Variant: NM_000156.6(GAMT):c.491dup (p.Val165fs)

Version: 1.0

CA9043628

495685 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: fdce6280-2ceb-4082-aa3b-48db0b1651f7
Approved on: 2022-06-06
Published on: 2022-10-07

HGVS expressions

NM_000156.6:c.491dup
NM_000156.6(GAMT):c.491dup (p.Val165fs)
NC_000019.10:g.1399000dup
CM000681.2:g.1399000dup
NC_000019.9:g.1398999dup
CM000681.1:g.1398999dup
NC_000019.8:g.1349999dup
NG_009785.1:g.7559dup
ENST00000252288.8:c.491dup
ENST00000447102.8:c.491dup
ENST00000591788.3:n.174dup
ENST00000640164.1:n.324dup
ENST00000640762.1:c.422dup
ENST00000252288.6:c.491dup
ENST00000447102.7:c.491dup
ENST00000591788.2:n.176dup
NM_000156.5:c.491dup
NM_138924.2:c.491dup
NM_138924.3:c.491dup

Pathogenic

Met criteria codes 4

PP4_Strong PM3_Supporting PM2_Supporting PVS1_Strong

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.491dup (p.Val165ArgfsTer26) variant in GAMT is a frameshift variant 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; PMID: 11136556). The highest population minor allele frequency in gnomAD v2.1.1 is 0.0001 in the East Asian population, which is less than the ClinGen CCDS VCEP's threshold (<0.0004) (PM2_Supporting). The variant was found in homozygosity in one patient who meets the ClinGen CCDS VCEP's PP4 specifications (PMID 12557293). This variant was also found in compound heterozygosity in two patients who meet ClinGen CCDS VCEP's PP4 specifications; one with the variant c.564G>T (p. Met188Ile) (PMID 28438604) or "IVS5-3C>G" (PMID 11136556). However, the in trans data from these two patients will be used in the assessment of the second variant and is not included here to avoid circular logic. (PM3_Supporting). Three patients have been reported with this variant and clinical and biochemical features consistent with GAMT deficiency including an adult patient with low creatine and elevated GAA in urine, plasma, and CSF, <10% normal GAMT activity in fibroblasts, and absent creatine peak with GAA detected on MRS (PMID 12557293), low creatine and elevated GAA in plasma and urine and absent creatine peak on MRS (PMID 28438604), and elevated GAA in plasma, urine, and CSF, and lacking creatine peak on brain MRS (PMID 1136556)(PP4_Strong). There is a ClinVar entry for this variant (Variation ID: 495685) In summary, this variant meets the criteria to be classified as 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 1.1.0): PVS1_Strong, PP4_Strong, PM2_Supporting, PM3_Supporting. (Classification approved by the ClinGen CCDS VCEP on June 6, 2022).

Met criteria codes

PP4_Strong	✔	Three patients have been reported with this variant and clinical and biochemical features consistent with GAMT deficiency including an adult patient with low creatine and elevated GAA in urine, plasma, and CSF, <10% normal GAMT activity in fibroblasts, and absent creatine peak with GAA detected on MRS (PMID 12557293), low creatine and elevated GAA in plasma and urine and absent creatine peak on MRS (PMID 28438604), and elevated GAA in plasma, urine, and CSF, and lacking creatine peak on brain MRS (PMID 1136556)(PP4_Strong).
PM3_Supporting	✔	Three patients have been reported with this variant and clinical and biochemical features consistent with GAMT deficiency including one patient who is homozygous for the variant (PMID 12557293; 0.5 points)(PM3_Supporting), and two patients who are compound heterozygous for the variant and either c.564G>T (p. Met188Ile), in trans (PMID 28438604) or "IVS5-3C>G" (PMID 11136556). The in trans data from these two patients will be used in the assessment of the second variant and is not included here to avoid circular logic.
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.0001 in the East Asian population, which is less than the ClinGen CCDS VCEP's threshold (<0.0004), meeting this criterion (PM2_Supporting).
PVS1_Strong	✔	The NM_000156.6:c.491dup (p.Val165ArgfsTer26) variant in GAMT is a frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 5/6, leading to nonsense-mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1; PMID 11136556).

Curation History

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