Variant: NM_001482.3(GATM):c.1022C>T (p.Pro341Leu)

Version: 2.1

CA392256442

917496 (ClinVar)

Gene: GATM (HGNC:2628)
Condition: AGAT deficiency (MONDO:0012996)
Inheritance Mode: Autosomal recessive inheritance
UUID: 83589d11-bc2c-4791-9b9b-1972e67680c5
Approved on: 2025-10-08
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HGVS expressions

NM_001482.3:c.1022C>T
NM_001482.3(GATM):c.1022C>T (p.Pro341Leu)
NC_000015.10:g.45364817G>A
CM000677.2:g.45364817G>A
NC_000015.9:g.45657015G>A
CM000677.1:g.45657015G>A
NC_000015.8:g.43444307G>A
NG_011674.1:g.18966C>T
NG_011674.2:g.42501C>T
ENST00000396659.8:c.1022C>T
ENST00000674905.1:c.1022C>T
ENST00000675158.1:c.1022C>T
ENST00000675323.1:c.1022C>T
ENST00000675701.1:c.962C>T
ENST00000675974.1:n.1113C>T
ENST00000676090.1:c.*1753C>T
ENST00000396659.7:c.1022C>T
ENST00000558336.5:c.1022C>T
ENST00000558362.5:n.2678C>T
ENST00000561376.1:n.69C>T
NM_001482.2:c.1022C>T
NM_001321015.1:c.635C>T
NM_001321015.2:c.635C>T

Uncertain Significance

Met criteria codes 1

PM2_Supporting

Not Met criteria codes 3

PM3 PP3 BP4

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.1022C>T variant in GATM is a missense variant predicted to cause substitution of proline by leucine at amino acid 341 (p.Pro341Leu). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.476 which is neither above nor below the thresholds predicting a damaging (>0.75) or benign (<0.15) impact on AGAT function. There is a ClinVar entry for this variant (Variation ID: 917496). To our knowledge, this variant has not been reported in an individual with phenotypic features of AGAT deficiency. It has been reported as a single heterozygous variant segregating in a family autosomal dominant renal Fanconi syndrome and kidney failure (PMID: 29654216, 39544690). However, classification with respect to this alternative disorder is outside the scope of this curation. There is a ClinVar entry for this variant (Variation ID: 917496). In summary, this variant meets the criteria to be classified as a variant of uncertain significance for AGAT deficiency based on the GATM-specific ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (Specifications Version 1.1.0): PM2_Supporting. (Classification approved by the ClinGen CCDS VCEP on October 8, 2025).

Met criteria codes

PM2_Supporting	✔	Absent from gnomAD v4.1.0.

Not Met criteria codes

PM3	✖	Identified in heterozygous individuals with renal Fanconi syndrome and kidney failure (PMID 29654216), but not reported in the homozygous or compound heterozygous state in individuals with a known or suspected cerebral creatine deficiency syndrome.
PP3	✖	The computational predictor REVEL gives a score of 0.476 which is neither above nor below the thresholds predicting a damaging (>0.644) or benign (<0.29) impact on IDUA function.
BP4	✖	The computational predictor REVEL gives a score of 0.476 which is neither above nor below the thresholds predicting a damaging (>0.644) or benign (<0.29) impact on IDUA function.

Curation History

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