The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000152.5(GAA):c.1004G>A (p.Gly335Glu)

Version: 1.0

CA273683

180142 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 177fc2f9-a81b-4d71-a203-302e68e815e4
Approved on: 2024/9/17
Published on: 2024/9/17

HGVS expressions

NM_000152.5:c.1004G>A
NM_000152.5(GAA):c.1004G>A (p.Gly335Glu)
NC_000017.11:g.80108338G>A
CM000679.2:g.80108338G>A
NC_000017.10:g.78082137G>A
CM000679.1:g.78082137G>A
NC_000017.9:g.75696732G>A
NG_009822.1:g.11783G>A
ENST00000570803.6:c.1004G>A
ENST00000572080.2:c.1004G>A
ENST00000577106.6:c.1004G>A
ENST00000302262.8:c.1004G>A
ENST00000302262.7:c.1004G>A
ENST00000390015.7:c.1004G>A
NM_000152.3:c.1004G>A
NM_001079803.1:c.1004G>A
NM_001079804.1:c.1004G>A
NM_000152.4:c.1004G>A
NM_001079803.2:c.1004G>A
NM_001079804.2:c.1004G>A
NM_001079803.3:c.1004G>A
NM_001079804.3:c.1004G>A

Likely Pathogenic

Met criteria codes 6

PM3_Supporting | PP3 | PP4_Moderate | PM2_Supporting | PM5_Supporting | PS3_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.1004G>A variant in GAA is a missense variant predicted to cause substitution of glycine by glutamic acid at amino acid #335 (p.Gly335Glu). At least two (2) patients with this variant had documented GAA deficiency with <10% of normal mean control level of GAA activity in leukocytes, lymphocytes, or muscle samples and were described as having infantile-onset Pompe disease (PMIDs: 30214072, 32711049). It has been reported in two patients described as having LOPD but without documented GAA deficiency (PMID: 36105079, 27649523). It has been reported in one patient with a positive newborn screen for Pompe disease with documented GAA enzyme deficiency in dried blood spot, but no clinical information is available (internal data, Duke Molecular Genetics Laboratory) (PP4_moderate). This variant has been reported in compound heterozygosity (phase unconfirmed) with a second variant in GAA classified as likely pathogenic by the ClinGen LD VCEP (c.1841C>A; PMID: 30214072). It has also been reported in compound heterozygosity in two patients with a variant in GAA classified as pathogenic by the LD VCEP (c.-32-13T>G; PMID: 27649523). Additionally, it has been reported in compound heterozygosity in two separate patients with two variants classified as likely pathogenic or pathogenic in ClinVar, but have not been reviewed by the ClinGen LD VCEP (c.797C>T and c.1634C>T; PMIDs: 32711049 and 36105079 respectively) (PM3_supporting). The highest population minor allele frequency in gnomAD v4.0. is 0.000001695 (2/118,0038 alleles) in the European 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 0.897 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense variant, c.1003G>A, p.Gly335Arg (ClinVar Variation ID: 972790, PMIDs: 31510962, 26497565, 31193175, 24685124) in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP. Data from p.Gly335Arg was not used in the classification of p.Gly335Glu to avoid a circular logic (PM5_Supporting). This variant results in 0.2% GAA activity (and is abnormally synthesized and/or processed) when expressed in COS cells, (and was classified as Class B (potentially less severe) by Kroos et al, 2012 (PMID 22644586), meeting the ClinGen LD VCEP specifications for PS3_moderate. There is a ClinVar entry for this variant (Variation ID: 180142, 1-star review status) with 4 submitters classifying the variant as pathogenic (3) or likely pathogenic (1). 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, PS3_moderate, PM3_supporting, PM5_supporting, PM2_supporting, PP3 (Classification approved by the ClinGen Variant Curation Expert Panel on September 17, 2024)

Met criteria codes

PM3_Supporting	✔	This variant has been reported in compound heterozygosity (phase unconfirmed) with a second variant in GAA classified as likely pathogenic by the ClinGen LD VCEP (c.1841C>A; PMID: 30214072). It has also been reported in compound heterozygosity in two patients with a variant in GAA classified as pathogenic by the LD VCEP (c.-32-13T>G; PMID: 27649523). Additionally, it has been reported in compound heterozygosity in two separate patients with two variants classified as likely pathogenic or pathogenic in ClinVar, but have not been reviewed by the ClinGen LD VCEP (c.797C>T and c.1634C>T; PMIDs: 32711049 and 36105079 respectively). (PM3_supporting)
PP3	✔	The computational predictor REVEL gives a score of 0.897 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PP4_Moderate	✔	At least two (2) patients with this variant had documented GAA deficiency with <10% of normal mean control level of GAA activity in leukocytes, lymphocytes, or muscle samples and were described as having infantile-onset Pompe disease (PMIDs: 30214072, 32711049). It has been reported in two patients described as having LOPD but without documented GAA deficiency (PMID: 36105079, 27649523). It has been reported in one patient with a positive newborn screen for Pompe disease with documented GAA enzyme deficiency in dried blood spot, but no clinical information is available (internal data, Duke Molecular Genetics Laboratory). (PP4_moderate)
PM2_Supporting	✔	

The highest population minor allele frequency in gnomAD v4.0. is 0.000001695 (2/118,0038 alleles) in the European population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

PM5_Supporting ✔

Another missense variant, c.1003G>A, p.Gly335Arg (ClinVar Variation ID: 972790, PMIDs: 31510962, 26497565, 31193175, 24685124) in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (PM5_Supporting). Data from p.Gly335Glu was not used in the classification of p.Gly335Arg to avoid a circular logic.

PS3_Moderate ✔

This variant results in 0.2% GAA activity (and is abnormally synthesized and/or processed) when expressed in COS cells, (and was classified as Class B (potentially less severe) by Kroos et al, 2012 (PMID 22644586), meeting the ClinGen LD VCEP specifications for PS3_moderate.

Curation History

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.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.