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.59G>C (p.Trp20Ser)

Version: 1.0

CA340769

8303 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: dc790a08-e798-46d6-ad31-772c3482c12b
Approved on: 2023/5/25
Published on: 2023/5/25

HGVS expressions

NM_000156.6:c.59G>C
NM_000156.6(GAMT):c.59G>C (p.Trp20Ser)
NC_000019.10:g.1401418C>G
CM000681.2:g.1401418C>G
NC_000019.9:g.1401417C>G
CM000681.1:g.1401417C>G
NC_000019.8:g.1352417C>G
NG_009785.1:g.5136G>C
ENST00000252288.8:c.59G>C
ENST00000447102.8:c.59G>C
ENST00000640762.1:c.59G>C
ENST00000252288.6:c.59G>C
ENST00000447102.7:c.59G>C
NM_000156.5:c.59G>C
NM_138924.2:c.59G>C
NM_138924.3:c.59G>C

Pathogenic

Met criteria codes 4

PP3 PM3_Strong PP4_Strong PS3_Supporting

Not Met criteria codes 3

PP1 PM5 PM2

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.59G>C variant in GAMT is a missense variant predicted to cause substitution of tryptophan by serine at amino acid 20 (p.Trp20Ser). This variant has been detected in at least 9 unrelated individuals with GAMT deficiency (PMID: 15651030, PMID: 16855203, PMID: 15108290). Of those individuals, one was compound heterozygous for the variant and a pathogenic variant, c.521G>A (p.Trp174*, in trans (PMID: 16855203) and eight individuals were homozygous for the variant (PMID: 15651030, PMID: 16855203, PMID: 15108290) (2 points total) (PM3_Strong). These individuals showed elevated plasma GAA and urine GAA (PMID: 15651030, PMID: 16855203, PMID: 15108290), three also showed deficient (<5% wild-type) GAMT enzyme activity in lymphoblasts (PMID: 15651030), and one also showed deficient (<5% wild-type) GAMT enzyme activity in fibroblasts and reduced creatine signal on brain MRS (PMID: 16855203, PMID: 21140503) (PP4_Strong). Expression of the variant in HeLa cells resulted in 3% wild type GAMT activity indicating that this variant may impact protein function (PMID: 17336114)(PS3_Supporting). The highest population minor allele frequency in gnomAD v2.1.1 is 0.0001 (3/27420 alleles) in the European (non-Finnish) population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004); however, as this variant is covered in <50% of individuals in gnomAD v2.1.1, allele frequency estimates may not be reliable and thus PM2_Supporting is not met. The computational predictor REVEL gives a score of 0.94 which is above the threshold of 0.75, evidence that correlates with impact to GAMT function (PP3). There is a ClinVar entry for this variant (Variation ID: 8303, 2 star review status) with 9 submitters classifying the variant as pathogenic and 1 submitter classifying the variant as likely pathogenic. In summary, this variant meets the criteria to be classified as 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): PS3_Supporting, PM3_Strong, PP3, PP4_Strong. (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on May 25, 2023)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.94 which is above the threshold of 0.75, evidence that correlates with impact to GAMT function (PP3).
PM3_Strong	✔	Of those individuals, one was compound heterozygous for the variant and a pathogenic variant, c.521G>A (p.Trp174*, in trans (PMID: 16855203) and eight individuals were homozygous for the variant (PMID: 15651030, PMID: 16855203, PMID: 15108290) (2 points total) (PM3_Strong).
PP4_Strong	✔	These individuals showed elevated plasma GAA and urine GAA (PMID: 15651030, PMID: 16855203, PMID: 15108290), three also showed deficient (<5% wild-type) GAMT enzyme activity in lymphoblasts (PMID: 15651030), and one also showed deficient (<5% wild-type) GAMT enzyme activity in fibroblasts and reduced creatine signal on brain MRS (PMID: 16855203, PMID: 21140503) (PP4_Strong).
PS3_Supporting	✔	PMID: 17336114: Variant expressed in HeLa cells and showed no difference in GAMT activity versus negative control (cells transfected with empty vector) and 3% of WT activity

Not Met criteria codes

PP1	✖	PP1 not used per VCEP specifications
PM5	✖	A different missense variant at the same site, p.Trp20Leu, has been reported in ClinVar with conflicting interpretations of pathogenicity (Variation ID: 588631) and has been classified as a VUS by the ClinGen CCDS.
PM2	✖	The highest population minor allele frequency in gnomAD v2.1.1 is 0.0001 (3/27420 alleles) in the European (non-Finnish) population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004); however, as this variant is covered in <50% of individuals in gnomAD v2.1.1, allele frequency estimates may not be reliable and thus PM2_Supporting is not met.

Curation History

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