Variant: NM_000156.6(GAMT):c.507_521dup (p.Cys169_Ser173dup)

Version: 1.1

CA9043617

431959 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6ad8131f-e940-4765-8021-25867dfc42c3
Approved on: 2024-09-11
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HGVS expressions

NM_000156.6:c.507_521dup
NM_000156.6(GAMT):c.507_521dup (p.Cys169_Ser173dup)
NC_000019.10:g.1398968_1398982dup
CM000681.2:g.1398968_1398982dup
NC_000019.9:g.1398967_1398981dup
CM000681.1:g.1398967_1398981dup
NC_000019.8:g.1349967_1349981dup
NG_009785.1:g.7575_7589dup
ENST00000252288.8:c.507_521dup
ENST00000447102.8:c.507_521dup
ENST00000591788.3:c.190_204dup
ENST00000640164.1:n.340_354dup
ENST00000640762.1:c.438_452dup
ENST00000252288.6:c.507_521dup
ENST00000447102.7:c.507_521dup
ENST00000591788.2:c.192_206dup
NM_000156.5:c.507_521dup
NM_138924.2:c.507_521dup
NM_138924.3:c.507_521dup

Likely Pathogenic

Met criteria codes 4

PM3 PM4 PP4_Strong PM2_Supporting

Not Met criteria codes 1

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 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.507_521dup (p.Cys169_Ser173dup) variant in GAMT is a protein length-changing variant (in-frame insertion) in a non-repeat region (PM4). This variant has been previously reported in at least two unrelated individuals with clinical symptoms consistent with GAMT deficiency. One individual had elevated plasma GAA and was compound heterozygous for the variant and a pathogenic variant in GAMT, c.327G>A (p.Lys109=, ClinVar ID: 21065), with the variants confirmed in trans by parental testing (PMID: 23583224, 29506905; personal communication) (PM3). The other individual had elevated plasma GAA and reduced cerebral creatine by MRS, pretreatment (PP4_Strong), and was compound heterozygous for the variant and c.403G>T (p.Asp135Tyr) (PMID: 19027335, 23660394); however, the allelic data for the latter patient will be used in the classification of p.Asp135Tyr and was not included here to avoid circular logic and thus this individual was not counted towards PM3 evidence. The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001525 (14/1180016 alleles; no homozygotes) 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 computational predictor PROVEAN predicts a damaging effect on GAMT function, but MutationTaster suggested no impact, such that PP3 is not met. There is a ClinVar entry for this variant (Variation ID: 431959). In summary, this variant meets the criteria to be classified as likely 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 2.0.0): PP4_Strong, PM3, PM4, PM2_supporting. (Classification approved by the ClinGen Creatine Deficiency Syndromes Variant Curation Expert Panel on September 11, 2024).

Met criteria codes

PM3	✔	This variant has been previously reported in at least two cases with clinical symptoms consistent with GAMT deficiency. One proband had elevated plasma GAA and was compound heterozygous for the variant and another pathogenic variant in GAMT, c.327G>A (p.Lys109=), with the variants confirmed in trans by parental testing (PMID: 23583224, 29506905; personal communication) (1 point). Another proband had elevated plasma GAA and reduced cerebral creatine by MRS, pretreatment, and was compound heterozygous for the variant and c.403G>T (p.Asp135Tyr) (PMID: 19027335). The allelic data for this latter patient will be used in the assessment of p.Asp135Tyr and is not included here to avoid circular logic. Total 1 point (PM3).
PM4	✔	The c.507_521dup (p.Cys169_Ser173dup) variant in GAMT is a protein length-changing variant (in-frame insertion) in a non-repeat region (PM4).
PP4_Strong	✔	This variant has been reported in at least two cases: one proband with elevated plasma guanidinoacetate and reduced cerebral creatine by brain magnetic resonance spectroscopy (PMID: 19027335, 2950690); and in one proband with elevated plasma guanidinoacetate (PMID: 23583224, 29506905) (PP4_Strong).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001525 (18/1180016 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).

Not Met criteria codes

PP3	✖	The computational predictor PROVEAN gives a score of -7.095 (below the threshold of -2.5), MutPred-Indel gives a score of 0.69307 (>0.50 suggests pathogenicity with a false positive rate of 10%, > 0.70 yields a false positive rate of 5%), but MutationTaster predicts it to be a "polymorphism". PP3 not applied because the predictors do not agree.

Curation History

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