

Variant: NM_000156.6(GAMT):c.587C>T (p.Ala196Val)

Version: 1.0

CA314820 [↗](#)

205588 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 48f641c9-b475-4f6d-85fc-a2b3a05ba365

Approved on: 2024/9/11

Published on: 2025/3/13

HGVS expressions

NM_000156.6(GAMT):c.587C>T (p.Ala196Val)

NM_000156.6:c.587C>T

NC_000019.10:g.1397483G>A

CM000681.2:g.1397483G>A

NC_000019.9:g.1397482G>A

CM000681.1:g.1397482G>A

NC_000019.8:g.1348482G>A

NG_008283.1:g.18600G>A

NG_009785.1:g.9071C>T

ENST00000252288.8:c.587C>T

ENST00000640164.1:n.420C>T

ENST00000640762.1:c.518C>T

ENST00000252288.6:c.587C>T

NM_000156.5:c.587C>T

Likely Benign

Met criteria codes **3**

BS3_Supporting

BP4

PM2_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.587C>T variant in GAMT is a missense variant that is predicted to cause the substitution of an alanine by a valine at amino acid position 196 (p.Ala196Val). This variant has been previously reported as a heterozygous variant detected in the context of newborn screening in Dutch newborns (PMID: 26319512). Expression of the variant in GAMT-deficient fibroblasts resulted in similar activity

as wild type GAMT indicating that this variant does not impact protein function (PMID: 26319512) (BS3_Supporting). The highest population minor allele frequency in gnomAD v4.1.0. is 0.0001043 (123/1179840 alleles; no homozygotes) in the European (Non-Finnish) population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.267 which is below the threshold of 0.29, evidence that does not predict a damaging effect on GAMT function (BP4). There is a ClinVar entry for this variant (Variation ID: 205588). Although there is conflicting evidence, with two benign criteria met (BP4 and BS3_Supporting) and one pathogenic criterion met (PM2_Supporting), the consensus from the ClinGen CCDS VCEP is that this variant is likely benign for GAMT deficiency, based upon the in silico and functional evidence. GAMT-specific ACMG/AMP codes met, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes VCEP (Specifications Version 2.0.0): PM2_Supporting, BS3_Supporting, BP4 (classification modified to likely benign) (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on September 11, 2024)

Met criteria codes

BS3_Supporting			Expression of the variant in GAMT-deficient fibroblasts resulted in similar activity as wild type GAMT indicating that this variant does not impact protein function (PMID: 26319512) (BS3_Supporting).
BP4			The computational predictor REVEL gives a score of 0.267 which is below the threshold of 0.29, evidence that does not predict a damaging effect on GAMT function (BP4).
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0. is 0.0001043 (123/1179840 alleles; no homozygotes) in the European (Non-Finnish) population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting).

Not Met criteria codes

PM5			c.586G>A (p.Ala196Thr) is classified as a VUS in ClinVar (ID: 971375)
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Curation History



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