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_001079804.3:c.2174G>C

Version: 1.0

CA401370634

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6fdddd25-8646-479f-8eaa-070a73e409ba
Approved on: 2025/8/31
Published on: 2025/9/16

HGVS expressions

NM_001079804.3:c.2174G>C
NC_000017.11:g.80113351G>C
CM000679.2:g.80113351G>C
NC_000017.10:g.78087150G>C
CM000679.1:g.78087150G>C
NC_000017.9:g.75701745G>C
NG_009822.1:g.16796G>C
ENST00000570803.6:c.2174G>C
ENST00000572080.2:c.*312G>C
ENST00000577106.6:c.2174G>C
ENST00000302262.8:c.2174G>C
ENST00000302262.7:c.2174G>C
ENST00000390015.7:c.2174G>C
ENST00000572080.1:c.593G>C
NM_000152.3:c.2174G>C
NM_001079803.1:c.2174G>C
NM_001079804.1:c.2174G>C
NM_000152.4:c.2174G>C
NM_001079803.2:c.2174G>C
NM_001079804.2:c.2174G>C
NM_000152.5:c.2174G>C
NM_001079803.3:c.2174G>C

Likely Pathogenic

Met criteria codes 5

PM3_Supporting | PP3 | PM5 | 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.2174G>C variant in GAA is a missense variant that results in the substitution of arginine by proline at amino acid 725 (p.Arg725Pro). This variant has been reported in one patient, in a study from China, diagnosed with infantile onset Pompe disease with <1% GAA activity in fibroblasts (PMID: 18458862) (PP4_Moderate). This patient was compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP, c.1935C>A (p.Asp645Glu) (ClinVar Variation ID: 4029) (PMID: 18458862); the phase is unknown. 0.5 points (PM3_Supporting). The variant is absent in gnomAD v4.1.0. (PM2_Supporting). The computational predictor REVEL gives a score of 0.973 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense change at the same amino acid position, c.2173C>T (p.Arg725Trp) (ClinVar Variation ID: 4024), has been classified as pathogenic by the LD VCEP (PM5). In addition, c.2174G>A (p.Arg725Gln) (ClinVar Variation ID: 555727) has been identified in an individuals with a positive newborn screen for Pompe disease and is classified as a VUS by the LD VCEP. In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0.0.): PM5, PP4_Moderate, PP3, PM2_Supporting, PM3_Supporting (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel, August 31, 2025)

Met criteria codes

PM3_Supporting	✔	One patient is compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP, c.1935C>A (p.Asp645Glu) (ClinVar Variation ID: 4029) (PMID: 18458862); the phase is unknown. 0.5 points (PM3_Supporting)
PP3	✔	The computational predictor REVEL gives a score of 0.973 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM5	✔	Another missense change at the same amino acid position, c.2173C>T (p.Arg725Trp) (ClinVar Variation ID: 4024), has been classified as pathogenic by the LD VCEP (PM5). In addition, c.2174G>A (p.Arg725Gln) (ClinVar Variation ID: 555727) has been identified in an individuals with a positive newborn screen for Pompe disease and is classified as a VUS by the LD VCEP.
PP4_Moderate	✔	One patient diagnosed with infantile onset Pompe disease, and reported to have <1% GAA activity in fibroblasts, was reported in a study from China (PMID: 18458862) (PP4_Moderate)
PM2_Supporting	✔	The 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.