

Variant: *NM_000152.5(GAA):c.1642G>T (p.Val548Phe)*

Version: 1.2

CA401368744 [↗](#)

597381 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 3b6543e9-192e-4d7d-9986-a4ae6baf2190

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HGVS expressions

NM_000152.5(GAA):c.1642G>T (p.Val548Phe)

NM_000152.5:c.1642G>T

NC_000017.11:g.80111988G>T

CM000679.2:g.80111988G>T

NC_000017.10:g.78085787G>T

CM000679.1:g.78085787G>T

NC_000017.9:g.75700382G>T

NG_009822.1:g.15433G>T

ENST00000570803.6:c.1642G>T

ENST00000572080.2:c.1642G>T

ENST00000577106.6:c.1642G>T

ENST00000302262.8:c.1642G>T

ENST00000302262.7:c.1642G>T

ENST00000390015.7:c.1642G>T

ENST00000572080.1:c.30G>T

ENST00000572803.1:n.256G>T

NM_000152.3:c.1642G>T

NM_001079803.1:c.1642G>T

NM_001079804.1:c.1642G>T

NM_000152.4:c.1642G>T

NM_001079803.2:c.1642G>T

NM_001079804.2:c.1642G>T

NM_001079803.3:c.1642G>T

NM_001079804.3:c.1642G>T

Likely Benign

Met criteria codes **4**

BS3_Supporting

PM2_Supporting

BP4

BP2

Not Met criteria codes **2**

PP3

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

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1642G>T variant in GAA is a missense variant predicted to cause substitution of valine by phenylalanine at amino acid 548 (p.Val548Phe). This variant has been observed in cis with the variant c.1880C>T (p.Ser627Phe) (PMID 28763149, ClinVar #000597382.19), which is classified as pathogenic by ClinGen LD VCEP, in two individuals with Pompe disease. The phase of variant was confirmed by parental testing (BP2). The computational predictor REVEL gives a score of 0.269, which is below the threshold of 0.5, evidence that does not predict a damaging effect on GAA function (BP4). This variant is absent in gnomAD v4.1.0, meeting this criterion (PM2_Supporting). Expression of the variant in HEK293 cells resulted in normal activity and processing, indicating that variant does not impact protein function ((unpublished data from the laboratory that published PMID: 36246652) (BS3_supporting). There is a ClinVar entry for this variant (Variation ID: 597381). Although PM2_Supporting is met, this is the only pathogenic criterion that was met. Overall, the evidence indicates that this variant is likely benign (BS3_Supporting, BP2, BP4) and thus the ClinGen LD VCEP classified this variant as likely benign. GAA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Lysosomal Diseases VCEP (Specifications Version 2.0): BS3_supporting, BP2, BP4, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on June 3, 2025)

Met criteria codes

BS3_Supporting			This variant demonstrated normal GAA expression and enzyme activity (unpublished data from the laboratory that published PMID: 36246652).
PM2_Supporting			This variant is absent in gnomAD v4.1.0 or v2.1.1. (PM2_Supporting).
BP4			The computational predictor REVEL gives a score of 0.269, which is below the threshold of 0.5, evidence that does not predict a damaging effect on GAA function.
BP2			The variant has been observed in cis with the variant c.1880C>T(p.Ser627Thr) (ClinVar # VCV000597382.19), (PMID:28763149), which is classified as Pathogenic by the ClinGen LD VCEP , in an individual with Pompe disease. The phase of variants was confirmed by parental testing.

Not Met criteria codes

PP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP4			At least 1 IOPD patient with this variant was reported to be on enzyme replacement therapy for Pompe disease (PMID: 31193175) (PP4).

