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Variant: NM_138924.3:c.58dup

Version: 1.0

CA504731701

2570637 (ClinVar)

Gene: GAMT (HGNC:2593)
Condition: guanidinoacetate methyltransferase deficiency (MONDO:0012999)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0cfc1fe1-1f59-49f3-aea2-c45dd7e81a0f
Approved on: 2023/5/25
Published on: 2023/5/25

HGVS expressions

NM_138924.3:c.58dup
NC_000019.10:g.1401419dup
CM000681.2:g.1401419dup
NC_000019.9:g.1401418dup
CM000681.1:g.1401418dup
NC_000019.8:g.1352418dup
NG_009785.1:g.5135dup
ENST00000252288.8:c.58dup
ENST00000447102.8:c.58dup
ENST00000640762.1:c.58dup
ENST00000252288.6:c.58dup
ENST00000447102.7:c.58dup
NM_000156.5:c.58dup
NM_138924.2:c.58dup
NM_000156.6:c.58dup

Pathogenic

Met criteria codes 3
PM3 PVS1 PP4_Strong

Not Met criteria codes 1
PM2

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.58dup (p.Trp20LeufsTer65) variant in GAMT is a frameshift variant predicted to cause a premature stop codon in biologically relevant exon 2/6 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism

(PVS1). This variant has been detected in one individual with GAMT deficiency, who was compound heterozygous for the variant and a pathogenic variant, with the phase confirmed in trans by family testing (PMID: 24766785). This individual had elevated urine GAA, deficient GAMT activity in fibroblasts and reduced creatine peak on brain MRS (PMID: 24766785) (PP4_Strong). This variant is not present in gnomAD v2.1.1 but the coverage is <20X and therefore PM2_Supporting is not met. There is no ClinVar entry for this variant. 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, PM3, PP4_Strong. (Classification approved by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel on May 25, 2023)

Met criteria codes

PM3	✔	One patient with GAMT deficiency has been reported with this variant. This patient is compound heterozygous for a pathogenic variant, c.327G>A, in trans (PMID 24766785)(1 point)(PM3)
PVS1	✔	The NM_000156.6:c.58dup (p.Trp20LeufsTer65) variant in GAMT is a frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 2/6 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PP4_Strong	✔	One patient with this variant and features consistent with GAMT deficiency has been reported. This patient has global developmental delay and history of seizures with elevated urine GAA, deficient GAMT activity in fibroblasts and reduced creatine peak on MRS (PMID 24766785) (PP4_Strong).

Not Met criteria codes

PM2	✖	This variant is not present in gnomAD v2.1.1 but the coverage is <20X and therefore PM2 is not met.

Curation History

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