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Variant: NM_000156.6(GAMT):c.402C>G (p.Tyr134Ter)

Version: 1.0

CA9043673

947458 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4e4553fb-c35a-404e-a0ad-de1af2055bab
Approved on: 2023/5/25
Published on: 2023/5/25

HGVS expressions

NM_000156.6:c.402C>G
NM_000156.6(GAMT):c.402C>G (p.Tyr134Ter)
NC_000019.10:g.1399185G>C
CM000681.2:g.1399185G>C
NC_000019.9:g.1399184G>C
CM000681.1:g.1399184G>C
NC_000019.8:g.1350184G>C
NG_009785.1:g.7369C>G
ENST00000252288.8:c.402C>G
ENST00000447102.8:c.402C>G
ENST00000591788.3:c.85C>G
ENST00000640164.1:n.235C>G
ENST00000640762.1:c.333C>G
ENST00000252288.6:c.402C>G
ENST00000447102.7:c.402C>G
ENST00000591788.2:c.87C>G
NM_000156.5:c.402C>G
NM_138924.2:c.402C>G
NM_138924.3:c.402C>G

Pathogenic

Met criteria codes 3

PVS1 PP4_Strong PM2_Supporting

Not Met criteria codes 1

PM3

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 1.1.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Cerebral Creatine Deficiency Syndromes VCEP

The NM_000156.6:c.402C>G (p.Tyr134Ter) variant in GAMT is a nonsense variant predicted to cause a premature stop codon in biologically relevant exon 4/6 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003 in the South Asian population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting, meeting this criterion (PM2_Supporting). This variant has been detected in one individual with GAMT deficiency (PMID: 19027335). This individual had elevated GAA and low creatine in plasma and significantly decreased creatine peak and visible GAA peak on brain MRS with full GAMT gene sequencing (PMID: 19027335) (PP4_Strong). There is a ClinVar entry for this variant (Variation ID: 947458, 2 star review status) with 3 submitters classifying the variant as pathogenic. In summary, this variant meets the criteria to be classified as 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 1.1.0): PVS1, PM2_Supporting, PP4_Strong. (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on May 25, 2023)

Met criteria codes

PVS1	✔	The NM_000156.6:c.402C>G (p.Tyr134Ter) variant in GAMT is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 4/6 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PP4_Strong	✔	Patient 8 (Table 2) is a male, diagnosed with GAMT deficiency at 14 years old; serum creatine (pre-treatment) 4.2 uM/L (normal range) 34–130 uM/L; serum GAA (pre-treatment 33.3 uM/L (normal range 0.7–5.4 uM/L)(2 points); on MRS he had a decreased creatine peak with slight elevation of GAA peak (3 points) (PMID: 19027335). Full GAMT gene sequencing done.
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003 in the South Asian population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting, meeting this criterion (PM2_Supporting).

Not Met criteria codes

PM3	✖	Patient 8 is compound heterozygous for the variant and c.610_611delAGinsGAA (p.Arg204GlufsTer63), phase unknown. The in trans data from this patient will be used in the assessment of c.610_611delAGinsGAA and is not included here to avoid circular logic.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000156.6(GAMT):c.402C>G (p.Tyr1…	Pathogenic	Guanidinoacetate Methyltransferase Deficiency	2023-05-25	1.0	ClinGen Cerebral Creatine Deficiency Syndromes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GAMT Version 1.1.0	GAMT

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