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Variant: NM_000156.6:c.595dup

Version: 2.0

CA2579753928

2570639 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 700cbe30-d33b-4aa5-9cd1-05806d9e00c9
Approved on: 2025/10/7
Published on: 2025/10/7

HGVS expressions

NM_000156.6:c.595dup
NC_000019.10:g.1397476dup
CM000681.2:g.1397476dup
NC_000019.9:g.1397475dup
CM000681.1:g.1397475dup
NC_000019.8:g.1348475dup
NG_008283.1:g.18593dup
NG_009785.1:g.9079dup
ENST00000252288.8:c.595dup
ENST00000640164.1:n.428dup
ENST00000640762.1:c.526dup
ENST00000252288.6:c.595dup
NM_000156.5:c.595dup

Likely Pathogenic

Met criteria codes 4

PM3_Supporting PVS1_Moderate PP4_Moderate PM2_Supporting

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 GATM 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_000156.6:595dupG (p.Glu199GlyfsTer68) variant in GAMT is a frameshift variant predicted to cause a premature stop codon in the last exon of the gene and therefore to escape nonsense mediated decay. Less than 10% of the protein is predicted to be removed (PVS1_Moderate). This variant has been detected in one individual with an absent creatine peak on brain MRS and low plasma creatine (PMID: 32606525) (PP4_Moderate). This individual was homozygous for the variant (PMID: 32606525) (0.5pts, PM3_Supporting). This

individual had an absent creatine peak on brain MRS (PMID: 32606525) (PP4_Moderate). This variant is absent in gnomAD v4.1.0. (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 2570639). In summary, this variant meets the criteria to be classified as likely pathogenic for GAMT deficiency based on the 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_Moderate, PM2_Supporting, PM3_Supporting, PP4_Moderate. (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on October 7, 2025)

Met criteria codes

PM3_Supporting	✔	This variant has been detected in one individual with GAMT deficiency (PMID: 32606525). This individual was homozygous for the variant (PMID: 32606525) (0.5pts, PM3_Supporting).
PVS1_Moderate	✔	The NM_000156.6:595dupG (p.Glu199GlyfsTer68) variant in GAMT is a frameshift variant predicted to cause a premature stop codon in the last exon of the gene and therefore to escape nonsense mediated decay. Less than 10% of the protein is predicted to be removed. (PVS1_Moderate).
PP4_Moderate	✔	This individual had an absent creatine peak on brain MRS and low plasma creatine; no plasma or urine GAA level available (PMID: 32606525) (PP4_Moderate).
PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0. (PM2_Supporting).

Curation History

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