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.1216G>A (p.Asp406Asn)

Version: 1.0

CA401365200

552776 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 3c39713f-0ccb-408a-8809-616479b46a90
Approved on: 2025/6/17
Published on: 2025/9/16

HGVS expressions

NM_000152.5:c.1216G>A
NM_000152.5(GAA):c.1216G>A (p.Asp406Asn)
NC_000017.11:g.80108718G>A
CM000679.2:g.80108718G>A
NC_000017.10:g.78082517G>A
CM000679.1:g.78082517G>A
NC_000017.9:g.75697112G>A
NG_009822.1:g.12163G>A
ENST00000570803.6:c.1216G>A
ENST00000572080.2:c.1216G>A
ENST00000577106.6:c.1216G>A
ENST00000302262.8:c.1216G>A
ENST00000302262.7:c.1216G>A
ENST00000390015.7:c.1216G>A
NM_000152.3:c.1216G>A
NM_001079803.1:c.1216G>A
NM_001079804.1:c.1216G>A
NM_000152.4:c.1216G>A
NM_001079803.2:c.1216G>A
NM_001079804.2:c.1216G>A
NM_001079803.3:c.1216G>A
NM_001079804.3:c.1216G>A

Likely Pathogenic

Met criteria codes 4

PM3 PP4_Moderate PP3 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.1216G>A variant in GAA is a missense variant predicted to cause substitution of aspartic acid by asparagine at amino acid 406 (p.Asp406Asn). At least 2 patients with this variant have been reported to have Pompe disease. The patients were siblings from the same family and were both reported to have symptoms consistent with Pompe disease. One of the siblings had documented GAA deficiency with <10% of normal mean control level of GAA activity in leukocytes (PMID: 31966564, 31439017) (PP4_Moderate). Both siblings were compound heterozygous for the variant and c.1935C>A (p.Asp645Glu), which is classified as pathogenic by the ClinGen LD VCEP, confirmed in trans by parental testing (PMID: 31966564, 31439017) (PM3). This variant has also been reported in one case identified as affected by newborn screening, but GAA enzyme activity and clinical information were not provided (PMID: 23430949). This variant is absent in gnomAD v4.1.0. (PM2_Supporting). The computational predictor REVEL gives a score of 0.81 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). There is a ClinVar entry for this variant (Variation ID: 552776). 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, PM3, PP3, PP4_Moderate (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel, June 17, 2025)

Met criteria codes

PM3	✔	This variant has been detected in at least 2 individuals (siblings) with Pompe disease. Both siblings were compound heterozygous for the variant and c.1935C>A (p.Asp645Glu) (ClinVar Variation ID: 4029), which is classified as pathogenic by the ClinGen LD VCEP, confirmed in trans by parental testing (PMID: 31966564, 31439017) (1 point) (PM3).
PP4_Moderate	✔	At least 2 patients with this variant have been reported to have Pompe disease. The patients were siblings from the same family and were both reported to have left ventricular hypertrophy and muscle weakness with juvenile onset and were on enzyme replacement therapy. One of the siblings had documented GAA deficiency with <10% of normal mean control level of GAA activity in leukocytes, and the other sibling had GAA activity 10.4% of normal controls in leukocytes (PMID: 31966564, 31439017). This variant has also been reported in one case identified as affected by newborn screening, but GAA enzyme activity and clinical information were not provided (PMID: 23430949) (PP4_Moderate).
PP3	✔	The computational predictor REVEL gives a score of 0.81 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0. (PM2_Supporting).

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.