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Variant: NM_138924.3:c.152A>C

Version: 2.0

CA402998053

2138184 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 666f3a4c-7076-43ec-8c81-965928812a1e
Approved on: 2025/12/10
Published on: 2025/12/10

HGVS expressions

NM_138924.3:c.152A>C
NC_000019.10:g.1401325T>G
CM000681.2:g.1401325T>G
NC_000019.9:g.1401324T>G
CM000681.1:g.1401324T>G
NC_000019.8:g.1352324T>G
NG_009785.1:g.5229A>C
ENST00000252288.8:c.152A>C
ENST00000447102.8:c.152A>C
ENST00000640762.1:c.112+40A>C
ENST00000252288.6:c.152A>C
ENST00000447102.7:c.152A>C
NM_000156.5:c.152A>C
NM_138924.2:c.152A>C
NM_000156.6:c.152A>C

Pathogenic

Met criteria codes 5

PM3 PS3_Supporting PP3_Moderate PP4_Strong PM2_Supporting

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.152A>C variant in GAMT is a missense variant that is predicted to result in the substitution of histidine by proline at amino acid 51 (p.His51Pro). One proband has been reported with mild developmental delay, anti-epileptic drug responsive seizures, and

autistic features, with a normal brain MRI. This individual had elevated guanidinoacetate in urine and, on MRS, creatine peak was partially absent and guanidinoacetate peak was absent (PMID: 15108290, 24415674) (PP4_Strong). This individual is compound heterozygous for the variant and another variant in GAMT that has been classified as pathogenic by the ClinGen CCDS VCEP, c.526dupG. The variants were confirmed to be in trans by parental testing (PM3). The variant is absent in gnomAD v4.1.0. (PM2_Supporting). When the variant was expressed in a primary GAMT-deficient human fibroblast cell line, no detectable expression could be seen on Western blot and the GAMT activity was very low (<4%) (PMID 24415674) (PS3_Supporting). The computational predictor REVEL gives a score of 0.814 which is in the range of 0.773-0.932, evidence that correlates with impact to GAMT function at the moderate level (PMID: 36413997) (PP3_Moderate). There is a ClinVar entry for this variant (Variation ID: 2138184). 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 Variant Curation Expert Panel (Specifications Version 2.0.0): PP4_Strong, PM3, PP3_Moderate, PS3_Supporting, PM2_Supporting. (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on December 10, 2025)

Met criteria codes

PM3	✔	One patient has been reported who is compound heterozygous for the variant and another variant in GAMT that has been classified as pathogenic for GAMT deficiency by the ClinGen CCDS VCEP; the variants were confirmed to be in trans (PMID: 15108290). 1 point, (PM3)
PS3_Supporting	✔	When the variant was expressed in a primary GAMT-deficient human fibroblast cell line, no detectable expression could be seen on Western blot and the GAMT activity was very low (<4% WT) (PMID 24415674) (PS3_Supporting). When the variant was expressed in a primary GAMT-deficient human fibroblast cell line (homozygous for a frameshift mutation), no detectable expression could be seen on Western blot and the GAMT activity was very low (<4%). PubMed:24415674
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.814 which is in the range of 0.773-0.932, evidence that correlates with impact to GAMT function at the moderate level (PMID: 36413997) (PP3_Moderate).
PP4_Strong	✔	One proband has been reported with mild developmental delay, anti-epileptic drug responsive seizures, and autistic features, with a normal brain MRI. This individual had elevated guanidinoacetate in urine, 1.1-12 x normal (1 point), and on MRS, creatine peak was partially absent and guanidinoacetate peak was absent (3 points) (PMID: 15108290, 24415674) (PP4_Strong).
PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0. (PM2_Supporting).

Curation History

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