

Variant: NM_138924.3:c.115A>G

Version: 1.1

CA402998134 [↗](#)

2683727 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: c4f27b5f-831e-4fe5-987b-293447d83b40

Approved on: 2026/4/20

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HGVS expressions

NM_138924.3:c.115A>G

NC_000019.10:g.1401362T>C

CM000681.2:g.1401362T>C

NC_000019.9:g.1401361T>C

CM000681.1:g.1401361T>C

NC_000019.8:g.1352361T>C

NG_009785.1:g.5192A>G

ENST00000252288.8:c.115A>G

ENST00000447102.8:c.115A>G

ENST00000640762.1:c.112+3A>G

ENST00000252288.6:c.115A>G

ENST00000447102.7:c.115A>G

NM_000156.5:c.115A>G

NM_138924.2:c.115A>G

NM_000156.6:c.115A>G

Likely Pathogenic

Met criteria codes **4**

PM2_Supporting

PP4_Strong

PM3_Supporting

PP3

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.115A>G variant in GAMT is predicted to results in the missense substitution of lysine by glutamate at amino acid 39 (p.Lys39Glu). One proband with this variant has been reported with moderate global developmental delay, increased guanidinoacetate and

significantly reduced creatine in dried blood spots, and significantly decreased creatine peak on MRS (PMID:37305710) (PP4_Strong). 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.328-2A>G (ClinVar Variation ID: 854099); the phase is unknown (PMID:3730571) (0.5 points) (PM3_Supporting). The variant is absent from gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.721, evidence that correlates with impact to GAMT function at the supporting level (PMID: 36413997) (PP3). 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). PM2_Supporting, PP4_Strong, PP3, PM3_Supporting. (Classification approved by the ClinGen CCDS VCEP on April 20, 2026).

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v4 (PM2_Supporting).
PP4_Strong			One male proband reported with moderate global developmental delay. Dried blood spot analysis measured increased GAA with significantly reduced creatine (2 points), patient has significantly decreased creatine peak via MRS (3 points). (PMID:37305710) (PP4_Strong).
PM3_Supporting			One proband 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.328-2A>G (ClinVar Variation ID: 854099); the phase is unknown (PMID:3730571) (0.5 points) (PM3_Supporting).
PP3			The computational predictor REVEL gives a score of 0.721, which meets the threshold set in Pejaver et al. 2022 (PMID:36413997) for PP3.

Not Met criteria codes

PM5			Another missense variant (c.115A>C p.Lys39Gln) in the same codon has been classified as of uncertain significance by a clinical lab, but it was absent literature evidence (ClinVar ID:1051517) (PM5 not met).
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Curation History

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