

Variant: *NM_000156.6(GAMT):c.505T>C (p.Cys169Arg)*

Version: 2.0

CA402994533 [↗](#)

818179 (ClinVar) [↗](#)

Gene: GAMT ([HGNC:2593](#))

Condition: guanidinoacetate methyltransferase deficiency
([MONDO:0012999](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: f7d9b26e-41e5-47ec-846a-8e99d0e376f6

Approved on: 2024/6/13

Published on: 2024/6/24

HGVS expressions

NM_000156.6(GAMT):c.505T>C (p.Cys169Arg)

NM_000156.6:c.505T>C

NC_000019.10:g.1398981A>G

CM000681.2:g.1398981A>G

NC_000019.9:g.1398980A>G

CM000681.1:g.1398980A>G

NC_000019.8:g.1349980A>G

NG_009785.1:g.7573T>C

ENST00000252288.8:c.505T>C

ENST00000447102.8:c.505T>C

ENST00000591788.3:c.188T>C

ENST00000640164.1:n.338T>C

ENST00000640762.1:c.436T>C

ENST00000252288.6:c.505T>C

ENST00000447102.7:c.505T>C

ENST00000591788.2:c.190T>C

NM_000156.5:c.505T>C

NM_138924.2:c.505T>C

NM_138924.3:c.505T>C

Pathogenic

Met criteria codes **5**

PM3_Strong

PP3

PM5_Supporting

PP4_Strong

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 1.1.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Cerebral Creatine Deficiency Syndromes VCEP

The NM_000156.6:c.505T>C variant in GAMT is a missense variant predicted to cause substitution of cysteine by arginine at amino acid 169 (p.Cys169Arg). This variant has been identified in 3 individuals with a diagnosis of GAMT deficiency. One of these individuals had pretreatment marked elevation of guanidinoacetate and low/low normal creatine in plasma, urine, and CSF, and diminished creatine peak on brain MRS (ACD registry). Another proband was reported with elevated guanidinoacetate in plasma (PMID: 23660394, PMID: 24268530) (PP4_Strong). These individuals are all compound heterozygous for the variant and another variant in GAMT that has been classified as pathogenic by the ClinGen CCDS VCEP including c.522G>A (p.Trp174Ter) (ClinVar Variation ID: 205584, SCV002600143.1), confirmed in trans by parental testing (PMID: 23660394, PMID: 24268530) (1 point), c.299_311dup (ClinVar Variation ID: 8302, SCV002600154.1) confirmed in trans by parental testing (Association for Creatine Deficiencies registry) (1 point), and c.59G>C (p.Trp20Ser) (ClinVar Variation ID: 8303, SCV004009593.1), phase unconfirmed (Association for Creatine Deficiencies registry) (0.5 points) (PM3_Strong). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.828, evidence that correlates with impact to GAMT function (PP3). A different missense variant at the same codon, c.506G>A (p.Cys169Tyr) (ClinVar ID: 8304, SCV004009598.1),has been classified as likely pathogenic by the ClinGen CCDS VCEP (PM5_Supporting) There is a ClinVar entry for this variant (Variation ID: 818179). In summary, this variant meets the criteria to be classified as 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 1.1.0): PM3_Strong, PP4_Strong, PP3, PM2_Supporting, PM5_Supporting. (Classification approved by the ClinGen CCDS VCEP on June 13, 2024)

Met criteria codes

PM3_Strong			This variant was detected in three individuals with GAMT deficiency (PMID: 23660394, PMID: 24268530). These individuals are all compound heterozygous for the variant and another variant in GAMT that has been classified as pathogenic by the ClinGen CCDS VCEP including c.522G>A (p.Trp174Ter) (ClinVar Variation ID: 205584, SCV002600143.1), confirmed in trans by parental testing (PMID: 23660394, PMID: 24268530) (1 point), c.299_311dup (ClinVar Variation ID: 8302, SCV002600154.1) confirmed in trans by parental testing (Association for Creatine Deficiencies registry) (1 point), and c.59G>C (p.Trp20Ser) (ClinVar Variation ID: 8303, SCV004009593.1), phase unconfirmed (Association for Creatine Deficiencies registry) 0.5 points). Total 2.5 points (PM3_Strong)
PP3			The computational predictor REVEL gives a score of 0.828, evidence that correlates with impact to GAMT function (PP3).
PM5_Supporting			A different missense variant at the same codon, c.506G>A (p.Cys169Tyr) (ClinVar ID: 8304, SCV004009598.1),has been classified as likely pathogenic by the ClinGen CCDS VCEP.
PP4_Strong			This variant has been identified in 3 individuals with a diagnosis of GAMT deficiency. One of these individuals had pretreatment marked elevation of guanidinoacetate and low/low normal creatine in plasma, urine, and CSF, and diminished creatine peak on brain MRS (ACD registry). Another proband was reported with elevated guanidinoacetate in plasma (PMID: 23660394, PMID: 24268530) (PP4_Strong).
PM2_Supporting			This variant is absent in gnomAD v2.1.1 (PM2_Supporting).

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