Guanidinoacetate Methyltransferase (GAMT) Deficiency

Also known as:

- Creatine deficiency syndrome due to GAMT deficiency
- GAMT deficiency

Definition:

The *GAMT* gene provides instructions for making the enzyme guanidinoacetate methyltransferase. This enzyme works to produce creatine, which is needed for the body to store and use energy correctly. When mutations exist in the *GAMT* gene, not enough creatine gets produced in the body. This causes symptoms to appear in parts of the body that require lots of energy, like the brain and muscles.

Diagnosis:

Sequencing of the *GAMT* gene will be performed as part of the screening algorithm. Diagnostic confirmation, under the direction of a specialist, may include measurement of guanidinoacetate (GUAC), creatine, and/or creatinine in urine and plasma. Cerebral creatine deficiency in brain MR spectroscopy is a hallmark characteristic of GAMT deficiency.

How is it inherited:

GAMT deficiency is inherited in an autosomal recessive pattern. Normally a person has two functional copies of the *GAMT* gene. In people with GAMT deficiency, both genes have a mutation. Each parent of a newborn with GAMT deficiency typically has one functional gene and one mutated gene, and is considered a carrier. When both parents are carriers, the chance of a newborn inheriting two mutated genes is 25%.

Newborn Screening:

- **Incidence:** The estimated incidence of GAMT deficiency in the general population ranges from 1 in 2,640,000 to 1 in 550,000.
- **New York State Method of Screening (First Tier):** Screening for GAMT is accomplished by analysis of GUAC and creatine by mass spectrometry. If concentrations are normal, the sample is deemed within acceptable limits. If abnormal, second tier testing is performed.
- **Second Tier Screening:** Samples with GUAC concentrations above a certain threshold will be tested a second time using a more specific assay. If concentrations are normal, the sample is deemed within acceptable limits. If abnormal, third tier screening is performed.

- **Third Tier Screening:** Sequencing of the *GAMT* gene.
- **Testing can be affected by:** Timing of sample collection; samples collected at less than 24 hours of age will be considered unsuitable. This is an enzyme reaction that may require time for the marker to accumulate.
- **Interpretation/reporting of data:** Results are reported as screen negative, borderline or as a referral. A repeat specimen should be collected for a borderline result. Prompt consultation with a specialist is required for a referral.
- **Referral to Specialty Care Center:** Babies with an abnormal newborn screen for GAMT are referred to an Inherited Metabolic Disease Specialty Care Center for a diagnostic evaluation.

Prognosis:

Prognosis is best for individuals who are diagnosed early in life, and begin treatment before the onset of symptoms. If individuals are diagnosed and treated later in life, intellectual disabilities and developmental delays cannot be reversed. However, treatment can prevent symptoms from worsening, and can help with movement coordination and behavioral problems. GAMT deficiency has not been shown to reduce an individual's lifespan.

Symptoms:

Symptoms of this disease may include mild to severe developmental delays, intellectual disabilities, poor muscle tone, seizures, speech delays, hyperactivity, and involuntary movements. These symptoms usually appear between three months and three years of life.

Symptoms in carriers:

Carriers do not typically have symptoms.

Treatment:

Treatment includes taking an oral creatine to supplement the amount of creatine in an individual's system. GUAC levels can be reduced by ornithine supplementation and Benzoate to reduce glycine levels and GUAC synthesis.

Educational materials:

More information:

https://ghr.nlm.nih.gov/condition/guanidinoacetate-methyltransferase-deficiency

https://creatineinfo.org/

https://rarediseases.info.nih.gov/diseases/2578/guanidinoacetate-methyltransferase-deficiency