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.883C>A (p.His295Asn)

Version: 1.0

CA8815081

953728 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 493e1b07-3ab0-4ef5-b867-8f6471131faa
Approved on: 2024/12/19
Published on: 2025/2/28

HGVS expressions

NM_000152.5:c.883C>A
NM_000152.5(GAA):c.883C>A (p.His295Asn)
NC_000017.11:g.80107824C>A
CM000679.2:g.80107824C>A
NC_000017.10:g.78081623C>A
CM000679.1:g.78081623C>A
NC_000017.9:g.75696218C>A
NG_009822.1:g.11269C>A
ENST00000570803.6:c.883C>A
ENST00000572080.2:c.883C>A
ENST00000577106.6:c.883C>A
ENST00000302262.8:c.883C>A
ENST00000302262.7:c.883C>A
ENST00000390015.7:c.883C>A
NM_000152.3:c.883C>A
NM_001079803.1:c.883C>A
NM_001079804.1:c.883C>A
NM_000152.4:c.883C>A
NM_001079803.2:c.883C>A
NM_001079804.2:c.883C>A
NM_001079803.3:c.883C>A
NM_001079804.3:c.883C>A

Likely Pathogenic

Met criteria codes 4

PP3 PM3 PP4_Moderate PM2_Supporting

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.883C>A variant in GAA is a missense variant predicted to cause substitution of His by Asn at amino acid 295 (p.His295Asn). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00012 (3/24448 alleles) in the African population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2 (<0.001), meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.716 which is above the thresholds predicting a damaging (>0.7) impact on GAA function (PP3. This variant has been detected in 1 individual with Pompe disease, who was compound heterozygous for the variant and variant c.2560C>T (VCEP Pathogenic) with unknown phase (PMID: 37087815). It has also been detected in 1 individual with low GAA enzyme activity with compound heterozygous for the variant and variant c.1962_1964delAGA; p.Glu655del (VCEP Pathogenic) with unknown phase (Clinical lab data), thus met PM3. At least 2 patient with this variant had documented GAA activity in blood (PMID: 37087815; clinical lab), meeting PP4_Moderate. There is a ClinVar entry for this variant (Variation ID: 953728). 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): PM2_supporting, PP3, PM3, PP4_moderate. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 19, 2024)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.716 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM3	✔	This variant has been detected in 1 individual with Pompe disease, who was compound heterozygous for the variant and variant c.2560C>T (VCEP Pathogenic) with unknown phase (PMID: 37087815). It has also been detected in 1 individual with low GAA enzyme activity with compound heterozygous for the variant and variant c.1962_1964delAGA; p.Glu655del (VCEP Pathogenic) with unknown phase (Clinical lab data). (PM3).
PP4_Moderate	✔	At least 2 patients with this variant had documented GAA activity in blood (PMID: 37087815; clinical lab) (PP4_Moderate).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00012 (3/24448 alleles) in the African population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2 (<0.001), meeting this criterion (PM2_Supporting).

Curation History

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