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Variant: NM_000152.5(GAA):c.1003G>A (p.Gly335Arg)

Version: 1.1

CA501005

972790 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: bd812e5a-6029-409c-83d1-c4b17227ac7c
Approved on: 2025/6/17
Published on: 2025/7/30

HGVS expressions

NM_000152.5(GAA):c.1003G>A (p.Gly335Arg)
NM_000152.5:c.1003G>A
NC_000017.11:g.80108337G>A
CM000679.2:g.80108337G>A
NC_000017.10:g.78082136G>A
CM000679.1:g.78082136G>A
NC_000017.9:g.75696731G>A
NG_009822.1:g.11782G>A
ENST00000570803.6:c.1003G>A
ENST00000572080.2:c.1003G>A
ENST00000577106.6:c.1003G>A
ENST00000302262.8:c.1003G>A
ENST00000302262.7:c.1003G>A
ENST00000390015.7:c.1003G>A
NM_000152.3:c.1003G>A
NM_001079803.1:c.1003G>A
NM_001079804.1:c.1003G>A
NM_000152.4:c.1003G>A
NM_001079803.2:c.1003G>A
NM_001079804.2:c.1003G>A
NM_001079803.3:c.1003G>A
NM_001079804.3:c.1003G>A

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PM3 PS3_Moderate PP4_Moderate

Not Met criteria codes 1

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

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1003G>A variant in GAA is a missense variant predicted to cause substitution of glycine by arginine at amino acid 335 (p.Gly335Arg). At least 4 patient(s) with this variant had documented GAA deficiency with <10% of normal mean control level of GAA activity in leukocytes, lymphocytes, muscle samples or were reported to be on enzyme replacement therapy for Pompe disease (PP4_Moderate) (PMIDs 31510962, 26497565, 31193175, 24685124). One of these probands is compound heterozygous for the variant and a variant classified as pathogenic by the ClinGen LSD VCEP, c.876C>G p.Tyr292X (PMID 31510962); the variants were confirmed in trans by familial testing (PM3). The highest population minor allele frequency in gnomAD v4.1.0 for this variant is 0.000011 (1/91090) alleles) in the South Asian 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 HEK293 cells resulted in 0.8% GAA activity in cells and evidence of abnormal synthesis and processing on Western blot, indicating that this variant may impact protein function (PMID 22644586) (PS3_Moderate). The computational predictor REVEL gives a score of 0.919 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense variant, c.1004G>A (p.Gly335Glu), in the same codon has been reported in a patient with Pompe disease (PMIDs 22644586, 32711049). This variant has been classified as likely pathogenic by the ClinGen Lysosomal Diseases VCEP. Since c.1003G>A (p.Gly335Arg) was used to apply PM5 in the classification of c.1004G>A (p.Gly335Glu), PM5 is not included here to avoid circular logic (PM5 not met). There is a ClinVar entry for this variant (Variation ID: 972790; 3 star review status) with six submitters classifying the variant as pathogenic. 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 VCEP (Specifications Version 2.0.0): PM3, PS3_Moderate, PP4_Moderate, PP3, PM2_Supporting. (Classification approved by the Lysosomal Diseases VCEP, June 17, 2025).

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.0.1 is 0.000011 (1/91090) alleles) in the South 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 0.919, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM3	✔	This variant has been detected in at least 4 individuals with Pompe disease. Of those individuals, one was compound heterozygous for the variant and a pathogenic or likely pathogenic variant and confirmed in trans by parental/family testing (c.876C>G p.Tyr292X, PMID 31510962, 1 pt).
PS3_Moderate	✔	Expression of the variant in COS-7 cells resulted in 0.8% wild type GAA activity and evidence of abnormal GAA synthesis and processing, leading the variant to be described as Class B ("potentially less severe"), indicating that this variant may impact protein function (PMID 22644586)(PS3_Moderate).
PP4_Moderate	✔	At least 4 patient(s) with this variant had documented GAA deficiency with <10% of normal mean control level of GAA activity in leukocytes, lymphocytes, muscle samples or were reported to be on enzyme replacement therapy for Pompe disease (PP4_Moderate) (PMIDs 31510962, 26497565, 31193175, 24685124).

Not Met criteria codes

PM5	✖	Another missense variant, c.1004G>A, p.Gly335Glu (ClinVar Variation ID:180142, PMIDs:30214072, 32711049) in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP.

Since c.1003G>A (p.Gly335Arg) was used to apply PM5 in the classification of c.1004G>A (p.Gly335Glu), PM5 is not applied here to avoid circular logic (PM5 not met).

Curation History

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