

Variant: *NM_000156.6(GAMT):c.148A>C (p.Met50Leu)*

Version: 2.0

CA254380 [↗](#)

8305 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 562504e1-86d3-4fa5-818a-0eecd910d7b4

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HGVS expressions

NM_000156.6:c.148A>C

NM_000156.6(GAMT):c.148A>C (p.Met50Leu)

NC_000019.10:g.1401329T>G

CM000681.2:g.1401329T>G

NC_000019.9:g.1401328T>G

CM000681.1:g.1401328T>G

NC_000019.8:g.1352328T>G

NG_009785.1:g.5225A>C

ENST00000252288.8:c.148A>C

ENST00000447102.8:c.148A>C

ENST00000640762.1:c.112+36A>C

ENST00000252288.6:c.148A>C

ENST00000447102.7:c.148A>C

NM_000156.5:c.148A>C

NM_138924.2:c.148A>C

NM_138924.3:c.148A>C

Likely Pathogenic

Met criteria codes **5**

PS3_Supporting

PM3_Supporting

PP3_Moderate

PP4_Strong

PM2_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 GATM 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.148A>C variant in GAMT is predicted to result in the substitution of methionine by leucine at amino acid 50 (p.Met50Leu). One individual has been reported who was homozygous for the variant and had a low creatine peak on brain MRS, elevated urinary GAA, low creatine/creatinine ratio, with DNA sequence analysis of GAMT (PMID: 17101918, 24415674) (PM3_Supporting, PP4_Strong). The variant is absent in gnomAD v4.1.0. (PM2_Supporting). The computational predictor REVEL gives a score of 0.923 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). This variant was shown to result in undetectable GAMT enzymatic activity when transfected into GAMT-deficient fibroblasts (PMID: 24415674) (PS3_Supporting). 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): PP4_Strong, PP3_Moderate, PS3_Supporting, PM2_Supporting, PM3_Supporting. (Classification approved by the ClinGen CCDS VCEP on October 7, 2025)

Met criteria codes

PS3_Supporting			The p.Met50Leu variant was shown to result in undetectable GAMT enzymatic activity when transfected into GAMT-deficient fibroblasts (PMID: 24415674)
			The p.Met50Leu variant was shown to result in undetectable GAMT enzymatic activity when transfected into GAMT-deficient fibroblasts PubMed:24415674 
PM3_Supporting			PMID: 17101918: Reported in the homozygous state in one patient with guanidinoacetate methyltransferase deficiency (0.5pts)
PP3_Moderate			The computational predictor REVEL gives a score of 0.923 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			Found in proband with low creatine peak on brain MRS (3pts), elevated urinary GAA (1pts), low creatine/creatinine ratio, with DNA sequence analysis of GAMT (PMID: 17101918, 24415674) (PP4_Strong)
PM2_Supporting			The variant is absent in gnomAD v4.1.0. (PM2_Supporting).

Not Met criteria codes

PM5			A different missense variant at the same amino acid residue, p.Met50Ile, has been previously reported and interpreted as a VUS in ClinVar (Variation ID: 566179)
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Curation History 

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