

Variant: *NM\_000156.6(GAMT):c.507\_521dup*  
(*p.Cys169\_Ser173dup*)

Version: 1.1

[CA9043617](#)

[431959 \(ClinVar\)](#)

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

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** 6ad8131f-e940-4765-8021-25867dfc42c3

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### *HGVS expressions*

#### **NM\_000156.6:c.507\_521dup**

NM\_000156.6(GAMT):c.507\_521dup (*p.Cys169\_Ser173dup*)

NC\_000019.10:g.1398968\_1398982dup

CM000681.2:g.1398968\_1398982dup

NC\_000019.9:g.1398967\_1398981dup

CM000681.1:g.1398967\_1398981dup

NC\_000019.8:g.1349967\_1349981dup

NG\_009785.1:g.7575\_7589dup

ENST00000252288.8:c.507\_521dup

ENST00000447102.8:c.507\_521dup

ENST00000591788.3:c.190\_204dup

ENST00000640164.1:n.340\_354dup

ENST00000640762.1:c.438\_452dup

ENST00000252288.6:c.507\_521dup

ENST00000447102.7:c.507\_521dup

ENST00000591788.2:c.192\_206dup

NM\_000156.5:c.507\_521dup

NM\_138924.2:c.507\_521dup

NM\_138924.3:c.507\_521dup

**Likely Pathogenic**

**Met criteria codes** **4**

**PP4\_Strong** **PM3** **PM4**

**PM2\_Supporting**

**Not Met criteria codes** **1**

**PP3**

**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**





## Cerebral Creatine Deficiency Syndromes VCEP

The NM\_000156.6:c.507\_521dup (p.Cys169\_Ser173dup) variant in *GAMT* is a protein length-changing variant (in-frame insertion) in a non-repeat region (PM4). This variant has been previously reported in at least two unrelated individuals with clinical symptoms consistent with *GAMT* deficiency. One individual had elevated plasma GAA and was compound heterozygous for the variant and a pathogenic variant in *GAMT*, c.327G>A (p.Lys109=, ClinVar ID: 21065), with the variants confirmed in trans by parental testing (PMID: 23583224, 29506905; personal communication) (PM3). The other individual had elevated plasma GAA and reduced cerebral creatine by MRS, pretreatment (PP4\_Strong), and was compound heterozygous for the variant and c.403G>T (p.Asp135Tyr) (PMID: 19027335, 23660394); however, the allelic data for the latter patient will be used in the classification of p.Asp135Tyr and was not included here to avoid circular logic and thus this individual was not counted towards PM3 evidence. The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001525 (14/1180016 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 PROVEAN predicts a damaging effect on *GAMT* function, but MutationTaster suggested no impact, such that PP3 is not met. There is a ClinVar entry for this variant (Variation ID: 431959). 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): PP4\_Strong, PM3, PM4, PM2\_supporting. (Classification approved by the ClinGen Creatine Deficiency Syndromes Variant Curation Expert Panel on September 11, 2024).

### Met criteria codes

<b>PP4_Strong</b>	 	This variant has been reported in at least two cases: one proband with elevated plasma guanidinoacetate and reduced cerebral creatine by brain magnetic resonance spectroscopy (PMID: 19027335, 2950690); and in one proband with elevated plasma guanidinoacetate (PMID: 23583224, 29506905) (PP4_Strong).
<b>PM3</b>	 	This variant has been previously reported in at least two cases with clinical symptoms consistent with <i>GAMT</i> deficiency. One proband had elevated plasma GAA and was compound heterozygous for the variant and another pathogenic variant in <i>GAMT</i> , c.327G>A (p.Lys109=), with the variants confirmed in trans by parental testing (PMID: 23583224, 29506905; personal communication) (1 point). Another proband had elevated plasma GAA and reduced cerebral creatine by MRS, pretreatment, and was compound heterozygous for the variant and c.403G>T (p.Asp135Tyr) (PMID: 19027335). The allelic data for this latter patient will be used in the assessment of p.Asp135Tyr and is not included here to avoid circular logic. Total 1 point (PM3).
<b>PM4</b>	 	The c.507_521dup (p.Cys169_Ser173dup) variant in <i>GAMT</i> is a protein length-changing variant (in-frame insertion) in a non-repeat region (PM4).
<b>PM2_Supporting</b>	 	The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001525 (18/1180016 alleles) 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

<b>PP3</b>	 	The computational predictor PROVEAN gives a score of -7.095 (below the threshold of -2.5), MutPred-Indel gives a score of 0.69307 (>0.50 suggests pathogenicity with a false positive rate of 10%, > 0.70 yields a false positive rate of 5%), but MutationTaster predicts it to be a "polymorphism". PP3 not applied because the predictors do not agree.
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