The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_138924.3:c.235C>T

Version: 1.0

CA402996840

2675837 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: d72b25b2-7f46-40bd-acd7-02a8139788a0
Approved on: 2023/10/12
Published on: 2023/11/8

HGVS expressions

NM_138924.3:c.235C>T
NC_000019.10:g.1399885G>A
CM000681.2:g.1399885G>A
NC_000019.9:g.1399884G>A
CM000681.1:g.1399884G>A
NC_000019.8:g.1350884G>A
NG_009785.1:g.6669C>T
ENST00000252288.8:c.235C>T
ENST00000447102.8:c.235C>T
ENST00000640762.1:c.166C>T
ENST00000252288.6:c.235C>T
ENST00000447102.7:c.235C>T
NM_000156.5:c.235C>T
NM_138924.2:c.235C>T
NM_000156.6:c.235C>T

Pathogenic

Met criteria codes 4

PVS1 PP4_Strong PM3_Supporting PM2_Supporting

Not Met criteria codes 2

BA1 BS1

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.235C>T (p.Gln79Ter) 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).

This variant has been detected in at least one patient with GAMT deficiency. This individual was homozygous for the variant (PMIDs 32606564) (PM3_Supporting). The patient reported with this variant had elevated GAA in plasma and significantly decreased creatine peak (PP4_Strong). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). 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, PM3_Supporting, PM2_Supporting. (Classification approved by the ClinGen CCDS VCEP on Oct. 12, 2023)

Met criteria codes

PVS1	✔	Nonsense variant in exon 2 of 6
PP4_Strong	✔	Variant observed homozygous in patient with absent creatine peak on brain MRS, elevated plasma GAA, and elevated urine GAA
PM3_Supporting	✔	Variant observed in homozygous state in one affected patient
PM2_Supporting	✔	Absent from gnomAD

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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