

Variant: *NM\_138924.3:c.48C>A*

Version: 1.0

CA402998364 [↗](#)

2412845 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** 3a761134-fdab-4d0f-a4da-dcb7b040a030

**Approved on:** 2023/8/8

**Published on:** 2023/9/13

## HGVS expressions

**NM\_138924.3:c.48C>A**

NC\_000019.10:g.1401429G>T

CM000681.2:g.1401429G>T

NC\_000019.9:g.1401428G>T

CM000681.1:g.1401428G>T

NC\_000019.8:g.1352428G>T

NG\_009785.1:g.5125C>A

ENST00000252288.8:c.48C>A

ENST00000447102.8:c.48C>A

ENST00000640762.1:c.48C>A

ENST00000252288.6:c.48C>A

ENST00000447102.7:c.48C>A

NM\_000156.5:c.48C>A

NM\_138924.2:c.48C>A

NM\_000156.6:c.48C>A

**Pathogenic**

**Met criteria codes** **3**

PVS1

PP4\_Strong

PM3

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

PM2

**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 1.1.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

### Cerebral Creatine Deficiency Syndromes VCEP

The NM\_000156.6:c.48C>A (p.Cys16Ter) variant in GAMT is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 1/6, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).

This variant is absent in gnomAD v2.1.1 but coverage of this region is <20X and therefore PM2\_Supporting is not met. First cousins who are homozygous for the variant (PMID 31559727), and siblings who are compound heterozygous for the variant and another variant in GAMT that has been classified as pathogenic by the ClinGen CCDS VCEP, c.327G>A, phase unknown, have been reported (PMID: 24268530) (PM3). These individuals all had clinical symptoms consistent with GAMT deficiency; in one of them elevated guanidinoacetate values were documented in urine and creatine peak was "sharply" decreased on MRS (PP4\_Strong). There is a ClinVar entry for this variant (Variation ID: 2412845). In summary, this variant meets the criteria to be classified as pathogenic for GAMT deficiency. GAMT-specific criteria met, as specified by the ClinGen CCDS Variant Curation Expert Panel (Specifications Version 1.1.0), PVS1, PP4\_Strong, PM3. (Classification approved by the ClinGen CCDS VCEP, August 8, 2023)

Met criteria codes

|            |                                                                                   |                                                                                   |                                                                                                                                                                                                                                                                                                                                      |
|------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PVS1       |  |  | The NM_000156.6:c.48C>A (p.Cys16Ter) variant in GAMT is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 1/6 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).                                                            |
| PP4_Strong |  |  | First cousins, who are homozygous for the variant, have been reported. One of these individuals had elevated guanidinoacetate in urine and decreased creatine peak on MRS (PP4_Strong).                                                                                                                                              |
| PM3        |  |  | First cousins who are homozygous for the variant (PMID 31559727; 0.5 points), and siblings who are compound heterozygous for the variant and another variant in GAMT that has been classified as pathogenic by the ClinGen CCDS VCEP, c.327G>A, phase unknown, have been reported (PMID: 24268530; 0.5 points). Total 1 point (PM3). |

Not Met criteria codes

|     |  |                                                                                     |                                                                                                                      |
|-----|--|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|
| PM2 |  |  | This variant is absent in gnomAD v2.1.1 but coverage of this region is <20X and therefore PM2_Supporting is not met. |
|-----|--|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|

Curation History 



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