

Variant: NM_138924.3:c.202G>T

Version: 1.1

CA402997207 [↗](#)

2446456 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 9982600a-815b-4869-aaa0-c9456f12008e

Approved on: 2025/10/15

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HGVS expressions

NM_138924.3:c.202G>T

NC_000019.10:g.1399918C>A

CM000681.2:g.1399918C>A

NC_000019.9:g.1399917C>A

CM000681.1:g.1399917C>A

NC_000019.8:g.1350917C>A

NG_009785.1:g.6636G>T

ENST00000252288.8:c.202G>T

ENST00000447102.8:c.202G>T

ENST00000640762.1:c.133G>T

ENST00000252288.6:c.202G>T

ENST00000447102.7:c.202G>T

NM_000156.5:c.202G>T

NM_138924.2:c.202G>T

NM_000156.6:c.202G>T

Likely Pathogenic

Met criteria codes **5**

PP4_Moderate

PS3_Supporting

PM3_Supporting

PP3_Strong

PM2_Supporting

Evidence Links **1**

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.202G>T variant in GAMT is predicted to result in the missense substitution of glycine by cysteine at amino acid 68 (p.Gly68Cys). The variant has been reported in homozygosity in a proband and sibling with clinical symptoms consistent with GAMT

deficiency (PM3_Supporting). The proband has absent creatine peak and guanidinoacetate peak on brain MRS. Urine guanidinoacetate levels were elevated in all patients and were between 1.1 and 12 times above the upper limit of reference range, but specific values for each patient were not provided (PP4_Moderate) (PMID: 24415674). This variant is absent in gnomAD v4.1.0. (PM2_Supporting). The computational predictor REVEL gives a score of 0.994 which is above the threshold of 0.932, evidence that correlates with impact to GAMT function at the strong level (PMID: 36413997) (PP3_Strong). This variant was shown to result in undetectable GAMT enzymatic activity when transfected into GAMT-deficient fibroblasts (PMID: 24415674) (PS3_Supporting). There is a ClinVar entry for this variant (Variation ID: 2446456). In summary, this variant meets criteria to be classified as likely 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_Moderate, PS3_Supporting, PM2_Supporting, PM3_Supporting (Classification approved by the ClinGen Cerebral Creatine Deficiencies Variant Curation Expert Panel on October 15, 2025

Met criteria codes

PP4_Moderate			A proband and sibling with clinical symptoms consistent with GAMT deficiency are homozygous for the variant. The proband has absent creatine peak and guanidinoacetate peak on brain MRS (3pts). Urine guanidinoacetate levels were elevated in all patients and were between 1.1 and 12 times above the upper limit of reference range, but specific values for each patient were not provided (PM4_Moderate) (PMID: 24415674).
PS3_Supporting			PMID: 24415674: shown to result in undetectable GAMT enzyme activity in GAMT-deficient fibroblasts. <div>PMID: 24415674: shown to result in undetectable GAMT enzyme activity in GAMT-deficient fibroblasts.<div>PubMed:24415674 </div></div>
PM3_Supporting			Identified in one homozygous proband (0.5pts) (PMID: 24415674)
PP3_Strong			The computational predictor REVEL gives a score of 0.994 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			Variant is absent in gnomAD v4.1.0 (PM2_Supporting)

Curation History

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