

Variant: *NM_000152.5(GAA):c.1562A>T (p.Glu521Val)*

Version: 1.0

CA401367205 [↗](#)

972760 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: baaa2e82-4341-4b56-894f-b9546270aa06

Approved on: 2025/12/16

Published on: 2025/12/16

HGVS expressions

NM_000152.5(GAA):c.1562A>T (p.Glu521Val)

NM_000152.5:c.1562A>T

NC_000017.11:g.80110951A>T

CM000679.2:g.80110951A>T

NC_000017.10:g.78084750A>T

CM000679.1:g.78084750A>T

NC_000017.9:g.75699345A>T

NG_009822.1:g.14396A>T

ENST00000570803.6:c.1562A>T

ENST00000572080.2:c.1562A>T

ENST00000577106.6:c.1562A>T

ENST00000302262.8:c.1562A>T

ENST00000302262.7:c.1562A>T

ENST00000390015.7:c.1562A>T

NM_000152.3:c.1562A>T

NM_001079803.1:c.1562A>T

NM_001079804.1:c.1562A>T

NM_000152.4:c.1562A>T

NM_001079803.2:c.1562A>T

NM_001079804.2:c.1562A>T

NM_001079803.3:c.1562A>T

NM_001079804.3:c.1562A>T

Pathogenic

Met criteria codes **5**

PM2_Supporting

PP3

PP4_Moderate

PM5

PM3_Strong

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_000152.5:c.1562A>T variant in GAA is a missense variant predicted to cause substitution of glutamic acid by valine at amino acid 521 (p.Glu521Val). At least six individuals diagnosed with Pompe disease have been reported to have this variant, including one individual with clinical features consistent with infantile-onset Pompe disease and on enzyme replacement therapy (PMID: 35833019), one individual with GAA activity in the affected range in dried blood spot (PMID: 34072668), two individuals with GAA activity reported to be deficient but the data were not provided (PMID: 39010129), and two individuals with muscle histology consistent with Pompe disease (PMIDs: 25526786, 29786057) (PP4_Moderate). Five of these individuals were compound heterozygous for this variant and another pathogenic/likely pathogenic variant in GAA, phase unknown, including c.-32-13T>G (PMID: 34072668), c.796C>T (p.Pro266Ser) (PMID: 35833019), c.1309C>T (p.Arg437Cys) (PMID: 29786057), c.1781G>A (p.Arg594His) (PMID: 25526786), and c.2238G>C (p.Trp746Cys) (PMID: 39010129) (PM3_Strong). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00002228 (1/44878 alleles) in the East Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.992 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Additionally, another missense variant in the same codon, c.1561G>A (p.Glu521Lys) (ClinVar Variation ID: 4022), has been classified as pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (PM5). In summary, this variant meets the criteria to be classified as 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): PM2_Supporting, PM3_Strong, PM5, PP3, PP4_Moderate. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 16, 2025)

Met criteria codes

PM2_Supporting		The highest population minor allele frequency in gnomAD v4.1.0. is 0.00002228 (1/44878 alleles) in the East Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PP3	 	The computational predictor REVEL gives a score of 0.992 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PP4_Moderate	 	At least six individuals diagnosed with Pompe disease have been reported to have this variant including one individual with clinical features consistent with infantile-onset Pompe disease and on enzyme replacement therapy (PMID: 35833019), one individual with GAA activity in the affected range in dried blood spot (PMID: 34072668), two individuals with GAA activity reported to be deficient but the data were not provided (PMID: 39010129), and two individuals with muscle histology consistent with Pompe disease (PMIDs: 25526786, 29786057) (PP4_Moderate).
PM5	 	Another missense variant in the same codon, c.1561G>A (p.Glu521Lys) (ClinVar Variation ID: 4022), has been classified as pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (PM5).
PM3_Strong	 	This variant has been detected in at least five individuals with Pompe disease who were compound heterozygous for this variant and another pathogenic/likely pathogenic variant in GAA, phase unknown, including c.-32-13T>G (PMID: 34072668) (0.5 points), c.796C>T (p.Pro266Ser) (PMID: 35833019) (0.25 points), c.1309C>T (p.Arg437Cys) (PMID: 29786057) (0.5 points), c.1781G>A (p.Arg594His) (PMID: 25526786) (0.25 points), and c.2238G>C (p.Trp746Cys) (PMID: 39010129) (0.5 points). (Total of 2.0 points; PM3_Strong).

▼

▼

Showing 1 to 1 of 1 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.