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_000156.6(GAMT):c.22C>A (p.Pro8Thr)

Version: 2.0

CA314840

205598 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 88895225-665c-4e9b-bf17-ca9fe729cf9c
Approved on: 2025/10/8
Published on: 2025/10/8

HGVS expressions

NM_000156.6:c.22C>A
NM_000156.6(GAMT):c.22C>A (p.Pro8Thr)
NC_000019.10:g.1401455G>T
CM000681.2:g.1401455G>T
NC_000019.9:g.1401454G>T
CM000681.1:g.1401454G>T
NC_000019.8:g.1352454G>T
NG_009785.1:g.5099C>A
ENST00000252288.8:c.22C>A
ENST00000447102.8:c.22C>A
ENST00000640762.1:c.22C>A
ENST00000252288.6:c.22C>A
ENST00000447102.7:c.22C>A
NM_000156.5:c.22C>A
NM_138924.2:c.22C>A
NM_138924.3:c.22C>A

Likely Benign

Met criteria codes 2

BS2 BS3_Supporting

Not Met criteria codes 5

PM2 PM3 BP4 PP3 PP4

Evidence Links 1

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 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:c.22C>A variant in GAMT is a missense variant that is predicted to result in the substitution of proline by threonine at amino acid 8 (p.Pro8Thr). One patient, who is heterozygous for the variant, has been reported. This individual, who presented with severe global developmental delay, hypotonia, and intractable seizures, died at 11 months of age. Urine and plasma guanidinoacetate were elevated 2.5 and 1.8 times, respectively. However, on 1H-MRS, creatine peak was about 90% of normal, marginally low, which was not suggestive of GAMT deficiency(PMID: 24415674) (PP4 not applied). GAA-deficient fibroblasts overexpressing the c.22C>A (p.Pro8Thr) variant showed similar GAMT enzyme activity as those transfected with wild-type cDNA (PMID: 24415674) (BS3_Supporting). The computational predictor REVEL gives a score of 0.479 which is below the threshold of 0.5, evidence that does not predict a damaging effect on GAMT function (BP4). The highest population minor allele frequency (MAF) in gnomAD v4.1.0 is 0.002564 (10/3900 alleles) in the Middle Eastern population; there is one homozygote in the European non-Finnish population, in gnomAD v4.1.0. While the MAF is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), PM2_Supporting is not met due to presence of a homozygote. Because GAMT deficiency is a severe, pediatric onset condition, the presence of a homozygote supports benignity (BS2). There is a ClinVar entry for this variant (Variation ID: 205598). In summary, this variant meets the criteria to be classified as likely benign for GAMT deficiency. GAMT-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Cerebral Creatine Deficiencies VCEP (Specifications Version 2.0.0.): BS2, BS3_Supporting (Classification approved by the ClinGen Cerebral Creatine Deficiencies VCEP on October 8, 2025)

Met criteria codes

BS2	✔	There is one homozygote, in the European non-Finnish population, in gnomAD v4.1.0.
BS3_Supporting	✔	GAMT-deficient fibroblasts overexpressing the c.22C>A (p.Pro8Thr) variant showed similar GAMT enzyme activity as those transfected with wild-type enzyme (PMID: 24415674). Fibroblasts overexpressing cells the c.22C>A (p.Pro8Thr) variant showed similar GAMT enzyme activity as those transfected with wild-type enzyme (PMID: 24415674). PubMed:24415674

Not Met criteria codes

PM2	✖	The highest population minor allele frequency in gnomAD v4.1.0 is 0.002564 (10/3900 alleles) in the Middle Eastern population. While this is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), PM2_Supporting is not met due to presence of a homozygote.
PM3	✖	PMID: 24415674: Found as a single heterozygous variant in one patient, no second variant identified
BP4	✖	The computational predictor REVEL gives a score of 0.479 which is neither above nor below the thresholds predicting a damaging (>0.644) or benign (<0.29) impact on GAMT function.
PP3	✖	The computational predictor REVEL gives a score of 0.479 which is neither above nor below the thresholds predicting a damaging (>0.644) or benign (<0.29) impact on GAMT function.
PP4	✖	One patient, heterozygous for the variant, with urine guanidinoacetate elevated 2.5 times and plasma guanidinoacetate 1.8 times above the upper limit of reference range. However, on 1H-MRS, creatine peak was about 90% of normal, marginally low, which was not suggestive of GAMT deficiency (Note: 1H-MRS data overrides biochemical findings) (PMID: 24415674).

Curation History

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