Variant: NM_001482.3(GATM):c.778C>T (p.Arg260Ter)

Version: 1.1

CA314876

205617 (ClinVar)

Gene: GATM (HGNC:2628)
Condition: AGAT deficiency (MONDO:0012996)
Inheritance Mode: Autosomal recessive inheritance
UUID: a786cc98-612e-43dc-b59e-2261626694d0
Approved on: 2025-05-22
Published on: 2025-05-22

HGVS expressions

NM_001482.3:c.778C>T
NM_001482.3(GATM):c.778C>T (p.Arg260Ter)
NC_000015.10:g.45366406G>A
CM000677.2:g.45366406G>A
NC_000015.9:g.45658604G>A
CM000677.1:g.45658604G>A
NC_000015.8:g.43445896G>A
NG_011674.1:g.17377C>T
NG_011674.2:g.40912C>T
ENST00000396659.8:c.778C>T
ENST00000674905.1:c.778C>T
ENST00000675158.1:c.778C>T
ENST00000675323.1:c.778C>T
ENST00000675701.1:c.718C>T
ENST00000675974.1:n.869C>T
ENST00000676090.1:c.*1509C>T
ENST00000396659.7:c.778C>T
ENST00000558336.5:c.778C>T
ENST00000558362.5:n.2434C>T
ENST00000558916.1:n.676C>T
NM_001482.2:c.778C>T
NM_001321015.1:c.391C>T
NM_001321015.2:c.391C>T

Likely Pathogenic

Met criteria codes 2
PM2_Supporting PVS1

Not Met criteria codes 2
PM3 PP4

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_001482.3: c.778C>T (p.Arg260Ter) variant in GATM is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 5 out of a total of 9 exons, 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 v4.1.0. is 8.474e-7 (1/1180024 alleles) in the European non-Finnish population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.000055), meeting this criterion (PM2_Supporting). To our knowledge, this variant has not been reported in the published literature. However, there is a ClinVar entry for this variant (Variation ID: 205617). The variant has been observed in a child with seizures referred for an epilepsy panel (GeneDx); no second variant in GATM was identified (insufficient evidence for PP4 or PM3). 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). GATM-specific ACMG/AMP codes met, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes VCEP (Specifications Version 2.0.0): PVS1, PM2_Supporting. (Classification approved by the ClinGen CCDS VCEP on May 22, 2025).

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 8.474e-7 (1/1180024 alleles) in the European non-Finnish population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.000055), meeting this criterion (PM2_Supporting).
PVS1	✔	The NM_001482.3: c.778C>T (p.Arg260Ter) variant in GATM is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 5 out of a total of 9 exons, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).

Not Met criteria codes

PM3	✖	The variant has been observed in a child with seizures referred for an epilepsy panel; no second variant in GATM was identified (insufficient evidence for PP4 or PM3)
PP4	✖	The variant has been observed in a child with seizures referred for an epilepsy panel; no second variant in GATM was identified (insufficient evidence for PP4 or PM3)

Curation History

Showing 1 to 2 of 2 rows