

Variant: *NM_000152.5(GAA):c.1445C>T (p.Pro482Leu)*

Version: 1.1

CA401366796 [↗](#)

982297 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 0b43e608-9622-456f-a358-b4d29ab793e0

Approved on: 2025/10/28

Published on: 2025/10/28

HGVS expressions

NM_000152.5(GAA):c.1445C>T (p.Pro482Leu)

NM_000152.5:c.1445C>T

NC_000017.11:g.80110734C>T

CM000679.2:g.80110734C>T

NC_000017.10:g.78084533C>T

CM000679.1:g.78084533C>T

NC_000017.9:g.75699128C>T

NG_009822.1:g.14179C>T

ENST00000570803.6:c.1445C>T

ENST00000572080.2:c.1445C>T

ENST00000577106.6:c.1445C>T

ENST00000302262.8:c.1445C>T

ENST00000302262.7:c.1445C>T

ENST00000390015.7:c.1445C>T

NM_000152.3:c.1445C>T

NM_001079803.1:c.1445C>T

NM_001079804.1:c.1445C>T

NM_000152.4:c.1445C>T

NM_001079803.2:c.1445C>T

NM_001079804.2:c.1445C>T

NM_001079803.3:c.1445C>T

NM_001079804.3:c.1445C>T

Likely Pathogenic

Met criteria codes **5**

PP4_Moderate

PM3_Strong

PP3

PM5_Supporting

PM2_Supporting

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.1445C>T variant in GAA is a missense variant predicted to cause substitution of proline by leucine at amino acid 482 (p.Pro482Leu). At least 5 patient(s) with this variant had documented GAA deficiency with <10% of normal mean control level of GAA activity in leukocytes, activity in the affected range in muscle, cultured skin fibroblasts, leukocytes, lymphocytes, whole blood or dried blood spot, or were noted to have deficient GAA activity but results were not provided (PMID: 17616415, 31086307, 34530085, 33741225, 31931849) (PP4_Moderate). This variant has been detected in at least 6 individuals with Pompe disease. Of those individuals, 4 were compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic for Pompe disease by the ClinGen LD VCEP. The phase is unconfirmed in all cases. The second variant includes c.1674_1675delTG (ClinVar Variation ID: 1397833) (PMID: 38958145, 0.5 points), c.258dup (ClinVar Variation ID: 282842) (PMID: 31931849, 0.5 points), c.1210G>A (p.Asp404Asn) (ClinVar Variation ID: 657348) (PMID: 31086307, 0.5 points), and c.343C>T (p.Gln115Ter) (ClinVar Variation ID: 188996) (PMID: 17616415, 0.5 points). Two individuals from different geographical areas were homozygous for the variant (2 x 0.5 pt) (PMID: 33741225, 38958145). Total 3 points (PM3_Strong). The highest population minor allele frequency in gnomAD v4.1.0. is 8.475e-7 (1/1179992 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). The computational predictor REVEL gives a score of 0.918 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense variant c.1445C>G (p.Pro482Arg) (PMID: 31392188, 22644586, ClinVar Variation ID 1067574) in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen LD VCEP (PM5_Supporting). There is a ClinVar entry for this variant (Variation ID: 982297). 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 LD VCEP (Specifications Version 2.0): PM3_Strong, PP4_Moderate, PP3, PM2_Supporting, PM5_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on October 28, 2025).

Met criteria codes

PP4_Moderate			At least 5 patient(s) with this variant had documented GAA deficiency with <10% of normal mean control level of GAA activity in leukocytes, lymphocytes, muscle samples, activity in the affected range in muscle, cultured skin fibroblasts, leukocytes, lymphocytes, whole blood or dried blood spot, or were noted to have deficient GAA activity but results were not provided (PMID: 17616415, 31086307, 34530085, 33741225, 31931849) (PP4_Moderate).
PM3_Strong			This variant has been detected in at least 6 individuals with Pompe disease. Of those individuals, 4 were compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic for Pompe disease by the ClinGen LD VCEP. The phase is unconfirmed in all cases. The second variant includes c.1674_1675delTG (ClinVar Variation ID: 1397833) (PMID: 38958145, 0.5 points), c.258dup (ClinVar Variation ID: 282842) (PMID: 31931849, 0.5 points), c.1210G>A (p.Asp404Asn) (ClinVar Variation ID: 657348) (PMID: 31086307, 0.5 points), and c.343C>T (p.Gln115Ter) (ClinVar Variation ID: 188996) (PMID: 17616415, 0.5 points). Two individuals from different geographical areas were homozygous for the variant (2 x 0.5 pt) (PMID: 33741225, 38958145). Total 3 points (PM3_Strong).
PP3			The computational predictor REVEL gives a score of [0.918] which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM5_Supporting			Another missense variant c.1445C>G (p.Pro482Arg) (PMID: 31392188, 22644586, ClinVar Variation ID 1067574) in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen LD VCEP without requiring the use of PM5 data from p.Pro482Leu (PM5_Supporting).
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0. is 8.475e-7 (1/1179992 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).

Curation History

▼

▼

Showing 1 to 2 of 2 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.