

Variant: *NM\_138924.3:c.403G>T*

Version: 2.0

CA402995388 [↗](#)

2446459 (ClinVar) [↗](#)

**Gene:** GAMT ([HGNC:2593](#))

**Condition:** guanidinoacetate methyltransferase deficiency  
([MONDO:0012999](#))

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** d2085e1a-c394-464c-89b1-2934e44601b4

**Approved on:** 2025/12/10

**Published on:** 2025/12/10

## HGVS expressions

**NM\_138924.3:c.403G>T**

NC\_000019.10:g.1399184C>A

CM000681.2:g.1399184C>A

NC\_000019.9:g.1399183C>A

CM000681.1:g.1399183C>A

NC\_000019.8:g.1350183C>A

NG\_009785.1:g.7370G>T

ENST00000252288.8:c.403G>T

ENST00000447102.8:c.403G>T

ENST00000591788.3:c.86G>T

ENST00000640164.1:n.236G>T

ENST00000640762.1:c.334G>T

ENST00000252288.6:c.403G>T

ENST00000447102.7:c.403G>T

ENST00000591788.2:c.88G>T

NM\_000156.5:c.403G>T

NM\_138924.2:c.403G>T

NM\_000156.6:c.403G>T

**Pathogenic**

Met criteria codes **5**

PP4\_Strong

PM3\_Supporting

PP3\_Strong

PM2\_Supporting

PM5

Evidence Links **0**

## Expert Panel

Cerebral Creatine Deficiency Syndromes VCEP [↗](#)

## Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Cerebral Creatine Deficiency Syndromes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GAMT Version 2.0.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Cerebral Creatine Deficiency Syndromes VCEP

The NM\_000156.6:c.403G>T variant in GAMT is predicted to result in the missense substitution of aspartate at amino acid 135 (p.Asp135Tyr). This variant has been identified in one individual with guanidinoacetate methyltransferase deficiency with reduced creatine peak and visible guanidinoacetate peak on brain magnetic resonance spectroscopy, and elevated plasma guanidinoacetate with low creatine, with full GAMT gene sequencing (PMID: 19027335). This individual was a reported to be compound heterozygous for the variant and another variant in GAMT that has been classified as pathogenic for GAMT deficiency by the ClinGen CCDS VCEP, c.507\_521dup15 (p.Cys169\_Ser173dup), (ClinVar Variation ID: 431959) in unknown phase (0.5pts) (PMID: 19027335) (PM3\_Supporting). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001098 (1/91064 alleles) in the South Asian population, which is lower than the ClinGen CCDS VCEP’s threshold for PM2\_Supporting (<0.0004), meeting this criterion (PM2\_Supporting). The computational predictor REVEL gives a score of 0.938 which is above the threshold of 0.932, evidence that correlates with impact to GAMT function at the strong level (PMID: 36413997) (PP3\_Strong). A different missense variant at the same amino acid residue, c.403G>A (p.Asp135Asn) (ClinVar Variation ID: 573140), has been classified as pathogenic by the ClinGen CCDS VCEP (PM5). There is a ClinVar entry for this variant (Variation ID: 2446459). In summary, this variant meets criteria to be classified as pathogenic for guanidinoacetate methyltransferase (GAMT) deficiency. GAMT-specific ACMG/AMP Criteria applied, as specified by the ClinGen Cerebral Creatine Deficiencies Variant Curation Expert Panel (CCDS VCEP) (Specifications version 2.0.0): PP3\_Strong, PP4\_Strong, PM5, PM2\_Supporting, PM3\_Supporting, PM5, PP3, PP4\_Strong (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on December 10, 2025)

Met criteria codes

|                |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                                                               |
|----------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PP4_Strong     |    |    | The variant has been identified in one individual who showed elevated plasma guanidinoacetate with low creatine (2pts) and reduced ('small') creatine peak with evidence of guanidinoacetate peak on MRS (3pts) with full GAMT gene sequencing (PMID: 19027335) (PP4_Strong)                                                                  |
| PM3_Supporting |  |  | One individual with GAMT deficiency was reported to be compound heterozygous for the variant and another variant in GAMT that has been classified as pathogenic for GAMT deficiency by the ClinGen CCDS VCEP, c.507_521dup15 (p.Cys169_Ser173dup), (ClinVar Variation ID: 431959) in unknown phase (0.5pts) (PMID: 19027335) (PM3_Supporting) |
| PP3_Strong     |  |  | The computational predictor REVEL gives a score of 0.938 which is above the threshold of 0.932, evidence that correlates with impact to GAMT function at the strong level (PMID: 36413997) (PP3_Strong).                                                                                                                                      |
| PM2_Supporting |  |  | The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001098 (1/91064 alleles) in the South Asian population, which is lower than the ClinGen CCDS VCEP’s threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting).                                                                                   |
| PM5            |  |  | A different missense variant at the same amino acid residue, c.403G>A (p.Asp135Asn) (ClinVar Variation ID: 573140), has been classified as pathogenic by the ClinGen CCDS VCEP (PM5).                                                                                                                                                         |

Curation History 

