

Variant: NM_138924.3:c.160G>C

Version: 1.2

CA402998035 [↗](#)

2446454 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: df177d38-29ce-4a53-8bc0-8131ab4fe8da

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HGVS expressions

NM_138924.3:c.160G>C

NC_000019.10:g.1401317C>G

CM000681.2:g.1401317C>G

NC_000019.9:g.1401316C>G

CM000681.1:g.1401316C>G

NC_000019.8:g.1352316C>G

NG_009785.1:g.5237G>C

ENST00000252288.8:c.160G>C

ENST00000447102.8:c.160G>C

ENST00000640762.1:c.112+48G>C

ENST00000252288.6:c.160G>C

ENST00000447102.7:c.160G>C

NM_000156.5:c.160G>C

NM_138924.2:c.160G>C

NM_000156.6:c.160G>C

Likely Pathogenic

Met criteria codes **4**

PM3_Supporting

PP3_Moderate

PP4_Strong

PM2_Supporting

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.160G>C variant in GAMT is predicted to result in the substitution of alanine by proline at amino acid 54 (p.Ala54Pro). Three probands with clinical symptoms consistent with GAMT deficiency have been reported to be homozygous for this variant. One of

these individuals had elevated urinary guanidinoacetate, and GAMT enzymatic activity <0.1 nmol/h/mg in lymphoblasts, with full GAMT gene sequencing performed (PMID: 15108290) (PP4_Strong). This individual harbored the variant in cis with two homozygous variants that have been classified as benign by the ClinGen CCDS VCEP, c.626C>T (p.Thr209Met) (ClinVar ID: 21068) and c.459+71G>A (aka c.460-31G>A, ClinVar ID: 21067). For the other two probands, neither biochemical nor MRS data were available (PMID: 38020815, 39006040); therefore, their data was not included for PM3 (total 0.5 points, PM3_Supporting). The variant is absent in gnomAD v4.1.0. (PM2_Supporting). The computational predictor REVEL gives a score of 0.894 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: 2446454). In summary, this variant meets the 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): PP4_Strong, PP3_Moderate, PM2_Supporting, PM3_Supporting (Classification approved by the ClinGen Cerebral Creatine Deficiencies Variant Curation Expert Panel on October 8, 2025)

Met criteria codes

PM3_Supporting			Identified in one homozygous proband, in cis with two benign variants (c.626C>T (p.Thr209Met) (ClinVar ID: 21068) and c.459+71G>A (ClinVar ID: 21067)) (PMID: 15108290) (0.5 points). Two additional homozygous probands have been identified with clinical symptoms consistent with GAMT deficiency. However, because no biochemical or MRS data is available, this data was not included (PMID: 38020815, 39006040). Total 0.5 points (PM3_Supporting)
PP3_Moderate			The computational predictor REVEL gives a score of 0.894 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).
PP4_Strong			Identified in one individual who showed elevated urinary GAA (1pt), GAMT enzymatic activity <0.1 nmol/h/mg in lymphoblasts (3pts), with full GAMT gene sequencing performed (PMID: 15108290) (total - 4pts, PP4_Strong). Two additional individuals have been reported with clinical symptoms consistent with GAMT deficiency but no biochemical or MRS data is available (PMID: 38020815, 39006040).
PM2_Supporting			The variant is absent in gnomAD v4.1.0. (PM2_Supporting).

Curation History

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