

Variant: NM_000156.6(GAMT):c.467C>A (p.Ala156Asp)

Version: 1.0

CA9043637 [↗](#)

801415 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 5c72c382-0f01-44d1-aa6a-d90d93639061

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HGVS expressions

NM_000156.6(GAMT):c.467C>A (p.Ala156Asp)

NM_000156.6:c.467C>A

NC_000019.10:g.1399019G>T

CM000681.2:g.1399019G>T

NC_000019.9:g.1399018G>T

CM000681.1:g.1399018G>T

NC_000019.8:g.1350018G>T

NG_009785.1:g.7535C>A

ENST00000252288.8:c.467C>A

ENST00000447102.8:c.467C>A

ENST00000591788.3:c.150C>A

ENST00000640164.1:n.300C>A

ENST00000640762.1:c.398C>A

ENST00000252288.6:c.467C>A

ENST00000447102.7:c.467C>A

ENST00000591788.2:c.152C>A

NM_000156.5:c.467C>A

NM_138924.2:c.467C>A

NM_138924.3:c.467C>A

Likely Pathogenic

Met criteria codes **4**

PP3_Moderate

PM3

PP4_Strong

PM2_Supporting

Not Met criteria codes **1**

PS3

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**

Cerebral Creatine Deficiency Syndromes VCEP

The NM_000156.6:c.467C>A variant in GAMT is a missense variant that is predicted to cause the substitution of an alanine by an aspartic acid at amino acid position 156 (p.Ala156Asp). This variant has been detected in at least one individual with GAMT deficiency (Lei et al. Journal of Clinical Pediatrics, 2024, 42(12): 1039-1046), who was compound heterozygous for the variant and a pathogenic or likely pathogenic variant, c.194T>C (p.Leu65Pro), which was confirmed in trans by parental testing (PM3). The individual with this variant (Lei et al. Journal of Clinical Pediatrics, 2024, 42(12): 1039-1046) had elevated GAA and low or low normal creatine in urine and significantly decreased creatine peak (GAA not reported) on brain MRS (4 points; PP4_Strong). The highest population minor allele frequency in gnomAD v4.1.0. is 0.000015 (18/1180024 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). The computational predictor REVEL gives a score of 0.864 which is in the range of 0.773-0.932, evidence that correlates with impact to GAMT function at the moderate level (PP3_Moderate). Expression of the variant in HeLa cells resulted in <15% wild type GAMT activity indicating that this variant may impact protein function (PMID: 26003046); however, due to uncertainty regarding variant annotation in the publication, this was not used for PS3 evidence. There is a ClinVar entry for this variant (Variation ID: 801415). 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): PP4_Strong, PP3_Moderate, PM3, PM2_Supporting. (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on December 10, 2025)

Met criteria codes

PP3_Moderate			The computational predictor REVEL gives a score of 0.864 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). No impact on splicing is predicted by SpliceAI.
PM3			One patient with features consistent with GAMT deficiency has been reported to be compound heterozygous for the variant and another variant in GAMT that has been classified as pathogenic for GAMT deficiency, c.194T>C (p.Leu65Pro); the variants were confirmed to be in trans by parents testing (Journal of Clinical Pediatrics, 2024 Vol.42 No.12 1039-1046 (article in Chinese), link to article - https://jcp.xinhuamed.com.cn/EN/10.12372/jcp.2024.24e0300). (1pt, PM3).
PP4_Strong			The individual with this variant (PMID: 40105081) had elevated GAA and low or low normal creatine in urine and significantly decreased creatine peak (GAA not reported) on brain MRS (4 points; PP4_Strong).
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0. is 0.000015 (18/1180024 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

PS3			According to Table 2, when expressed in HeLa cells, the variant resulted in a significant decrease in enzyme activity (PMID: 26003046). However, due to various typos throughout the article when referring to this variant, the evidence is not included.
			According to Table 2, when expressed in HeLa cells, the variant resulted in a significant decrease in enzyme activity (PS3_Supporting). (Possible typos, with variant as either c.467C>A, c.467C>G, p.Thr156Asp, p.Ala156Asp, and p.Ala156Arg) PubMed:26003046 

Curation History

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