

Variant: *NM_000156.6:c.623G>C*

Version: 1.0

CA9043555 [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: e89e7d7a-db98-4496-85e0-5e86e6cfeab3

Approved on: 2025/3/18

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HGVS expressions

NM_000156.6:c.623G>C

NC_000019.10:g.1397447C>G

CM000681.2:g.1397447C>G

NC_000019.9:g.1397446C>G

CM000681.1:g.1397446C>G

NC_000019.8:g.1348446C>G

NG_008283.1:g.18564C>G

NG_009785.1:g.9107G>C

ENST00000252288.8:c.623G>C

ENST00000640164.1:n.456G>C

ENST00000640762.1:c.554G>C

ENST00000252288.6:c.623G>C

NM_000156.5:c.623G>C

Likely Pathogenic

Met criteria codes **5**

PM3_Supporting

PP3

PP4_Strong

PM2_Supporting

PS3_Supporting

Not Met criteria codes **1**

PM5

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.623G>C variant in GAMT is a missense variant predicted to cause substitution of arginine by proline at amino acid 208 (p.Arg208Pro). This variant is absent in gnomAD v4.1.0. (PM2_Supporting). It has been reported in homozygosity in one individual with clinical symptoms consistent with GAMT deficiency (severe intellectual impairment, intractable seizures, movement disorder), deficient GAMT activity, and reduction of creatine on brain MRS, who showed clinical improvement on dietary treatment (PMID 24415674,

29506905) (PM3_Supporting, PP4_Strong). When expressed in GAMT-deficient fibroblasts, the variant resulted in ~4% wild type GAMT activity (PMID 24415674) (PS3_Supporting). The computational predictor REVEL gives a score of 0.751, which is in the range (0.644-0.773) that predicts impact to GAMT function at the supporting level (Pejaver et al, 2022, PMID: 36413997) (PP3). Two additional missense variants at this amino acid position have been reported; c.623G>A (p.Arg208His) (ClinVarID: 577478), and c.622C>T (p.Arg208Cys) (ClinVar ID: 544261). Both of these variants have been classified as variants of uncertain significance by the ClinGen CCDS VCEP. There is no ClinVar entry for this variant. In summary, this variant meets the criteria to be classified as likely pathogenic for GAMT deficiency. GAMT-specific ACMG/AMP criteria applied, as specified by the ClinGen CCDS VCEP (Specifications Version 2.0.0): PP4_Strong, PP3, PS3_Supporting, PM2_Supporting, PM3_Supporting. (Classification approved by the ClinGen Cerebral Creatine Deficiencies Variant Curation Expert Panel on March 18, 2025)

Met criteria codes

PM3_Supporting			One individual with symptoms consistent with GAMT deficiency is homozygous for the variant (0.5 points) (PMID: 24415674) (PM3_Supporting).
PP3			The computational predictor REVEL gives a score of 0.751, which is in the range (0.644-0.773) that predicts impact to GAMT function at the supporting level (Pejaver et al, 2022, PMID: 36413997) (PP3).
PP4_Strong			One patient has been reported with clinical symptoms consistent with GAMT deficiency (severe intellectual impairment, intractable seizures, movement disorder), deficient GAMT activity, and reduction of creatine on brain MRS (PMID 24415674) (PP4_Strong).
PM2_Supporting			This variant is absent in gnomAD v4.1.0. (PM2_Supporting).
PS3_Supporting			When expressed in GAMT-deficient fibroblasts, the variant resulted in ~4% wild type GAMT activity (PMID 24415674).
			When expressed in GAMT-deficient fibroblasts, the variant resulted in ~4% wild type GAMT activity (Fig 1). All transfections were done in triplicate, and green fluorescence of a EGFP tag was used to estimate the transfection efficiency. PubMed:24415674 

Not Met criteria codes

PM5			Two additional missense variants at this amino acid position have been reported; c.623G>A (p.Arg208His) (ClinVarID: 577478), and c.622C>T (p.Arg208Cys) (ClinVar ID: 544261). Both of these variants have been classified as variants of uncertain significance by the ClinGen CCDS VCEP.
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Curation History 

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