The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000156.6(GAMT):c.650C>T (p.Pro217Leu)

Version: 1.1

CA314828

205592 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8d568e0a-6ff6-4008-b41c-6e3af28d6f2d
Approved on: 2025/4/28
Published on: 2025/4/28

HGVS expressions

NM_000156.6:c.650C>T
NM_000156.6(GAMT):c.650C>T (p.Pro217Leu)
NC_000019.10:g.1397420G>A
CM000681.2:g.1397420G>A
NC_000019.9:g.1397419G>A
CM000681.1:g.1397419G>A
NC_000019.8:g.1348419G>A
NG_008283.1:g.18537G>A
NG_009785.1:g.9134C>T
ENST00000252288.8:c.650C>T
ENST00000640164.1:n.483C>T
ENST00000640762.1:c.581C>T
ENST00000252288.6:c.650C>T
NM_000156.5:c.650C>T

Uncertain Significance

Met criteria codes 2

PM2_Supporting PP3

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.650C>T variant in GAMT is a missense variant predicted to result in the substitution of proline for leucine at amino acid 217 (p.Pro217Leu). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00006674 (5/74922 alleles) in the African African American 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 0.773, in the range of 0.644-0.773, evidence that correlates with impact to GAMT function at the supporting level (PMID: 36413997) (PP3). SpliceAI predicts that the variant has no impact on splicing. To our knowledge, this variant has not been reported in published literature in individuals with GAMT deficiency, and the results of functional studies are unavailable. This variant has been previously reported in ClinVar (Variation ID: 205592). In summary, this variant meets the criteria to be classified as a variant of uncertain significance for GAMT deficiency. GAMT-specific ACMG/AMP codes met, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes VCEP (Specifications Version 2.0.0): PP3, PM2_Supporting. (Classification approved by the ClinGen CCDS VCEP on April 28, 2025).

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.00006674 (5/74922 alleles) in the African African American population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.773, in the range of 0.644-0.773, evidence that correlates with impact to GAMT function at the supporting level (PMID: 36413997) (PP3). SpliceAI predicts that the variant has no impact on splicing.

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.650C>T (p.Pro2...	Uncertain Significance	Guanidinoacetate Methyltransferase Deficiency	2025-04-28	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.650C>T (p.Pro2...	Uncertain Significance	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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