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Variant: NM_000156.6(GAMT):c.261G>A (p.Trp87Ter)

Version: 1.1

CA9043754

849693 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 13302787-d703-433f-9904-a20fb6beb318
Approved on: 2025/10/7
Published on: 2025/10/7

HGVS expressions

NM_000156.6:c.261G>A
NM_000156.6(GAMT):c.261G>A (p.Trp87Ter)
NC_000019.10:g.1399859C>T
CM000681.2:g.1399859C>T
NC_000019.9:g.1399858C>T
CM000681.1:g.1399858C>T
NC_000019.8:g.1350858C>T
NG_009785.1:g.6695G>A
ENST00000252288.8:c.261G>A
ENST00000447102.8:c.261G>A
ENST00000640762.1:c.192G>A
ENST00000252288.6:c.261G>A
ENST00000447102.7:c.261G>A
NM_000156.5:c.261G>A
NM_138924.2:c.261G>A
NM_138924.3:c.261G>A

Likely Pathogenic

Met criteria codes 2

PVS1 PM2_Supporting

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.261G>A (p.Trp87Ter) variant in GAMT is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 2/6, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001338 (1/74748 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). To our knowledge, this variant has not been reported in the literature in individuals with GAMT deficiency. There is a ClinVar entry for this variant (Variation ID: 849693). The classification of this variant has been upgraded from Variant of Uncertain Significance to Likely Pathogenic based on the recommendations of the ClinGen Sequence Variant Interpretation Working Group, that a variant meeting PVS1 and PM2_Supporting is classified as Likely Pathogenic (https://clinicalgenome.org/site/assets/files/5182/pm2_-_svi_recommendation_-_approved_sept2020.pdf). In summary, this variant meets the criteria to be classified as likely pathogenic for GAMT deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (Specifications Version 2.0.0): PVS1, PM2_Supporting. (Classification approved by the ClinGen Creatine Deficiency Syndromes Variant Curation Expert Panel on October 7, 2025)

Met criteria codes

PVS1	✔	The NM_000156.6:c.261G>A (p.Trp87Ter) variant in GAMT is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 2 out of a total of 6 exons, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001338 (1/74748 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).

Curation History

Showing 1 to 2 of 2 rows

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