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Variant: NM_000156.6(GAMT):c.481A>T (p.Lys161Ter)

Version: 1.1

CA16608969

392462 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 88568db0-9192-4742-8199-f7371c8a2255
Approved on: 2025/10/7
Published on: 2025/10/7

HGVS expressions

NM_000156.6(GAMT):c.481A>T (p.Lys161Ter)
NM_000156.6:c.481A>T
NC_000019.10:g.1399005T>A
CM000681.2:g.1399005T>A
NC_000019.9:g.1399004T>A
CM000681.1:g.1399004T>A
NC_000019.8:g.1350004T>A
NG_009785.1:g.7549A>T
ENST00000252288.8:c.481A>T
ENST00000447102.8:c.481A>T
ENST00000591788.3:c.164A>T
ENST00000640164.1:n.314A>T
ENST00000640762.1:c.412A>T
ENST00000252288.6:c.481A>T
ENST00000447102.7:c.481A>T
ENST00000591788.2:c.166A>T
NM_000156.5:c.481A>T
NM_138924.2:c.481A>T
NM_138924.3:c.481A>T

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.481A>T (p.Lys161Ter) variant in GAMT is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 5 out of a total of 6 exons. While the variant is in the penultimate exon of GAMT, it is upstream of the region predicted to be missed by nonsense-mediated decay; this is expected to lead 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 0.00001335 (1/74906 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). There is a ClinVar entry for this variant (Variation ID: 392462). To our knowledge, this variant has not been reported in an individual with GAMT deficiency in the published literature. 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 CCDS VCEP on October 7, 2025)

Met criteria codes

PVS1	✔	The NM_000156.6:c.481A>T (p.Lys161Ter) variant in GAMT is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 5 out of a total of 6 exons. While the variant is in the penultimate exon of GAMT, it is upstream of the region predicted to be missed by nonsense-mediated decay, and this is expected to lead 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 0.00001335 (1/74906 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

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