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Variant: NM_138924.3:c.439C>T

Version: 1.1

CA402995088

2446460 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 578f0aa4-5ea7-4f9b-a584-c6607d0cf64d
Approved on: 2025/10/15
Published on: 2025/10/15

HGVS expressions

NM_138924.3:c.439C>T
NC_000019.10:g.1399148G>A
CM000681.2:g.1399148G>A
NC_000019.9:g.1399147G>A
CM000681.1:g.1399147G>A
NC_000019.8:g.1350147G>A
NG_009785.1:g.7406C>T
ENST00000252288.8:c.439C>T
ENST00000447102.8:c.439C>T
ENST00000591788.3:c.122C>T
ENST00000640164.1:n.272C>T
ENST00000640762.1:c.370C>T
ENST00000252288.6:c.439C>T
ENST00000447102.7:c.439C>T
ENST00000591788.2:c.124C>T
NM_000156.5:c.439C>T
NM_138924.2:c.439C>T
NM_000156.6:c.439C>T

Likely Pathogenic

Met criteria codes 5

PP3_Moderate PM3_Supporting PP4_Moderate PM2_Supporting PS3_Supporting

Not Met criteria codes 1

PM5

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.439C>T variant in GAMT is predicted to result in the substitution of histidine by tyrosine at amino acid 147 (p.His147Tyr). This variant has been identified in an individual with a diagnosis of guanidinoacetate methyltransferase deficiency confirmed by deficient enzyme activity in cultured fibroblasts (PMID: 24415674) (PP4_Moderate). This individual is compound heterozygous for the variant and another variant in GAMT that has been classified as pathogenic for GAMT deficiency by the ClinGen CCDS VCEP, c.11_36dup (p.Gly13fs) (ClinVar Variation ID: 858462); the phase is unconfirmed (PMID: 24415674) (0.5 points) (PM3_Supporting). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001335 (1/74918 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). This variant was shown to result in 4% of wild-type enzyme activity in GAMT-deficient fibroblasts (PMID: 24415674) (PS3_Supporting). The computational predictor REVEL gives a score of 0.888 which is in the range of 0.773-0.932, evidence that correlates with impact to GAMT function at the moderate level (PMID: 36413997) (PP3_Moderate). There is a ClinVar entry for this variant (Variation ID: 2446460). 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_Moderate, PP4_Moderate, PS3_Supporting, PM2_Supporting, PM3_Supporting (Classification approved by the ClinGen Cerebral Creatine Deficiencies Variant Curation Expert Panel on October 15, 2025)

Met criteria codes

PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.888 which is in the range of 0.773-0.932, evidence that correlates with impact to GAMT function at the moderate level (PMID: 36413997) (PP3_Moderate).
PM3_Supporting	✔	One individual with GAMT deficiency is compound heterozygous for the variant and another variant in GAMT that has been classified as pathogenic for GAMT deficiency by the ClinGen CCDS VCEP, c.11_36dup (p.Gly13fs) (ClinVar Variation ID: 858462); the phase is unconfirmed (PMID: 24415674) (0.5 points) (PM3_Supporting)
PP4_Moderate	✔	PMID: 24415674: Identified in one patient who showed deficient GAMT enzyme activity in cultured skin fibroblasts (3pts)
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001335 (1/74918 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).
PS3_Supporting	✔	When expressed in GAMT-deficient fibroblasts, the variant was shown to result in 4% of wild-type GAMT enzyme activity (PMID: 24415674:). Variant shown to result in 4% of wild-type GAMT enzyme activity when expressed in GAMT-deficient fibroblasts PubMed:24415674

Not Met criteria codes

PM5	✖	A different missense variant at the same amino acid residue, p.His147Gln has been previously reported as a variant of uncertain significance (ClinVar Variation ID: 450331).

Curation History

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