

Variant: *NM_000156.6(GAMT):c.407C>T (p.Thr136Met)*

Version: 2.0

CA9043669 [↗](#)

544257 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: b1540be4-deab-4ef4-b3d1-260e5e246046

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HGVS expressions

NM_000156.6(GAMT):c.407C>T (p.Thr136Met)

NM_000156.6:c.407C>T

NC_000019.10:g.1399180G>A

CM000681.2:g.1399180G>A

NC_000019.9:g.1399179G>A

CM000681.1:g.1399179G>A

NC_000019.8:g.1350179G>A

NG_009785.1:g.7374C>T

ENST00000252288.8:c.407C>T

ENST00000447102.8:c.407C>T

ENST00000591788.3:c.90C>T

ENST00000640164.1:n.240C>T

ENST00000640762.1:c.338C>T

ENST00000252288.6:c.407C>T

ENST00000447102.7:c.407C>T

ENST00000591788.2:c.92C>T

NM_000156.5:c.407C>T

NM_138924.2:c.407C>T

NM_138924.3:c.407C>T

Pathogenic

Met criteria codes **5**

PM2_Supporting

PS3_Supporting

PP4_Strong

PP3_Moderate

PM3

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 1.1.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Cerebral Creatine Deficiency Syndromes VCEP

The NM_000156.6:c.407C>T variant in GAMT is a missense variant predicted to cause substitution of threonine by methionine at amino acid 136 (p.Thr136Met). This variant has been detected in 3 unrelated individuals with GAMT deficiency (PMID: 24415674, PMID: 21140503, ClinVar SCV001428825.1). Of those individuals, two were compound heterozygous for the variant and a pathogenic variant, c.316C>T (p.Q106*) in unknown phase (PMID: 24415674, PMID: 21140503) and 1 was homozygous for the variant (ClinVar SCV001428825.1) (1.5pts total, PM3). One of these individuals had elevated GAA in plasma, deficient GAMT enzyme activity (<5% wild-type enzyme) in fibroblasts, and significantly reduced creatine peak on brain MRS (PMID: 21140503) and one individual had an absent creatine peak with visible GAA peak on brain MRS (PMID: 24415674) (PP4_Strong). Expression of the variant in GAMT-deficient fibroblasts resulted in <5% wild type GAMT activity indicating that this variant may impact protein function (PMID: 24415674)(PS3_Supporting). The highest population minor allele frequency in gnomAD v2.1.1 is 0.000009 (1/113420 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). The computational predictor REVEL gives a score of 0.976 which is above the threshold of 0.75, evidence that correlates with impact to GAMT function (PP3_Moderate). There is a ClinVar entry for this variant (Variation ID: 544257). In summary, this variant meets the criteria to be classified as pathogenic for GAMT deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (Specifications Version 1.1.0): PP4_Strong, PM3, PP3_Moderate, PS3_Supporting, PM2_Supporting. (Classification approved by the ClinGen CCDS VCEP on Oct. 2026, 2023)

Met criteria codes

PM2_Supporting			The highest population minor allele frequency in gnomAD v2.1.1 is 0.000009 (1/113420 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).
PS3_Supporting			GAMT deficient fibroblasts transfected with the variant showed <5% of wild-type enzyme activity (PMID: 24415674) GAMT deficient fibroblasts transfected with the variant showed <5% of wild-type enzyme activity (PMID: 24415674) PubMed:24415674 
PP4_Strong			One of these individuals had elevated GAA in plasma, deficient GAMT enzyme activity (<5% wild-type enzyme) in fibroblasts, and significantly reduced creatine peak on brain MRS (PMID: 21140503) and one individual had an absent creatine peak with visible GAA peak on brain MRS (PMID: 24415674) (PP4_Strong).
PP3_Moderate			The computational predictor REVEL gives a score of 0.976 which is above the threshold of 0.75, evidence that correlates with impact to GAMT function, based on specifications of the CCDS VCEP (PP3_Moderate).
PM3			This variant has been detected in 3 unrelated individuals with GAMT deficiency (PMID: 24415674, PMID: 21140503, ClinVar SCV001428825.1). Of those individuals, two were compound heterozygous for the variant and a pathogenic variant, c.316C>T (p.Q106*) in unknown phase and 1 was homozygous for the variant (1.5pts total, PM3).

Curation History 

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