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Variant: NM_000156.6(GAMT):c.476T>C (p.Leu159Pro)

Version: 1.2

CA402994686

1335317 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7ed0a7a6-a85c-4faf-8a42-5ac1a5559d6b
Approved on: 2026/4/21
Published on: 2026/4/21

HGVS expressions

NM_000156.6(GAMT):c.476T>C (p.Leu159Pro)
NM_000156.6:c.476T>C
NC_000019.10:g.1399010A>G
CM000681.2:g.1399010A>G
NC_000019.9:g.1399009A>G
CM000681.1:g.1399009A>G
NC_000019.8:g.1350009A>G
NG_009785.1:g.7544T>C
ENST00000252288.8:c.476T>C
ENST00000447102.8:c.476T>C
ENST00000591788.3:c.159T>C
ENST00000640164.1:n.309T>C
ENST00000640762.1:c.407T>C
ENST00000252288.6:c.476T>C
ENST00000447102.7:c.476T>C
ENST00000591788.2:c.161T>C
NM_000156.5:c.476T>C
NM_138924.2:c.476T>C
NM_138924.3:c.476T>C

Likely Pathogenic

Met criteria codes 5

PP3_Strong PM3_Supporting PS3_Supporting PP4_Moderate PM2_Supporting

Evidence Links 1

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.476T>C variant in GAMT is predicted to result in the substitution of leucine by proline at amino acid 159 (p.Leu159Pro). This variant has been identified in one homozygous individual with an absent creatine peak on brain MRS and elevated urine guanidinoacetate (value not provided) (PM3_Supporting, PP4_Moderate) (PMID: 24415674). This variant is absent in gnomAD v4.1.0. (PM2_Supporting). The computational predictor REVEL gives a score of 0.947 which is above the threshold of 0.932, evidence that correlates with impact to GAMT function at the strong level (PMID: 36413997) (PP3_Strong). This variant was shown to result in undetectable GAMT enzyme activity in GAMT-deficient fibroblasts (PMID: 24415674) (PS3_Supporting). In summary, this variant meets criteria to be classified as likely pathogenic for guanidinoacetate methyltransferase (GAMT) deficiency. GAMT-specific ACMG/AMP Criteria applied, as specified by the ClinGen Cerebral Creatine Deficiencies Variant Curation Expert Panel (CCDS VCEP) (Specifications version 2.0.0): PP3_Strong, PP4_Moderate, PS3_Supporting, PM2_Supporting, PM3_Supporting (Classification approved by the ClinGen CCDS VCEP on April 21, 2026)

Met criteria codes

PP3_Strong	✔	The computational predictor REVEL gives a score of 0.947 which is above the threshold of 0.932, evidence that correlates with impact to GAMT function at the strong level (PMID: 36413997) (PP3_Strong).
PM3_Supporting	✔	PMID: 24415674: Identified in one homozygous proband (0.5pts)
PS3_Supporting	✔	PMID: 24415674: Variant shown to result in undetectable GAMT enzymatic activity when expressed in GAMT-deficient fibroblasts PMID: 24415674: Variant shown to result in undetectable GAMT enzymatic activity when expressed in GAMT-deficient fibroblasts PubMed:24415674
PP4_Moderate	✔	One proband who is homozygous for the variant has clinical symptoms consistent with GAMT deficiency, showed an absent creatine peak on brain MRS (3pts) (PMID: 24415674) (PP4_Moderate).
PM2_Supporting	✔	The variant is absent in gnomAD v4.1.0. (PM2_Supporting)

Curation History

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