

Variant: *NM_000152.5(GAA):c.1103G>A (p.Gly368Asp)*

Version: 1.1

CA294892175 [↗](#)

1037598 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 7f0a1bfb-4260-4646-bb97-f8efe0cf7c22

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HGVS expressions

NM_000152.5(GAA):c.1103G>A (p.Gly368Asp)

NM_000152.5:c.1103G>A

NC_000017.11:g.80108516G>A

CM000679.2:g.80108516G>A

NC_000017.10:g.78082315G>A

CM000679.1:g.78082315G>A

NC_000017.9:g.75696910G>A

NG_009822.1:g.11961G>A

ENST00000570803.6:c.1103G>A

ENST00000572080.2:c.1103G>A

ENST00000577106.6:c.1103G>A

ENST00000302262.8:c.1103G>A

ENST00000302262.7:c.1103G>A

ENST00000390015.7:c.1103G>A

NM_000152.3:c.1103G>A

NM_001079803.1:c.1103G>A

NM_001079804.1:c.1103G>A

NM_000152.4:c.1103G>A

NM_001079803.2:c.1103G>A

NM_001079804.2:c.1103G>A

NM_001079803.3:c.1103G>A

NM_001079804.3:c.1103G>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting

PS3_Supporting

PP4_Moderate

PM3

Not Met criteria codes 2

BP4

PP3

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(GAA):c.1103G>A variant in GAA is a missense variant predicted to cause substitution of glycine by aspartic acid at amino acid 368 (p.Gly368Asp). This variant has been detected in at least 4 individuals with Pompe disease and deficient GAA activity (PP4_Moderate). Of those individuals, 4 were compound heterozygous for the variant and c.-32-13T>G (ClinVar Variation ID: 4027), a variant that has been classified by the LD VCEP as pathogenic for Pompe disease, c.-32-13T>G; one of those were confirmed in trans by parental/family testing (PMID: 36246652, 33202836, internal lab data) (max 2 patients counted, 1 point for confirmed in trans and 0.5 points for unconfirmed phase, 1.5 points) (PM3)(PMID: 36246652, 33202836, internal lab data). This variant is absent in gnomAD v4.1.0 (PM2_Supporting). Expression of the variant in HEK293 cells resulted in 2.8% wild type GAA activity and evidence of abnormal GAA synthesis and processing, indicating that this variant may impact protein function (PMID: 36246652) (PS3_Supporting). The computational predictor REVEL gives a score of 0.647 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function. There is a ClinVar entry for this variant (Variation ID: 1037598, 1 star review status) with 3 other submitters including 1 classifying the variant as a VUS, 1 as Likely Pathogenic and 1 as Pathogenic. In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease based on the GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0.0): PM3, PP4_Moderate, PM2_Supporting, PS3_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on August 2, 2025).

Met criteria codes

PM2_Supporting		This variant is absent in gnomAD v4.1.0 (PM2_Supporting).
PS3_Supporting	 	Expression of the variant in HEK293 cells resulted in 2.8% wild type GAA activity - and evidence of abnormal GAA synthesis and processing, indicating that this variant may impact protein function (PMID: 36246652) (PS3_Supporting).
PP4_Moderate	 	At least 4 patients with this variant had documented GAA deficiency with activity in the affected range in dried blood spot. (PMID: 33202836, 36246652, internal lab data) (PP4_Moderate).
PM3	 	This variant has been detected in at least 4 individuals with Pompe disease. Of those individuals, 4 were compound heterozygous for the variant and c.-32-13T>G, a variant that has been classified by the LD VCEP as pathogenic for Pompe disease, c.-32-13T>G; one of those were confirmed in trans by parental/family testing (PMID: 36246652, 33202836, internal lab data) (max 2 patient counted, 1 point for confirmed in trans and 0.5 points for unconfirmed phase, 1.5 points) (PM3).

Not Met criteria codes

BP4	 	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	 	The computational predictor REVEL gives a score of 0.647 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function.

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