A visual guide to understand
CEREBRAL CREATINE DEFICIENCY SYNDROMES (CCDS)

CCDS are 3 rare genetic diseases that involve problems with making creatine or transporting creatine to brain cells.

MEET CREATINE

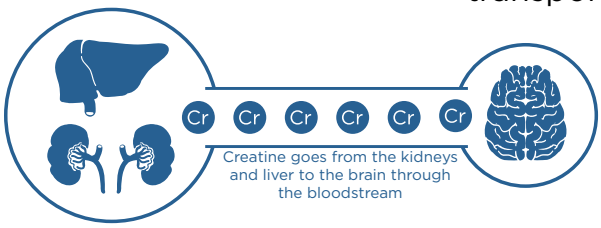
Creatine (Cr) is a substance the body needs to store and produce energy. About half of our creatine comes from food, mainly meat and dairy products. The other half is produced in the kidney and the liver.

CRITICAL FOR BRAIN ENERGY AND PERFORMANCE

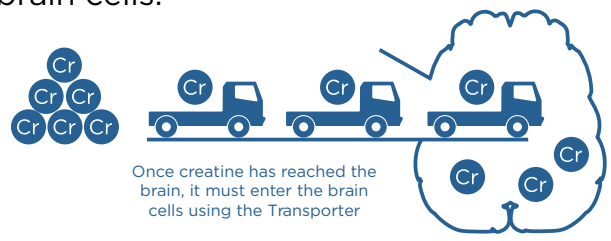
It is needed for energy and performance by the brain and muscles.

HOW IS CREATINE MADE AND HOW DOES IT GET TO BRAIN CELLS?

It takes 3 steps to get creatine made and transported to brain cells and muscles. The first 2 steps make creatine in the kidneys and liver and the 3rd step involves transporting creatine to brain cells.



Creatine goes from the kidneys and liver to the brain through the bloodstream



Once creatine has reached the brain, it must enter the brain cells using the Transporter

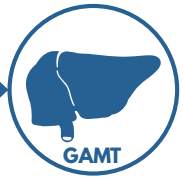
NORMAL CREATINE PRODUCTION LOOKS LIKE THIS

Step 1

- Produces GAA (Guanidinoacetate)
- Involves the AGAT enzyme
- Takes place in the kidneys

GAA

Step 2



- Transforms GAA through a process called methylation
- Involves the GAMT enzyme
- Takes place in the liver

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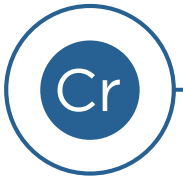
Creatine Produced!



- Needed for energy
- Needed for performance

Step 3

- Creatine Transporter (made by the SLC6A8 gene) is needed to transport creatine to brain cells

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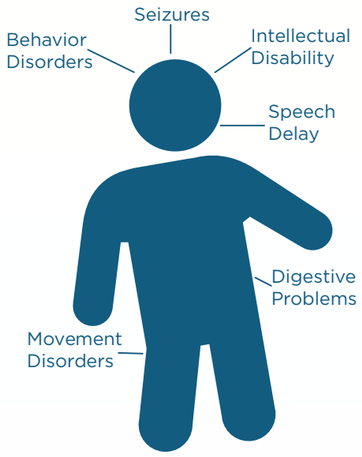
Creatine in the Brain!

- Supports normal intellectual development and performance

WHAT DO CEREBRAL CREATINE DEFICIENCY SYNDROMES LOOK LIKE?

The 3 CCDS share many of the same signs and symptoms



Global developmental delay, or GDD (delay in meeting 2 or more developmental milestones, including body movements, large and small; speech and language; ability to think; social and personal skills; and daily life skills). GDD is a term applied to children under 5 years and typically predicts a future diagnosis of intellectual disability.[1]

Intellectual disability, or ID (marked by serious limitations in intellectual functioning and behaviors and skills needed to function in daily life). ID is a term applied to older children whose intelligence can be measured with an IQ test. It appears before age 18 years.[1]

CTD

CTD (creatine transporter deficiency) is caused by a genetic mutation in the SLC6A8 gene. CTD is a rare condition that is described as the second-most common cause of X-linked intellectual disability.

The most common CTD signs and symptoms are:

- Speech/language development delay[2]
- Seizures involving muscle stiffening and/or jerking[2]
- Behavior disorders such as autism and attention deficit and/or hyperactivity disorders[2]
- Movement disorders involving lack of coordination and delays in crawling, sitting, and walking[2,3]
- Vomiting and digestive problems[3]
- Failure to thrive[3]

GAMT

GAMT (guanadinoacetate methyltransferase) deficiency is a rare condition caused by an alteration of the GAMT gene. Early symptoms of GAMT deficiency appear in children aged 3 months to 3 years. Here are the most common signs and symptoms:[2]

- Intellectual disability, mild to severe
- Language delay
- Epilepsy or seizures ranging from occasional to severe and not responsive to anti-seizure medications
- Movement disorders involving uncontrollable jerking or slowness and delays in crawling, sitting, and walking
- Behavior disorders involving hyperactivity, autism, or self-injury

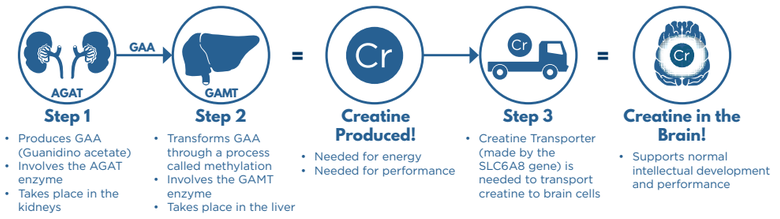
AGAT

AGAT (arginine:glycine amidinotransferase) deficiency is a very rare disorder caused by an alteration of the GATM gene. Here are the two most common signs and symptoms:[2]

- Intellectual disability, mild to moderate
- Muscle weakness

Missing enzymes or the creatine transporter can lead to CCDS

Normal Creatine Production



AGAT Deficiency

GAMT Deficiency

Creatine Transporter Deficiency

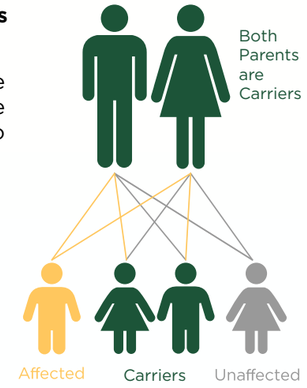
GAMT and AGAT deficiencies are treatable conditions. Supplementary creatine, supplementary ornithine (an important amino acid), and a protein-restricted diet are often prescribed. Early diagnosis and treatment may prevent development of intellectual disability and other symptoms of GAMT and AGAT deficiency.[2]

CTD-Appropriate symptomatic therapies may include occupational therapy, physiotherapy, speech-language therapy, and behavior therapy. Anti-seizure medications may be used for seizure management.

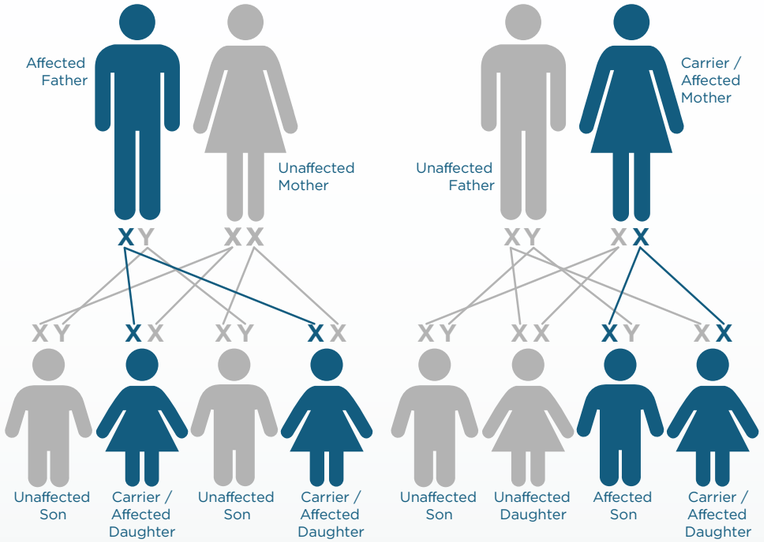
This is how CCDS get inherited in families

GAMT and AGAT - Autosomal Recessive Disorders

- If your child has either GAMT deficiency or AGAT deficiency, both you and your partner are carriers of the genetic alteration that causes the disorder. Carriers do not have symptoms nor do they develop the disorder themselves but they can pass the disorder on to their children.
- If your child has one of these disorders, each sibling has a 25% chance of having the same disorder, a 50% chance of being a carrier without symptoms, and a 25% chance of being unaffected and not a carrier.
- Siblings of a parent whose child has GAMT or AGAT deficiency are at 50% risk of being carriers of the disorder.



CTD - X-linked Disorder



Here's how X-linked disorders are passed from parents to children:[2,7]

In an X-linked disorder, an affected father can pass the mutation to his daughter (who inherits her father's X chromosome) but not to his son (who inherits his father's Y chromosome). Genetic testing has shown that most children with CTD have either inherited the mutation from their mother or they are the first person in their family to have it (de novo mutation). Mothers who have the mutation may have a mild intellectual disability or a history of learning disabilities. They may also show no sign of CTD at all. If a mother has the mutation, every one of her children has a 50% chance of inheriting it. Girls who inherit the mutation will become carriers and may or may not experience mild symptoms of CTD. Boys who inherit the mutation will develop CTD.

Learn More About CCDS at SCREENCREATINE.ORG

CCDS are 3 rare genetic diseases that involve problems with making creatine or transporting creatine to brain cells.

SPECIALISTS

Healthcare professionals who specialize in the diagnosis and/or management of CCDS may include the following:

- Metabolic Geneticists
- Pediatric Neurologists
- Genetic Counselors
- Developmental-Behavioral Pediatricians

LABS

If a child is missing early developmental milestones, a healthcare professional may order several tests. When CCDS are suspected, these tests may be used to confirm (or not) the diagnosis:

- A urine test
- A blood test
- An imaging procedure called magnetic resonance spectroscopy (MRS)
- Genetic testing

CONNECT WITH CCDS PATIENT ADVOCACY GROUPS

Go to **ScreenCreatine.org** to get the latest update on patient organizations and resources available throughout the world on CCDS.

Be a Creatine Hero and remember to Screen for Creatine!

References:

1. AAP Definitions of ID and GDD accessed from:
Moeschler et al. Comprehensive Evaluation of the Child with Intellectual Disability or Global Developmental Delays. Pediatrics September 2014 http://pediatrics.aappublications.org/content/134/3/e903

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3. Miller JS et al. Red Flags for Creatine Transporter Deficiency, and Potential Outcome Variables for the Severely Impaired. Poster first presented at Society for Developmental Behavioral Pediatrics (SDBP) 2016 Annual Meeting Savannah, GA September 2016.

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5. U.S. National Library of Medicine, Medline Plus. https://medlineplus.gov/ency/article/002052.htm

6. Kurosawa Y, DeGrauw TJ, Lindquist DM et al. Cyclocreatine treatment improves cognition in mice with creatine transporter deficiency. J Clin Invest. 2012;122(8):2837-2846. doi:10.1172/JCI59373.

7. NIH National Human Genome Research Institute, https://www.genome.gov/glossary/index.cfm?id=209

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