This is Creatine

Creatine is formed in the **liver** and **kidneys**. It is also found in some of the foods we eat, such as fish, meat, and dairy. Creatine is necessary for energy usage in all cells of the body and is crucial for brain development.

Our Bodies Need Creatine

Production and transportation of creatine are essential to its use in the body. Two enzymes make creatine, AGAT (L-Arginine:glycine amidinotransferase) and GAMT (guanidinoacetate methyltranserase).

It Requires a Transporter

The CrT transporters allow creatine to be transported into the cells of the body. Without this transporter, creatine can't get into the brain and muscles.

Diagnostic Testing

Proper diagnosis and early intervention is critical to establish treatments needed to improve life quality and longevity for CCDS patients.

METABOLITE SCREENING

- Testing of both urine and plasma is necessary to screen for all three disorders.
- The concentration of creatine (CR), guanidinoacetate (GAA), and creatinine (Crn) are measured.
- Gene sequencing should be considered if there is a suspicion of CTD in a female with normal metabolite screening.

PROTON MAGNETIC RESONANCE SPECTROSCOPY (1H-MRS) OF THE BRAIN

- Can be requested at the same time as brain MRI. Useful for measuring creatine levels in the brain.
- Decreased/absent creatine peak in the brain for all three disorders. Creatine level is low in females heterozygous for CTD, but may overlap with unaffected individuals.
- Brain MRI may show non-specific findings such as delayed myelination, hyperintensities of the globus pallidus, and cerebral atrophy.

GENE SEQUENCING

Sequencing of the genes GATM, GAMT, and SLC6A8

ENZYME ASSAYS

Cultured skin fibroblasts are not usually required for diagnosis, but may be helpful when metabolite and gene sequencing test results are unclear. This includes measurement of AGAT and GAMT activity and creatine uptake studies for CTD.

LABORATORY TESTING

Resources offering CCDS testing information:
Association for Creatine Deficiencies: creatineinfo.org/screening/
ScreenCreatine: screencreatine.org/labs/
Genetic Testing Registry (GTR): www.ncbi.nlm.nih.gov/gtr/

Metabolite Screening Test Results:

AGAT	
Plasma	
GAA:	Low
Creatine:	Low/normal
Urine[a]	
GAA:	Low
Creatine:	Low/normal

GAMT	
Plasma	
GAA:	Elevated
Creatine:	Low
Urine[a]	
GAA:	Elevated
Creatine:	Low/normal

CTD	
Plasma	
GAA:	Normal
Creatine:	Normal[b]
Urine[a]	
GAA:	Normal
Creatine:	Elevated in males; may be normal in females[c]

[a]Urine metabolites are measured relative to creatinine.

[b]Urine is needed to diagnose creatine transporter deficiency (CTD) in males, CTD will be missed in males if only plasma is screened.

[c]Urine creatine can be normal in females who are heterozygous for CTD. Sequencing of the SLC6A8 gene is needed for assessment of females for CTD.

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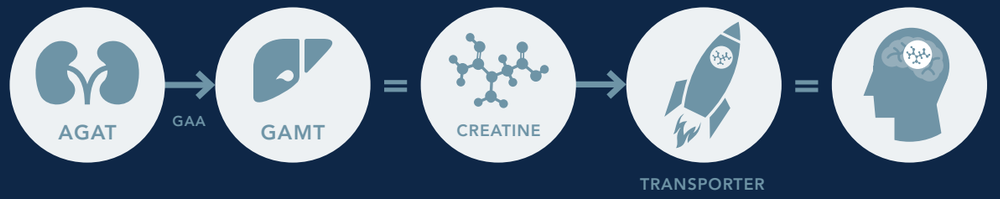
A Guide to Understanding CCDS

Cerebral Creatine Deficiency Syndromes

ACD
ASSOCIATION FOR CREATINE DEFICIENCIES

CEREBRAL CREATINE DEFICIENCY SYNDROMES (CCDS) are three rare, inborn errors of creatine metabolism, in which the body's production or transportation of creatine is impaired.

NORMAL CREATINE PRODUCTION



AGAT DEFICIENCY

Arginine: Glycine Amidinotransferase Deficiency is an impairment of the first enzyme necessary for creatine production. Glycine and Arginine in the diet cannot combine to form guanidinoacetate (GAA). No creatine is produced.

MUTATED GENE: GATM

INHERITANCE: Autosomal Recessive (Two copies of an abnormal gene are present. Typically one from each parent.)

GAMT DEFICIENCY

Guanidinoacetate Methyltransferase Deficiency is an impairment of the second enzyme necessary for metabolizing guanidinoacetate into creatine, resulting in a buildup of unused guanidinoacetate (GAA). No creatine is produced.

MUTATED GENE: GAMT

INHERITANCE: Autosomal Recessive (Two copies of an abnormal gene are present. Typically one from each parent.)

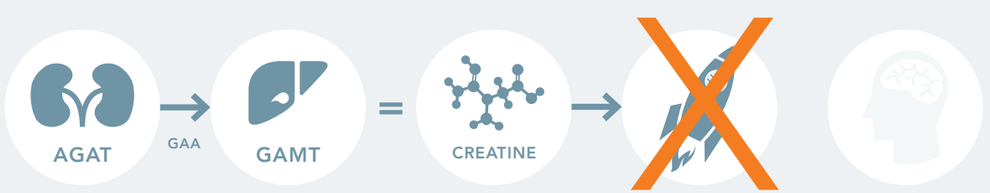
CTD

Creatine Transporter Deficiency is a mutation in the creatine transporter gene. This results in a blockage in the transportation of creatine to the brain. No creatine is utilized.

MUTATED GENE: SLC6A8

INHERITANCE: X-linked (Mutated gene is located on the X chromosome. Typically inherited from the mother or a "de novo mutation" that is not inherited, but is the first occurrence in a family.)

CTD FEMALES: About half of females with one mutated copy of the SLC6A8 gene (heterozygous) have intellectual disability, learning difficulties, or behavioral problems. The other half are unaffected carriers.



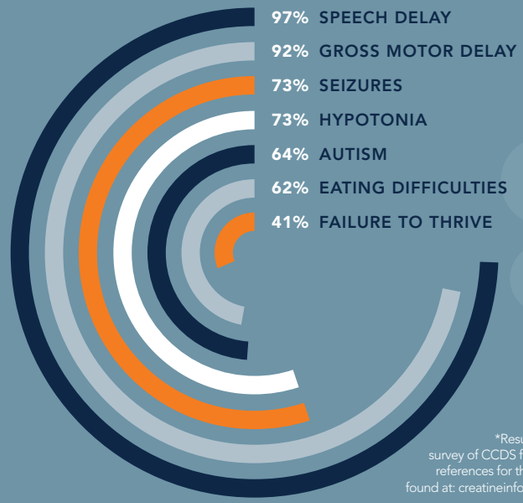
EARLY DIAGNOSES

It is encouraged that all individuals with Global Developmental Delay, Speech Delay, Hypotonia, Autism, or Epilepsy be screened for CCDS as early as possible.

Speech Delay may be particularly severe and is present in all affected children. Many individuals develop no speech, or speak only in single words.

Intellectual Disability of variable severity is typically present in all affected older children and adults.

CCDS CLINICAL SYMPTOMS



*Results from ACD 2017 survey of CCDS families. Additional references for this brochure can be found at: creatineinfo.org/acd-resources

TREATMENTS:

Treatment with oral supplementation is effective, if initiated early for AGAT and GAMT deficiencies. To date, supplementation has not been proven to be effective in individuals with CTD.

- Oral creatine monohydrate is given to replenish creatine levels in the brain and other tissues in individuals with AGAT and GAMT deficiencies.
- Low arginine/protein diet, l-ornithine supplementation, and sodium benzoate are used to reduce toxic levels of guanidinoacetate in individuals with GAMT deficiency.
- There may be some clinical benefit to a subset of individuals with CTD when treated with creatine monohydrate, l-arginine, and glycine. Additional treatments for CTD are under investigation.

FIND SUPPORT, CCDS RESOURCES, AND JOIN OUR PATIENT REGISTRY AT: CREATINEINFO.ORG