

Variant: *NM_000152.5(GAA):c.1000G>T (p.Gly334Cys)*

Version: 1.0

CA10604927 [↗](#)

284864 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 18ee75c4-d779-4cc0-bba9-7a9617f7410f

Approved on: 2025/9/2

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HGVS expressions

NM_000152.5:c.1000G>T

NM_000152.5(GAA):c.1000G>T (p.Gly334Cys)

NC_000017.11:g.80108334G>T

CM000679.2:g.80108334G>T

NC_000017.10:g.78082133G>T

CM000679.1:g.78082133G>T

NC_000017.9:g.75696728G>T

NG_009822.1:g.11779G>T

ENST00000570803.6:c.1000G>T

ENST00000572080.2:c.1000G>T

ENST00000577106.6:c.1000G>T

ENST00000302262.8:c.1000G>T

ENST00000302262.7:c.1000G>T

ENST00000390015.7:c.1000G>T

NM_000152.3:c.1000G>T

NM_001079803.1:c.1000G>T

NM_001079804.1:c.1000G>T

NM_000152.4:c.1000G>T

NM_001079803.2:c.1000G>T

NM_001079804.2:c.1000G>T

NM_001079803.3:c.1000G>T

NM_001079804.3:c.1000G>T

Likely Pathogenic

Met criteria codes **5**

PM2_Supporting

PS3_Moderate

PP3

PP4_Moderate

PM3

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.1000G>T variant in GAA is a missense variant predicted to cause substitution of glycine by cysteine at amino acid 334 (p.Gly334Cys). It has been reported in two individuals in the literature with infantile-onset Pompe disease, at least one of whom is receiving enzyme replacement therapy (PMIDs: 28196920, 39835171) (PP4_moderate). Both individuals were compound heterozygous for the variant and c.[271G>A, 307T>G] p.[Asp91Asn, Cys103Gly], phase unreported; c.307T>G (p.Cys103Gly) is classified as pathogenic by the ClinGen LD VCEP (PM3). This variant has also been reported in infantile-onset Pompe disease in the Pompe Variant Database (PMIDs: 31342611, 33560568). The highest population minor allele frequency in gnomAD v4.1.0. is 0.0000025 (3/1180038 alleles) in the Non-Finnish European population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). When expressed in HEK293 cells using a previously published in vitro assay (PMID: 36246652), GAA enzyme activity was undetectable when compared to wild type and no GAA protein was detectable on western blot (unpublished data) (PS3_moderate). The computational predictor REVEL gives a score of 0.854, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). There is a ClinVar entry for this variant (Variation ID: 284864). In summary, this variant meets the criteria to be classified as likely pathogenic 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): PP4_moderate, PM3, PS3_moderate, PM2_supporting, PP3. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel, Sept. 2, 2025)

Met criteria codes

PM2_Supporting		Highest MAF in Non-Finnish European population is 0.0000025, which is lower than the threshold of 0.001 and meeting criteria for PM2_Supporting.
PS3_Moderate		No detectable enzyme activity in HEK293 cells when compared to wild type in previously established functional assay (Goomber et al. 2022). No precursor, indeterminate, or mature GAA protein seen on western blot. Data unpublished.
PP3		REVEL score is 0.854. greater than threshold of 0.7, meeting criteria for PP3.
PP4_Moderate		No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3		Two individuals with Pompe disease were reported with this variant and a second pathogenic variant in compound heterozygosity (PMIDs: 28196920, 39835171). Both individuals were compound heterozygous for the variant and c. [271G>A, 307T>G] p.[Asp91Asn, Cys103Gly], phase unreported. The variant c.307T>G (p.Cys103Gly) is classified as pathogenic by the LD VCEP (0.5 pt/each, total 1 pt)

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