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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

PP3 PP4_Moderate PS3_Supporting PM2_Supporting PM5_Supporting

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

Evidence submitted by expert panel

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

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).
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.
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.
PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0 (PM2_Supporting). This variant is absent in gnomAD v4.1.0 (PM2_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).

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

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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