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Variant: NM_000152.5(GAA):c.1445C>G (p.Pro482Arg)

Version: 1.2

CA401366794

1067574 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 32998b1b-724b-48dd-8e77-ff28373954c1
Approved on: 2025/10/28
Published on: 2025/10/28

HGVS expressions

NM_000152.5(GAA):c.1445C>G (p.Pro482Arg)
NM_000152.5:c.1445C>G
NC_000017.11:g.80110734C>G
CM000679.2:g.80110734C>G
NC_000017.10:g.78084533C>G
CM000679.1:g.78084533C>G
NC_000017.9:g.75699128C>G
NG_009822.1:g.14179C>G
ENST00000570803.6:c.1445C>G
ENST00000572080.2:c.1445C>G
ENST00000577106.6:c.1445C>G
ENST00000302262.8:c.1445C>G
ENST00000302262.7:c.1445C>G
ENST00000390015.7:c.1445C>G
NM_000152.3:c.1445C>G
NM_001079803.1:c.1445C>G
NM_001079804.1:c.1445C>G
NM_000152.4:c.1445C>G
NM_001079803.2:c.1445C>G
NM_001079804.2:c.1445C>G
NM_001079803.3:c.1445C>G
NM_001079804.3:c.1445C>G

Likely Pathogenic

Met criteria codes 6

PM2_Supporting | PP3 | PP4 | PM3 | PS3_Moderate | PM5_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**

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1445C>G variant in GAA is a missense variant predicted to cause substitution of proline by arginine at amino acid 482 (p.Pro482Arg). One proband with this variant was reported to be on enzyme replacement therapy for Pompe disease (PMID: 31392188) (PP4). This variant has been detected two apparently unrelated probands and one sibling with late onset Pompe disease who 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, c.-32-13T>G; the phase is unknown (PMID: 24383498, 29122469, 31392188, 31710733, 38313679); 2 x 0.5pt) (PM3). This variant is absent in gnomAD v4.1.0.. (PM2_Supporting). Expression of the variant in COS7 or HEK293 cells resulted in 0% GAA activity in cells and 0% in medium, and evidence of abnormal synthesis and processing on Western blot, indicating that this variant may impact protein function (PMID 22644586) (PS3_Moderate). The computational predictor REVEL gives a score of 0.948 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Two other missense variants at the same amino acids have been reported in patients with Pompe disease; c.1445C>T (p.Pro482Leu) (ClinVar Variation ID: 982297) has been classified as likely pathogenic by the ClinGen LD VCEP, c.1444C>T (p.Pro482Ser) has not yet been classified by the VCEP (PM5_Supporting). There is a ClinVar entry for this variant (Variation ID: 1067574). 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 2.0.0): PM3, PS3_Moderate, PP3, PP4, PM2_Supporting, PM5_Supporting (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on October 28, 2025).

Met criteria codes

PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0 (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.948 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PP4	✔	At least 1 patient(s) with this variant was reported to be on enzyme replacement therapy for Pompe disease (PMID: 31392188) (PP4).
PM3	✔	This variant has been detected two apparently unrelated probands and one sibling with late onset Pompe disease who 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, c.-32-13T>G; the phase is unknown (PMID: 24383498, 29122469, 31392188, 31710733, 38313679); 2 x 0.5pt) (PM3).
PS3_Moderate	✔	Expression of the variant in COS7 cells resulted in 0% wild type GAA activity and evidence of abnormal GAA synthesis and processing leading the variant to be described as Class B (“potentially less severe”), indicating that this variant may impact protein function (PMID 22644586) (PS3_Moderate).
PM5_Supporting	✔	Two other missense variants at the same amino acids have been reported in patients with Pompe disease; c.1445C>T (p.Pro482Leu) (ClinVar Variation ID: 982297) has been classified as likely pathogenic by the ClinGen LD VCEP, c.1444C>T (p.Pro482Ser) has not yet been classified by the VCEP (PM5_Supporting).

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000152.5(GAA):c.1445C>G (p.Pro4...	Likely Pathogenic	Glycogen Storage Disease II	2025-10-28	1.2	ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2	GAA
View	NM_000152.5(GAA):c.1445C>G (p.Pro4...	Likely Pathogenic	Glycogen Storage Disease II	2025-10-28	1.1	ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2	GAA
View	NM_000152.5(GAA):c.1445C>G (p.Pro4...	Likely Pathogenic	Glycogen Storage Disease II	2023-03-03	1.0	ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 2	GAA

Showing 1 to 3 of 3 rows

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