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Variant: NM_000152.5(GAA):c.1000G>A (p.Gly334Ser)

Version: 1.0

CA401364531

843318 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 9be95ff6-d68d-4313-b7ce-822ec265bcaf
Approved on: 2025/9/16
Published on: 2025/9/16

HGVS expressions

NM_000152.5:c.1000G>A
NM_000152.5(GAA):c.1000G>A (p.Gly334Ser)
NC_000017.11:g.80108334G>A
CM000679.2:g.80108334G>A
NC_000017.10:g.78082133G>A
CM000679.1:g.78082133G>A
NC_000017.9:g.75696728G>A
NG_009822.1:g.11779G>A
ENST00000570803.6:c.1000G>A
ENST00000572080.2:c.1000G>A
ENST00000577106.6:c.1000G>A
ENST00000302262.8:c.1000G>A
ENST00000302262.7:c.1000G>A
ENST00000390015.7:c.1000G>A
NM_000152.3:c.1000G>A
NM_001079803.1:c.1000G>A
NM_001079804.1:c.1000G>A
NM_000152.4:c.1000G>A
NM_001079803.2:c.1000G>A
NM_001079804.2:c.1000G>A
NM_001079803.3:c.1000G>A
NM_001079804.3:c.1000G>A

Likely Pathogenic

Met criteria codes 5

PM3_Supporting PM5_Supporting PM2_Supporting PP3 PP4_Moderate

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.1000G>A variant in GAA is a missense variant predicted to cause substitution of glycine by serine at amino acid 334 (p.Gly334Ser). Two individuals with LOPD and this variant have been reported in the literature (PMID: 21687968, 33741225) with one individual having deficient GAA enzyme activity in leukocytes (PMID: 33741225) (PP4_moderate). Both individuals were compound heterozygous for the variant and a second pathogenic or likely pathogenic GAA variant, phase not reported (PM3_Supporting). This variant is absent in gnomAD v4.1.0. (PM2_Supporting). The computational predictor REVEL gives a score of 0.855 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense variant [c.1000G>T, p.Gly334Ser] [ClinVar Variation ID: 843318] in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (PM5_Supporting). There is a ClinVar entry for this variant (Variation ID:843318). 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): PP4_moderate, PM3_supporting, PM2_supporting, PP3, PM5_supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel, Sept. 16, 2025)

Met criteria codes

PM3_Supporting	✔	Two individuals with LOPD have been reported with this variant and a second likely pathogenic or pathogenic GAA variant in compound heterozygosity. One individual (PMID: 21687968) has this variant and c.1222A>G (p.Met208Val) classified as likely pathogenic by the LD VCEP (0.25 pt), and one individual (PMID: 33741225) has this variant and c.2238G>A (p.Trp746Ter), classified as Pathogenic by the LD VCEP (0.5 pt). (0.75 pts for PM3_Supporting).
PM5_Supporting	✔	Another missense variant [c.1000G>T, p.Gly334Ser] [ClinVar Variation ID: 843318] in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (PM5_Supporting).
PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0. (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.855 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PP4_Moderate	✔	Two individuals with LOPD and this variant have been reported in the literature (PMID: 21687968, 33741225) with one individual having deficient GAA enzyme activity in leukocytes (PMID: 33741225) (PP4_moderate).

Curation History

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