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Variant: NM_138924.3:c.391G>C

Version: 2.0

CA402995480

2446458 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: ddd3d58a-031d-4fb9-b992-a9be27c33545
Approved on: 2025/12/10
Published on: 2025/12/10

HGVS expressions

NM_138924.3:c.391G>C
NC_000019.10:g.1399524C>G
CM000681.2:g.1399524C>G
NC_000019.9:g.1399523C>G
CM000681.1:g.1399523C>G
NC_000019.8:g.1350523C>G
NG_009785.1:g.7030G>C
ENST00000252288.8:c.391G>C
ENST00000447102.8:c.391G>C
ENST00000591788.3:c.74G>C
ENST00000640164.1:n.224G>C
ENST00000640762.1:c.322G>C
ENST00000252288.6:c.391G>C
ENST00000447102.7:c.391G>C
ENST00000591788.2:c.76G>C
NM_000156.5:c.391G>C
NM_138924.2:c.391G>C
NM_000156.6:c.391G>C

Pathogenic

Met criteria codes 3

PP3_Strong PM2_Supporting PP4_Strong

Not Met criteria codes 3

PS3 PM3 PVS1

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.391G>C variant in GAMT is a missense variant that is predicted to cause the substitution of a glycine with an arginine at amino acid position 131 (p.Gly131Arg). This variant has been previously reported in at least one individual with GAMT deficiency (PMID: 23846910), who was compound heterozygous for this variant and a variant of uncertain significance c.578A>G (p.Gln193Arg) (ClinVar Variation ID: 1328978) with unknown phase. This individual showed an absent creatine peak on brain magnetic resonance spectroscopy and elevated urine GAA with low creatine with full GAMT gene sequencing (PMID: 23846910) (PP4_Strong). The highest population minor allele frequency in gnomAD v4.1.0. is 0.0000223 (1/44874 alleles) in the East Asian population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting). The computational splicing predictor SpliceAI gives a score of 0.8 for donor loss, predicting that the variant disrupts the donor splice site of intron 3 of GAMT. If any protein is made, the variant is predicted to result in a missense, p.Gly131Arg. The computational predictor REVEL gives a score of 0.958 for this missense variant, which is above the threshold of 0.75, evidence that correlates with impact to GAMT function (PP3_Strong). This variant was shown to result in abnormal splicing, frameshift, and premature termination based on cDNA analysis from an affected individual (PMID: 23846910). Based on the chromatograms shown in the publication, the altered splicing seems incomplete; however, the report does not specify the percentage of alternately spliced transcript. Given the uncertainty about the degree of altered splicing, PVS1 was not applied. There is a ClinVar entry for this variant (Variation ID: 2446458). In summary, this variant meets criteria to be classified as pathogenic for guanidinoacetate methyltransferase GAMT) deficiency. GAMT-specific ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiencies Variant Curation Expert Panel (CCDS VCEP) (Specifications version 2.0.0): PM2_Supporting, PP3_Strong, PP4_Strong. (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on December 10, 2025)

Met criteria codes

PP3_Strong	✔	The NM_000156.6:c.391G>C variant in GAMT alters the last nucleotide of exon 3. The computational splicing predictor SpliceAI gives a score of 0.8 for donor loss, predicting that the variant disrupts the donor splice site of intron 3 of GAMT. If any protein is made, the variant is predicted to result in a missense, p.Gly131Arg. The computational predictor REVEL gives a score of 0.958 for this missense variant, which is above the threshold of 0.75, evidence that correlates with impact to GAMT function.
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.0000223 (1/44874 alleles) in the East Asian population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting).
PP4_Strong	✔	Patient reported showed absent creatine peak on brain magnetic resonance spectroscopy (3pts) and elevated urine guanidinoacetate with low creatine (1pt) with full GAMT gene sequencing (PP4_Strong, 4pts total) (PMID: 23846910).

Not Met criteria codes

PS3	✖	Data moved to PVS1 per Walker et al. Shown to result in abnormal splicing based on RT-PCR and cDNA analysis: ['One transcript had the complete exon 3 (64-bp) deletion by exon skipping and the other transcript was aberrantly spliced at exon 2 involving intron 2 insertion (44-bp) followed by exon 3 skipping, resulting in a 20-bp deletion. Both transcripts are expected to result in frame shift and premature termination of p.Val110Glyfs*30 and p.Ile111Profs*73, respectively.'] PubMed:23846910
PM3	✖	Reported in one patient (PMID: 23846910) who was a reported compound heterozygote and harbored a variant of uncertain significance (c.578A>G (p.Gln193Arg, ClinVar Variation ID: 1328978) in unknown phase.

PVS1		✖	Shown to result in abnormal splicing, frameshift, and premature termination based on cDNA analysis from an affected individual (PMID: 23846910). Based on the chromatograms shown in the publication, the altered splicing seems incomplete; however, the report does not specify the percentage of alternately spliced transcript. Given the uncertainty about the degree of altered splicing, PVS1 was not applied.

Curation History

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