The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000156.6(GAMT):c.506G>A (p.Cys169Tyr)

Version: 1.1

CA254379

8304 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 14a32c81-d293-49d1-afb2-82210e4986ba
Approved on: 2025/10/16
Published on: 2025/10/16

HGVS expressions

NM_000156.6:c.506G>A
NM_000156.6(GAMT):c.506G>A (p.Cys169Tyr)
NC_000019.10:g.1398980C>T
CM000681.2:g.1398980C>T
NC_000019.9:g.1398979C>T
CM000681.1:g.1398979C>T
NC_000019.8:g.1349979C>T
NG_009785.1:g.7574G>A
ENST00000252288.8:c.506G>A
ENST00000447102.8:c.506G>A
ENST00000591788.3:c.189G>A
ENST00000640164.1:n.339G>A
ENST00000640762.1:c.437G>A
ENST00000252288.6:c.506G>A
ENST00000447102.7:c.506G>A
ENST00000591788.2:c.191G>A
NM_000156.5:c.506G>A
NM_138924.2:c.506G>A
NM_138924.3:c.506G>A

Likely Pathogenic

Met criteria codes 5

PP3 PM3 PP4_Strong PM2_Supporting PS3_Supporting

Not Met criteria codes 1

PM5

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.505T>A variant in GAMT is a missense variant predicted to cause substitution of a cysteine by tyrosine at amino acid 169 (p.Cys169Tyr). At least 4 unrelated probands and one sibling were found to be homozygous for the variant (PMID: 15651030, 2323426424415674, 24268530, 32606525) (max 2 x 0.5, PM3). Three individuals with the variant had elevated guanidinoacetate in plasma and/or urine); in addition, one individual showed absent creatine peak on brain MRS; another had deficient (<5% wild-type) GAMT activity in lymphoblasts (PMID: 15651030, 24268530, 24415674). Two sibs had absent creatine peak on brain MRS (PMID: 32606525) (PP4_Strong). The highest population minor allele frequency in gnomAD v4.1.0. is 0.0000333 (2/60014 alleles) in the Admixed American population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting). Expression of the variant in GAMT-deficient fibroblasts resulted in <5% wild type GAMT activity indicating that this variant may impact protein function (PMID: 24415674)(PS3_Supporting). The computational predictor REVEL gives a score of 0.754 which is in the range of 0.644-0.773, evidence that correlates with impact to GAMT function at the supporting level (PP3). There is a ClinVar entry for this variant (Variation ID: 8304). 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): PP4_Strong, PM3, PP3, PS3_Supporting, PM2_Supporting (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on October 16, 2025)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.754 which is in the range of 0.644-0.773, evidence that correlates with impact to GAMT function at the supporting level (PP3).
PM3	✔	At least 4 unrelated probands and one sibling were found to be homozygous for the variant (PMID: 15651030, 2323426424415674, 24268530, 32606525) (max 2 x 0.5, PM3)
PP4_Strong	✔	Three individuals with the variant had elevated guanidinoacetate in plasma and/or urine); in addition, one individual showed absent creatine peak on brain MRS; another had deficient (<5% wild-type) GAMT activity in lymphoblasts (PMID: 15651030, 24268530, 24415674). Two sibs had absent creatine peak on brain MRS (PMID: 32606525) (PP4_Strong).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.0000333 (2/60014 alleles) in the Admixed American population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting).
PS3_Supporting	✔	GAMT-deficient fibroblasts transfected with the variant showed <5% of wild-type GAMT enzyme activity (PMID: 24415674)

Not Met criteria codes

PM5	✖	A different missense variant at the same codon, p.Cys169Arg (ClinVar ID: 818179), has been reported likely pathogenic in ClinVar; since p.Cys169Tyr was used for PM5 evidence for p.Cys169Arg, this is not used here to prevent circularity.

Curation History

Showing 1 to 2 of 2 rows

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