

Variant: NM_000152.5:c.1106T>C

Version: 1.0

CA401364964 [↗](#)

1034639 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 58c05f56-40b8-4963-87f3-9720ac6f893c

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HGVS expressions

NM_000152.5:c.1106T>C

NC_000017.11:g.80108519T>C

CM000679.2:g.80108519T>C

NC_000017.10:g.78082318T>C

CM000679.1:g.78082318T>C

NC_000017.9:g.75696913T>C

NG_009822.1:g.11964T>C

ENST00000570803.6:c.1106T>C

ENST00000572080.2:c.1106T>C

ENST00000577106.6:c.1106T>C

ENST00000302262.8:c.1106T>C

ENST00000302262.7:c.1106T>C

ENST00000390015.7:c.1106T>C

NM_000152.3:c.1106T>C

NM_001079803.1:c.1106T>C

NM_001079804.1:c.1106T>C

NM_000152.4:c.1106T>C

NM_001079803.2:c.1106T>C

NM_001079804.2:c.1106T>C

NM_001079803.3:c.1106T>C

NM_001079804.3:c.1106T>C

Likely Pathogenic

Met criteria codes 5

PM2_Supporting

PP4_Moderate

PM3_Supporting

PS3_Moderate

PP3

Not Met criteria codes 1

PM5

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**

Lysosomal Diseases VCEP

The NM_000152.5:c.1106T>C variant in GAA is a missense variant predicted to cause substitution of leucine by proline at amino acid 369 (p.Leu369Pro). At least 2 patients with a diagnosis of Pompe disease have been reported to have this variant, including one individual with documented GAA activity in the affected range in dried blood spot. This patient was also treated with enzyme replacement therapy for Pompe disease (Duke University; PMID: 23430493) (PP4_Moderate). This individual was compound heterozygous for this variant, c.2704C>T (p.Gln902Ter) (likely pathogenic based on classification by the ClinGen Lysosomal Diseases VCEP), and c.2064C>G (p.Ser688Arg) (not yet evaluated by the ClinGen Lysosomal Diseases VCEP); phase unconfirmed (Duke University). Another individual was compound heterozygous for this variant and c.1064T>C (p.Leu355Pro) (pathogenic based on classification by the ClinGen Lysosomal Diseases VCEP); phase unconfirmed (PMID: 23430493) (PM3_Supporting). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001666 (1/60010 alleles) in the Admixed American population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). Additionally, expression of the variant in HEK293 cells resulted in 3.1% wild type GAA activity and evidence of abnormal GAA synthesis and processing, leading the variant to be described as Class B (“potentially less severe”), indicating that this variant may impact protein function (PMID: 23430493) (PS3_Moderate). The computational predictor REVEL gives a score of 0.976, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense variant in the same codon, c.1106T>A (p.Leu369Gln), has been reported in a patient with Pompe disease (PMID: 31342611). However, this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen Lysosomal Diseases VCEP (PM5 not met). In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert panel (specifications Version 2.0): PS3_Moderate, PM2_Supporting, PM3_Supporting, PP3, PP4_Moderate. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on October 21, 2025).

Met criteria codes

PM2_Supporting	✓	The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001666 (1/60010 alleles) in the Admixed American population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PP4_Moderate	 ✓	At least 2 patients with a diagnosis of Pompe disease have been reported to have this variant, including one individual with documented GAA activity in the affected range in dried blood spot. This patient was also treated with enzyme replacement therapy for Pompe disease (Duke University; PMID: 23430493) (PP4_Moderate).
PM3_Supporting	 ✓	This variant has been detected in at least 2 individuals with Pompe disease. Of those individuals, one was compound heterozygous for this variant and c.1064T>C (p.Leu355Pro) (pathogenic based on classification by the ClinGen Lysosomal Diseases VCEP); phase unconfirmed (PMID: 23430493) (0.5 points). Another individual was compound heterozygous for this variant, c.2704C>T (p.Gln902Ter) (likely pathogenic based on classification by the ClinGen Lysosomal Diseases VCEP), and c.2064C>G (p.Ser688Arg) (not yet evaluated by the ClinGen Lysosomal Diseases VCEP); phase unconfirmed (Duke University) (PM3_Supporting).
PS3_Moderate	 ✓	Expression of the variant in HEK293 cells resulted in 3.1% wild type GAA activity and evidence of abnormal GAA synthesis and processing, leading the variant to be described as Class B (“potentially less severe”), indicating that this variant may impact protein function (PMID: 23430493) (PS3_Moderate).
PP3	 ✓	The computational predictor REVEL gives a score of 0.976, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

Not Met criteria codes

PM5



Another missense variant in the same codon, c.1106T>A (p.Leu369Gln), has been reported in a patient with Pompe disease (PMID: 31342611). However, this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen Lysosomal Diseases VCEP (PM5 not met).

Curation History [↗](#)

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See Report	Preferred Variant Title	Classification ⓘ	Condition	Published Date	Version ⓘ	Criteria Specification	Gene
View	NM_000152.5:c.1106T>C	Likely Pathogenic	Glycogen Storage Disease II ↗	2025-12-02	1.0	ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2 ↗	GAA ↗

Showing 1 to 1 of 1 rows

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