

Variant: *NM_000156.6(GAMT):c.520T>C (p.Trp174Arg)*

Version: 1.2

CA304065950 [↗](#)

1420866 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 94bbe47d-781a-4378-ba79-2455475b5394

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HGVS expressions

NM_000156.6(GAMT):c.520T>C (p.Trp174Arg)

NM_000156.6:c.520T>C

NC_000019.10:g.1398966A>G

CM000681.2:g.1398966A>G

NC_000019.9:g.1398965A>G

CM000681.1:g.1398965A>G

NC_000019.8:g.1349965A>G

NG_009785.1:g.7588T>C

ENST00000252288.8:c.520T>C

ENST00000447102.8:c.520T>C

ENST00000591788.3:c.203T>C

ENST00000640164.1:n.353T>C

ENST00000640762.1:c.451T>C

ENST00000252288.6:c.520T>C

ENST00000447102.7:c.520T>C

ENST00000591788.2:c.205T>C

NM_000156.5:c.520T>C

NM_138924.2:c.520T>C

NM_138924.3:c.520T>C

Likely Pathogenic

Met criteria codes **4**

PP3_Moderate

PP4

PM2_Supporting

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.520T>C variant in GAMT is a missense variant predicted to cause substitution of tryptophan by arginine at amino acid 174 (p.Trp174Arg). Two probands have been reported with clinical symptoms consistent with GAMT deficiency, elevated guanidinoacetate and low creatine in dried blood spot, and improvement in seizures frequency on creatine treatment (PMID: 35588794) (PP4). One proband was compound heterozygous for the variant and another variant in GAMT that has been classified as pathogenic for GAMT deficiency by the ClinGen CCDS VCEP, c.403G>A (p.Asp135Asn) (ClinVar Variation ID: 573140), and confirmed in trans by parental DNA testing (PMID: 35588794) (1 point) (PM3). Another patient was compound heterozygous for the variant and c.444_448del (p.Phe149LeufsTer40) (ClinVar Variation ID: 2831012) (PMID: 35588794). The allelic data from this patient will be used in the classification of the second variant and was not included here to avoid circular logic. In addition a patient with atypical developmental epileptic encephalopathy is homozygous for the variant (PMID: 41751517). However, because no biochemical details are available, no points were given for PM3 for this patient. The highest population minor allele frequency in gnomAD v4.1.0. is 0.0000076 (9/1179976 alleles) in the non-Finnish European 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 0.808 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: 1420866). In summary, this variant meets the criteria to be classified as likely 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): PM3, PP3_Moderate, PP4, PM2_Supporting. (Classification approved by the ClinGen CCDS VCEP on April 21, 2026)

Met criteria codes

PP3_Moderate			The computational predictor REVEL gives a score of 0.808 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			Two probands have been reported with clinical symptoms consistent with GAMT deficiency, elevated guanidinoacetate and low creatine in dried blood spot, and improvement in seizures frequency on creatine treatment (PMID: 35588794) (PP4)
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0. is 0.0000076 (9/1179976 alleles) in the non-Finnish European population, which is lower than the ClinGen CCDS VCEP’s threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting).
PM3			One proband was compound heterozygous for the variant and another variant in GAMT that has been classified as pathogenic for GAMT deficiency by the ClinGen CCDS VCEP, c.403G>A (p.Asp135Asn) (ClinVar Variation ID: 573140), and confirmed in trans by parental DNA testing (PMID: 35588794) (1 point) (PM3). Another patient was compound heterozygous for the variant and c.444_448del (p.Phe149LeufsTer40) (ClinVar Variation ID: 2831012) (PMID: 35588794). The allelic data from this patient will be used in the classification of the second variant and was not included here to avoid circular logic. In addition a patient with atypical developmental epileptic encephalopathy is homozygous for the variant (PMID: 41751517). However, because no biochemical details are available, no points were given for PM3 for this patient.

Curation History 

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