Variant: NM_000156.6(GAMT):c.316C>T (p.Gln106Ter)

Version: 1.0

CA402996122

566624 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3452b82d-9e59-452b-9384-d0d089d383be
Approved on: 2022-06-06
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HGVS expressions

NM_000156.6:c.316C>T
NM_000156.6(GAMT):c.316C>T (p.Gln106Ter)
NC_000019.10:g.1399804G>A
CM000681.2:g.1399804G>A
NC_000019.9:g.1399803G>A
CM000681.1:g.1399803G>A
NC_000019.8:g.1350803G>A
NG_009785.1:g.6750C>T
ENST00000252288.8:c.316C>T
ENST00000447102.8:c.316C>T
ENST00000640762.1:c.247C>T
ENST00000252288.6:c.316C>T
ENST00000447102.7:c.316C>T
ENST00000591788.2:c.1C>T
NM_000156.5:c.316C>T
NM_138924.2:c.316C>T
NM_138924.3:c.316C>T

Pathogenic

Met criteria codes 3

PM2_Supporting PVS1 PP4_Strong

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*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Cerebral Creatine Deficiency Syndromes VCEP

The NM_000156.6:c.316C>T variant in GAMT is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 2/6 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). Two patients with this variant have been reported with clinical features consistent with GAMT deficiency, elevated guanidinoacetate in urine or plasma, and low or absent creatine peak on brain magnetic resonance spectroscopy (MRS), and one of these patients also had evidence of a guanidinoacetate peak on brain MRS (PMID: 20049533, 24415674, 29506905) (PP4_Strong). Both patients (who have different descriptions) are compound heterozygous for the variant and c.407C>T (p.Thr136Met), phase unknown (PMID 20049533, 24415674, 29506905). The allelic data from these patients will be used in the assessment of p.Thr136Met and is not included here to avoid circular logic. This variant is absent in gnomAD v2.1.1 (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 566624). 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, PP4_strong, PM2_supporting. (Classification approved by the ClinGen CCDS VCEP on June 6, 2022).

Met criteria codes

PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).
PVS1	✔	The NM_000156.6:c.316C>T (p.Gln106Ter) variant in GAMT is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 2/6 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PP4_Strong	✔	At least 2 patients with this variant have been reported with clinical features consistent with GAMT deficiency, elevated guanidinoacetate in urine or plasma, and low or absent creatine peak on brain magnetic resonance spectroscopy (MRS) (PMID: 20049533, 24415674, 29506905); one of these patients also had evidence of a guanidinoacetate peak on brain MRS (PP4_Strong).

Not Met criteria codes

PM3	✖	Two patients with this variant (with different descriptions) are compound heterozygous for the variant and c.407C>T (p.Thr136Met); phase unknown (PMID 20049533, 29506905). The in trans data from this patient will be used in the assessment of p.Thr136Met and is not included here to avoid circular logic. Therefore, PM3 is not met at the current time.

Curation History

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