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Variant: NM_000156.6(GAMT):c.64dup (p.Ala22fs)

Version: 1.0

CA631301051

1402763 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9eb5a533-ebbe-4fc3-82b4-92fffdb9847c
Approved on: 2023/3/9
Published on: 2023/3/29

HGVS expressions

NM_000156.6(GAMT):c.64dup (p.Ala22fs)
NM_000156.6:c.64dup
NC_000019.10:g.1401418dup
CM000681.2:g.1401418dup
NC_000019.9:g.1401417dup
CM000681.1:g.1401417dup
NC_000019.8:g.1352417dup
NG_009785.1:g.5141dup
ENST00000252288.8:c.64dup
ENST00000447102.8:c.64dup
ENST00000640762.1:c.64dup
ENST00000252288.6:c.64dup
ENST00000447102.7:c.64dup
NM_000156.5:c.64dup
NM_138924.2:c.64dup
NM_138924.3:c.64dup

Pathogenic

Met criteria codes 4

PM3 PVS1 PM2_Supporting PP4_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 1.1.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Cerebral Creatine Deficiency Syndromes VCEP

The NM_000156.6:c.64dup (p.Ala22GlyfsTer63) variant in GAMT is a frameshift variant predicted to cause a premature stop codon, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). Two affected unrelated individuals, previously reported (PMID: 27650626, PMID: 15108290), were homozygous for the variant; one of these individuals (PMID: 15108290) had elevated urinary guanidinoacetate and absent GAMT enzyme activity in fibroblasts with full GAMT gene sequencing performed, and the other proband (PMID: 27650626) had low serum and urine creatinine and absent creatine peak on brain MRS. (PM3, PP4_Strong), This variant is absent from population databases (PM2_Supporting). This variant has also been reported in ClinVar (Variation ID: 1402763). In summary, this variant meets criteria to be classified as pathogenic for guanidinoacetate methyltransferase deficiency. GAMT-specific ACMG/AMP criteria applied (Specifications Version 1.1.0): PVS1, PP4_Strong, PM2_Supporting, PM3, PP4_Strong. (Classification approved by the ClinGen CCDS VCEP on March 9, 2023)

Met criteria codes

PM3	✔	Identified in two affected individuals, both of whom were homozygous for the variant (PMID: 27650626, PMID: 15108290) (1pt).
PVS1	✔	This variant is predicted to cause a frameshift, which alters the protein's amino acid sequence beginning at position 22 and leads to a premature termination codon 63 amino acids downstream. This alteration is then predicted to lead to a truncated or absent protein. Loss of function of the GAMT gene is an established disease mechanism in guanidinoacetate methyltransferase deficiency.
PM2_Supporting	✔	Absent in gnomAD
PP4_Strong	✔	Identified in one proband (PMID: 15108290) with elevated urinary GAA and absent GAMT enzyme activity in fibroblasts with full GAMT gene sequencing performed (4pts; PP4_Strong); also identified in another proband (PMID: 27650626) with low serum and urine creatinine and absent creatine peak on brain MRS (3pts; PP4_Moderate).

Curation History

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