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# *Variant: NM_000156.6(GAMT):c.1A>G (p.Met1Val)*

Version: 1.0

*CA314826*

*205591 (ClinVar)*

**Gene**: GAMT (HGNC:2593)
**Condition**: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 23ae4aee-9294-46f0-8431-d7435c40c602
**Approved on**: 2024/9/11
**Published on**: 2024/9/12

## *HGVS expressions*

**NM_000156.6:c.1A>G**
**NM_000156.6(GAMT):c.1A>G (p.Met1Val)**
NC_000019.10:g.1401476T>C
CM000681.2:g.1401476T>C
NC_000019.9:g.1401475T>C
CM000681.1:g.1401475T>C
NC_000019.8:g.1352475T>C
NG_009785.1:g.5078A>G
ENST00000252288.8:c.1A>G
ENST00000447102.8:c.1A>G
ENST00000640762.1:c.1A>G
ENST00000252288.6:c.1A>G
ENST00000447102.7:c.1A>G
NM_000156.5:c.1A>G
NM_138924.2:c.1A>G
NM_138924.3:c.1A>G

**Likely Pathogenic**

**Met criteria codes** 3

PVS1_Moderate PP4_Strong PM2_Supporting

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.1A>G (p.Met1Val) variant in GAMT may cause a truncated or absent protein by altering the start codon of the coding sequence and is predicted to lead to the omission of a critical region of the protein (PVS1_Moderate). This variant is reported in an individual with elevated GAA and low creatine in plasma, elevated guanidinoacetate in urine, and diminished creatine peak on magnetic resonance spectroscopy (GAA not reported) (CreatineInfo, Association for Creatine Deficiencies registry). The variant is also reported in one individual with epilepsy and/or neurodevelopmental delay without reported biochemical evidence of GAMT deficiency (PMID: 29655203; unknown if these cases may be the same individual) (PP4_Strong). The highest population minor allele frequency in gnomAD v4.1.0. is 9.588e-7 (1/1042950 alleles; no homozygotes) 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). There is a ClinVar entry for this variant (Variation ID: 205591). 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): PVS1_Moderate, PM2_Supporting, PP4_Strong. (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on September 11, 2024).**

**Met criteria codes**

| | | |
|---|---|---|
| **PVS1_Moderate** | ✔ | The NM_000156.6:c.1A>G (p.Met1Val) variant in GAMT may cause a truncated or absent protein by altering the start codon of the coding sequence and is predicted to lead to the omission of a critical region of the protein (PVS1_Moderate). |
| **PP4_Strong** | ✔ | Reported in one individual with elevated GAA and low creatine in plasma, elevated guanidinoacetate in urine, and diminished creatine peak on magnetic resonance spectroscopy (GAA not reported) (CreatineInfo, Association for Creatine Deficiencies registry)(PP4_Strong). |
| **PM2_Supporting** | ✔ | The highest population minor allele frequency in gnomAD v4.1.0. is 9.588e-7 (1/1042950 alleles; no homozygotes) 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). |

Curation History

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