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.2015G>T (p.Arg672Leu)*

Version: 1.0

*CA401370075*

*2675756 (ClinVar)*

**Gene**: GAA (HGNC:2548)
**Condition**: glycogen storage disease II (MONDO:0009290)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 19aeda92-c0d1-42d4-8c8c-4c4c76b3a4ce
**Approved on**: 2025/8/31
**Published on**: 2025/9/16

## *HGVS expressions*

**NM_000152.5(GAA):c.2015G>T (p.Arg672Leu)**
**NM_000152.5:c.2015G>T**
NC_000017.11:g.80113002G>T
CM000679.2:g.80113002G>T
NC_000017.10:g.78086801G>T
CM000679.1:g.78086801G>T
NC_000017.9:g.75701396G>T
NG_009822.1:g.16447G>T
ENST00000570803.6:c.2015G>T
ENST00000572080.2:c.*153G>T
ENST00000577106.6:c.2015G>T
ENST00000302262.8:c.2015G>T
ENST00000302262.7:c.2015G>T
ENST00000390015.7:c.2015G>T
ENST00000570716.1:n.455G>T
ENST00000572080.1:c.434G>T
NM_000152.3:c.2015G>T
NM_001079803.1:c.2015G>T
NM_001079804.1:c.2015G>T
NM_000152.4:c.2015G>T
NM_001079803.2:c.2015G>T
NM_001079804.2:c.2015G>T
NM_001079803.3:c.2015G>T
NM_001079804.3:c.2015G>T

**Likely Pathogenic**

**Met criteria codes** 4

PP3 PM5 PP4_Moderate PM2_Supporting

**Not Met criteria codes** 1

PM3

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.2015G>T variant in GAA is a missense variant that results in the substitution of an arginine for a leucine at amino acid 672 (p.Arg672Leu). One Indian patient with late onset Pompe disease has been reported, with <1% normal GAA activity in skin fibroblasts, and muscle histology consistent with the condition (PMID: 33741225) (PP4_Moderate). This individual is compound heterozygous for the variant and another variant in GAA that has been classified as likely pathogenic for Pompe disease by the ClinGen LD VCEP, c.2783A>G (p.Tyr928Cys); phase unconfirmed (0.25 points) (Insufficient to apply PM3). The variant is absent in gnomAD v4.1.0. (PM2_Supporting). Two other variants at the same amino acid position have been classified as pathogenic (c.2014C>T, p.Arg672Trp, ClinVar Variation ID: 188773) or likely pathogenic (c.2015G>A p.Arg672Gln, ClinVar Variation ID: 371126) for Pompe disease by the ClinGen LD VCEP (PM5). The computational predictor REVEL gives a score of 0.955 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). SpliceAI predicts no impact on splicing. There is a ClinVar entry for this variant (Variation ID: 2675756) with one submitter classifying the variant as pathogenic. In summary, these variant meets the criteria to be classified a likely pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LD VCEP (Specifications Version 2.0.0.): PM5, PP4_Moderate, PP3, PM2_Supporting (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel, August 31, 2025)**

**Met criteria codes**

| | | |
|---|---|---|
| **PP3** | ✔ | The computational predictor REVEL gives a score of 0.955 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). |
| **PM5** | ✔ | Two other variants at the same amino acid position have been classified as pathogenic (c.2014C>T, p.Arg672Trp, ClinVar Variation ID: 188773) or likely pathogenic (c.2015G>A p.Arg672Gln, ClinVar Variation ID: 371126) for Pompe disease by the ClinGen LD VCEP (PM5). |
| **PP4_Moderate** | ✔ | One Indian patient with late onset Pompe disease has been reported, with <1% normal GAA activity in skin fibroblasts, and muscle histology consistent with the condition (PMID: 33741225) (PP4_Moderate). |
| **PM2_Supporting** | ✔ | The variant is absent in gnomAD v4.1.0. (PM2_Supporting). |

**Not Met criteria codes**

| | | |
|---|---|---|
| **PM3** | ✖ | This individual is compound heterozygous for the variant and another variant in GAA that has been classified as likely pathogenic for Pompe disease by the ClinGen LD VCEP, c.2783A>G (p.Tyr928Cys); phase unconfirmed (0.25 points) (Insufficient to apply PM3). |

Curation History

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