatine levels by supplementation with creatine monohydrate in oral doses ranging from 300-400 mg to 2 g/kg BW/day in three to six divided doses. The dose of 350 mg/kg BW/day is about 20 times the daily creatine requirement and has not been associated with side effects in healthy volunteers [Greenhaff et al 1993].

The accumulation of GAA cannot be sufficiently corrected by creatine monohydrate supplementation alone and requires:

- Dietary restriction of arginine (the rate-limiting substrate for GAA synthesis) to 15-25 mg/kg/day that corresponds to 0.4-0.7 g/kg/day protein intake;
- Dietary supplementation of ornithine ranging from a low dose of 100 mg/kg/day (given in order to prevent shortage of arginine supply to the urea cycle) to a high dose of 800 mg/kg/day (which may have an additional effect on further decreasing GAA levels by competitive inhibition of AGAT activity). High-dose ornithine supplementation did not decrease plasma and urinary GAA concentrations in an individual with GAMT deficiency [Stöckler et al 1996]. Verbruggen et al [2007b] reported successful treatment and decrease in GAA levels in plasma and in urine after 29 months of oral ornithine substitution in 2007. Administration of ornithine is divided into three to six daily doses [Schulze et al 1998, Schulze et al 2001].

Oral creatine substitution has been effective in replenishing the cerebral creatine pool to approximately 70% of normal. Of the 23 individuals treated, 18 were treated with creatine monohydrate alone and five were treated with creatine monohydrate and dietary restriction of arginine [Mercimek-Mahmutoglu et al 2006]. Of the 18 treated with creatine monohydrate alone, clinical severity score improved from severe to moderate in four and from moderate to mild in five. Improvement was observed in epileptic seizures and movement disorder. Behavioral disorders improved in all. Neither intellectual ability nor speech improved; irreversible brain damage prior to treatment onset is the most probable explanation for these findings.

Determination of cerebral creatine level by in vivo MRS should be performed for individuals with GAMT deficiency to monitor cerebral creatine levels during creatine supplementation therapy.

Whether early treatment prevents disease manifestations totally is under investigation. Some examples of short-term outcomes following early diagnosis and treatment follow:

- A child, diagnosed at birth (due to a history of GAMT deficiency in an older sib) and treated with arginine-restricted diet and creatine monohydrate and ornithine supplementation at age three weeks prior to the onset of symptoms, had age appropriate development at age 14 months [Schulze et al 2006]. The index case in this family (Patient 9 in Mercimek-Mahmutoglu et al [2006]), who was diagnosed with GAMT deficiency at age 2.5 years, had a mild phenotype: developmental delay was noted about age six to nine months; the infant had speech delay and mild intellectual disability with occasional febrile seizures.
- In one individual with GAMT deficiency and epileptic seizures refractory to oral creatine substitution alone, additional measures to restrict dietary arginine and supplement dietary ornithine resulted in a significant decrease of urinary and plasma GAA concentrations and a significant improvement of epilepsy and EEG findings [Schulze et al 1998, Schulze et al 2001, Schulze et al 2003].
- In another individual treated with oral creatine substitution, dietary arginine restriction, and dietary ornithine supplementation, plasma GAA concentrations normalized and positive behavioral changes, increased alertness and attentiveness, and improved motor abilities were noted [Ensenauer et al 2004].

AGAT (GATM) deficiency. Treatment of AGAT deficiency aims to increase cerebral creatine levels by supplementation with creatine monohydrate in oral doses ranging from 300 to 400 mg to 2 g/kg BW/day in three to six divided doses. The dose of 350 mg/kg BW/day is about 20 times the daily creatine requirement and has not been associated with side effects in healthy volunteers [Greenhaff et al 1993].

Determination of cerebral creatine level by in vivo MRS should be performed for individuals with AGAT deficiency to monitor cerebral creatine levels during creatine supplementation therapy [Battini et al 2002, Battini et al 2006].

In the three individuals with AGAT deficiency treated with oral creatine supplementation, normalization of extremely low pretreatment cerebral creatine levels was accompanied by significant improvement of highly abnormal developmental scores [Bianchi et al 2000, Battini et al 2002]. Nonetheless, despite improvement and stabilization of their overall condition after six years of treatment, the two sisters, ages 13 and 11 years, continued to have moderate intellectual deficiency. In this same family, AGAT deficiency was diagnosed prenatally in a younger sib who was begun on creatine supplementation at age four months. Development in this child was normal at age 18 months, in contrast to his sisters who had already shown signs of developmental delay at this age [Battini et al 2006].

After nine to 17 months of treatment with 400-600 mg/kg/day creatine monohydrate, the child reported by Johnston et al [2005] showed acceleration of growth rate into the normal range, improved psychomotor development, and partial normalization of cerebral creatine levels.

These observations suggest that AGAT deficiency seems to respond better to creatine supplementation than does GAMT deficiency. As GAA concentration in the plasma is not elevated in AGAT deficiency, creatine substitution alone may effectively prevent neurologic sequelae in affected children who are treated early [Stöckler-Ipsiroglu et al 2005].

SLC6A8 deficiency does not appear to respond to the approaches that are effective in GAMT deficiency and AGAT deficiency. Treatment of both males and females with SLC6A8 deficiency with creatine-monohydrate was not successful [Stöckler-Ipsiroglu & Salomons 2006]. Only one heterozygous female with learning disability and mildly decreased creatine concentration on brain MRS showed mild improvement on neuropsychological testing after 18 weeks of treatment with creatine-monohydrate (250-750 mg/kg/day) [Cecil et al 2001].

Since the enzymes for creatine biosynthesis are present in the brain [Braissant & Henry 2008], individuals with SLC6A8 deficiency have been treated with L-arginine and L-glycine, precursors in the biosynthesis of creatine. Four individuals with SLC6A8 deficiency who were treated with oral L-arginine substitution for nine months had no improvement in neuropsychological outcome and cerebral creatine in MRS [Fons et al 2008]. However, in another report an individual with SLC6A8 deficiency showed improved neurologic, language, and behavioral status and an increase of brain creatine and phosphocreatine in MRS [Chilosi et al 2008].

Combined L-arginine and L-glycine supplementation therapy to enhance intra-cerebral creatine synthesis successfully treated intractable epilepsy in a female with SLC6A8 deficiency; however, intellectual disability had not improved after one year of treatment [Mercimek-Mahmutoglu et al 2010a].

Nine males with SLC6A8 deficiency and long-term treatment outcome on L-arginine and glycine along with creatine supplementation therapies initially showed improvement in locomotor and personal social IQ subscales; however, IQ declined after the initial improvement [van de Kamp et al 2011b].

Four males and two females with creatine deficiency treated for 42 months with creatine, L-arginine, and L-glycine did not show improvement in cognitive and psychiatric functions or cerebral creatine levels; however, increased muscle mass and improved gross motor skills were observed [Valayannopoulos et al 2011].

Determination of cerebral creatine level by in vivo MRS should be performed for individuals with SLC6A8 deficiency to monitor cerebral creatine levels for the assessment of treatment outcome during experimental therapies [Mercimek-Mahmutoglu et al 2010b, van de Kamp et al 2011b].

Prevention of Primary Manifestations

See Treatment of Manifestations.

Surveillance

GFR for baseline assessment of kidney function prior to initiation of creatine monohydrate supplementation is recommended. Repeat yearly while on creatine supplementation therapy to detect possible creatine-associated nephropathy [Barisic et al 2002].

Evaluation of Relatives at Risk

For GAMT deficiency and AGAT deficiency early diagnosis of at-risk neonates by biochemical or molecular genetic testing (if the family-specific mutations are known) allows early diagnosis and treatment.

See [Genetic Counseling](#) for issues related to evaluation of at-risk relatives for genetic counseling purposes.

Therapies under Investigation

In SLC6A8 deficiency, creatine is not delivered into the brain due to its deficient transporter.

- Dietary supplementation with high dose L-arginine and L-glycine, the primary substrates for creatine biosynthesis, combined with high doses of creatine-monohydrate are being investigated for treatment of SLC6A8 deficiency. The rationale behind this approach is that increased cerebral uptake of both amino acids may enhance intracerebral creatine synthesis [Mancini, van der Knaap, Salomons; unpublished].
- Creatine-derived compounds that cross the blood-brain barrier in a transporter-independent fashion would be useful in the therapy of SLC6A8 deficiency. In vitro, mouse hippocampal slices incubated with creatine benzyl ester or phosphocreatine-Mg-complex acetate, creatine-derived compounds, showed increased tissue creatine content despite functional blockage of creatine transporter with guanidinopropionic acid.

Search [ClinicalTrials.gov](#) for access to information on clinical studies for a wide range of diseases and conditions.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the [GeneTests Clinic Directory](#).

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the [GeneTests Clinic Directory](#).

Mode of Inheritance

GAMT deficiency and AGAT (GATM) deficiency are inherited in an autosomal recessive manner.

SLC6A8 deficiency is inherited in an X-linked manner.

Risk to Family Members – Autosomal Recessive Inheritance

Parents of a proband

- The parents of a child with GAMT or AGAT deficiency are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

Sibs of a proband

- At conception, each sib of an individual with GAMT or AGAT deficiency has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. To date, individuals with GAMT or AGAT deficiency have not reproduced.

Other family members of a proband. Each sib of the proband's parents is at 50% risk of being a carrier.

Carrier Detection

Molecular genetic testing. Carrier testing for at-risk family members is possible if the disease-causing mutations have been identified in a family member.

Risk to Family Members –X-linked Inheritance

Parents of a Proband

- The father of a male with SLC6A8 deficiency will not have the disease nor will he be a carrier of the mutation.
- In a family with more than one affected male, the mother of an affected male is either an obligate carrier or has germline mosaicism. However, low level somatic mosaicism cannot be excluded [Betsalel et al 2008]. No data are available on the possibility or frequency of germline mosaicism in the mothers.
- If pedigree analysis reveals that the proband is the only affected family member, the mother may be a carrier or the affected male may have a *de novo* mutation and, thus, the mother is not a carrier [Stöckler-Ipsiroglu & Salomons 2006].
- Heterozygous mothers may have a history of learning disability. Skewed X-chromosome inactivation may cause pronounced clinical manifestations in these cases similar to the male phenotype, whereas others remain completely asymptomatic [van de Kamp et al 2011a, Stöckler-Ipsiroglu & Salomons 2006]. One female with severe phenotype of SLC6A8 deficiency had no evidence of skewed X-chromosome inactivation in a peripheral blood sample [Mercimek-Mahmutoglu et al 2010a].
- When an affected male represents a simplex case, several possibilities regarding his mother's carrier status need to be considered:
 - He has a *de novo* disease-causing SLC6A8 mutation and his mother is not a carrier.
 - His mother has a *de novo* disease-causing SLC6A8 mutation, either (a) as a "germline mutation" (i.e., present at the time of her conception and therefore in every cell of her body); or (b) as "germline mosaicism" (i.e., present in some of her germ cells only) [Betsalel et al 2008].
 - His mother has a disease-causing SLC6A8 mutation.

Sibs of a proband

- The risk to sibs depends on the carrier status of the mother.
- If the mother of the proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Males who inherit the mutation will be affected; females who inherit the mutation will be carriers. Some of the heterozygous females have learning and behavioral problems [van de Kamp et al 2011a]. Skewed X-chromosome inactivation may cause pronounced clinical manifestations in some females, whereas others remain completely asymptomatic [Stöckler-Ipsiroglu & Salomons 2006].
- If the disease-causing mutation cannot be detected in the DNA of the mother of the only affected male in the family, the risk to sibs is low but greater than that of the general population because of possible germline mosaicism [Betsalel et al 2008].

Offspring of a proband. Males will pass the disease-causing mutation to all of their daughters and none of their sons. To date, no individuals with SLC6A8 deficiency have reproduced.

Other family members of a proband

- The proband's maternal aunts may be at risk of being carriers. The aunts' offspring, depending upon their gender, may be at risk of being carriers or of being affected.
- In one family, the maternal aunt was described with verbal memory deficit and a mild confrontational naming weakness [deGrauw et al 2003].

Carrier Detection

Molecular genetic testing. Carrier testing of at-risk female relatives is possible if the disease-causing mutation has been identified in the family.

Related Genetic Counseling Issues

See [Management, Evaluation of Relatives at Risk](#) for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See [Testing](#) for a list of laboratories offering DNA banking.

Prenatal Testing

Molecular genetic testing

- Prenatal diagnosis for pregnancies at risk for GAMT deficiency or AGAT deficiency is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified before prenatal testing can be performed.
- Prenatal testing is possible for pregnancies at increased risk for SLC6A8 deficiency if the *SLC6A8* mutation has been identified in a family member. The usual procedure is to determine fetal sex by performing chromosome analysis on fetal cells obtained by chorionic villus sampling (CVS) at about ten to 12 weeks' gestation or by amniocentesis usually performed at about 15 to 18 weeks' gestation. If the karyotype is 46, XY, DNA from fetal cells can be analyzed for the known disease-causing mutation.

Biochemical genetic testing. Prenatal diagnosis for pregnancies at increased risk for GAMT deficiency is possible by analysis of guanidinoacetate and creatine in amniotic fluid. Amniocentesis was performed in a mother with a ten-year-old child with GAMT deficiency at 15 weeks' gestation for prenatal diagnosis. Guanidinoacetate was 11.43 $\mu\text{mol/L}$ (normal range for 15 weeks of amenorrhea was $2.96 \pm 0.70 \mu\text{mol/L}$) [Cheillan et al 2006].

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see [Testing](#).

Note: It is the policy of *GeneReviews* to include in *GeneReviews*[™] chapters any clinical uses of testing available from laboratories listed in the GeneTests[™] Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Creatine Deficiency Syndromes: Genes and Databases

Gene Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
<i>SLC6A8</i>	Xq28	Sodium- and chloride-dependent creatine transporter 1	SLC6A8 @ LOVD	SLC6A8
<i>GAMT</i>	19p13.3	Guanidinoacetate N-methyltransferase	GAMT @ LOVD	GAMT
<i>GATM</i>	15q15.3	Glycine amidinotransferase, mitochondrial	GATM @ LOVD	GATM

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) linked to, click here.

Table B. OMIM Entries for Creatine Deficiency Syndromes (View All in OMIM)

300036	SOLUTE CARRIER FAMILY 6 (NEUROTRANSMITTER TRANSPORTER, CREATINE), MEMBER 8; SLC6A8
300352	CREATINE DEFICIENCY SYNDROME, X-LINKED
601240	GUANIDINOACETATE METHYLTRANSFERASE; GAMT
602360	L-ARGININE:GLYCINE AMIDINOTRANSFERASE; GATM

Molecular Genetic Pathogenesis

Creatine is synthesized by two enzymatic reactions: (1) transfer of the amidino group from arginine to glycine, yielding guanidinoacetic acid and catalyzed by L-arginine:glycine amidinotransferase (also known as glycine amidinotransferase, mitochondrial, AGAT, or GATM); or (2) methylation of the amidino group in the guanidinoacetic acid molecule by S-adenosyl-L-methionine:N-guanidinoacetate methyltransferase (also known as guanidinoacetate N-methyltransferase or GAMT). Creatine is synthesized primarily in the kidney and pancreas which have high AGAT activity and in liver which has high GAMT activity. Both genes and enzymes have been detected in brain as well [Braissant & Henry 2008]

Synthesized creatine is transported via the bloodstream to the organs of utilization (mainly muscle and brain), where it is taken up via sodium- and chloride-dependent creatine transporter 1 (SLC6A8 protein) (Figure 2) [Wyss & Kaddurah-Daouk 2000]. This protein is predominantly expressed in skeletal muscle and kidney, but also found in brain, heart, colon, testis, and prostate. The creatine-phosphocreatine shuttle has a key function in the maintenance of the energy supply to skeletal and cardiac muscle. Muscle cells do not synthesize creatine, but take it up via a special sodium-dependent transporter, the creatine transporter.

GAMT

Normal allelic variants. *GAMT* comprises six exons spanning about 5 kb, forming an open reading frame of 711 nucleotides.

Six different genetic variations (three in intron 5 and two in 3' flanking region 1) were found in *GAMT* in the Japanese population; none predicted an amino acid substitution [Saito et al 2001].

Pathologic allelic variants. Thirty-one different mutations located in various exons have been found in individuals with *GAMT* deficiency [Carducci et al 2000, Item et al 2004, Cheillan et al 2006, Mercimek-Mahmutoglu et al 2006, Lion-François et al 2006, Verbruggen et al 2007a, Vodopiutz et al 2007, Dhar et al 2009, O'Rourke et al 2009, Sempere et al 2009].

GAMT mutations are nonsense and missense mutations, splice errors, insertions, deletions, and frameshifts.

The most frequent mutations were c.327G>A (24%; 23/94 alleles) and c.59G>C (21%; 20/94 alleles) detected in 47 affected individuals. Twenty seven of the 47 affected individuals were homozygous [Carducci et al 2000, Item et al 2004, Cheillan et al 2006, Lion-François et al 2006, Mercimek-Mahmutoglu et al 2006, Verbruggen et al 2007a, Vodopituz et al 2007, Dhar et al 2009, O'Rourke et al 2009, Sempere et al 2009].

Table 7. Selected *GAMT* Pathologic Allelic Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.59G>C	p.Trp20Ser	NM_000156.4 NP_000147.1
c.327G>A ¹	See footnote 1	
c.297_309dup13	p.Arg105GlyfsX26	

See [Quick Reference](#) for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. The mutation c.327G>A changes the last nucleotide of the splice donor site of exon 2. Although no amino acid change is predicted, experimental analysis demonstrated that this one base substitution affects RNA-processing and yields two abnormal transcripts, one from skipping of exon 2 and the other from use of a cryptic splice site in intron 2 [Stöckler et al 1996].

Normal gene product. *GAMT*, a cytosolic protein, catalyzes the second step of creatine biosynthesis. This enzyme converts guanidinoacetate and S-adenosylmethionine to creatine and S-adenosylhomocysteine. In humans, *GAMT* is expressed with highest activity in the liver and the pancreas and with lower activity in kidney. It is a monomeric protein of 236 amino acids with a relative molecular mass of 26,000-31,000 [Velichkova & Himo 2006].

Abnormal gene product. The first affected individual described had severe deficiency of *GAMT* enzyme activity in the liver [Stöckler et al 1996]. Following development of an assay for *GAMT* enzyme activity in skin fibroblasts or Epstein-Barr virus transformed lymphoblasts [Ilas et al 2000], undetectable *GAMT* enzyme activity was identified in 20 individuals with *GAMT* deficiency [Mercimek-Mahmutoglu et al 2006].

GATM

Normal allelic variants. The normal *GATM* genomic DNA is 16,858 bp in length and comprises nine exons [Battini et al 2002]. No normal allelic variants have been reported in the SNP database.

Pathologic allelic variants. Only two *GATM* mutations causing AGAT deficiency have been reported (see Table 8). Both mutations occurred in the homozygous state.

Table 8. Selected *GATM* Pathologic Allelic Variants

DNA Nucleotide Change (Alias ¹)	Protein Amino Acid Change	Reference Sequences
c.446G>A ² (9297G>A)	p.Trp149X	NM_001482.2 NP_001473.1
c.484+1G>T (IVS3+1G>T) ³	--	
c.1111_1112insA ⁴	p.Met371AsnfsX6	

See [Quick Reference](#) for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Variant designation that does not conform to current naming conventions

2. The c.446G>A nonsense mutation predicts a severely truncated protein lacking the active-site cysteine residue 407 [Item et al 2001].

3. Nucleotide change results in skipping of exon 3 at the RNA level (r.289_484del196) [Johnston et al 2005].

4. Edvardson et al [2010]

Normal gene product. AGAT (GATM) catalyzes the first reaction in creatine biosynthesis and transfers amidino group from arginine to glycine to form ornithine and guanidinoacetate. Guanidinoacetate is the precursor of creatine. Mainly found in kidney, AGAT is located in the cytosol and in the intermembrane space of mitochondria. AGAT is the rate-limiting enzyme of creatine biosynthesis. AGAT enzyme activity is inhibited by creatine via expression of the protein in mRNA level. AGAT enzyme activity is inhibited by ornithine allosterically.

Human mitochondrial AGAT is synthesized as a precursor of 423 amino acids from which the N-terminal 37 residues are cleaved off when the protein is transported to the mitochondrial intermembrane space, yielding a mature protein of 386 amino acid residues. The cytosolic form of AGAT consists of 391 amino acids [Humm et al 1997].

Abnormal gene product. The effect of two reported pathologic alleles was investigated on the protein level by the measurement of AGAT enzyme activity in cultivated fibroblasts and in virus-transformed lymphoblasts from affected individuals; no detectable enzyme activity was found in the cell extracts [Item et al 2001, Battini et al 2002, Johnston et al 2005]. Cell extracts from the obligate carrier parents of the first described Italian family showed intermediate residual enzyme activity, as would be expected for the heterozygous state [Item et al 2001, Battini et al 2002].

SLC6A8

Normal allelic variants. *SLC6A8* comprises 13 exons and spans 8.4 kb. The *SLC6A8* mRNA is 3580 bp (reference sequence NM_005629.3) [Salomons et al 2001]. Previously, 18 non-disease associated variants were reported in *SLC6A8* [Rosenberg et al 2004]. Of these, 65 variants were later studied extensively and reported as most likely normal benign variants [Betsalel et al 2011]. These variants are all included in the LOVD database (www.LOVD.nl/SLC6A8 or through the Variation Databases page of the Human Genome Variation Society [www.hgvs.org]). *SLC6A8*, on chromosome Xq28, has a pseudogene, *SLC6A10* on chromosome 16p11.2, which has a premature stop codon in exon 4 [Clark et al 2006].

Pathologic allelic variants. The LOVD database (www.LOVD.nl/SLC6A8 or through the Variation Databases page of the Human Genome Variation Society [www.hgvs.org]) lists 38 reported pathogenic mutations from 44 families with *SLC6A8* deficiency [Betsalel et al 2011]. There is no evidence for a mutational hotspot region in *SLC6A8*; however, certain mutations have been detected in several unrelated families. For example, c.321_323delCTT and c.1222_1224delTTC both result in the deletion of a three-nucleotide duplication [Stöckler-Ipsiroglu & Salomons 2006]. The pathogenic nature of many missense variants has been established by overexpression in primary *SLC6A8*-deficient cells [Rosenberg et al 2007].

Table 9. Selected *SLC6A8* Pathologic Allelic Variants

DNA Nucleotide Change (Alias ¹)	Protein Amino Acid Change	Reference Sequences
c.321_323delCTT (319_321delCTT)	p.Phe107del	
c.1222_1224delTTC (1221_1223delTTC)	p.Phe408del	NM_005629.3 NP_005620.1
c.1631C>T	p.Pro544Leu	
c.1661C>T	p.Pro554Leu	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Variant designation that does not conform to current naming conventions

Normal gene product. The *SLC6A8* protein is a member of a solute carrier family of Na⁺ and Cl⁻ dependent transporters responsible for the uptake of certain neurotransmitters (noradrenalin, serotonin, GABA, dopamine) and amino acids (glycine, proline, taurine) [Nash et al 1994]. The *SLC6A8* protein comprises 635 amino acids with a molecular weight of 70 kd.

Abnormal gene product. All mutations resulted in impaired creatine uptake in fibroblasts when cultured at physiologic levels of creatine [Salomons et al 2003].

Resources

See *Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.*—ED.

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page [PubMed](#)

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Suggested Reading

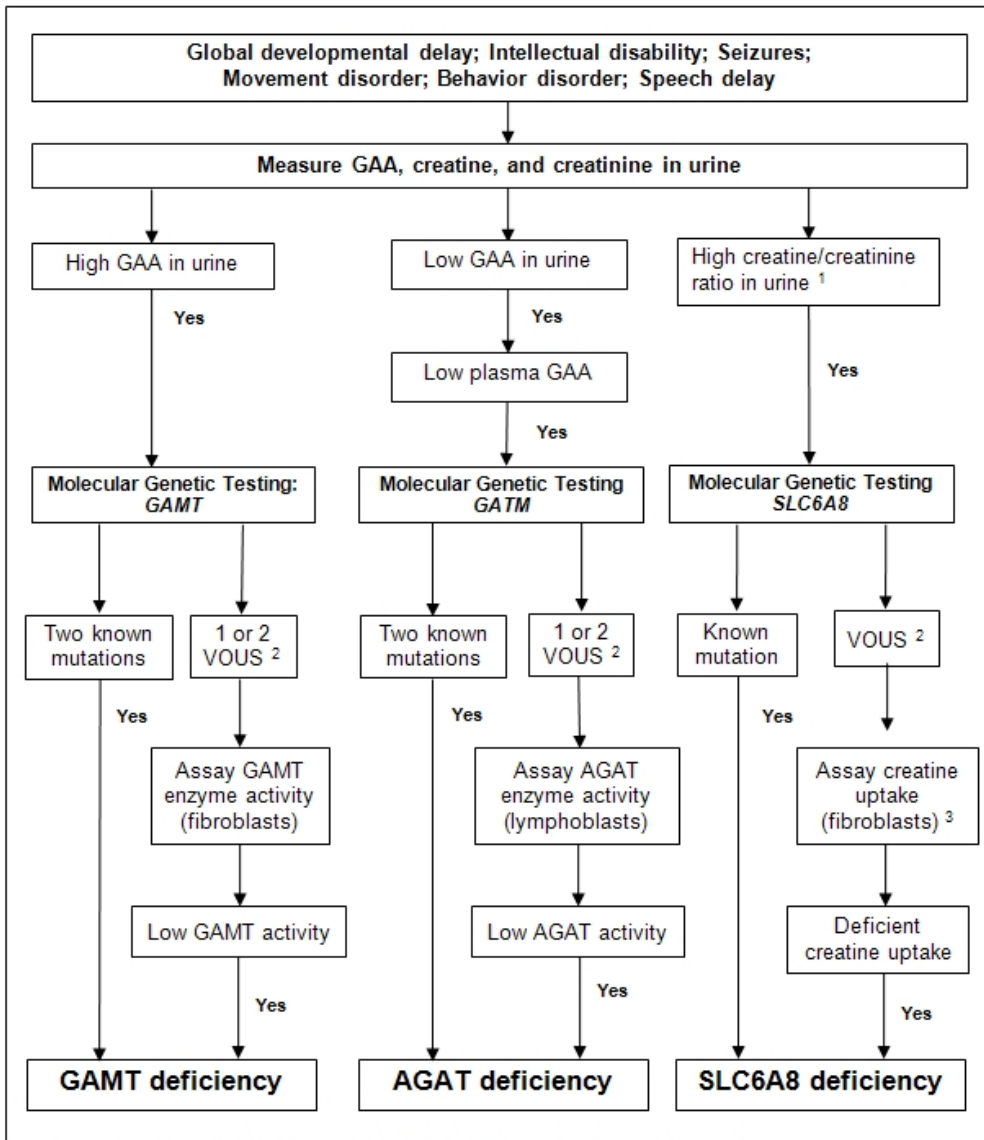
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Chapter Notes

Revision History

- 18 August 2011 (me) Comprehensive update posted live
- 15 January 2009 (me) Review posted live
- 24 July 2008 (smm) Original submission

Figures



1. Males only. The only reliable testing for females is molecular genetic testing.

2. VOUS= Variant of unknown significance

3. Creatine uptake can be used in females when molecular genetic testing has identified either a novel mutation of uncertain clinical significance or no mutation despite strong clinical suspicion. Note: In some heterozygous females, creatine uptake studies are normal because X-chromosome inactivation results in expression of only the normal *SLC6A8* allele.

Figure 1. Algorithm for diagnosis of the cerebral creatine deficiency syndromes. Note: Urinary creatine/creatinine ratio and creatine uptake studies in cultured skin fibroblasts are often not informative in females with *SLC6A8* deficiency; hence, molecular genetic testing is the preferred method of diagnosis of females with this disorder [van de Kamp et al 2011a].

CREATINE SYNTHESIS (liver, pancreas & kidney)

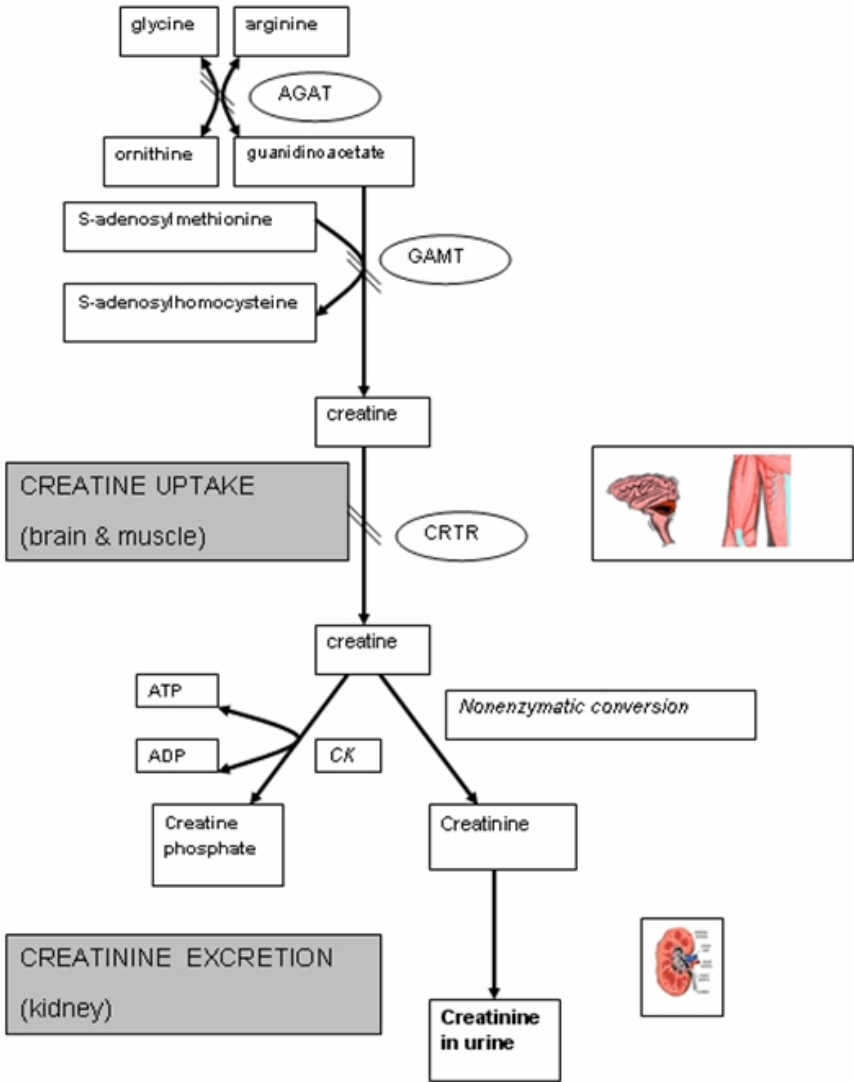


Figure 2. Schema illustrating (1) creatine synthesis that occurs mainly in liver, pancreas, and kidney; (2) creatine uptake into muscle and brain by the creatine transporter (CRTR); and (3) non-enzymatic conversion of creatine to creatinine for excretion in the urine