

Variant: *NM_000156.6(GAMT):c.526del (p.Glu176fs)*

Version: 1.1

CA2499225402 [↗](#)

1067935 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: df780bbd-6d93-4670-9d0e-121f7e0c44d9

Approved on: 2025/10/7

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HGVS expressions

NM_000156.6(GAMT):c.526del (p.Glu176fs)

NM_000156.6:c.526del

NC_000019.10:g.1398965del

CM000681.2:g.1398965del

NC_000019.9:g.1398964del

CM000681.1:g.1398964del

NC_000019.8:g.1349964del

NG_009785.1:g.7594del

ENST00000252288.8:c.526del

ENST00000447102.8:c.526del

ENST00000591788.3:c.209del

ENST00000640164.1:n.359del

ENST00000640762.1:c.457del

ENST00000252288.6:c.526del

ENST00000447102.7:c.526del

ENST00000591788.2:c.211del

NM_000156.5:c.526del

NM_138924.2:c.526del

NM_138924.3:c.526del

Likely Pathogenic

Met criteria codes **3**

PM2_Supporting

PP4_Moderate

PVS1_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**

Cerebral Creatine Deficiency Syndromes VCEP

The NM_000156.6:c.526del (p.Glu176SerfsTer2) variant in GAMT is a frameshift variant predicted to cause a premature stop codon in the last 50 nucleotides of the penultimate exon/the last exon of the gene and therefore to escape nonsense mediated decay. More than 10% of the protein is predicted to be removed (PVS1_Strong). This variant has been reported in one individual with GAMT deficiency who had elevated GAA and low creatine in plasma and in urine (PMID: 19288536) (PP4_Moderate). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00002229 (1/44860 alleles) in the East Asian 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: 1067935). In summary, this variant meets the criteria to be classified as likely 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): PVS1_Strong, PM2_Supporting, PP4_Moderate. (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on October 7, 2025)

Met criteria codes

PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0. is 0.00002229 (1/44860 alleles) in the East Asian population, which is lower than the ClinGen CCDS VCEP’s threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting).
PP4_Moderate			PMID: 19288536: identified in one patient with elevated plasma GAA with low creatine and elevated urine GAA with low creatine (3pts total, PP4_Mod)
PVS1_Strong			Frameshift variant in exon 5/6 in the last 50bp of the penultimate exon (c.526), such that NMD is not predicted. Predicted to result in frameshift at amino acid position 176 and premature termination at amino acid position 178/236, resulting in removal of 58 amino acids (24.5% of the protein, >10% of the protein), such that PVS1_Strong applies per CCDS specifications.

Not Met criteria codes

PM3			Patient 3: comp het for c.590T>C (p.L197P)/c.526delG (p.E176SfsX2); did not count for PM3 here because this occurrence was counted for PM3 for the p.L197P variant, thereby preventing circularity in use of PM3
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Curation History

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