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Variant: NM_000152.5(GAA):c.971dup (p.Ser325fs)

Version: 2.0

CA1585329339

1327501 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: c4d64323-3172-41bd-b904-0c782103ce70
Approved on: 2024/3/6
Published on: 2024/3/26

HGVS expressions

NM_000152.5(GAA):c.971dup (p.Ser325fs)
NM_000152.5:c.971dup
NC_000017.11:g.80108305dup
CM000679.2:g.80108305dup
NC_000017.10:g.78082104dup
CM000679.1:g.78082104dup
NC_000017.9:g.75696699dup
NG_009822.1:g.11750dup
ENST00000570803.6:c.971dup
ENST00000572080.2:c.971dup
ENST00000577106.6:c.971dup
ENST00000302262.8:c.971dup
ENST00000302262.7:c.971dup
ENST00000390015.7:c.971dup
NM_000152.3:c.971dup
NM_001079803.1:c.971dup
NM_001079804.1:c.971dup
NM_000152.4:c.971dup
NM_001079803.2:c.971dup
NM_001079804.2:c.971dup
NM_001079803.3:c.971dup
NM_001079804.3:c.971dup

Pathogenic

Met criteria codes 3

PM3_Supporting PVS1 PM2_Supporting

Not Met criteria codes 1

PP4

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.971dupC (p.Ser325GlufsTer5) variant in GAA is a frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 6 out of 20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). One patient reported to have infantile-onset Pompe disease is compound heterozygous for the variant and a variant that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP, c.1802C>T (p.Ser601Leu) (ClinVar Variation ID: 194154; SCV002032130.1); the phase is unconfirmed (PMID: 28394184) (PM3_Supporting). There is insufficient data to apply PP4. The variant is absent in gnomAD v2.1.1. (PM2_Supporting). In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. Initially, the variant was classified a likely pathogenic by the ClinGen Lysosomal Diseases VCEP on August 17, 2021, but it was reclassified as pathogenic on Jan 15, 2024, due to the application of PM3_Supporting. GAA-specific ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PVS1, PM2_Supporting, PM3_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on Feb 6, 2024).

Met criteria codes

PM3_Supporting	✔	One patient reported to have infantile-onset Pompe disease is compound heterozygous for the variant and a variant that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP, c.1802C>T (p.Ser601Leu) (ClinVar Variation ID: 194154; SCV002032130.1); the phase is unconfirmed (PMID: 28394184) (0.5 points) (PM3_Supporting). Note that the pathogenic classification of p.Ser601Leu does not require the allelic data from this patient.
PVS1	✔	The NM_000152.5:c.971dupC (p.Ser325GlufsTer5) variant in GAA is a frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 6 out of 20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1. and v4.0. (PM2_Supporting)

Not Met criteria codes

PP4	✖	A Chinese patient with this variant and infantile onset Pompe disease has been reported (PMID 28394184). While the diagnosis was based on clinical presentation and GAA enzyme activity assay, details for the individual patient are not available (PP4 was not applied).

Curation History

Showing 1 to 7 of 7 rows

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