

Variant: NM_000156.6:c.590T>C

Version: 2.0

CA402990982 [↗](#)

2570638 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 70289cf1-f13c-4317-b172-1ab3d6434b82

Approved on: 2025/12/10

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HGVS expressions

NM_000156.6:c.590T>C

NC_000019.10:g.1397480A>G

CM000681.2:g.1397480A>G

NC_000019.9:g.1397479A>G

CM000681.1:g.1397479A>G

NC_000019.8:g.1348479A>G

NG_008283.1:g.18597A>G

NG_009785.1:g.9074T>C

ENST00000252288.8:c.590T>C

ENST00000640164.1:n.423T>C

ENST00000640762.1:c.521T>C

ENST00000252288.6:c.590T>C

NM_000156.5:c.590T>C

Pathogenic

Met criteria codes **5**

PM2_Supporting

PP4_Strong

PS3_Supporting

PP3_Moderate

PM3

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.590T>C variant in GAMT is a missense variant predicted to cause substitution of leucine by proline at amino acid 197 (p.Leu197Pro). This variant has been detected in two unrelated individuals with elevated guanidinoacetate with low creatine in both plasma and urine; in addition, one of these individuals had a brain MRS which revealed no creatine peak (PMID: 16293431, 19288536) (PP4_Strong). One of these patients was reported to be compound heterozygous for the variant and another variant in GAMT that has been

classified as likely pathogenic by the ClinGen CCDS VCEP, c.526delG; the phase was confirmed by parental testing (PMID: 19288536, 19461121) (1 point). Another patient was reported to be homozygous for the variant PMID: 16293431 (0.5 points). Total 1.5 points (PM3). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00000339 (4/1179854 alleles) in the European non-Finnish population, which is lower than the ClinGen CCDS VCEP’s threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting). Expression of the variant in a GAMT-deficient human fibroblast cell line resulted in <5% wild type GAMT activity indicating that this variant may impact protein function (PMID: 24415674) (PS3_Supporting). The computational predictor REVEL gives a score of 0.925 which is in the range of 0.773-0.932, evidence that correlates with impact to GAMT function at the moderate level (PMID: 36413997) (PP3_Moderate). There is a ClinVar entry for this variant (Variation ID: 2570638). In summary, this variant meets the criteria to be classified as pathogenic for GAMT deficiency based on the GAMT-specific ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (Specifications Version 2.0.0): PP4_Strong, PM3, PP3_Moderate, PS3_Supporting, PM2_Supporting. (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on December 10, 2025)

Met criteria codes

PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0. is 0.00000339 (4/1179854 alleles) in the European non-Finnish population, which is lower than the ClinGen CCDS VCEP’s threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting).
PP4_Strong			Two patients with this variant had elevated guanidinoacetate with low creatine in plasma and elevated guanidinoacetate with low creatine in urine; one of these individuals had a brain MRS which revealed no creatine peak (PMID: 16293431, 19288536).
PS3_Supporting			Expression of the variant in GAMT-deficient human fibroblast cell line resulted in <5% wild type GAMT activity indicating that this variant may impact protein function (PMID: 24415674) (PS3_Supporting)
PP3_Moderate			The computational predictor REVEL gives a score of 0.925 which is in the range of 0.773-0.932, evidence that correlates with impact to GAMT function at the moderate level (PMID: 36413997) (PP3_Moderate). No impact on splicing was predicted by SpliceAI.
PM3			One patient was reported to be compound heterozygous for the variant and another variant in GAMT that has been classified as likely pathogenic by the ClinGen CCDS VCEP, c.526delG; the phase was confirmed by parental testing (PMID: 19288536, 19461121) (1 point). Another patient was reported to be homozygous for the variant PMID: 16293431 (0.5 points). Total 1.5 points (PM3)

Curation History

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