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Variant: NM_000156.6(GAMT):c.526dup (p.Glu176fs)

Version: 1.0

CA913184710

1409758 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2b6ecaf4-3191-458c-80c0-9dfdabed4486
Approved on: 2023/3/23
Published on: 2023/3/29

HGVS expressions

NM_000156.6:c.526dup
NM_000156.6(GAMT):c.526dup (p.Glu176fs)
NC_000019.10:g.1398965dup
CM000681.2:g.1398965dup
NC_000019.9:g.1398964dup
CM000681.1:g.1398964dup
NC_000019.8:g.1349964dup
NG_009785.1:g.7594dup
ENST00000252288.8:c.526dup
ENST00000447102.8:c.526dup
ENST00000591788.3:c.209dup
ENST00000640164.1:n.359dup
ENST00000640762.1:c.457dup
ENST00000252288.6:c.526dup
ENST00000447102.7:c.526dup
ENST00000591788.2:c.211dup
NM_000156.5:c.526dup
NM_138924.2:c.526dup
NM_138924.3:c.526dup

Pathogenic

Met criteria codes 3

PVS1_Strong PP4_Strong PM2_Supporting

Not Met criteria codes 1

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:c.526dup (p.Glu176GlyfsTer15) variant in GAMT has been previously reported in at least one individual with guanidinoacetate methyltransferase deficiency (PMID: 15108290). This variant is absent in population databases (PM2_Supporting). This variant has been reported in ClinVar (Variation ID: 1409758) and has been interpreted as pathogenic by Invitae. The individual who was previously reported was a compound heterozygote; however, this occurrence was counted for evidence for PM3 for the other variant and thus not used here to prevent circularity in the use of PM3 (PMID: 15108290). This individual showed elevated urinary GAA and partially absent creatine peak and absent GAA peak on brain MRS with full GAMT gene sequencing (PMID: 15108290) (PP4_Strong). The p.Glu176GlyfsTer15 variant is a frameshift variant at amino acid position 176 that is predicted to lead to premature termination 15 amino acids downstream. As the variant results in termination downstream of the last 50 base pairs of the penultimate exon of the GAMT gene, nonsense-mediated decay is not predicted; however, the variant results in removal of >10% of the encoded protein (PVS1_Strong). In summary, this variant meets criteria to be classified as pathogenic for guanidinoacetate methyltransferase (GAMT) deficiency. GAMT-specific ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiencies Variant Curation Expert Panel (CCDS VCEP) (Specifications version 1.1.0): PVS1_Strong, PM2_Supporting, PP4_Strong (Richards 2015). (Classification approved by the ClinGen CCDS VCEP on March 23, 2023)

Met criteria codes

PVS1_Strong	✔	Frameshift variant in exon 5/6 in the last 50bp of the penultimate exon (c.526), such that NMD is not predicted. Predicted to result in frameshift at amino acid position 176 and premature termination at amino acid position 191/236, resulting in removal of 45 amino acids (19.1% of the protein, >10% of the protein), such that PVS1_Strong applies per CCDS specifications.
PP4_Strong	✔	PMID: 15108290: Identified in one proband who showed elevated urinary GAA (1pt) and partially absent creatine peak and absent GAA peak on brain MRS (3pts) with full GAMT gene sequencing (4pts total)
PM2_Supporting	✔	Absent in population databases.

Not Met criteria codes

PM3	✖	Identified in at least one individual with guanidinoacetate methyltransferase deficiency, who was a compound heterozygote (PMID: 24415674, PMID: 15108290); this occurrence was not counted for PM3 so that it could be counted for PM3 for the other variant, thereby preventing circularity in use of PM3.

Curation History

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