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Variant: NM_000156.6(GAMT):c.328G>T (p.Val110Phe)

Version: 1.1

CA314806

205580 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2b15edee-9933-4217-b969-7b86bf30c14b
Approved on: 2025/4/18
Published on: 2025/4/18

HGVS expressions

NM_000156.6(GAMT):c.328G>T (p.Val110Phe)
NM_000156.6:c.328G>T
NC_000019.10:g.1399587C>A
CM000681.2:g.1399587C>A
NC_000019.9:g.1399586C>A
CM000681.1:g.1399586C>A
NC_000019.8:g.1350586C>A
NG_009785.1:g.6967G>T
ENST00000252288.8:c.328G>T
ENST00000447102.8:c.328G>T
ENST00000591788.3:c.11G>T
ENST00000640164.1:n.161G>T
ENST00000640762.1:c.259G>T
ENST00000252288.6:c.328G>T
ENST00000447102.7:c.328G>T
ENST00000591788.2:c.13G>T
NM_000156.5:c.328G>T
NM_138924.2:c.328G>T
NM_138924.3:c.328G>T

Likely Pathogenic

Met criteria codes 5

PP3_Moderate PS3_Supporting PM3_Supporting PM2_Supporting PP4_Strong

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.328G>T variant in GAMT is a missense variant predicted to cause substitution of valine by phenylalanine at amino acid 110 (p.Val110Phe). Two patient(s) with this variant had elevated guanidinoacetate in urine and decreased creatine peak on MRS (PMID: 24415674; CreatineInfo Registry) (PP4_Strong). Both individuals with GAMT deficiency were heterozygous for the variant and another variant in GAMT that has been classified as pathogenic (c.327G>A, PMID: 24415674) or likely pathogenic (CreatineInfo Registry data) by the ClinGen CCDS VCEP. The phase was unconfirmed in both cases (PM3_Supporting). The variant has also been reported in an individual with neurodevelopmental disorder/epilepsy but further details are unavailable, and it is unknown if this case may overlap with either of the other 2 cases (PMID: 29655203). Expression of the variant in GAMT-deficient fibroblasts resulted in extremely low GAMT activity, and no detectable expression of the protein (Figure 1, PMID 24415674) indicating that this variant may impact protein function (PS3_Supporting). The computational predictor REVEL gives a score of 0.928 which is in the range of 0.773-0.932, evidence that correlates with impact to GAMT function at the moderate level. Furthermore, SpliceAI predicts that this variant, which alters the first nucleotide of exon 3, impacts normal splicing (score = 0.4 for acceptor loss) (PP3_Moderate). The highest population minor allele frequency in gnomAD v4.1.0 is 0.000009326 (11/1179478 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). There is a ClinVar entry for this variant (Variation ID: 205580. In summary, this variant meets the criteria to be classified as likely pathogenic for GAMT deficiency. GAMT-specific ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (Specifications Version 1.1.0): PP4_strong, PP3_Moderate, PS3_Supporting, PM3_Supporting, PM2_Supporting. (Classification approved by the ClinGen CCDS VCEP on April 18, 2025).

Met criteria codes

PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.928 which is in the range of 0.773-0.932, evidence that correlates with impact to GAMT function at the moderate level. Furthermore, SpliceAI predicts that this variant, which alters the first nucleotide of exon 3, impacts normal splicing (score = 0.4 for acceptor loss) (PP3_Moderate).
PS3_Supporting	✔	Expression of the variant in GAMT-deficient fibroblasts resulted in extremely low GAMT activity, and no detectable expression of the protein (Figure 1, PMID 24415674) indicating that this variant may impact protein function (PS3_Supporting).
PM3_Supporting	✔	This variant has been detected in 2 individuals with GAMT deficiency who were heterozygous for the variant and another variant in GAMT that has been classified as pathogenic (c.327G>A, PMID: 24415674) or likely pathogenic (CreatineInfo Registry data) by the ClinGen CCDS VCEP. The phase is unconfirmed in both cases (0.5 + 0.25 points = 0.75 points) (PM3_Supporting).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.000009326 (11/1179478 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	✔	At least 2 patient(s) with this variant had elevated guanidinoacetate in urine and significantly decreased creatine peak (PMID: 24415674; CreatineInfo Registry) (PP4_Strong)

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000156.6(GAMT):c.328G>T (p.Val1...	Likely Pathogenic	Guanidinoacetate Methyltransferase Deficiency	2025-04-18	1.1	ClinGen Cerebral Creatine Deficiency Syndromes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GAMT Version 2.0.0	GAMT
View	NM_000156.6(GAMT):c.328G>T (p.Val1...	Likely Pathogenic	Guanidinoacetate Methyltransferase Deficiency	2022-10-07	1.0	ClinGen Cerebral Creatine Deficiency Syndromes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GAMT Version 1	GAMT

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