

Variant: NM_138924.3:c.194T>C

Version: 1.0

CA402997251 [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 2101061a-262e-4550-9772-60f0c0923f03

Approved on: 2025/12/10

Published on: 2025/12/10

HGVS expressions

NM_138924.3:c.194T>C

NC_000019.10:g.1399926A>G

CM000681.2:g.1399926A>G

NC_000019.9:g.1399925A>G

CM000681.1:g.1399925A>G

NC_000019.8:g.1350925A>G

NG_009785.1:g.6628T>C

ENST00000252288.8:c.194T>C

ENST00000447102.8:c.194T>C

ENST00000640762.1:c.125T>C

ENST00000252288.6:c.194T>C

ENST00000447102.7:c.194T>C

NM_000156.5:c.194T>C

NM_138924.2:c.194T>C

NM_000156.6:c.194T>C

Pathogenic

Met criteria codes **3**

PM2_Supporting

PP4_Strong

PP3_Strong

Not Met criteria codes **1**

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.194T>C variant in GAMT is a missense variant that is predicted to cause the substitution of a leucine by a proline at amino acid position 65 (p.Leu65Pro). This variant has been detected in at least one individual with GAMT deficiency (Lei et al. Journal of

Clinical Pediatrics, 2024, 42(12): 1039-1046), who was compound heterozygous for the variant and a pathogenic or likely pathogenic variant, c.467C>A (p.Ala156Asp), which was confirmed in trans by parental testing. This occurrence was not counted for PM3 evidence as it was used for PM3 evidence for the c.467C>A (p.Ala156Asp) variant, thereby preventing circularity. The individual with this variant (Lei et al. Journal of Clinical Pediatrics, 2024, 42(12): 1039-1046) had elevated GAA and low or low normal creatine in urine and significantly decreased creatine peak (GAA not reported) on brain MRS (4 points; PP4_Strong). The highest population minor allele frequency in gnomAD v4.1.0. is 8.49e-7 (1/1178058 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 0.981 which is above the threshold of 0.932, evidence that correlates with impact to GAMT function at the strong level (PMID: 36413997) (PP3_Strong). There is no ClinVar entry for this variant. In summary, this variant meets the criteria to be classified as pathogenic for GAMT deficiency based on the GAMT-specific ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (Specifications Version 2.0.0): PP4_Strong, PP3_Strong, PM2_Supporting. (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on December 10, 2025)

Met criteria codes

PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0. is 8.49e-7 (1/1178058 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			The individual with this variant (PMID: 40105081) had elevated GAA and low or low normal creatine in urine and significantly decreased creatine peak (GAA not reported) on brain MRS (4 points; PP4_Strong).
PP3_Strong			The computational predictor REVEL gives a score of 0.981 which is above the threshold of 0.932, evidence that correlates with impact to GAMT function at the strong level (PMID: 36413997) (PP3_Strong).

Not Met criteria codes

PM3			Patient 1 is compound heterozygous for the variant and another variant in GAMT (c.467C>A (p.Ala156Asp). This occurrence was not counted for PM3 evidence as it was used for PM3 evidence for c.467C>A (p.Ala156Asp), thereby preventing circularity.
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Curation History

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