Variant: NM_000156.6(GAMT):c.328-1G>A

Version: 1.0

CA9043720

844968 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: bd348752-8812-41c2-8014-b97f14b9dff5
Approved on: 2023-02-03
Published on: 2023-03-09

HGVS expressions

NM_000156.6:c.328-1G>A
NM_000156.6(GAMT):c.328-1G>A
NC_000019.10:g.1399588C>T
CM000681.2:g.1399588C>T
NC_000019.9:g.1399587C>T
CM000681.1:g.1399587C>T
NC_000019.8:g.1350587C>T
NG_009785.1:g.6966G>A
ENST00000252288.8:c.328-1G>A
ENST00000447102.8:c.328-1G>A
ENST00000591788.3:c.11-1G>A
ENST00000640164.1:n.160G>A
ENST00000640762.1:c.259-1G>A
ENST00000252288.6:c.328-1G>A
ENST00000447102.7:c.328-1G>A
ENST00000591788.2:c.13-1G>A
NM_000156.5:c.328-1G>A
NM_138924.2:c.328-1G>A
NM_138924.3:c.328-1G>A

Likely Pathogenic

Met criteria codes 2

PM2_Supporting PVS1

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.328-1G>A variant in GAMT occurs within the canonical splice acceptor site of intron 2. It is predicted to cause skipping of biologically-relevant-exon 3/6, resulting in a frameshift 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 0.00006 (1/15792 alleles) in the African population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 844968). 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). In summary, this variant meets the criteria to be classified as likely 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.

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is [0.00006] (1/15792 alleles) in the African population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting). SpliceAI indocates that this variant abolishes splicing but also that a new aceptor site may be created 1 nucleotide upstream. Even if this new site is used, the consequence would still be a frameshift.
PVS1	✔	The NM_000156.6:c.328-1G>A variant in GAMT occurs within the canonical splice acceptor site of intron 2. It is predicted to cause skipping of biologically-relevant-exon 3/6, resulting in a frameshift leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).

Curation History

Showing 1 to 2 of 2 rows