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Variant: NM_138924.3:c.220G>C

Version: 1.1

CA402997017

2446457 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9262800f-6b30-4ede-af2c-601847eaadf7
Approved on: 2025/10/15
Published on: 2025/10/15

HGVS expressions

NM_138924.3:c.220G>C
NC_000019.10:g.1399900C>G
CM000681.2:g.1399900C>G
NC_000019.9:g.1399899C>G
CM000681.1:g.1399899C>G
NC_000019.8:g.1350899C>G
NG_009785.1:g.6654G>C
ENST00000252288.8:c.220G>C
ENST00000447102.8:c.220G>C
ENST00000640762.1:c.151G>C
ENST00000252288.6:c.220G>C
ENST00000447102.7:c.220G>C
NM_000156.5:c.220G>C
NM_138924.2:c.220G>C
NM_000156.6:c.220G>C

Likely Pathogenic

Met criteria codes 5

PS3_Supporting PP4_Moderate PM2_Supporting PM3 PP3_Moderate

Not Met criteria codes 1

PM5

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.220G>C variant in GAMT is predicted to result in a missense substitution of alanine by proline at amino acid 74 (p.Ala74Pro). This variant has been identified in two unrelated probands with clinical features consistent with GAMT deficiency; one with

absent creatine peak on MRS, the other with deficient GAMT activity. Both had urine guanidinoacetate levels 1.1 - 12 times above the upper limit of reference range, but specific values for each patient were not provided (PMID: 24415674) (PP4_Moderate). One of these individuals was reported to be compound heterozygous, phase unconfirmed, for the variant and another variant in GAMT that has been classified as pathogenic by the ClinGen CCDS VCEP, c.327G>A (ClinVar Variation ID: 21065) (0.5 points) and another patient was homozygous for the variant (0.5 points) (PMID: 24415674) Total 1 point (PM3). The highest population minor allele frequency in gnomAD v4.1.0. is 0.0000033945 (4/1178374 alleles) 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 0.930 which is in the range of 0.773-0.932, evidence that correlates with impact to GAMT function at the moderate level (PMID: 36413997) (PP3_Moderate). This variant was shown to result in undetectable GAMT enzymatic activity when transfected into GAMT-deficient fibroblasts (PMID: 24415674) (PS3_Supporting). In summary, this variant meets criteria to be classified as likely pathogenic for guanidinoacetate methyltransferase deficiency. GAMT-specific ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiencies Variant Curation Expert Panel (CCDS VCEP) (Specifications version 1.1.0): PM3, PP3_Moderate, PP4_Moderate PS3_Supporting, PM2_Supporting. (Classification approved by the ClinGen Cerebral Creatine Deficiencies Variant Curation Expert Panel on October 15, 2025)

Met criteria codes

PS3_Supporting	✔	The p.Ala74Pro variant was shown to result in undetectable GAMT enzyme activity, and no protein expression on Western blot, when expressed in GAMT-deficient fibroblasts (PMID: 24415674) The p.Ala74Pro variant was shown to result in undetectable GAMT enzyme activity in GAMT-deficient fibroblasts (PMID: 24415674) **PubMed:24415674**
PP4_Moderate	✔	The variant has been identified in two unrelated probands with clinical features consistent with GAMT deficiency; one with absent creatine peak on MRS, the other with deficient GAMT activity. Both had urine guanidinoacetate levels 1.1 - 12 times above the upper limit of reference range, but specific values for each patient were not provided (PMID: 24415674) (PP4_Moderate)
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.0000033945 (4/1178374 alleles) 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).
PM3	✔	One individual was reported to be compound heterozygous, phase unconfirmed, for the variant and another variant in GAMT that has been classified as pathogenic by the ClinGen CCDS VCEP, c.327G>A (ClinVar Variation ID: 21065) (0.5 points) and another patient is homozygous for the variant (0.5 points) (PMID: 24415674) Total 1 point, PM3.
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.930 which is in the range of 0.773-0.932, evidence that correlates with impact to GAMT function at the moderate level (PMID: 36413997) (PP3_Moderate).

Not Met criteria codes

PM5	✖	A different missense variant at the same amino acid residue, p.Ala74Thr has been reported as a VUS in ClinVar (Variation ID:651193)

Curation History

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