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Variant: NM_000152.5(GAA):c.1115A>T (p.His372Leu)

Version: 1.0

CA16041889

370483 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: a67f8a03-785c-44c2-b912-13cdb9ffef8b
Approved on: 2026/4/7
Published on: 2026/4/8

HGVS expressions

NM_000152.5(GAA):c.1115A>T (p.His372Leu)
NM_000152.5:c.1115A>T
NC_000017.11:g.80108528A>T
CM000679.2:g.80108528A>T
NC_000017.10:g.78082327A>T
CM000679.1:g.78082327A>T
NC_000017.9:g.75696922A>T
NG_009822.1:g.11973A>T
ENST00000570803.6:c.1115A>T
ENST00000572080.2:c.1115A>T
ENST00000577106.6:c.1115A>T
ENST00000302262.8:c.1115A>T
ENST00000302262.7:c.1115A>T
ENST00000390015.7:c.1115A>T
NM_000152.3:c.1115A>T
NM_001079803.1:c.1115A>T
NM_001079804.1:c.1115A>T
NM_000152.4:c.1115A>T
NM_001079803.2:c.1115A>T
NM_001079804.2:c.1115A>T
NM_001079803.3:c.1115A>T
NM_001079804.3:c.1115A>T

Likely Pathogenic

Met criteria codes 5

PP4_Moderate | PP3 | PM3_Strong | PM2_Supporting | PS3_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.1115A>T variant in GAA is a missense variant predicted to cause substitution of histidine by leucine at amino acid 557 (p.Ile557Phe). Five probands with symptoms consistent with Pompe disease have been reported with this variant (PMID: 15121988, 18607768, 24715333, 28196920, 28394184, 31467850), three with documented deficiency of GAA activity (PMID: 15121988, 24715333, 28196920, 31467850) (PP4_Moderate). Each of these individuals was compound heterozygous for the variant and another variant that has been classified as pathogenic for Pompe disease by the ClinGen LD VCEP, including c.-32-13T>G (ClinVar Variation ID: 4027) (PMID: 18607768, 28196920, 3 patients, max 2 x 0.5 points), c.258dup (ClinVar Variation ID: 282842) (0.5 points, PMID: 31467850), and c.525del (Variation ID: 4033) (0.5 points, PMID: 15121988, 24715333); phase was not confirmed for any of these individuals. Another patient was compound heterozygous for the variant and c.2563G>C (p.Gly855Arg). The allelic data will be used to classify the second variant and is not included here to avoid circular logic. Total 2 points (PM3_Strong). The highest population minor allele frequency for this variant in gnomAD v4.1.0. is 0.000007628 (9/1179890 alleles) in the European (non-Finnish) population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). Expression of the variant in COS7 or HEK293T cells resulted in evidence of abnormal synthesis and processing on Western blot, indicating that this variant may impact protein function (PMID: 15121988, 24715333) (PS3_Supporting). The computational predictor REVEL gives a score of 0.928 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). There is a ClinVar entry for this variant (Variation ID: 370483). 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 Variant Curation Expert Panel (Specifications Version 2.0): PP4_Moderate, PM2_Supporting, PM3_Strong, PP3, PS3_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on April 7, 2026)

Met criteria codes

PP4_Moderate	✔	At least five patients with this variant had documented GAA deficiency. One patient showed <30% of normal mean control level of GAA activity in cultured fibroblasts and skeletal muscle. This patient was also reported to be on enzyme replacement therapy for Pompe disease (PMID: 15121988, 247153333). Two patients showed <30% normal mean control level of GAA activity in dried blood spot, one of which was reported to be on enzyme replacement therapy for Pompe disease (PMID: 28196920, 31467850). Two patients were noted to have deficient GAA activity but results were not reported (PMID: 18607768, 28394184). PP4_Moderate.
PP3	✔	The computational predictor REVEL gives a score of 0.928 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM3_Strong	✔	Five individuals were compound heterozygous for the variant and another variant that has been classified as pathogenic for Pompe disease by the ClinGen LD VCEP, including c.-32-13T>G (ClinVar Variation ID: 4027) (PMID: 18607768, 28196920, 3 patients, max 2 x 0.5 points), c.258dup (ClinVar Variation ID: 282842) (0.5 points, PMID: 31467850), and c.525del (Variation ID: 4033) (0.5 points, PMID: 15121988, 24715333); phase was not confirmed for any of these individuals. Another patient was compound heterozygous for the variant and c.2563G>C (p.Gly855Arg). The allelic data will be used to classify the second variant and is not included here to avoid circular logic. Total 2 points (PM3_Strong)
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.000007628 (9/1179890 alleles) in the European (non-Finnish) population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PS3_Supporting	✔	Expression of the variant in COS cells resulted in low-level synthesis of the 110 kDa precursor but did show some degradation. The mutant allele did not generate catalytically active α-glucosidase, despite overexpression (PMID:

15121988). Expression of the variant in HEK293T cells showed synthesis of the 110 kDa acid α-glucosidase precursor with normal molecular mass in cells. The c.1115A>T (p.His372Leu) encoded precursor was not present in culture medium when analyzed by Western blot (PMID: 24715333). PS3_Supporting.

Curation History

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