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.403G>A (p.Asp135Asn)

Version: 1.0

CA9043671

573140 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8a818f12-30b9-40f0-9411-9be1e355f21b
Approved on: 2023/6/8
Published on: 2023/6/8

HGVS expressions

NM_000156.6:c.403G>A
NM_000156.6(GAMT):c.403G>A (p.Asp135Asn)
NC_000019.10:g.1399184C>T
CM000681.2:g.1399184C>T
NC_000019.9:g.1399183C>T
CM000681.1:g.1399183C>T
NC_000019.8:g.1350183C>T
NG_009785.1:g.7370G>A
ENST00000252288.8:c.403G>A
ENST00000447102.8:c.403G>A
ENST00000591788.3:c.86G>A
ENST00000640164.1:n.236G>A
ENST00000640762.1:c.334G>A
ENST00000252288.6:c.403G>A
ENST00000447102.7:c.403G>A
ENST00000591788.2:c.88G>A
NM_000156.5:c.403G>A
NM_138924.2:c.403G>A
NM_138924.3:c.403G>A

Pathogenic

Met criteria codes 6

PS3_Supporting PP4_Strong PM5_Supporting PP3 PM2_Supporting PM3

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(GAMT):c.403G>A variant in GAMT is predicted to result in the substitution of aspartate by asparagine at amino acid 135 (p.Asp135Asn). Four probands and one affected sibling have been reported with this variant, all with clinical symptoms consistent with GAMT deficiency, evidence of elevated guanidinoacetate and low creatine in plasma and/or urine, and reduced creatine on brain MRS with guanidinoacetate peak also noted for two patients. In addition, one proband was shown to have deficient GAMT activity in fibroblasts (PMID: 19027335, 19388150, 24071436, 24268530, 24415674) (PP4_Strong). Each of these individuals is compound heterozygous for the variant and another variant in GAMT that has been classified as pathogenic or likely pathogenic by the ClinGen CCDS VCEP including c.327G>A (2 patients; PMID: 24071436, 24268530, 24415674), c.299dup13 (a.k.a. c.299_311dup) (PMID: 19388150), and c.507_521dup15 (p.Cys169_Ser173dup) (PMID: 19027335)(PM3). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00011 (2/18390 alleles) in the East Asian population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting). When the variant was expressed in GAMT-deficient fibroblasts, GAMT enzyme activity was undetectable (PMID: 24415674). The computational predictor REVEL gives a score of 0.856 which is above the threshold of 0.75, evidence that correlates with impact to GAMT function (PP3). Another variant at the same amino acid position, c.403G>T (p.Asp135Tyr), has been classified as likely pathogenic by the ClinGen CCDS VCEP (and would be likely pathogenic even without the use of PM5, therefore avoiding circular logic) (PM5_Supporting). There is a ClinVar entry for this variant (Variation ID: 573140). In summary, this variant meets the criteria to be classified as pathogenic for GAMT deficiency. GAMT-specific ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (Specifications Version 1.1.0); PP4_Strong, PM3, PP3, PS3_Supporting, PM2_Supporting, PM5_Supporting. (Classification approved by the ClinGen CCDS VCEP on June 8, 2023)

Met criteria codes

PS3_Supporting	✔	When the variant was expressed in GAMT-deficient fibroblasts, GAMT enzyme activity was undetectable (PMID: 24415674).
PP4_Strong	✔	Four probands and one affected sibling have been reported with this variant and clincal symptoms consistent with GAMT defciiency. All reported patients had evidence of elevated guanidinoacetate and low creatine in plasma and/or urine, and reduced creatine on brain MRS with guanidinoacetate peak also noted for two patients. In addition, one proband was shown to have deficient GAMT activity in fibroblasts (PMID: 19027335, 19388150, 24071436, 24268530, 24415674 (PP4_Strong).
PM5_Supporting	✔	Another variant at the same amino acid position, c.403G>T (p.Asp135Tyr), has been classified as likely pathogenic by the ClinGen CCDS VCEP (and would be likely pathogenic even without the use of PM5, therefore avoiding circular logic) (PM5_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.856 which is above the threshold of 0.75, evidence that correlates with impact to GAMT function (PP3). No impact on splicing predicted by SpliceAI.
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00011 (2/18390 alleles) in the East Asian population, which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting).
PM3	✔	Four patients have been reported who are compound heterozygous, phase unknown, for the variant and another variant in GAMT that has been classified as pathogenic or likely pathogenic by the ClinGen CCDS VCEP including c.327G>A (2 patients; 2 x 0.5 points, PMID: 24071436, 24268530, 24415674), c.299dup13 (a.k.a. c.299_311dup) (0.5 points) (PMID: 19388150), and c.507_521dup15 (p.Cys169_Ser173dup) (PMID: 19027335) (0.25 points). Total 1.75 points (PM3)

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.