

Variant: NM_000152.5(GAA):c.1392G>C (p.Arg464Ser)

Version: 1.1

CA8815303 [↗](#)

432217 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 5ff4c67a-40fc-4de5-ac2f-2d74e46aee54

Approved on: 2025/11/17

Published on: 2025/12/2

HGVS expressions

NM_000152.5:c.1392G>C

NM_000152.5(GAA):c.1392G>C (p.Arg464Ser)

NC_000017.11:g.80110010G>C

CM000679.2:g.80110010G>C

NC_000017.10:g.78083809G>C

CM000679.1:g.78083809G>C

NC_000017.9:g.75698404G>C

NG_009822.1:g.13455G>C

ENST00000570803.6:c.1392G>C

ENST00000572080.2:c.1392G>C

ENST00000577106.6:c.1392G>C

ENST00000302262.8:c.1392G>C

ENST00000302262.7:c.1392G>C

ENST00000390015.7:c.1392G>C

NM_000152.3:c.1392G>C

NM_001079803.1:c.1392G>C

NM_001079804.1:c.1392G>C

NM_000152.4:c.1392G>C

NM_001079803.2:c.1392G>C

NM_001079804.2:c.1392G>C

NM_001079803.3:c.1392G>C

NM_001079804.3:c.1392G>C

Uncertain Significance

Met criteria codes **1**

PM2_Supporting

Not Met criteria codes **3**

PP3

PM3

PM5

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_000152.5c.1392G>C variant in GAA is a missense variant predicted to cause substitution of Arginine by Serine at amino acid 464 (p.Arg464Ser). The highest population minor allele frequency in gnomAD v4.1.0 is 0.00019 (219/1179922 alleles) in the European (non-Finnish) population, which is lower than the ClinGen LD VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion. The computational predictor REVEL gives a score of 0.631 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function. Another missense variant c.1390A>T, p.Arg464Trp in the same codon has been reported in a patient with Pompe disease (ClinVar Variation ID: 843677). However, this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen LD VCEP. There is a ClinVar entry for this variant (Variation ID: 432217, 3-star review status) with 6 submitters classifying the variant as Uncertain Significance and 1 submitter classifying the variant as Likely Pathogenic. In summary, this variant meets the criteria to be classified as Uncertain Significance for Pompe disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Disease Variant Curation Expert Panel (Specifications Version 2.0): PM2_Supporting. (Classification approved by the ClinGen Lysosomal Disease Variant Curation Expert Panel on November 17, 2025)

Met criteria codes

PM2_Supporting		The highest population minor allele frequency in gnomAD v4.1.0 is 0.00019 (219/1179922 alleles) in the European (non-Finnish) population, which is lower than the ClinGen LD VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
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Not Met criteria codes

PP3	 	The computational predictor REVEL gives a score of 0.634 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function.
PM3	 	A patient with suspected LOPD based on newborn screening was heterozygous for this variant and an additional variant c.784G>A. However, confirmatory GAA activity testing result of 4.00 (N>3.88) suggested that GAA activity is not deficient (PMID: 33202836).
PM5	 	Another missense variant c.1390A>T, p.Arg464Trp in the same codon has been reported in a patient with Pompe disease (ClinVar Variation ID: 843677). However, this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen LD VCEP (PM5 not met).



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