

Variant: NM_000152.5(GAA):c.1626C>G (p.Pro542=)

Version: 1.4

CA294895065 [↗](#)

430167 (ClinVar) [↗](#)

Gene: GAA ([HGNC:2548](#))

Condition: glycogen storage disease II ([MONDO:0009290](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 783e5337-87d6-4332-9cc6-e5f88f18df24

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HGVS expressions

NM_000152.5(GAA):c.1626C>G (p.Pro542=)

NM_000152.5:c.1626C>G

NC_000017.11:g.80111015C>G

CM000679.2:g.80111015C>G

NC_000017.10:g.78084814C>G

CM000679.1:g.78084814C>G

NC_000017.9:g.75699409C>G

NG_009822.1:g.14460C>G

ENST00000570803.6:c.1626C>G

ENST00000572080.2:c.1626C>G

ENST00000577106.6:c.1626C>G

ENST00000302262.8:c.1626C>G

ENST00000302262.7:c.1626C>G

ENST00000390015.7:c.1626C>G

ENST00000572080.1:c.14C>G

NM_000152.3:c.1626C>G

NM_001079803.1:c.1626C>G

NM_001079804.1:c.1626C>G

NM_000152.4:c.1626C>G

NM_001079803.2:c.1626C>G

NM_001079804.2:c.1626C>G

NM_001079803.3:c.1626C>G

NM_001079804.3:c.1626C>G

Uncertain Significance

Met criteria codes **3**

PM3_Supporting

PVS1_Moderate

PM2_Supporting

Not Met criteria codes **3**

PS3

PP3

PP4

Evidence Links **1**

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

Lysosomal Diseases VCEP

The NM_000152.5:c.1626C>G variant is a synonymous (silent) variant in exon 11 of GAA (p.Pro542=). A minigene assay demonstrated that the variant impacts splicing by creating a de novo donor site in exon 11 as well as activating a cryptic acceptor site in exon 12. This results in the deletion of 11 nucleotides from exon 11 and 46 nucleotides from exon 12. A low level of normal transcript was also detected (PMID 21179066). PVS1_moderate was applied because the resulting deletion is predicted to be in frame (57 nucleotides, 29 amino acids deleted; none of which have been designated by the Lysosomal Diseases VCEP as critical residues). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00000254 (3/1179982 alleles) in the European non-Finnish population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). The variant was found homozygous in one patient with late-onset Pompe disease (PM3_supporting); there was insufficient evidence to apply PP4 (PMID 16917947). There is a ClinVar entry for this variant (Variation ID: 430167). In summary, this variant currently meets the criteria to be classified as a variant of uncertain significance for Pompe disease based on the GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0.0): PVS1_Moderate, PM2_Supporting, PM3_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on June 26, 2025).

Met criteria codes

PM3_Supporting			This variant has been detected in the homozygous state in one individual with Pompe disease (0.5 pt, PMID 16917947) (PM3_Supporting).
PVS1_Moderate			The NM_000152.5:c.1626C>G variant in GAA is a synonymous variant (p.Pro542=). A minigene assay demonstrated that the variant impacts splicing by creating a de novo donor site in exon 11 as well as activating a cryptic acceptor site in exon 12. This results in the deletion of 11 nucleotides from exon 11 and 46 nucleotides from exon 12. A low level of normal transcripts was also detected (PMID 21179066). SpliceAI prediction is consistent with these results, indicating that that a donor splice site will be created at the position of the altered nucleotide (score = 0.99). PVS1_moderate was applied because the resulting deletion is predicted to be in frame (29 amino acids deleted; none of which have been designated by the Lysosomal Diseases VCEP as critical residues) (PMID: 37352859).
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0. is 0.00000254 (3/1179982 alleles) in the European non-Finnish population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

Not Met criteria codes

PS3			Minigene assay data is recorded under PVS1 based on recommendations published by Walker et al, PMID: 37352859. Minigene assay showed variant results in abnormal transcripts and a low level of normal WT transcripts. RT-PCR analysis showed the abnormal transcripts lacked 11 nt of exon 11 and 46 nt of exon 12 due to activation of a cryptic acceptor site in exon 12 and a de novo donor site in exon 11. This would be predicted to be in-frame. PubMed:21179066 
PP3			The computational splicing predictor SpliceAI gives a score of 0.99 for gain of a de novo donor site. However, PP3 is not applied because PVS1_Moderate has been applied (based on the recommendations of Walker et al, PMID: 37352859).

PP4



At least 1 patient with this variant was noted to have deficient GAA activity but results were not provided (0.5 pt, PMID 16917947).

Curation History [↗](#)

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