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.522G>A (p.Trp174Ter)

Version: 1.0

CA314812

205584 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 8d75afff-17c2-458d-86bd-cf700e13320b
Approved on: 2022/6/6
Published on: 2022/10/7

HGVS expressions

NM_000156.6:c.522G>A
NM_000156.6(GAMT):c.522G>A (p.Trp174Ter)
NC_000019.10:g.1398964C>T
CM000681.2:g.1398964C>T
NC_000019.9:g.1398963C>T
CM000681.1:g.1398963C>T
NC_000019.8:g.1349963C>T
NG_009785.1:g.7590G>A
ENST00000252288.8:c.522G>A
ENST00000447102.8:c.522G>A
ENST00000591788.3:c.205G>A
ENST00000640164.1:n.355G>A
ENST00000640762.1:c.453G>A
ENST00000252288.6:c.522G>A
ENST00000447102.7:c.522G>A
ENST00000591788.2:c.207G>A
NM_000156.5:c.522G>A
NM_138924.2:c.522G>A
NM_138924.3:c.522G>A

Pathogenic

Met criteria codes 4

PVS1_Strong PM3 PP4_Strong PM2_Supporting

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.522G>A (p.Trp174Ter) variant is a nonsense variant in the last 50bp of the penultimate exon of GAMT, predicted to cause a premature stop codon in the last 50 nucleotides of the penultimate exon of the gene and therefore to escape nonsense mediated decay. More than 10% of the protein is predicted to be removed (PVS1_Strong). At least six probands and two siblings have been reported with clinical and biochemical features consistent with GAMT deficiency including 3 probands and one sibling with elevated plasma GAA (PMID 23660394, https://adc.bmj.com/content/103/2/e1.24), 1 proband with enzyme deficiency (PMID 17171576), 2 probands with reduced plasma creatine, elevated plasma GAA, and reduced creatine peak on MRS (PMID 23583224, 24071436), and a sibling of one of these patients with reduced plasma creatine and elevated plasma GAA (PMID 23583224) (PP4_Strong). Of these probands 4 are compound heterozygous for the variant and a variant that is classified as pathogenic by the ClinGen CCDS VCEP, c.327G>A, phase unknown (PMIDs 17171576, 19027335, 23583224, 23660394, 24071436, 24268530, https://adc.bmj.com/content/103/2/e1.24 (PM3). Another two probands are compound heterozygous for the variant and a missense variant, either c.491G>A (p.Gly164Asp) or c.505T>C (p.Cys169Arg) (PMID 23660394, 24268530). The in trans data from these patients will be used in the assessment of the missense variants and is not included here to avoid circular logic. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006 (7/113306 alleles) in the European non-Finnish population, which is less that the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 205584). 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 CCDS VCEP (Specifications Version 1.1.0): PVS1_Strong, PP4_Strong, PM3, PM2_Supporting. (Classification approved by the ClinGen CCDS VCEP on June 6, 2022).

Met criteria codes

PVS1_Strong	✔	The NM_000156.6:c.522G>A (p.Trp174Ter) variant is a nonsense variant in the last 50bp of the penultimate exon of GAMT, predicted to cause a premature stop codon in the last 50 nucleotides of the penultimate exon of the gene and therefore to escape nonsense mediated decay. More than 10% of the protein is predicted to be removed (PVS1_Strong).
PM3	✔	At least six probands have been reported with clinical and biochemical features consistent with GAMT deficiency. Of these probands 4 are compound heterozygous for the variant and a variant that is classified as pathogenic by the ClinGen CCDS VCEP, c.327G>A, phase unknown (PMIDs 17171576, 19027335, 23583224, 23660394, 24071436, 24268530, https://adc.bmj.com/content/103/2/e1.24 (max 1 point; PM3). Another two probands are compound heterozygous for the variant and a missense variant, either c.491G>A (p.Gly164Asp) or c.505T>C (p.Cys169Arg) (PMID 23660394, 24268530). The in trans data from these patients will be used in the assessment of the missense variants and is not included here to avoid circular logic.
PP4_Strong	✔	At least six probands and two siblings have been reported with clinical and biochemical features consistent with GAMT deficiency including 3 probands and one sibling with elevated plasma GAA (PMID 23660394, https://adc.bmj.com/content/103/2/e1.24), 1 proband with enzyme deficiency (PMID 17171576), 2 probands with reduced plasma creatine, elevated plasma GAA, and reduced creatine peak on MRS (PMID 23583224, 24071436), and a sibling of one of these patients with reduced plasma creatine and elevated plasma GAA (PMID 23583224) (PP4_Strong).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006 (7/113306 alleles) in the European non-Finnish population, which is less that the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.0004), meeting this criterion (PM2_Supporting).

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.