

Variant: NM_001321015.2:c.166G>C

Version: 1.1

CA392261143 [↗](#)

1478699 (ClinVar) [↗](#)

Gene: GATM ([HGNC:2628](#))

Condition: AGAT deficiency ([MONDO:0012996](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 34e85701-31a5-45f8-8d77-23cb3e6b7e82

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HGVS expressions

NM_001321015.2:c.166G>C

NC_000015.10:g.45368192C>G

CM000677.2:g.45368192C>G

NC_000015.9:g.45660390C>G

CM000677.1:g.45660390C>G

NC_000015.8:g.43447682C>G

NG_011674.1:g.15591G>C

NG_011674.2:g.39126G>C

ENST00000396659.8:c.553G>C

ENST00000674905.1:c.553G>C

ENST00000675158.1:c.553G>C

ENST00000675323.1:c.553G>C

ENST00000675701.1:c.493G>C

ENST00000675974.1:n.644G>C

ENST00000676090.1:c.*1284G>C

ENST00000396659.7:c.553G>C

ENST00000558163.1:c.334G>C

ENST00000558336.5:c.553G>C

ENST00000558362.5:n.2209G>C

ENST00000558916.1:n.451G>C

NM_001482.2:c.553G>C

NM_001321015.1:c.166G>C

NM_001482.3:c.553G>C

Likely Pathogenic

Met criteria codes **4**

PS3_Supporting

PP4_Strong

PM3_Supporting

PM2_Supporting

Not Met criteria codes **2**

BP4

PP3

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 GATM Version 2.0.0

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

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

Cerebral Creatine Deficiency Syndromes VCEP

The NM_001482.3:c.553G>C variant in GATM is a missense variant that is predicted to result in the substitution of alanine by proline at amino acid 185 (p.Ala185Pro). One patient, with one episode of seizure, myopathy, intellectual disability, and abnormal EMG, has been reported with absent creatine on brain MRS, as well as low urine guanidinoacetate, and low plasma guanidinoacetate with low plasma creatine (PMID: 26490222) (PP4_Strong). This individual is homozygous for the variant (PM3_Supporting). The highest population minor allele frequency in gnomAD v4.1.0 is 0.00001562 (1/64012 alleles) in the Finnish population, which is lower than the ClinGen CCDS VCEP’s threshold for PM2_Supporting (<0.000055), meeting this criterion. This allele is the only allele in gnomAD v4.1.0. (PM2_Supporting). When overexpressed in HeLa cells, the variant resulted in <15% wild-type enzyme activity (PMID: 27233232) (PS3_Supporting). The computational predictor REVEL gives a score of 0.528 which is neither above nor below the thresholds predicting a damaging (>0.644) or benign (<0.29) impact on AGAT function. SpliceAI predicts that the variant has no impact on splicing. In summary, this variant meets the criteria to be classified as likely pathogenic for AGAT deficiency. GATM-specific ACMG/AMP criteria applied, as specified by the ClinGen CCDS VCEP (Specifications Version 2.0.0): PP4_Strong, PS3_Supporting, PM3_Supporting, PM2_Supporting. (Classification approved by the ClinGen CCDS VCEP on April 11, 2025).

Met criteria codes

PS3_Supporting			When overexpressed in HeLa cells, the variant resulted in <15% wild-type enzyme activity (PMID: 27233232)
			When overexpressed in HeLa cells, the variant resulted in <15% wild-type enzyme activity (PMID: 27233232). PubMed:27233232 
PP4_Strong			One patient, with one episode of seizure, myopathy, intellectual disability, and abnormal EMG, had absent creatine on brain MRS, as well as low urine guanidinoacetate, and low plasma guanidinoacetate with low plasma creatine (PMID: 26490222) (PP4_Strong).
PM3_Supporting			PMID: 26490222: Found in a single patient who was homozygous for the variant (0.5pts)
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0 is 0.00001562 (1/64012 alleles) in the Finnish population, which is lower than the ClinGen CCDS VCEP’s threshold for PM2_Supporting (<0.000055), meeting this criterion. This allele is the only allele in gnomAD v4.1.0. (PM2_Supporting).

Not Met criteria codes

BP4			The computational predictor REVEL gives a score of 0.528 which is neither above nor below the thresholds predicting a damaging (>0.644) or benign (<0.29) impact on AGAT function. SpliceAI predicts that the variant has no impact on splicing.
PP3			The computational predictor REVEL gives a score of 0.528 which is neither above nor below the thresholds predicting a damaging (>0.644) or benign (<0.29) impact on AGAT function.

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