

Variant: NM\_000156.6(GAMT):c.491G>A (p.Gly164Asp)

Version: 2.0

CA314807 [↗](#)

205581 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** fd7e045d-f8c5-457a-bfef-c535608351ea

**Approved on:** 2024/9/11

**Published on:** 2024/9/12

## HGVS expressions

NM\_000156.6:c.491G>A

NM\_000156.6(GAMT):c.491G>A (p.Gly164Asp)

NC\_000019.10:g.1398995C>T

CM000681.2:g.1398995C>T

NC\_000019.9:g.1398994C>T

CM000681.1:g.1398994C>T

NC\_000019.8:g.1349994C>T

NG\_009785.1:g.7559G>A

ENST00000252288.8:c.491G>A

ENST00000447102.8:c.491G>A

ENST00000591788.3:c.174G>A

ENST00000640164.1:n.324G>A

ENST00000640762.1:c.422G>A

ENST00000252288.6:c.491G>A

ENST00000447102.7:c.491G>A

ENST00000591788.2:c.176G>A

NM\_000156.5:c.491G>A

NM\_138924.2:c.491G>A

NM\_138924.3:c.491G>A

Likely Pathogenic

Met criteria codes **4**

PM2\_Supporting

PP3\_Moderate

PP4

PM3

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**

Cerebral Creatine Deficiency Syndromes VCEP

The NM\_000156.6:c.491G>A variant in GAMT is a missense variant predicted to cause the substitution of a glycine by an aspartate at amino acid position 164 (p.Gly164Asp). This variant has been previously reported in one patient who had elevated plasma guanidinoacetate levels on two occasions (PP4) and was compound heterozygous for the variant and a pathogenic variant in GAMT, c.522G>A (p.Trp174Ter, ClinVar ID: 205584), confirmed in trans by parental testing (PM3). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001667 (1/59992 alleles) in the Admixed American 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 0.919, evidence that correlates with impact to GAMT function (PP3\_Moderate applied for REVEL score range 0.773-0.932). There is a ClinVar entry for this variant (Variation ID: 203539). 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): PM3, PP4, PP3\_Moderate, PM2\_Supporting. (Classification approved by the ClinGen Creatine Deficiency Syndromes Variant Curation Expert Panel on September 11, 2024).

Met criteria codes

|                |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                              |
|----------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PM2_Supporting |    |    | The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001667 (1/59992 alleles) in the Admixed American population, which is lower than the ClinGen CCDS VCEP’s threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting).             |
| PP3_Moderate   |    |    | The computational predictor REVEL gives a score of 0.919, evidence that correlates with impact to GAMT function (PP3_Moderate applied for REVEL score range 0.773-0.932).                                                                                                    |
| PP4            |  |  | One patient with two elevated plasma guanidinoacetate levels has been reported (PMID: 23660394) (PP4).                                                                                                                                                                       |
| PM3            |  |  | This variant has been detected in 1 individual with GAMT deficiency. They were compound heterozygous for the variant and a pathogenic variant [c.522G>A (p.Trp174Ter); ClinVar ID: 205584] and confirmed in trans by parental testing (PMID : 23660394) Total 1 point (PM3). |

Not Met criteria codes

|     |                                                                                     |                                                                                     |                                                        |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------|
| PM5 |  |  | c.491G>T (p.Gly164Val) is VUS in ClinVar (ID: 1312507) |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------|

Curation History 

▼

▼

Showing 1 to 2 of 2 rows

|  |
|--|
|  |
|--|

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.