

Variant: *NM_138924.3:c.274A>G*

Version: 2.0

CA402996427 [↗](#)

2446453 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: a430849d-26c4-42f2-a413-c79e51cad973

Approved on: 2024/9/11

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HGVS expressions

NM_138924.3:c.274A>G

NC_000019.10:g.1399846T>C

CM000681.2:g.1399846T>C

NC_000019.9:g.1399845T>C

CM000681.1:g.1399845T>C

NC_000019.8:g.1350845T>C

NG_009785.1:g.6708A>G

ENST00000252288.8:c.274A>G

ENST00000447102.8:c.274A>G

ENST00000640762.1:c.205A>G

ENST00000252288.6:c.274A>G

ENST00000447102.7:c.274A>G

NM_000156.5:c.274A>G

NM_138924.2:c.274A>G

NM_000156.6:c.274A>G

Likely Pathogenic

Met criteria codes **5**

PS3_Supporting

PM3_Supporting

PP3_Moderate

PP4

PM2_Supporting

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**

Evidence submitted by expert panel

Cerebral Creatine Deficiency Syndromes VCEP

The NM_000156.6:c.274A>G variant in GAMT is a missense variant predicted to cause the substitution of an asparagine by an aspartate at amino acid position 92 (p.Asn92Asp). This variant has been previously reported in one individual with elevated urine guanidinoacetate and

low urine creatine (PP4) who was homozygous for the variant (PMID: 19288536, 24415674, 33996490) (PM3_Supporting). The highest population minor allele frequency in gnomAD v4.1.0. is 0.000001705 (2/1172782 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). The computational predictor REVEL gives a score of 0.92, evidence that correlates with impact to GAMT function (PP3_Moderate applied for REVEL score range 0.773-0.932). This variant was shown to result in <15% GAMT enzymatic activity when transfected into GAMT-deficient fibroblasts (PMID: 24415674) (PS3_Supporting). There is a ClinVar entry for this variant (Variation ID: 2446453). 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): PS3_Supporting, PM2_Supporting, PM3_Supporting, PP3_Moderate, PP4. (Classification approved by the ClinGen Creatine Deficiency Syndromes Variant Curation Expert Panel on September 11, 2024).

Met criteria codes

PS3_Supporting			PMID 24415674: Shown to result in <5% of wild-type GAMT enzyme activity in GAMT-deficient fibroblasts
			PMID 24415674: Shown to result in <5% of wild-type GAMT enzyme activity in GAMT-deficient fibroblasts PubMed:24415674 
PM3_Supporting			Identified in one individual with guanidinoacetate methyltransferase deficiency, who was a homozygote for the variant (0.5pts) (PMID: 19288536)
PP3_Moderate			The computational predictor REVEL gives a score of 0.92, evidence that correlates with impact to GAMT function (PP3_Moderate applied for REVEL score range 0.773-0.932).
PP4			Identified in one individual who showed elevated urine GAA with low creatine (1pt, PP4_Supporting) (PMID: 19288536, 24415674, 33996490)
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0 is 0.000001705 (2/1172782 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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