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Variant: NM_000156.6(GAMT):c.419C>A (p.Ser140Ter)

Version: 1.1

CA402995274

225369 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: e72bbdd6-26f5-45c3-99b3-e4e9b401ad27
Approved on: 2025/4/25
Published on: 2025/4/25

HGVS expressions

NM_000156.6(GAMT):c.419C>A (p.Ser140Ter)
NM_000156.6:c.419C>A
NC_000019.10:g.1399168G>T
CM000681.2:g.1399168G>T
NC_000019.9:g.1399167G>T
CM000681.1:g.1399167G>T
NC_000019.8:g.1350167G>T
NG_009785.1:g.7386C>A
ENST00000252288.8:c.419C>A
ENST00000447102.8:c.419C>A
ENST00000591788.3:c.102C>A
ENST00000640164.1:n.252C>A
ENST00000640762.1:c.350C>A
ENST00000252288.6:c.419C>A
ENST00000447102.7:c.419C>A
ENST00000591788.2:c.104C>A
NM_000156.5:c.419C>A
NM_138924.2:c.419C>A
NM_138924.3:c.419C>A

Likely Pathogenic

Met criteria codes 2

PVS1 PM2_Supporting

Not Met criteria codes 1

BA1

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.419C>A (p.Ser140Ter) variant in GAMT is a nonsense variant that is predicted to cause a premature stop codon in biologically-relevant exon 4 out of 6 exons that leads to nonsense mediated decay in a gene in which loss-of-function is an established mechanism (PVS1). This variant is absent from gnomAD v4.1.0. (PM2_Supporting). To our knowledge, this variant has not been reported in the literature in individuals with GAMT deficiency. There is a ClinVar entry for this variant (Variation ID: 225369). The classification of this variant has been upgraded from Variant of Uncertain Significance to Likely Pathogenic based on the recommendations of the ClinGen Sequence Variant Interpretation Working Group, that a variant meeting PVS1 and PM2_Supporting is classified as Likely Pathogenic (https://clinicalgenome.org/site/assets/files/5182/pm2_-_svi_recommendation_-_approved_sept2020.pdf). GAMT-specific ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (Specifications Version 2.0.0): PVS1, PM2_Supporting. (Classification approved by the ClinGen CCDS VCEP on April 25, 2025).

Met criteria codes

PVS1	✔	The NM_000156.6:c.419C>A (p.Ser140Ter) variant in GAMT is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 4 out of 6 exons, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1)
PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0. (PM2_Supporting).

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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