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.1710C>G (p.Asn570Lys)

Version: 1.3

CA401369044

555153 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: e7b9a367-b68f-4028-bcb6-0c0ddfa1fc7e
Approved on: 2024/11/22
Published on: 2024/12/17

HGVS expressions

NM_000152.5(GAA):c.1710C>G (p.Asn570Lys)
NM_000152.5:c.1710C>G
NC_000017.11:g.80112056C>G
CM000679.2:g.80112056C>G
NC_000017.10:g.78085855C>G
CM000679.1:g.78085855C>G
NC_000017.9:g.75700450C>G
NG_009822.1:g.15501C>G
ENST00000570803.6:c.1710C>G
ENST00000572080.2:c.1710C>G
ENST00000577106.6:c.1710C>G
ENST00000302262.8:c.1710C>G
ENST00000302262.7:c.1710C>G
ENST00000390015.7:c.1710C>G
ENST00000572080.1:c.98C>G
ENST00000572803.1:n.324C>G
NM_000152.3:c.1710C>G
NM_001079803.1:c.1710C>G
NM_001079804.1:c.1710C>G
NM_000152.4:c.1710C>G
NM_001079803.2:c.1710C>G
NM_001079804.2:c.1710C>G
NM_001079803.3:c.1710C>G
NM_001079804.3:c.1710C>G

Likely Pathogenic

Met criteria codes 4

PM3 PS3_Moderate PM2_Supporting PP4_Moderate

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

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1710C>G (p.Asn570Lys) variant in GAA has a minor allele frequency in gnomAD of 0.0001149 in the African population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion. At least three individuals have been reported with this variant and documented GAA activity in the affected range and/or were reported to be on enzyme replacement therapy for Pompe disease (PMID: 17151339, 22538254, 29122469, 32248831) (PP4_Moderate). This variant was found in compound heterozygosity with another variant in GAA that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP including c.2560C>T (p.Arg854Ter) (ClinVar Variation ID: 4034, SCV001371731.1), phase unconfirmed, in at least one patient with Pompe disease (PMID: 22538254, 22658377, 29122469, 31193175)(0.5 points), and confirmed in trans in a patient with c.953T>C (p.Met318Thr) (ClinVar Variation ID: 4021; SCV002583364.1) (PMID: 36636589) (1 point). Another patient with the variant, along with with c.-32-13T>G and a rare synonymous variant c.1923G>A (p.Leu641=) has been reported (PMID: 32248831). While the allelic data from the latter patient is likely supportive of pathogenicity for c.1710C>G (p.Asn570Lys), it is not included here because the impact of p.Leu641= is unknown (Total 1.5 points) (PM3). Functional assays support a deleterious effect of this variant. When expressed in COS cells, this variant was classified as Class B ("potentially less severe") by Kroos et al, 2012 (PMID:22644586). This includes 0.9% GAA activity in cells and 0.5% in medium, and evidence of abnormal synthesis and processing on Western blot (PS3_Moderate). Computational evidence is inconclusive, REVEL score = 0.662 which is lower than the LD VCEP threshold for PP3 (>0.7) but higher than the LD VCEP threshold for BP4 (<0.5), and therefore does not meet either criterion. There is a ClinVar entry for this variant (Variation ID: 555153). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Pompe disease based on the specifications of the ClinGen Lysosomal Diseases Variant Curation Expert Panel. GAA-specific GAA-specific ACMG/AMP criteria met (Specifications Version 2.0): PS3_Moderate, PM3, PP4_Moderate, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on November 22, 2024).

Met criteria codes

PM3	✔	This variant was found in compound heterozygosity with another variant in GAA that has been classified as pathogenic by the ClinGen Lysosomal Diseases VCEP including c.2560C>T (p.Arg854Ter) (ClinVar Variation ID: 4034, SCV001371731.1), phase unconfirmed, in at least one patient with Pompe disease (PMID: 22538254, 22658377, 29122469, 31193175)(0.5 points) and confirmed in trans with c.953T>C (p.Met318Thr) (ClinVar Variation ID: 4021; SCV002583364.1) (PMID: 36636589) (1 point). Another patient with the variant, along with with c.-32-13T>G and a rare synonymous variant c.1923G>A (p.Leu641=) has been reported (PMID: 32248831). While the allelic data from the latter patient is likely supportive of pathogenicity for c.1710C>G (p.Asn570Lys), it is not included here because the impact of p.Leu641= is unknown (Total 1.5 points) (PM3).
PS3_Moderate	✔	When expressed in COS cells, this variant was classified as Class B ("potentially less severe") by Kroos et al, 2012 (PMID:22644586). This includes 0.9% GAA activity in cells and 0.5% in medium, and evidence of abnormal synthesis and processing on Western blot. This meets the ClinGen Lysosomal Diseases VCEP's specifications for PS3_Moderate.
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1. is 0.0001149 (1/8702) in the African population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PP4_Moderate	✔	At least three individuals have been reported with this variant and documented GAA activity in the affected range and/or were reported to be on enzyme replacement therapy for Pompe disease (PMID: 17151339, 22538254, 29122469, 32248831) (PP4_Moderate).

Not Met criteria codes

BP4	✖	REVEL score = 0.662 which is higher than the Lysosomal Diseases VCEP's threshold for BP4 (<0.5), and therefore does not meet this criterion.

PP3		✖	REVEL score = 0.662 which is lower than the Lysosomal Diseases VCEP's threshold for PP3 (>0.7), and therefore does not meet this criterion.

Curation History

Showing 1 to 4 of 4 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.