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Creatine Deficiency Syndromes

Synonym: Cerebral Creatine Deficiency Syndromes

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Summary

Clinical 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) deficiency, and the creatine transporter (CRTR) 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; about 40% have movement disorder. Onset is between ages three months and three years. Only 14 individuals with AGAT deficiency have been reported. The phenotype of CRTR deficiency in affected males ranges from mild intellectual disability and speech delay to severe intellectual disability, seizures, movement disorder and behavior disorder; age at diagnosis ranges from two to 66 years. Clinical phenotype of females heterozygous for CRTR deficiency ranges from asymptomatic to severe phenotype resembling male phenotype.

Diagnosis/testing. Cerebral creatine deficiency in brain MR spectroscopy (^{1}H-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*, and *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 replenish cerebral creatine levels. Treatment of GAMT deficiency requires supplementation of ornithine and dietary restriction of arginine or protein. In males with CRTR deficiency creatine supplementation alone does not improve clinical outcome and does not result in replenished cerebral creatine levels; likewise, high-dose L-arginine and L-glycine supplementation so far has not consistently improve clinical or biochemical outcome in males although some have been reported to have increased muscle mass and improved motor and personal social IQ skills. One female with intractable epilepsy responded to high-dose L-arginine and L-glycine supplementation with cessation of seizures.

Prevention of primary manifestations: Early treatment at the asymptomatic stage of the disease in individuals with GAMT and AGAT deficiencies appears to be beneficial: treatment in newborn sibs of individuals with AGAT or GAMT deficiency prevented disease manifestations.

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

Evaluation of relatives at risk: Early diagnosis of neonates at risk for GAMT deficiency, AGAT deficiency, and CRTR 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. CRTR deficiency is inherited in an X-linked manner. Mothers who are carriers have a 50% chance of transmitting the pathogenic variant in each pregnancy; sons who inherit the pathogenic variant will be affected; daughters who inherit the pathogenic variant will be heterozygous and may have learning and behavior 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 pathogenic variants in the family are known.

GeneReview Scope

Creatine Deficiency Syndromes: Included Phenotypes
• Guanidinoacetate methyltransferase (GAMT) deficiency • L-arginine:glycine amidinotransferase (AGAT) deficiency • Creatine transporter (CRTR) deficiency

Diagnosis

The cerebral creatine deficiency syndromes (CCDS) are inborn errors of creatine metabolism that include [Stockler-Ipsiroglu et al 2012]:

- Two creatine biosynthesis defects (both inherited in an autosomal recessive manner):
  - Guanidinoacetate methyltransferase (GAMT) deficiency
  - L-arginine:glycine amidinotransferase (AGAT) deficiency
- One creatine transporter defect (inherited in an X-linked manner):
  - Creatine transporter (CRTR) deficiency

Suggestive Findings

Cerebral creatine deficiency syndromes (CCDS) **should be suspected** in:

- A young child with global developmental delay, hypotonia, seizures, and movement disorder;
- An older child with intellectual disability, epilepsy, movement disorder, and behavior problems.

See Table 1.

Table 1.

Clinical Features of GAMT, AGAT, and CRTR Deficiency

Deficiency	# of Affected Persons	ID	Epilepsy		Movement Disorder [1]		Behavior Problems
			Frequency	Drug Resistance	Frequency	Severity	
GAMT	110	Mild to severe	69/80 (86%) [2]	46% [2]	30/80 (37.5%) [2]	Mild to severe [2]	Hyperactivity, autism spectrum disorder, aggressive behavior, self-injurious behavior
AGAT	14	Mild to moderate	2/14 (14%)	None	None		None

Deficiency	# of Affected Persons	ID	Epilepsy		Movement Disorder		Behavior Problems
			Frequency	Drug Resistance	Frequency	Severity	
CRTR	>160 [3]	Mild to severe	59/101 (60%) males [3]	3/59 (5%) [3]	41/101 (40%) [3]	Mild to severe [4]	86/101 (85%) attention deficit hyperactivity, autism spectrum disorder [3]

ID = intellectual disability

1. Dystonia, chorea, choreoathetosis, ataxia
2. Based on the 80 patients reported by Mercimek-Mahmutoglu et al [2006], Stockler-Ipsiroglu et al [2014], and Mercimek-Mahmutoglu et al [2014a]
3. The authors are aware of more than 160 patients; however, the clinical characteristics have only been described for ~101 males from 85 families. The most recent international registry paper to review these data is van de Kamp et al [2013a].
4. 101 males reported by van de Kamp et al [2013b] had movement disorder including ataxia (29%) and dystonia or athetosis (11%).

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, van de Kamp et al 2014, Mørkrid et al 2015].

Table 2.

Urinary Metabolites by CCDS Disorder

Deficiency		GAA [1] Concentration	Creatine Concentration	Creatine/Creatinine Ratio
GAMT		Elevated [2]	Low to low normal [3]	Low normal
AGAT		Low to low normal [4]	Low normal [3]	Low normal
CRTR	**Males**	Normal [5]	Normal to elevated	Elevated [6]
	Females	Normal	Normal to elevated	Normal to mildly elevated

1. Guanidinoacetate
2. Pathognomonic finding
3. Battini et al [2002], Stockler-Ipsiroglu et al [2012]
4. Almeida et al [2004], Cognat et al [2004]
5. 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 CRTR deficiency.
6. Diagnostic finding [van de Kamp et al 2013a, van de Kamp et al 2014]

Table 3.

Plasma Concentration of Metabolites by CCDS Disorder

Deficiency		GAA [1]	Creatine	Creatinine
GAMT		Elevated [2]	Low	Low to normal [4]
AGAT		Low to low normal [3]	Low [3]	
CRTR	**Males**	Normal	Normal [3]	
	Females		Normal	
Normal		See age-related reference range [3]	Normal	Normal

1. Guanidinoacetate

2. Mercimek-Mahmutoglu et al [2006]
3. Almeida et al [2004], van de Kamp et al [2015]
4. 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		Elevated [2]	Low	Low
AGAT		No data	No data	No data
CRTR	**Males**	Normal to mildly elevated [3]	Normal to mildly elevated [3]	Low
	Females	No data	No data	No data
Normal		See age-related reference range [4]	Normal	Normal

1. Guanidinoacetate
2. Mercimek-Mahmutoglu et al [2006]
3. van de Kamp et al [2013b]
4. Almeida et al [2004], Cognat et al [2004]

Brain imaging for in vivo assessment of brain creatine levels. Proton magnetic resonance spectroscopy (^{1}H-MRS) reveals almost complete depletion of the cerebral creatine pool in all individuals with GAMT deficiency and AGAT deficiency and in males with CRTR deficiency. Partial depletion or even normal levels of the cerebral creatine pool are observed in female carriers with X-linked CRTR deficiency [van de Kamp et al 2011].

Note: Complete lack of creatine in the presence of a normal choline and N-acetyl aspartate (NAA) levels in ^{1}H-MRS is unique to CCDS [Stöckler et al 1996].

Establishing the Diagnosis

The diagnosis of CCDS **is established** in a proband with identification of biallelic pathogenic variants in *GAMT or GATM* or a hemizygous pathogenic variant (in males) of *SLC6A8* on molecular genetic testing (see Table 5) using the following algorithm for guidance.

The diagnostic testing algorithm for an individual with the listed clinical features and/or reduced creatine levels on brain ^{1}H-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 brain ^{1}H-MRS [van de Kamp et al 2011].
  - 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 [Item et al 2001, Verhoeven et al 2003, Verhoeven et al 2004].

Note: Methods for testing GAMT enzyme activity (in cultured fibroblast or lymphoblasts), AGAT enzyme activity (in lymphoblasts), or creatine uptake in cultured fibroblasts have been reported and may be helpful in the interpretation of

variants of unknown significance [Rosenberg et al 2007, Betsalel et al 2012, Mercimek-Mahmutoglu et al 2012a, Mercimek-Mahmutoglu et al 2014a, Desroches et al 2015]. See Molecular Genetics for details.

Molecular genetic testing approaches can include **serial single-gene testing**, use of a **multi-gene panel**, and **more comprehensive genomic testing**.

- ***GAMT*, *GATM*, and *SLC6A8* testing** is advised if biochemical features (e.g. creatine deficiency in brain ^{1}H-MRS) are suggestive of GAMT, AGAT, or CRTR deficiency.
- **Serial single gene testing** is advised in the case of specific abnormalities in metabolites of creatine metabolism in body fluids (Tables 2-4). Sequence analysis of the gene of interest is performed first, followed by gene-targeted deletion/duplication analysis and/or mRNA analysis if only one or no pathogenic variant is found.
- **A multi-gene panel** that includes *GAMT*, *GATM, SLC6A8,* and other genes of interest (see Differential Diagnosis) may also be considered in patients with global developmental delay, intellectual disability, and/or epilepsy and/or movement disorder who did not undergo biochemical investigations for CCDS. Note: The genes included and sensitivity of multi-gene panels vary by laboratory and over time.
- **More comprehensive genomic testing** (when available) including exome sequencing, genome sequencing, and mitochondrial sequencing may be considered if serial single-gene testing (and/or use of a multi-gene panel) fails to confirm a diagnosis in an individual with features of CCDS. For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 5.

Summary of Molecular Genetic Testing Used in CCDS

Gene [1]	Proportion of CCDS Attributed to Pathogenic Variants in This Gene	Proportion of Pathogenic Variants [2] Detected by Test Method [3]	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
GAMT	39% [6]	~100% [6]	Unknown [7]
GATM	5% [8]	~100% [8]	Unknown [7]
SLC6A8	56% [9]	~95% [9, 10]	~5% [11]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. In individuals with biochemical and/or enzymatic diagnosis of a specific CCDS
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods that may be used can include: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Mercimek-Mahmutoglu et al [2006], Mercimek-Mahmutoglu et al [2014a], Stockler-Ipsiroglu et al [2014]
7. No data on detection rate of gene-targeted deletion/duplication analysis are available.
8. Item et al [2001], Battini et l [2002], Battini et al [2006], Edvardson et al [2010], Verma [2010], Ndika et al [2012], Comeaux et al [2013], Nouioua et al [2013]
9. van de Kamp et al [2013a]
10. Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis.
11. Anselm et al [2006], van de Kamp et al [2015], Leiden Open Variation Database

Clinical Characteristics

Clinical Description

Intellectual disability and seizures are common to all three creatine deficiency syndromes. Intellectual disability is associated with expressive speech delay and behavior disorder [Stockler-Ipsiroglu et al 2012].

GAMT Deficiency

Approximately 110 affected individuals have been published either as single case reports or small groups of cases [Mercimek-Mahmutoglu et al 2006, Verbruggen et al 2007, Vodopiutz et al 2007, Dhar et al 2009, Engelke et al 2009, O'Rourke et al 2009, Sempere et al 2009a, Mercimek-Mahmutoglu et al 2010b, Cheillan et al 2012, Nasrallah et al 2012, Comeaux et al 2013, El-Gharbawy et al 2013, Viau et al 2013, Akiyama et al 2014, Mercimek-Mahmutoglu et al 2014a, Mercimek-Mahmutoglu et al 2014b, Stockler-Ipsiroglu et al 2014].

A review of 80 individuals with GAMT deficiency revealed that intellectual disability and epilepsy are the most consistent clinical features [Mercimek-Mahmutoglu et al 2006, Mercimek-Mahmutoglu et al 2014a, Stockler-Ipsiroglu et al 2014]. About 60% of individuals with GAMT deficiency have a severe phenotype characterized by severe intellectual disability, intractable epilepsy, and movement disorder [Mercimek-Mahmutoglu et al 2006, Mercimek-Mahmutoglu et al 2014a, Stockler-Ipsiroglu et al 2014].

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. About 60% of individuals with GAMT deficiency have severe global developmental delay or intellectual disability [Mercimek-Mahmutoglu et al 2006, Mercimek-Mahmutoglu et al 2014a, Stockler-Ipsiroglu et al 2014].

Language. Variable expressive language deficits were reported in two sibs 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 about 78% of affected individuals. Seizure types include myoclonic, generalized tonic-clonic, partial complex, head nodding, and atonic seizures. Seizure severity ranges from occasional seizures to seizures which are non-responsive to various antiepileptic drugs [Mercimek-Mahmutoglu et al 2006, Mercimek-Mahmutoglu et al 2014a, Stockler-Ipsiroglu et al 2014].

Movement disorders, observed in about 30% of individuals, are mainly chorea, athetosis, dystonia, or ataxia [Mercimek-Mahmutoglu et al 2006, Mercimek-Mahmutoglu et al 2014a, Stockler-Ipsiroglu et al 2014]. Pathologic signal intensities in the basal ganglia in brain MRI are observed in individuals with or without a movement disorder [Mercimek-Mahmutoglu et al 2006, Mercimek-Mahmutoglu et al 2014a, Stockler-Ipsiroglu et al 2014]. The onset is usually before age 12 years; however, recently a young woman with GAMT deficiency was reported to have onset of movement disorder (including ballistic and dystonic movements) at age 17 years [O'Rourke et al 2009].

A behavior disorder (e.g., hyperactivity, autism, or self-injurious behavior) is reported in about 77% of affected individuals [Mercimek-Mahmutoglu et al 2006, Mercimek-Mahmutoglu et al 2014a].

AGAT Deficiency

Fourteen individuals from seven families have been diagnosed with AGAT deficiency [Item et al 2001, Battini et al 2002, Battini et al 2006, Edvardson et al 2010, Verma 2010, Ndika et al 2012, Comeaux et al 2013, Nouioua et al 2013].

Intellectual disability, the most consistent clinical manifestation, is present in all affected individuals. The severity of intellectual disability ranges from mild to moderate.

Seizures, observed in only 9% of affected individuals, were occasional and associated with fever.

Muscle weakness or hypotonia was observed in 67% of affected individuals [Edvardson et al 2010, Verma 2010, Ndika et al 2012, Nouioua et al 2013].

Failure to thrive was reported in two sibs [Edvardson et al 2010].

A behavior disorder was present in 27% of affected individuals.

Movement disorders were not reported in any affected individuals.

CRTR Deficiency

Affected Males

Since the first description of SLC6A8 deficiency by Salomons et al [2001], 85 families comprising a total of 101 male individuals with an *SLC6A8* pathogenic variant have been reported in a single international registry study [van de Kamp et al 2013a]. The phenotype ranges from mild intellectual disability and speech delay to severe intellectual disability, seizures, and behavior disorder that may become more marked during the course of the disease.

The age at diagnosis ranges from one 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 three years of life.

Intellectual disability was present in all affected male individuals ranging from mild to severe: 85% of affected males had mild to moderate intellectual disability up to age four years; 75% of affected males older than age 18 years had severe intellectual disability [van de Kamp et al 2013a]. One adult had progressive cognitive dysfunction [Kleefstra et al 2005].

Speech-language disorder. Speech development was delayed in all affected males. First words were at a mean age of 3.1 years (age range: 9 months to 10 years). In affected males older than age ten years, 14% had no speech development, 55% were able to speak single words, and 31% were able to speak in sentences [van de Kamp et al 2013a].

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

Seizures were present in 59% of affected male individuals**.** The most common seizure type was generalized tonic-clonic and simple or complex partial seizures with or without secondary generalization. Absence and myoclonic seizures were rare. Age of seizure onset was between one and 21 years [van de Kamp et al 2013b]. Fewer than ten patients with intractable epilepsy have been reported [Mancardi et al 2007, Fons et al 2009, Mercimek-Mahmutoglu et al 2010a, van de Kamp et al 2013a].

Movement disorder. Wide-based gait or ataxia and dystonia or athetosis were reported in 29% and 11% of affected males respectively [van de Kamp et al 2013a].

Behavior disorder. Behavior disorder was reported in 85% of affected males. The most common behavior disorders were attention deficit and/or hyperactivity (55%) and autistic features (41%). Other behavior disorders reported in affected males include social anxiety or shyness (20%), stereotypic behavior (20%), impulsive behavior (27%), aggressive behavior (19%), self-injurious behavior (10%), and obsessive-compulsive behavior (8%) [van de Kamp et al 2013a].

Other neurologic clinical features. Hypotonia was present in 40% of affected males. Spasticity was reported in 26% of affected males. Four individuals had mild (sensorial-neural) hearing loss. Nine affected males were reported with strabismus or bilateral abducens nerve palsy. Myopathic face, ptosis, joint laxity (likely secondary to the hypotonia), and decreased muscle bulk were also reported [van de Kamp et al 2013a].

Other non-neurologic clinical features

- **Dysmorphic features** including microcephaly, broad forehead, midface retrusion, high palate, short nose, prominent nasal bridge, ear differences (underfolded helices, large ears, and/or cupped ears), deeply set eyes, fifth finger clinodactyly, and slender body build were reported in 45% of affected males [Anselm et al 2006, van de Kamp et al 2013a, van de Kamp et al 2013b].
- **Gastrointestinal findings** including failure to thrive, vomiting, constipation, ileus likely secondary to constipation, hepatitis, gastric and duodenal ulcers, and hiatal hernia (which may or may not be related to CRTR deficiency) were reported in 35% of affected males [van de Kamp et al 2013a].
- **Cardiac features.** One boy with CRTR deficiency developed multiple premature ventricular contractions in his second year [Anselm et al 2008]. Two affected males with mild cardiomyopathy were reported [Puusepp et al

2010]. One affected male had long QT syndrome [van de Kamp et al 2013a].

- **Medical concerns in adulthood.** Twenty-one of 101 affected males were adults (age >18 years). Adults affected with CRTR deficiency had intellectual disability ranging from moderate to severe [van de Kamp et al 2013b]. They presented with myopathic face, ptosis, external ophthalmoplegia, or parkinsonism. Chronic constipation leading to megacolon, ileus or bowel perforation, and/or gastric or duodenal ulcer disease have been reported in some adults [Hahn et al 2002, Kleefstra et al 2005, Sempere et al 2009b, van de Kamp et al 2013a].

Heterozygous Females

Females heterozygous for their family-specific *SLC6A8* pathogenic variant are either asymptomatic or have mild intellectual disability [van de Kamp et al 2011]. There was no clinical correlation between skewed X-inactivation in favor of the pathogenic variant allele and severity of clinical phenotype. There was no significant statistical correlation between intellectual ability and cerebral creatine level on brain ^{1}H-MRS [van de Kamp et al 2011]. A female with mild intellectual disability, intractable epilepsy, and behavior problems (a phenotype similar to affected males) 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 [Mercimek-Mahmutoglu et al 2010a].

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* pathogenic variants (c.59G>C and c.327G>A) range from mild to severe.

Prevalence

GAMT deficiency. Approximately 110 individuals with GAMT deficiency have been diagnosed worldwide.

The estimated incidence of GAMT deficiency in the general population ranges from 1:2,640,000 to 1:550,000 [Desroches et al 2015]. This is in agreement with information from pilot newborn screening programs for GAMT deficiency, which screened approximately 1,000,000 newborns; to date none of the newborns has a confirmed diagnosis of GAMT deficiency [Mercimek-Mahmutoglu et al 2012a, Pasquali et al 2014, Pitt et al 2014, Stockler-Ipsiroglu et al 2014].

In contrast, the estimated incidence of GAMT deficiency in the Utah newborn population was 1:114,072 [Viau et al 2013].

Smaller studies of individuals with neurologic disease or severe intellectual disability found GAMT deficiency present in 0.094% and 1.1% respectively [Caldeira Araújo et al 2005, Cheillan et al 2012].

AGAT deficiency. No prevalence studies have been performed to date.

CRTR deficiency. CRTR deficiency has been studied in many cohorts ranging from 49 to 4426 individuals with familial or non-familial intellectual disability. Recently these studies were summarized by van de Kamp et al [2014]:

- Three studies of X-linked families found CRTR deficiency in eight out of 408 cases, for a prevalence of 2.0% (CI 0.6-3.3);
- Six studies of cohorts with intellectual disability found CRTR deficiency in 15 out of 1102 cases, for a prevalence of 1.4% (CI 0.7-2.0).

These studies together with two miscellaneous cohorts resulted in 28 positive cases out of 7218, for a prevalence of 0.4% (CI 0.2-0.5).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *GAMT*, *GATM,* or *SLC6A8.*

Differential Diagnosis

Secondary (cerebral) creatine deficiencies have been observed in argininosuccinate lyase deficiency (ASL) and argininosuccinate synthetase deficiency (citrullinemia type 1) [van Spronsen et al 2006], ornithine aminotransferase deficiency (gyrate atrophy of the choroid and retina) [Nänto-Salonen et al 1999] and Δ(1)-pyrroline-5-carboxylate synthetase (P5CS) deficiency [Martinelli et al 2012].

Boenzi et al [2012] measured plasma creatine levels in individuals with ornithine transcarbamylase (OTC), argininosuccinate synthetase (ASS), and argininosuccinate lyase (ASL) deficiencies; hyperammonemia, hyperornithinemia, homocitrullinuria (HHH) syndrome, and lysinuric protein intolerance (LPI). Individuals with OTC and ASS deficiencies and HHH syndrome showed significant reduction of plasma creatine concentration, whereas individuals with ASL deficiency and LPI had high plasma creatine levels.

These disorders should be considered in individuals with partial cerebral creatine deficiency in the brain detected by ^{1}H-MRS, who have normal concentrations of guanidinoacetate (GAA) in the urine, plasma, and CSF and a normal creatine-to-creatinine ratio in urine.

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 the degree of global developmental delay or intellectual disability, epilepsy, movement disorder, and behavior problems
- Neuropsychological assessment of cognition and speech
- Video documentation of movement disorder
- EEG, if any clinical seizures
- Prior to initiation of creatine monohydrate supplementation, glomerular filtration rate (GFR) for baseline assessment of kidney function
- Baseline determination of cerebral creatine level by brain ^{1}H-MRS to document creatine deficiency [Stöckler et al 1996, Schulze et al 2001]
- ECG and echocardiogram for cardiac involvement
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

The following are appropriate:

- Occupational therapy, physiotherapy and speech-language therapy for global developmental delay by physiotherapist, occupational therapist, speech-language therapist
- Behavior therapy for behavior problems by developmental pediatrician
- Seizure management with antiepileptic drugs by epilepsy specialist
- Treatment of movement disorder by movement disorder specialist

GAMT Deficiency

Treatment of GAMT deficiency aims to replenish cerebral creatine levels by supplementation with creatine monohydrate and to decrease accumulation of neurotoxic GAA in the central nervous system by ornithine supplementation and protein- or arginine-restricted diet [Schulze et al 2001, Stockler-Ipsiroglu et al 2014]. Creatine monohydrate and ornithine supplementation decrease GAA accumulation by competitive inhibition of AGAT enzyme activity. A decrease in the level of GAA in cerebrospinal fluid was reported in two individuals with GAMT deficiency

treated with creatine monohydrate and ornithine supplementation and with arginine restriction [Mercimek-Mahmutoglu et al 2012b, Mercimek-Mahmutoglu et al 2014b].

Treatment is as follows:

- Creatine monohydrate in oral doses ranging from 400-800 mg/kg BW/day in three to six divided doses [Stockler-Ipsiroglu et al 2012, Stockler-Ipsiroglu et al 2014]
- Supplementation of ornithine ranging from 400-800 mg/kg BW/day. Administration of ornithine is divided into three to six daily doses [Schulze et al 1998, Schulze et al 2001].
- Dietary restriction of arginine to 15-25 mg/kg/day that corresponds to 0.4-0.7 g/kg/day protein intake [Schulze et al 1998, Schulze et al 2001, Schulze et al 2003]
    - To prevent protein malnutrition, essential amino acid medical formula should be supplemented (0.5-0.8g/kg/day). Available databases (e.g., the US Department of Agriculture National Nutrient Database) can be used to determine exact arginine content of foods to allow precise calculation of daily arginine intake in individuals with GAMT deficiency [Mercimek-Mahmutoglu et al 2012b].
    - Because of the challenges involved in understanding arginine restriction, reading dietary labels, and calculating arginine intake (particularly since arginine content is not always indicated), many centers use protein restriction instead [Mercimek-Mahmutoglu et al 2012b, Mercimek-Mahmutoglu et al 2014b].

Treatment outcome of symptomatic individuals with GAMT deficiency

- **Global developmental delay and intellectual disability** improved only in 21% of the individuals. None of the individuals achieved normal development or cognitive functions on treatment [Mercimek-Mahmutoglu et al 2006, Stockler-Ipsiroglu et al 2014].
- **Seizures.** In 18% of individuals seizures were eliminated; in 49% seizure frequency decreased; 33% of individuals had no improvement in seizures [Mercimek-Mahmutoglu et al 2006, Stockler-Ipsiroglu et al 2014].
- **Movement disorder.** Improvement was seen in 60% of individuals; in 40% of individuals, there was no change in the movement disorder [Mercimek-Mahmutoglu et al 2006, Stockler-Ipsiroglu et al 2014].

Treatment outcome of asymptomatic individuals with GAMT deficiency

- Normal neurodevelopmental outcome has been reported in three individuals with GAMT deficiency who were diagnosed and treated in the neonatal periodbased on a positive family history of GAMT deficiency in an older sib [Schulze et al 2006, El-Gharbawy et al 2013, Viau et al 2013].
- Another asymptomatic sib treated from age eight days showed global developmental delay and hypotonia at age 11 months. The authors suggested compliance problems in this family [Dhar et al 2009].

AGAT Deficiency

Treatment of AGAT deficiency aims to replenish cerebral creatine levels by supplementation with creatine monohydrate in oral doses ranging from 400 to 800 mg/kg BW/day in three to six divided doses.

Treatment outcome of symptomatic individuals with AGAT deficiency. Treatment outcome results were reported in 11 individuals with AGAT deficiency [Battini et al 2002, Edvardson et al 2010, Verma 2010, Nouioua et al 2013]. If initiation of treatment was after age ten years, no improvement in cognitive function or intellectual disability was seen [Battini et al 2002, Edvardson et al 2010, Verma 2010, Nouioua et al 2013]. Normal cognitive function was reported in a female whose treatment was initiated before age two years [Ndika et al 2012]. Muscle weakness was improved in all individuals treated with creatine monohydrate [Edvardson et al 2010, Verma 2010, Nouioua et al 2013].

Treatment outcome of asymptomatic individuals with AGAT deficiency. An asymptomatic sib treated from age four months with creatine monohydrate supplementation therapy had normal neurodevelopment at age 18 months; in contrast, his sisters had already shown signs of developmental delay at this age [Battini et al 2006].

CRTR Deficiency

The goal of treatment is to replenish cerebral creatine levels. Treatment of both males and females with CRTR deficiency with creatine-monohydrate was not successful [Stockler-Ipsiroglu et al 2012]. Only one heterozygous female with learning disability and mildly decreased creatine concentration on brain ^{1}H-MRS showed mild improvement on neuropsychological testing after 18 weeks of treatment with creatine-monohydrate (250-750 mg/kg/day) [Cecil et al 2001]. Additionally, combined arginine and glycine supplementation therapy successfully treated intractable epilepsy in a female with CRTR deficiency [Mercimek-Mahmutoglu et al 2010a].

Since the enzymes for creatine biosynthesis are present in the brain [Braissant & Henry 2008], individuals with CRTR deficiency have been treated with L-arginine and L-glycine, precursors in the biosynthesis of creatine.

Treatment has included:

- Creatine monohydrate 100-200 mg/kg BW/day in 3 doses
- Arginine (hydrochloride or base) 400 mg/kg BW/day in 3 doses
- Glycine 150 mg/kg BW/day in 3 doses

The authors recommend that all three of the supplements listed above be started together in new patients – especially in early childhood – to slow disease progression. The clinical effectiveness of treatment with three supplements has not been confirmed.

Treatment outcome of individuals with CRTR deficiency. To date 22 males and three females with CRTR deficiency have been treated with L-arginine with or without glycine supplementation [van de Kamp et al 2014].

- In some patients improvements were reported, but in general results appeared to be discouraging and cerebral creatine was not restored [van de Kamp et al 2014].
- Four males and two females with CRTR deficiency treated for 42 months with creatine, arginine, and glycine showed increased muscle mass and improved gross motor skills [Valayannopoulos et al 2012].
- Nine males with CRTR deficiency showed improvement in locomotor and personal social IQ subscales [van de Kamp et al 2012].
- Combined arginine and glycine supplementation therapy successfully treated intractable epilepsy in a female with CRTR deficiency [Mercimek-Mahmutoglu et al 2010a].

Prevention of Primary Manifestations

See Treatment of Manifestations.

Surveillance

For patients undergoing treatment:

- Determination of cerebral creatine level by in vivo ^{1}H-MRS should be performed:
  - For individuals with GAMT and AGAT deficiency to monitor cerebral creatine levels during creatine supplementation therapy;
  - For individuals with CRTR deficiency to monitor cerebral creatine levels for the assessment of treatment outcome [Mercimek-Mahmutoglu et al 2010b, van de Kamp et al 2012].
- For GAMT deficiency: growth and nutritional status (plasma GAA levels, amino acids, ammonia, protein, albumin, pre-albumin levels) should be monitored every three to six months.
- For CRTR deficiency: plasma GAA levels and plasma amino acids should be monitored every three to six months as high-dose arginine and glycine supplementation can result in increased GAA levels.
- Repeat GFR annually for assessment of kidney function while on creatine supplementation therapy to detect possible creatine-associated nephropathy [Barisic et al 2002].
- Perform neuropsychological assessment of cognitive functions and speech.

Evaluation of Relatives at Risk

It is appropriate to evaluate neonates at-risk for GAMT deficiency or AGAT deficiency to allow for early diagnosis and treatment.

Evaluations can include:

- Molecular genetic testing if the pathogenic variants in the family are known;
- Biochemical genetic testing if the pathogenic variants in the family are not known.

See Genetic Counseling for issues related to evaluation of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Transport of dodecyl creatine ester incorporated into lipid nanocapsules (LNCs) was investigated using an in vitro cell-based blood-brain barrier model. It has been shown that these LNCs can cross the blood-brain barrier and enter brain endothelial cells. In human fibroblasts with deficient SLC6A8 protein function, all or part of the dodecyl creatine ester was released from the LNCs and biotransformed to creatine [Trotier-Faurion et al 2015].

A brain-specific *Slc6a8* knockout mouse was successfully treated with the cyclocreatine, which is a creatine analog. Brain cyclocreatine and cyclocreatine phosphate were detected on cyclocreatine treatment in the brain-specific *Slc6a8* knockout mice at nine weeks of cyclocreatine treatment compared to the creatine and placebo treatment in the same mice. Cyclocreatine-treated brain-specific *Slc6a8* knockout mice showed improvements in cognitive abilities using novel object recognition and spatial learning and memory tests. Thus, cyclocreatine appears promising as a potential therapy for CRTR deficiency. Clinical trials are underway to prove its use in individuals with CRTR deficiency.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

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. —ED.

Mode of Inheritance

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

CRTR 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 (i.e., carriers of one *GAMT* or *GATM* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

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 that s/he is heterozygous for a *GAMT* or *GATM* pathogenic variant is 2/3.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

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 of a *GAMT* or *GATM* pathogenic variant.

Carrier Detection

Molecular genetic testing. Carrier testing for at-risk relatives requires prior identification of the *GAMT* or *GATM* pathogenic variants in the family.

Risk to Family Members – X-Linked Inheritance

Parents of a Proband

- The father of a male with CRTR deficiency will not have the disorder nor will he be hemizygous for the *SLC6A8* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected male, the mother of an affected male is an obligate heterozygote (carrier). Note: if a woman has more than one affected child and no other affected relatives and if the *SLC6A8* pathogenic variant cannot be detected in her leukocyte DNA, she has germline mosaicism; 7% of mothers in a retrospective study of 85 families had somatic/germline mosaicism [van de Kamp et al 2013a].
- If a male is the only affected family member (i.e., a simplex case), several possibilities regarding his mother's genetic status need to be considered:
    - The affected male has a *de novo SLC6A8* pathogenic variant and his mother is not heterozygous for the variant [Salomons et al 2003, van de Kamp et al 2013a, van de Kamp et al 2014]. *SLC6A8* pathogenic variants occurred *de novo* in 30% of the individuals with CRTR deficiency in the van de Kamp et al [2013a] retrospective study.
    - His mother has a *de novo SLC6A8* pathogenic variant, either (a) as a "germline pathogenic variant" (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, van de Kamp et al 2013a].
    - His mother is heterozygous for an *SLC6A8* pathogenic variant.
- Heterozygous mothers may have a history of learning disability or mild intellectual disability or seizures [Mercimek-Mahmutoglu et al 2010a, van de Kamp et al 2011] (see Clinical Description, CRTR Deficiency, **Heterozygous Females**).

Sibs of a proband

- The risk to sibs depends on the genetic status of the mother.
- If the mother of the proband has an *SLC6A8* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygous and may develop clinical findings related to the disorder (see Clinical Description, CRTR Deficiency, **Heterozygous Females**).
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *SLC6A8* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism [Betsalel et al 2008].

Offspring of a proband. No affected male has reproduced.

Other family members

- The proband's maternal aunts may be at risk of being heterozygotes (carriers) for the *SLC6A8* pathogenic variant and the aunts' offspring, depending on their gender, may be at risk of being heterozygous for the pathogenic variant or of being affected.
- In one family, a maternal aunt with verbal memory deficit and a mild confrontational naming weakness was described [deGrauw et al 2003].

Carrier Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the pathogenic variant has been identified in the proband.

Note: (1) Females who are heterozygous for an *SLC6A8* pathogenic variant may develop clinical findings related to the disorder (see Clinical Description, CRTR Deficiency, **Heterozygous Females**). (2) Identification of female carriers requires either (a) prior identification of the *SLC6A8* pathogenic variant in the family or, (b) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

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 genetic 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 heterozygous or are at risk of being heterozygous.

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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *GAMT, GATM, or SLC6A8* pathogenic variant(s) have been identified in an affected family member, prenatal testing or preimplantation genetic diagnosis for a pregnancy at increased risk may be an option that a couple may wish to consider.

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 for prenatal diagnosis was performed at 15 weeks' gestation in the mother of a child age ten years with GAMT deficiency. Guanidinoacetate was 11.43 µmol/L (normal range for 15 weeks of amenorrhea was 2.96 ± 0.70 µmol/L) [Cheillan et al 2006].

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Association for Creatine Deficiencies**
  1024 Bayside Drive
  Suite 532
  Newport Beach CA 92660
  Email: kim@creatineinfo.org
  www.creatineinfo.org
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  501 3rd Street Northwest
  Suite 200
  Washington DC 20001
  Phone: 202-387-1968
  Fax: 202-387-2193
  Email: sis@aaidd.org
  www.aaidd.org

- **American Epilepsy Society (AES)**
  www.aesnet.org
- **Children Living with Inherited Metabolic Diseases (CLIMB)**
  United Kingdom
  Phone: 0800-652-3181
  Email: info.svcs@climb.org.uk
  www.climb.org.uk
- **Epilepsy Foundation**
  8301 Professional Place East
  Suite 200
  Landover MD 20785-7223
  Phone: 800-332-1000 (toll-free)
  Email: ContactUs@efa.org
  www.epilepsy.com
- **Medline Plus**
  Intellectual Disability
- **National Center on Birth Defects and Developmental Disabilities**
  1600 Clifton Road
  MS E-87
  Atlanta GA 30333
  Phone: 800-232-4636 (toll-free); 888-232-6348 (TTY)
  Email: cdcinfo@cdc.gov
  Intellectual Disability
- **National Library of Medicine Genetics Home Reference**
  Guanidinoacetate methyltransferase deficiency
- **Association for Creatine Deficiencies Patient Registry**
  www.creatineinfo.org/patient-registry

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	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GAMT	19p13.3	Guanidinoacetate N-methyltransferase	GAMT @ LOVD	GAMT	GAMT
GATM	15q21.1	Glycine amidinotransferase, mitochondrial	GATM @ LOVD	GATM	GATM
SLC6A8	Xq28	Sodium- and chloride-dependent creatine transporter 1	SLC6A8 @ LOVD	SLC6A8	SLC6A8

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, 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	CEREBRAL CREATINE DEFICIENCY SYNDROME 1; CCDS1
601240	GUANIDINOACETATE METHYLTRANSFERASE; GAMT
602360	L-ARGININE:GLYCINE AMIDINOTRANSFERASE; GATM
612718	CEREBRAL CREATINE DEFICIENCY SYNDROME 3; CCDS3
612736	CEREBRAL CREATINE DEFICIENCY SYNDROME 2; CCDS2

Molecular Genetic Pathogenesis

Creatine is synthesized by one of two enzymatic reactions:

- 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)
- 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.

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 [Item et al 2001, Verhoeven et al 2003, Verhoeven et al 2004]. In addition, functional testing has been performed for many *GAMT* and *SLC6A8* variants [Rosenberg et al 2007, Betsalel et al 2012, Mercimek-Mahmutoglu et al 2012a, Mercimek-Mahmutoglu et al 2014a, Desroches et al 2015].

GAMT

Gene structure. *GAMT* comprises six exons spanning about 5 kb, forming an open reading frame of 711 nucleotides. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants. Five variants predicted to be possibly damaging (using in silico analysis tools including p.Pro8Thr, p.Tyr27His p.Met71Val, p.Val95Ile, and p.Thr146Arg) showed normal GAMT enzyme activity using site-directed mutagenesis, and were thus determined to be non-pathogenic [Mercimek-Mahmutoglu et al 2014a, Desroches et al 2015].

Pathogenic variants. See Table 6. About 60 different pathogenic variants located in various exons have been found in individuals with GAMT deficiency [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 2007, Vodopiutz et al 2007, Dhar et al 2009, O'Rourke et al 2009, Sempere et al 2009a, Mercimek-Mahmutoglu et al 2014a, Stockler-Ipsiroglu et al 2014].

GAMT pathogenic variants comprise nonsense and missense variants, splice errors, insertions, deletions, and frameshifts. The majority of pathogenic variants (>60%) are missense [Mercimek-Mahmutoglu et al 2014a, Stockler-Ipsiroglu et al 2014].

The most frequent pathogenic variants were c.327G>A (24%; 23/94 alleles) and c.59G>C (21%; 20/94 alleles), detected in 47 affected individuals; 27 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 2007, Vodopiutz et al 2007, Dhar et al 2009, O'Rourke et al 2009, Sempere et al 2009a].

Table 6.

Selected *GAMT* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.59G>C	p.Trp20Ser	NM_000156.4 NP_000147.1
c.327G>A [1]	See footnote 1	
c.299_311dup13	p.Arg105GlyfsTer26	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

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

1. The pathogenic variant 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

Gene structure. The normal *GATM* genomic DNA is 16,858 bp in length and comprises nine exons [Battini et al 2002]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Only seven *GATM* pathogenic variants causing AGAT deficiency have been reported (see Table 7). Five pathogenic variants occurred in the homozygous state.

Table 7.

Selected *GATM* Pathogenic Variants

DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Reference Sequences
c.446G>A [2] (9297G>A)	p.Trp149Ter	NM_001482.2 NP_001473.1
c.484+1G>T (IVS3+1G>T) [3]	--	
c.1111dupA [4]	p.Met371AsnfsTer6	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

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

1. Variant designation that does not conform to current naming conventions
2. The c.446G>A pathogenic nonsense variant 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 catalyzes the first reaction in creatine biosynthesis and transfers amidino group from arginine to glycine to form ornithine and guanidinoacetate. Guanidinocetate 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 pathogenic alleles (p.Trp149Ter and p.Ala97ValfsTer11) showed no detectable enzyme activity in the cultivated lymphoblasts [Item et al 2001, Battini et al 2002, Ndika et al 2012]. 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

Gene structure. *SLC6A8* comprises 13 exons and spans 8.4 kb. The SLC6A8 mRNA is 3580 bp (reference sequence NM_005629.3) [Salomons et al 2001]. *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]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The LOVD Database lists 65 reported pathogenic variants from 85 families with SLC6A8 deficiency [van de Kamp et al 2013b]. The most common pathogenic variants were missense (31%) and three-base pair (in-frame) deletions (24%) [van de Kamp et al 2013a]. Certain pathogenic variants have been detected in several unrelated families. For example, c.1006_1008delAAC (in 5 families) and c.1222_1224delTTC (in 7 families) both result in the deletion of a three-nucleotide duplication [van de Kamp et al 2013b]. The pathogenic nature of many missense variants has been established by overexpression in primary SLC6A8-deficient cells for 20 missense variants [Rosenberg et al 2007, Betsalel et al 2011, van de Kamp et al 2013a].

Single-exon deletions up to whole-gene deletions and even contiguous gene deletion have been reported [Anselm et al 2006, van de Kamp et al 2015, LOVD Database].

Table 8.

Selected *SLC6A8* Pathogenic Variants

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

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

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

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 pathogenic variants resulted in impaired creatine uptake in fibroblasts when cultured at physiologic levels of creatine [Salomons et al 2003, van de Kamp et al 2013a]. In the presence of a strong suspicion of CRTR deficiency in a male (e.g., elevated urine creatine-to-creatinine ratio or creatine deficiency in the brain ^{1}H-MRS) with no detected pathogenic variant or with a novel variant of uncertain pathogenicity, creatine uptake studies in cultured fibroblasts are important in the assessment of CRTR 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 valuable in a symptomatic heterozygous female with a novel variant of uncertain pathogenicity, but due to skewed X-inactivation a normal creatine uptake does not rule out CRTR deficiency.

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Suggested Reading

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Chapter Notes

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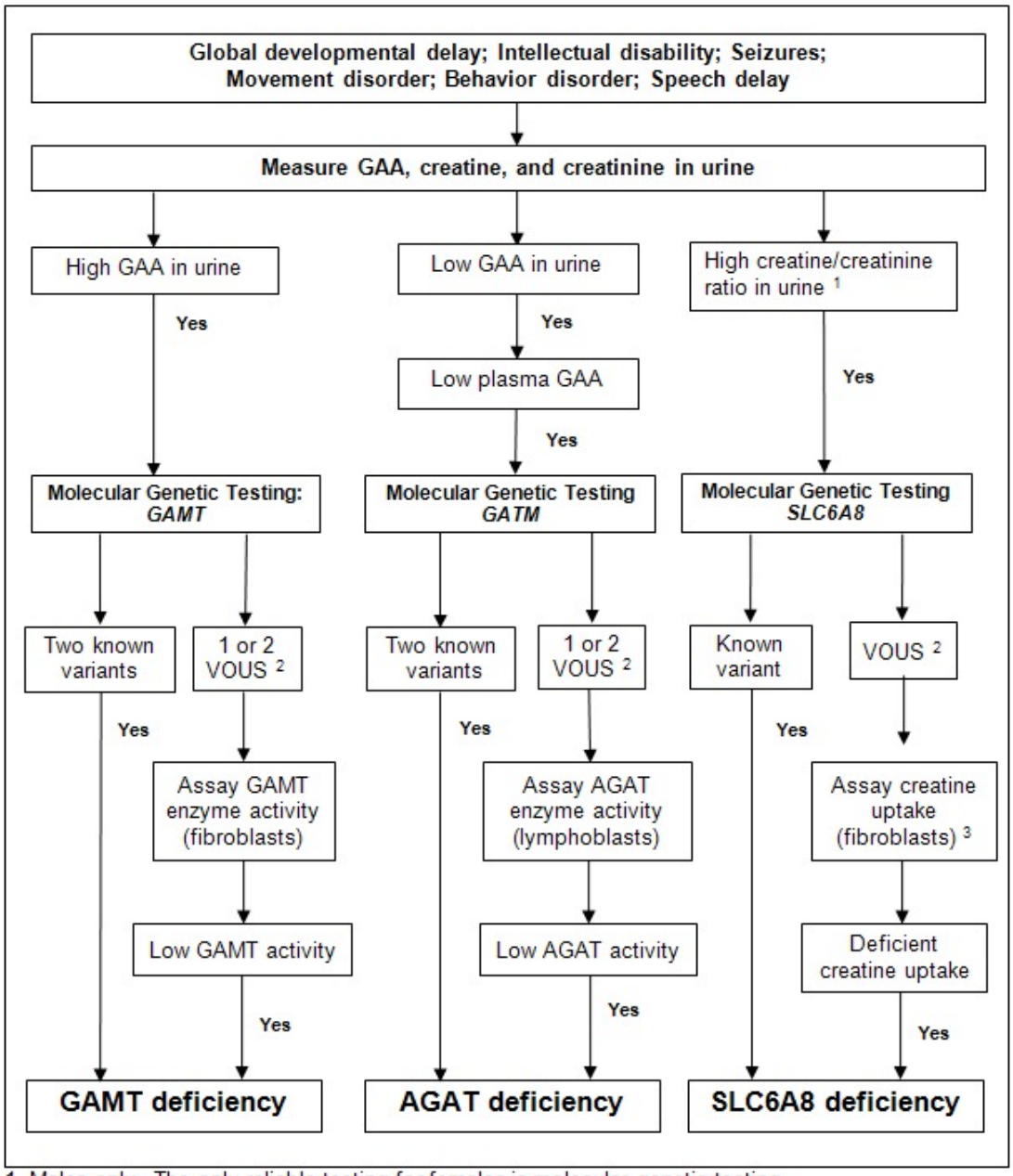
Figures



1. Males only. The only reliable testing for females is molecular genetic testing.
2. VOUS = variant of uncertain significance
3. Creatine uptake can be used in females when molecular genetic testing has identified either a novel variant of uncertain clinical significance or no variant 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 2011].

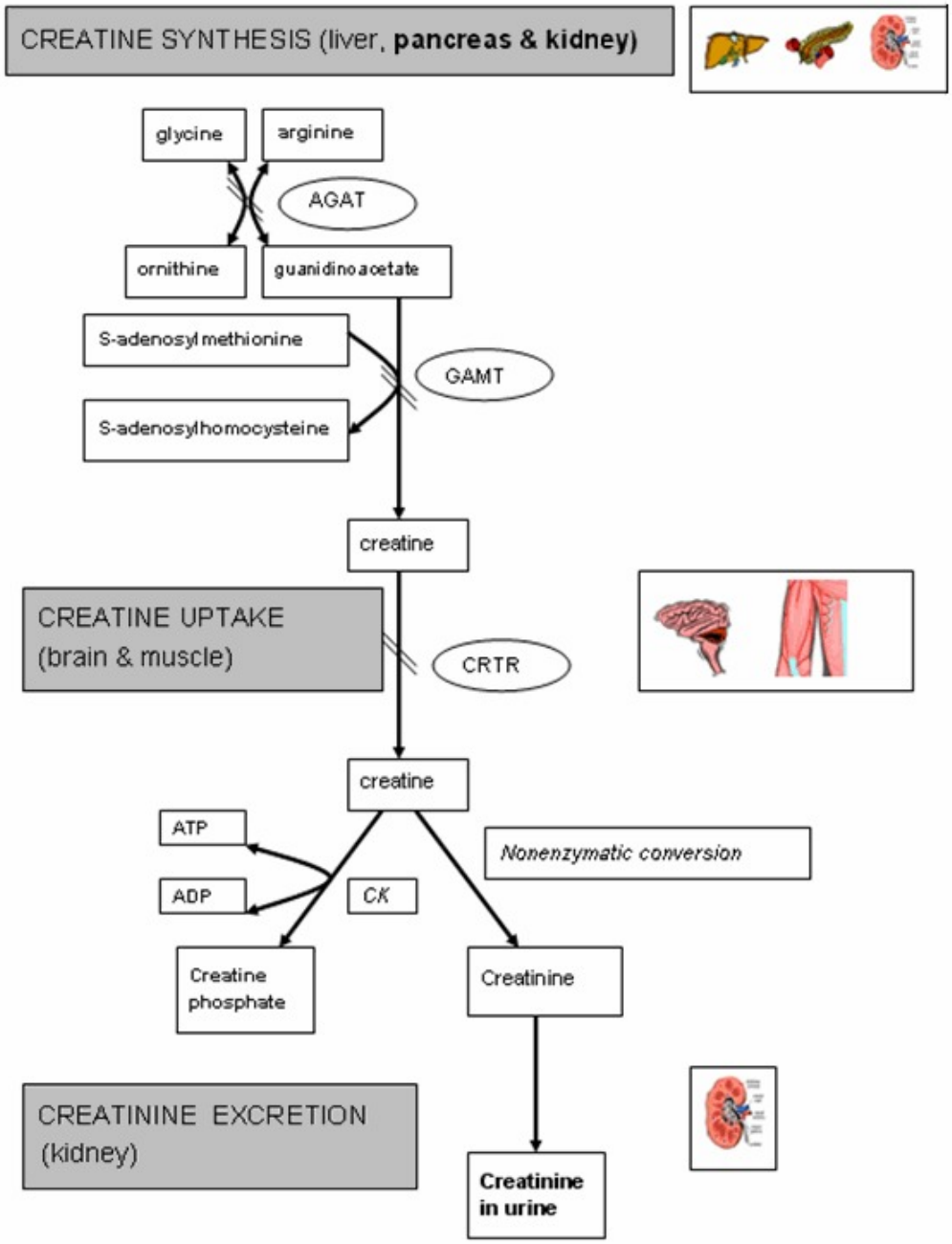


Figure 2.

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 CREATININE EXCRETION in the urine

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