

Variant: *NM\_000156.6(GAMT):c.59G>C (p.Trp20Ser)*

Version: 1.0

CA340769 [↗](#)

8303 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** dc790a08-e798-46d6-ad31-772c3482c12b

**Approved on:** 2023/5/25

**Published on:** 2023/5/25

### HGVS expressions

**NM\_000156.6:c.59G>C**

**NM\_000156.6(GAMT):c.59G>C (p.Trp20Ser)**

NC\_000019.10:g.1401418C>G

CM000681.2:g.1401418C>G

NC\_000019.9:g.1401417C>G

CM000681.1:g.1401417C>G

NC\_000019.8:g.1352417C>G

NG\_009785.1:g.5136G>C

ENST00000252288.8:c.59G>C

ENST00000447102.8:c.59G>C

ENST00000640762.1:c.59G>C

ENST00000252288.6:c.59G>C

ENST00000447102.7:c.59G>C

NM\_000156.5:c.59G>C

NM\_138924.2:c.59G>C

NM\_138924.3:c.59G>C

**Pathogenic**

**Met criteria codes** 4

PM3\_Strong

PP3

PS3\_Supporting

PP4\_Strong

**Not Met criteria codes** 3

PP1

PM2

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 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.59G>C variant in GAMT is a missense variant predicted to cause substitution of tryptophan by serine at amino acid 20 (p.Trp20Ser). This variant has been detected in at least 9 unrelated individuals with GAMT deficiency (PMID: 15651030, PMID: 16855203, PMID: 15108290). Of those individuals, one was compound heterozygous for the variant and a pathogenic variant, c.521G>A (p.Trp174\*, in trans (PMID: 16855203) and eight individuals were homozygous for the variant (PMID: 15651030, PMID: 16855203, PMID: 15108290) (2 points total) (PM3\_Strong). These individuals showed elevated plasma GAA and urine GAA (PMID: 15651030, PMID: 16855203, PMID: 15108290), three also showed deficient (<5% wild-type) GAMT enzyme activity in lymphoblasts (PMID: 15651030), and one also showed deficient (<5% wild-type) GAMT enzyme activity in fibroblasts and reduced creatine signal on brain MRS (PMID: 16855203, PMID: 21140503) (PP4\_Strong). Expression of the variant in HeLa cells resulted in 3% wild type GAMT activity indicating that this variant may impact protein function (PMID: 17336114)(PS3\_Supporting). The highest population minor allele frequency in gnomAD v2.1.1 is 0.0001 (3/27420 alleles) in the European (non-Finnish) population, which is lower than the ClinGen CCDS VCEP’s threshold for PM2\_Supporting (<0.0004); however, as this variant is covered in <50% of individuals in gnomAD v2.1.1, allele frequency estimates may not be reliable and thus PM2\_Supporting is not met. The computational predictor REVEL gives a score of 0.94 which is above the threshold of 0.75, evidence that correlates with impact to GAMT function (PP3). There is a ClinVar entry for this variant (Variation ID: 8303, 2 star review status) with 9 submitters classifying the variant as pathogenic and 1 submitter classifying the variant as likely pathogenic. In summary, this variant meets the criteria to be classified as 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 1.1.0): PS3\_Supporting, PM3\_Strong, PP3, PP4\_Strong. (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on May 25, 2023)

Met criteria codes

|                |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PM3_Strong     |    |    | Of those individuals, one was compound heterozygous for the variant and a pathogenic variant, c.521G>A (p.Trp174*, in trans (PMID: 16855203) and eight individuals were homozygous for the variant (PMID: 15651030, PMID: 16855203, PMID: 15108290) (2 points total) (PM3_Strong).                                                                                                        |
| PP3            |  |  | The computational predictor REVEL gives a score of 0.94 which is above the threshold of 0.75, evidence that correlates with impact to GAMT function (PP3).                                                                                                                                                                                                                                |
| PS3_Supporting |  |  | PMID: 17336114: Variant expressed in HeLa cells and showed no difference in GAMT activity versus negative control (cells transfected with empty vector) and 3% of WT activity                                                                                                                                                                                                             |
| PP4_Strong     |  |  | These individuals showed elevated plasma GAA and urine GAA (PMID: 15651030, PMID: 16855203, PMID: 15108290), three also showed deficient (<5% wild-type) GAMT enzyme activity in lymphoblasts (PMID: 15651030), and one also showed deficient (<5% wild-type) GAMT enzyme activity in fibroblasts and reduced creatine signal on brain MRS (PMID: 16855203, PMID: 21140503) (PP4_Strong). |

Not Met criteria codes

|     |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                          |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PP1 |                                                                                     |  | PP1 not used per VCEP specifications                                                                                                                                                                                                                                                                                                                                                     |
| PM2 |                                                                                     |  | The highest population minor allele frequency in gnomAD v2.1.1 is 0.0001 (3/27420 alleles) in the European (non-Finnish) population, which is lower than the ClinGen CCDS VCEP’s threshold for PM2_Supporting (<0.0004); however, as this variant is covered in <50% of individuals in gnomAD v2.1.1, allele frequency estimates may not be reliable and thus PM2_Supporting is not met. |
| PM5 |  |  | A different missense variant at the same site, p.Trp20Leu, has been reported in ClinVar with conflicting interpretations of pathogenicity (Variation ID: 588631) and has been classified as a VUS by the ClinGen CCDS.                                                                                                                                                                   |

Curation History 

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