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.327G>A (p.Lys109=)

Version: 1.0

CA314804

21065 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 824bc12b-2cd6-4821-b672-849f3748f174
Approved on: 2022/6/6
Published on: 2022/10/7

HGVS expressions

NM_000156.6:c.327G>A
NM_000156.6(GAMT):c.327G>A (p.Lys109=)
NC_000019.10:g.1399793C>T
CM000681.2:g.1399793C>T
NC_000019.9:g.1399792C>T
CM000681.1:g.1399792C>T
NC_000019.8:g.1350792C>T
NG_009785.1:g.6761G>A
ENST00000252288.8:c.327G>A
ENST00000447102.8:c.327G>A
ENST00000591788.3:c.10G>A
ENST00000640762.1:c.258G>A
ENST00000252288.6:c.327G>A
ENST00000447102.7:c.327G>A
ENST00000591788.2:c.12G>A
NM_000156.5:c.327G>A
NM_138924.2:c.327G>A
NM_138924.3:c.327G>A

Pathogenic

Met criteria codes 5

PM2_Supporting | PP4_Strong | PM3_Very Strong | PS3 | PP3

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*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Cerebral Creatine Deficiency Syndromes VCEP

The NM_000156.6:c.327G>A (p.Lys109=) variant in GAMT is a synonymous variant that alters the last nucleotide of exon 2. It is one of the most common variants associated with GAMT deficiency, accounting for 31-35% of alleles (PMID: 19027335, 24268530). The variant has been previously reported in at least 30 unrelated GAMT deficiency patients, including among those with elevated urine guanidinoacetate, reduced or absent cerebral creatine peak on MRS (some of whom also have evidence of guanidinoacetate peak on MRS, and GAMT deficiency in fibroblasts (PMIDs: 8651275, 17171576, 19027335, 22019491, 23660394, 24268530, 24766785) (PP4_Strong) including at least 8 homozygotes (PMID: 8651275, 11978605, 19027335, 22019491, 24268530), and in compound heterozygosity with another variant that has been classified as pathogenic by the ClinGen CCDS VCEP including c.58dupT (PMID 24766785, confirmed in trans), c.297_c.309dup13 (PMID: 8651275, confirmed in trans; PMID: 19027335), c.522G>A (p.Trp174Ter) (PMID: 17171576, 19027335, 24268530; 3 probands), or c.36_c.37ins26 (PMID: 19027335) as well as c.133T>A (p.Trp45Arg) (PMID 24268530), and c.403G>A (p.Asp135Asn) (PMID 24268530) (PM3_VeryStrong). Additional patients may be reported in the literature but the maximum evidence for PM3_VeryStrong has already been reached. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00039 (34/ 86230 alleles) in the European non-Finnish population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting). The c.327G>A variant was shown by RT-PCR and RNA sequencing analysis to result in two abnormal transcripts: in one transcript, the variant resulted in a cryptic splice site in intron 2 and deletion of 146bp, and in the other transcript, the variant resulted in a 44bp insertion leading to altered splicing and skipping of exon 2 (PMID: 8651275) (PS3). It is predicted to alter splicing by SpliceAI (donor loss, score 0.93) and varSEAK (splicing class 5) (PP3). There is a ClinVar entry for this variant (Variation ID: 21065). In summary, this variant meets the criteria to be classified as Pathogenic for GAMT deficiency. GAMT-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Cerebral Creatine Deficiencies VCEP (Specifications Version 1.1.0): PM3_VeryStrong, PS3, PP4_Strong, PP3, PM2_Supporting. (Classification approved by the ClinGen CCDS VCEP on June 6, 2022).

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00039 (34/ 86230 alleles) in the European non-Finnish population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting).
PP4_Strong	✔	The variant has been previously reported in at least 30 unrelated GAMT deficiency patients, including among those with elevated urine guanidinoacetate, reduced or absent cerebral creatine peak on MRS (some of whom also have evidence of guanidinoacetate peak on MRS, and GAMT deficiency in fibroblasts (PMIDs: 8651275, 17171576, 19027335, 22019491, 23660394, 24268530, 24766785) (PP4_Strong).
PM3_Very Strong	✔	The variant has been previously reported in at least 39 unrelated GAMT deficiency patients, including among those with elevated urine GAA and reduced or absent cerebral creatine peak on MRS and among those with GAMT deficiency shown in fibroblasts (PP4_Moderate), both in the homozygous state and in trans with Pathogenic or Likely Pathogenic variants (PM3_VeryStrong (10.5 points total)). (Please note that to avoid circularity for other variant classifications, we have counted only compound heterozygotes in whom the second variant qualifies as Pathogenic without using PM3. We have noted the evidence for PM3 use by listing the points assigned for each of the publications discussed below, in the in the format PM3; points assigned). It was first noted in two cases who showed elevated guanidinoacetate and severe creatine deficiency in the brain on MRS and GAMT deficiency in cultured fibroblasts: in one, as a homozygous variant, and in the other, as a heterozygous variant in trans with a frameshift insertion variant (c.309ins13; aka c.299_311dup (p.Arg105fs); ClinVar Pathogenic (ID 8302), Pathogenic per CCDS VCEP-specified ACMG/AMP guidelines (using PVS1, PM2_Supporting, PS3, PP4_Moderate) (PMID: 8651275) (PM3; 1.5 points total). The c.327G>A variant was shown by RT-PCR and RNA sequencing analysis in this publication to result in two abnormal transcripts: in one transcript, the variant resulted in a cryptic splice site in intron 2 and deletion of 146bp, and in the other transcript, the variant resulted in a 44bp insertion leading to altered splicing and skipping of exon 2 (PMID: 8651275) (PS3). It has been found in a patient as a homozygous variant (PMID: 22019491); the patient had elevated urine GAA, severe creatine deficiency in the brain on MRS, and GAMT deficiency in cultured fibroblasts (PM3: 0.5 points). It has also been noted (PMID: 24276113) in a patient in trans with the c.299_311dup (p.Arg105fs) variant (ClinVar Pathogenic (ID 8302), Pathogenic per CCDS VCEP-specified ACMG/AMP guidelines

(using PVS1, PM2_Supporting, PS3, PP4_Moderate) (PMID: 8651275) (PM3; 1 point). It has also been found (PMID: 24766785) in a patient with GAMT deficiency, including elevated urine GAA, deficient GAMT activity in cultured fibroblasts, and reduced creatine peak in the brain on MRS, in trans with the c.58dupT (p.Trp20LeufsX65) variant (Pathogenic per CCDS VCEP-specified ACMG/AMP guidelines (using PVS1, PM2, PS3, PP4_Moderate) (PMID: 8651275) (PM3; 1 point). It was noted in a case report (PMID: 17171576) of a patient with GAMT deficiency, as evinced by deficient GAMT activity in fibroblasts, who harbored it in trans with the c.522G>A (p.W174X) variant (ClinVar Pathogenic (ID 205584), Pathogenic per CCDS VCEP-specified ACMG/AMP guidelines (using PVS1, PM2_Supporting, PP4_Moderate) (PM3; 1 point). It has been noted in 7/28 alleles (PMID: 16169544), including two patients with elevated urinary GAA – one homozygous for the variant and one who harbored it in trans with the c.522G>A (p.W174X) variant (ClinVar Pathogenic (ID 205584), Pathogenic per CCDS VCEP-specified ACMG/AMP guidelines (using PVS1, PM2_Supporting, PP4_Moderate) (PM3; 1.5 points). It has been noted in six patients in another publication (PMID: 19027335): three homozygotes, two of whom had reduced or absent cerebral creatine peak on MRS; and three compound heterozygotes (with the following genotypes: c.327G>A/c.297_c.309dup13 (aka c.299_311dup (p.Arg105fs) variant (ClinVar Pathogenic (ID 8302), Pathogenic per CCDS VCEP-specified ACMG/AMP guidelines (using PVS1, PM2_Supporting, PS3, PP4_Moderate)); c.327G>A/c.522G>A (p.W174X; ClinVar Pathogenic (ID 205584), Pathogenic per CCDS VCEP-specified ACMG/AMP guidelines (using PVS1, PM2_Supporting, PP4_Moderate)); and c.327G>A/c.11_36dup (p.Gly13fs; ClinVar Pathogenic (ID 858462), Pathogenic per CCDS VCEP-specified ACMG/AMP guidelines (using PVS1, PM2, PP4_Moderate)), all three of whom had reduced had reduced or absent cerebral creatine peak on MRS (PM3; 3 points total). It has been found in two patients with GAMT deficiency (PMID: 24071436), including one patient who had low cerebral creatine peak on MRS and elevated urine GAA harbored it in trans with the c.522G>A (p.W174X; ClinVar Pathogenic (ID 205584), Pathogenic per CCDS VCEP-specified ACMG/AMP guidelines (using PVS1, PM2_Supporting, PP4_Moderate)) variant (PM3; 1 point). In another publication (PMID: 24268530), it was noted in nine previously unpublished cases (seven unrelated individuals and a pair of siblings), who had elevated urine GAA and reduced or absent cerebral creatine peak on MRS, which included: Patients 21, 30, 31, 33, 44, and 46 (all homozygous for the variant); and two siblings, Patient 12 and Patient 19, in trans with the c.48C>A (p.Cys16Ter) variant (Pathogenic per CCDS VCEP-specified ACMG/AMP guidelines (using PVS1, PM2, PP4_Moderate)) (PM3; 1 point).

PS3	✔	The c.327G>A variant was shown by RT-PCR and RNA sequencing analysis to result in two abnormal transcripts: in one transcript, the variant resulted in a cryptic splice site in intron 2 and deletion of 146bp, and in the other transcript, the variant resulted in a 44bp insertion leading to altered splicing and skipping of exon 2 (PMID: 8651275) (PS3).
PP3	✔	It is predicted to alter splicing by SpliceAI (donor loss, score 0.93) and varSEAK (splicing class 5).

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.