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Variant: NM_001079804.3:c.1075G>A

Version: 1.0

CA401364835

2727745 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: cd6b9616-4345-457b-bf52-3f2a5c8cd704
Approved on: 2025/11/4
Published on: 2026/1/26

HGVS expressions

NM_001079804.3:c.1075G>A
NC_000017.11:g.80108409G>A
CM000679.2:g.80108409G>A
NC_000017.10:g.78082208G>A
CM000679.1:g.78082208G>A
NC_000017.9:g.75696803G>A
NG_009822.1:g.11854G>A
ENST00000570803.6:c.1075G>A
ENST00000572080.2:c.1075G>A
ENST00000577106.6:c.1075G>A
ENST00000302262.8:c.1075G>A
ENST00000302262.7:c.1075G>A
ENST00000390015.7:c.1075G>A
NM_000152.3:c.1075G>A
NM_001079803.1:c.1075G>A
NM_001079804.1:c.1075G>A
NM_000152.4:c.1075G>A
NM_001079803.2:c.1075G>A
NM_001079804.2:c.1075G>A
NM_000152.5:c.1075G>A
NM_001079803.3:c.1075G>A

Pathogenic

Met criteria codes 4

PM3 PP4_Moderate PVS1 PM2_Supporting

Not Met criteria codes 1

BS3

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(GAA):c.1075G>A (p.Gly359Arg) variant alters the last nucleotide of exon 6 of in GAA. RT-PCR analysis of fibroblast RNA from a homozygous individual that showed that a cryptic splice donor site in exon 6, located four nucleotides upstream at c.1071 is used instead of the normal splice site. This results in loss of 4 nucleotides from the transcript (c.1071_1075del), causing a frameshift and premature termination codon, predicted to result in nonsense-mediated decay (p.Val358AspfsTer33) This cryptic splice site is also predicted by SpliceAI (score for donor gain 4 bp upstream = 0.86; score for donor loss at the normal slice junction = 0.71). Quantitative PCR revealed that all GAA exons were expressed at very low levels in this patient (PMID: 25243733) (PVS1). Two patients (PMID: 17573812/22613277 and 25243733) have been reported with this variant and GAA activity <10% in muscle samples or in the affected range in a clinically validated dried blood spot assay (PMID: 17573812/22613277 and 25243733). Additionally, two patients were reported to be on enzyme replacement therapy (PMID: 22613277, 32248831) (PP4_Moderate). At least two patients with late onset Pompe disease are compound heterozygous for the NM_000152.5(GAA):c.1075G>A (p.Gly359Arg) variant and another variant in GAA that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP, NM_000152.5(GAA):c.-32-13T>G. One patient is homozygous for the NM_000152.5(GAA):c.1075G>A (p.Gly359Arg) variant (PMID: 25243733) (PM3). This variant is absent in gnomAD v4.1.0. (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 2727745; 1 star review status) with one submitter classifying the variant as pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0.0): PVS1, PP4_Moderate, PM3, PM2_supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on November 4, 2025)

Met criteria codes

PM3	✔	At least two patients with late onset Pompe disease are compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP, c.-32-13T>G, phase unconfirmed (PMID: 17573812, 17643989, 22613277, 32248831) (2 x 0.5 points). One patient is homozygous for the variant (PMID: 25243733) (0.5 points). Total 1.5 points. PM3.
PP4_Moderate	✔	Two patients (PMID: 17573812/22613277 and 25243733) have been reported with this variant and GAA activity <10% in muscle samples or in the affected range in a clinically validated dried blood spot assay (PMID: 17573812/22613277 and 25243733). Additionally, two patients were reported to be on enzyme replacement therapy (PMID: 22613277, 32248831). 2 points. PP4_Moderate.
PVS1	✔	The NM_000152.5(GAA):c.1075G>A (p.Gly359Arg) variant alters the last nucleotide of exon 6 of in GAA. RT-PCR analysis of fibroblast RNA from a homozygous individual that showed that a cryptic splice donor site in exon 6, located four nucleotides upstream at c.1071 is used instead of the normal splice site. This results in loss of 4 nucleotides from the transcript (c.1071_1075del), causing a frameshift and premature termination codon, predicted to result in nonsense-mediated decay (p.Val358AspfsTer33) This cryptic splice site is also predicted by SpliceAI (score for donor gain 4 bp upstream = 0.86; score for donor loss at the normal slice junction = 0.71). Quantitative PCR revealed that all GAA exons were expressed at very low levels in this patient (PMID: 25243733) (PVS1).
PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0. (PM2_Supporting).

Not Met criteria codes

BS3	✖	Expression of the variant in COS-7 cells showed 54.3% GAA activity; media showed 14.2% GAA activity. Western blot showed normal processing and the variant was classified as class E. The study did note that the analysis does not

test for splicing defects and it is notable that c.1075G>A is located near a splice-site and is predicted by in silico analysis to cause abnormal splicing. As a result, this does not meet the requirements for applying BS3.

Curation History

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