

Variant: NM_000152.5(GAA):c.1477C>T (p.Pro493Ser)

Version: 1.0

CA401366926 [↗](#)

2160730 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 9bac4cac-ccd2-43d4-be60-88c23625224d

Approved on: 2025/5/6

Published on: 2025/5/20

HGVS expressions

NM_000152.5(GAA):c.1477C>T (p.Pro493Ser)

NM_000152.5:c.1477C>T

NC_000017.11:g.80110766C>T

CM000679.2:g.80110766C>T

NC_000017.10:g.78084565C>T

CM000679.1:g.78084565C>T

NC_000017.9:g.75699160C>T

NG_009822.1:g.14211C>T

ENST00000570803.6:c.1477C>T

ENST00000572080.2:c.1477C>T

ENST00000577106.6:c.1477C>T

ENST00000302262.8:c.1477C>T

ENST00000302262.7:c.1477C>T

ENST00000390015.7:c.1477C>T

NM_000152.3:c.1477C>T

NM_001079803.1:c.1477C>T

NM_001079804.1:c.1477C>T

NM_000152.4:c.1477C>T

NM_001079803.2:c.1477C>T

NM_001079804.2:c.1477C>T

NM_001079803.3:c.1477C>T

NM_001079804.3:c.1477C>T

Likely Pathogenic

Met criteria codes **5**

PP4_Moderate

PM2_Supporting

PS3_Supporting

PM5_Supporting

PP3

Not Met criteria codes **1**

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.1477C>T variant in GAA is a missense variant predicted to cause substitution of proline by serine at amino acid 493 (p.Pro493Ser). This variant has been detected in at least 1 patient reported to have Pompe disease with reported laboratory values demonstrating deficient GAA activity (Duke University; PMID: 31904026, 32518148) (PP4_moderate). This variant has been detected in at least one individual with Pompe disease. This individual was compound heterozygous for the variant, c.1477C>T (p.Pro493Ser), and two other variants: a variant classified as pathogenic by the ClinGen LD VCEP, c.1978C>T (p.Arg660Cys) (ClinVar Variation ID: 558604, SCV002540656.1), and a variant not classified by the by the ClinGen LD VCEP, c.2221G>A (p.Asp741Asn) (ClinVar Variation ID: 571521) (Duke University; PMID: 31904026, 32518148). The c.1477C>T (p.Pro493Ser) variant was confirmed in trans with the c.1978C>T (p.Arg660Cys) and c.2221G>A (p.Asp741Asn). The phase of these variants was confirmed in trans by parental testing (PM3_not met). Another missense variant, c.1478C>T, p.Pro493Leu (ClinVar Variation ID: 379593) in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (PM5_supporting). This variant is absent in gnomAD v4.1.0 (PM2_Supporting). Residual in vitro enzyme activity for the variant in 2 replicates resulted in a mean of 12.3% wild type GAA activity (within the pathogenic control range of <15%), indicating that this variant may impact protein function (Duke University) (PS3_Supporting). The computational predictor REVEL gives a score of 0.781 which is above the threshold predicting a damaging (>0.7) impact on GAA function (PP3_met). There is a ClinVar entry for this variant (Variation ID: 2160730; 1 star review status) with one submitter classifying the variant as likely pathogenic, and one as a variant of uncertain significance. In summary, this variant meets the criteria to be classified as Likely Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Lysosomal Diseases VCEP (Specifications Version 2.0): PP4_Moderate, PP3_met, PM2_supporting, PM5_supporting, PS3_supporting, PM3_not met). (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on May 6, 2025).

Met criteria codes

PP4_Moderate			This variant has been detected in at least 1 patient reported to have Pompe disease including with reported laboratory values demonstrating deficient GAA activity. This patient was also treated with enzyme replacement therapy (Clinical Diagnostic Laboratory; PMID: 31904026, 32518148). 2 points; PP4_Moderate.
PM2_Supporting			This variant is absent in gnomAD v4.1.0 (PM2_Supporting). This variant is absent in gnomAD v4.1.0 (PM2_Supporting).
PS3_Supporting			Residual in vitro enzyme activity for the variant in 2 replicates resulted in a mean of 12.3% wild type GAA activity (within the pathogenic control range of <15%), indicating that this variant may impact protein function (Duke University). PS3_Supporting.
PM5_Supporting			One different missense variant (c.1478C>T, p.Pro493Leu; ClinVar Variation ID: 379593, SCV001371749.2) in the same codon have been classified as likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (PM5_Supporting).
PP3			The computational predictor REVEL gives a score of 0.781 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

Not Met criteria codes

PM3			This variant has been detected in at least one individual with Pompe disease. This individual was compound heterozygous for the variant, c.1477C>T (p.Pro493Ser), and two other variants: a variant classified as pathogenic by
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the ClinGen LD VCEP, c.1978C>T (p.Arg660Cys) (ClinVar Variation ID: 558604, SCV002540656.1), and a variant not classified by the by the ClinGen LD VCEP, c.2221G>A (p.Asp741Asn) (ClinVar Variation ID: 571521) (Clinical Diagnostic Laboratory; PMID: 31904026, 32518148). The c.1477C>T (p.Pro493Ser) variant was confirmed in trans with the c.1978C>T (p.Arg660Cys) and c.2221G>A (p.Asp741Asn). The phase of these variants was confirmed in trans by parental testing. 0 points; PM3_Not Met.

Curation History [↗](#)



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