

Variant: *NM_000152.5(GAA):c.896T>G (p.Leu299Arg)*

Version: 1.1

CA116601 [↗](#)

4025 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: de7d68cb-c9ba-4921-b83f-24231dd47c5c

Approved on: 2026/9/1

Published on: 2026/9/1

HGVS expressions

NM_000152.5(GAA):c.896T>G (p.Leu299Arg)

NM_000152.5:c.896T>G

NC_000017.11:g.80107837T>G

CM000679.2:g.80107837T>G

NC_000017.10:g.78081636T>G

CM000679.1:g.78081636T>G

NC_000017.9:g.75696231T>G

NG_009822.1:g.11282T>G

ENST00000570803.6:c.896T>G

ENST00000572080.2:c.896T>G

ENST00000577106.6:c.896T>G

ENST00000302262.8:c.896T>G

ENST00000302262.7:c.896T>G

ENST00000390015.7:c.896T>G

NM_000152.3:c.896T>G

NM_001079803.1:c.896T>G

NM_001079804.1:c.896T>G

NM_000152.4:c.896T>G

NM_001079803.2:c.896T>G

NM_001079804.2:c.896T>G

NM_001079803.3:c.896T>G

NM_001079804.3:c.896T>G

Likely Pathogenic

Met criteria codes **6**

PP4_Moderate

PS3_Supporting

PP3

PM3

PM5

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 2.0*

[↗](#) **PDF**

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Lysosomal Diseases VCEP

The NM_000152.5:c.896T>G variant in GAA is a missense variant predicted to cause substitution of leucine by arginine at amino acid 299 (p.Leu299Arg). At least two individuals with this variant have been reported to have a diagnosis of Pompe disease. One of these individuals was diagnosed with late-onset Pompe disease and had documented GAA deficiency with <10% of normal mean control level of GAA activity in muscle and was on enzyme replacement therapy for Pompe disease. This individual was compound heterozygous for the variant and a variant classified as pathogenic by the ClinGen LD VCEP, c.1655T>C (p.Leu552Pro), phase unconfirmed (PMID: 38313679, Duke University Medical Center). Another individual with this variant was reported to have infantile-onset Pompe disease with <10% of normal mean control level of GAA activity in cultured fibroblasts, but exact values for the individual's GAA activity and laboratory control values for GAA activity were not provided. This individual was compound heterozygous for the variant and a variant classified as pathogenic by the ClinGen LD VCEP, a deletion of exon 18 (c.2481+110_2646+39del), phase unconfirmed (PMIDs: 7603531, 7717400) (PM3, PP4_Moderate). This variant is absent in gnomAD v4.1.1 (PM2_Supporting). Expression of the variant in COS-7 cells resulted in <2% wild type GAA activity, indicating that this variant may impact protein function (PMID: 19862843). Additionally, expression of the variant in TR4219 cells resulted in "complete loss of GAA activity". One positive and multiple negative controls were included, the experiment was replicated, and the cells were sequenced to ensure integrity of the variant (PMID: 7717400) (PS3_Supporting). The computational predictor REVEL gives a score of 0.93 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense variant in the same codon, c.896T>C (p.Leu299Pro) (ClinVar Variation ID: 180144), has been classified as pathogenic for Pompe disease by the ClinGen LD VCEP (PM5). There is a ClinVar entry for this variant (Variation ID: 4025). In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PS3_Supporting, PM2_Supporting, PM3, PM5, PP3, and PP4_Moderate. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on September 1, 2026).

Met criteria codes

PP4_Moderate			At least two individuals with this variant have been reported to have a diagnosis of Pompe disease. One of these individuals was diagnosed with late-onset Pompe disease and had documented GAA deficiency with <10% of normal mean control level of GAA activity in muscle and was on enzyme replacement therapy for Pompe disease (PMID: 38313679, Duke University Medical Center). Another individual with this variant was reported to have infantile-onset Pompe disease with <10% of normal mean control level of GAA activity in cultured fibroblasts, but exact values for the individual's GAA activity and laboratory control values for GAA activity were not provided (PMIDs: 7603531, 7717400) (PP4_Moderate).
PS3_Supporting			Expression of the variant in COS-7 cells resulted in <2% wild type GAA activity, indicating that this variant may impact protein function (PMID:19862843). Additionally, expression of the variant in TR4219 cells resulted in "complete loss of GAA activity". One positive and multiple negative controls were included, the experiment was replicated, and the cells were sequenced to ensure integrity of the variant (PMID:7717400)(PS3_Supporting).
PP3			The computational predictor REVEL gives a score of 0.93 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM3			This variant has been detected in at least two individuals with Pompe disease. Of those individuals, both were compound heterozygous for the variant and a variant classified as pathogenic by the ClinGen LD VCEP, either c.1655T>C (p.Leu552Pro) (PMID: 38313679, Duke University Medical Center) (0.5 points) or an exon 18 deletion (c.2481+110_2646+39del) (PMIDs: 7603531, 7717400) (0.5 points). Phase was unconfirmed in both cases (Total of 1.0 point, PM3).

PM5			Another missense variant in the same codon, c.896T>C (p.Leu299Pro) (ClinVar Variation ID: 180144), has been classified as pathogenic for Pompe disease by the ClinGen LD VCEP (PM5).
PM2_Supporting			This variant is absent in gnomAD v4.1.1 (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.