

Variant: *NM_000152.5(GAA):c.1352C>G (p.Pro451Arg)*

Version: 1.2

CA8815294 [↗](#)

281330 (ClinVar) [↗](#)

Gene: GAA ([HGNC:2548](#))

Condition: glycogen storage disease II ([MONDO:0009290](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: b11d7715-7a62-4071-9760-f92fefa72998

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HGVS expressions

NM_000152.5(GAA):c.1352C>G (p.Pro451Arg)

NM_000152.5:c.1352C>G

NC_000017.11:g.80109970C>G

CM000679.2:g.80109970C>G

NC_000017.10:g.78083769C>G

CM000679.1:g.78083769C>G

NC_000017.9:g.75698364C>G

NG_009822.1:g.13415C>G

ENST00000570803.6:c.1352C>G

ENST00000572080.2:c.1352C>G

ENST00000577106.6:c.1352C>G

ENST00000302262.8:c.1352C>G

ENST00000302262.7:c.1352C>G

ENST00000390015.7:c.1352C>G

NM_000152.3:c.1352C>G

NM_001079803.1:c.1352C>G

NM_001079804.1:c.1352C>G

NM_000152.4:c.1352C>G

NM_001079803.2:c.1352C>G

NM_001079804.2:c.1352C>G

NM_001079803.3:c.1352C>G

NM_001079804.3:c.1352C>G

Likely Benign

Met criteria codes 2

BP4 **BS1**

Not Met criteria codes 2

PP4 **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**

Lysosomal Diseases VCEP

The NM_000152.5:c.1352C>G variant in GAA is a missense variant predicted to result in the substitution of proline by arginine at amino acid 451 (p.Pro451Arg). The highest population minor allele frequency in gnomAD v4.1.0 is 0.004835 (363/75080) alleles, including 4 homozygotes) in the African/African-American population. This allele frequency meets the ClinGen LD VCEP threshold (>0.005) for BS1 (after rounding up). The variant was reported in a patient with limb-girdle muscle weakness but was not thought to be causative of the symptoms (PMID: 29149851). The variant was also reported in a patient with autism spectrum disorder but no reported diagnosis of Pompe disease (PMID: 37492102). The computational predictor REVEL gives a score of 0.449 which is below the threshold of 0.5, evidence that does not predict a damaging effect on GAA function, and SpliceAI predicts no impact on splicing (BP4). There is a ClinVar entry for this variant (Variation ID: 281330). In summary, this variant meets the criteria to be classified as likely benign for Pompe disease. ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases VCEP (Specifications Version 2.0): BS1, BP4. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert panel on May 20, 2025)

Met criteria codes

BP4			The computational predictor REVEL gives a score of 0.449 which is below the threshold of 0.5, evidence that does not predict a damaging effect on GAA function, and SpliceAI predicts no impact on splicing (BP4).
BS1			The highest population minor allele frequency in gnomAD v4.1.0 is 0.004835 (363/75080) alleles, including 4 homozygotes) in the African/African-American population. This allele frequency meets the ClinGen LD VCEP threshold (>0.005) for BS1 (after rounding up).

Not Met criteria codes

PP4			A patient with limb-girdle muscular dystrophy has been reported to be compound heterozygous for c.1352C>G (p.Pro451Arg) and an intronic variant, c.1438-7_1438-5delTGT (PMID 29149851). No GAA activity was provided for the patient. This variant was also identified in a cohort of patients with autism spectrum disorder in compound heterozygosity with a second GAA variant, c.277G>A (p.Ala93Thr) (PMID: 37492102). However, this individual is not reported to be diagnosed with Pompe disease and no GAA activity is provided. Therefore, this criterion is not met.
PM3			A patient with limb-girdle muscular dystrophy has been reported to be compound heterozygous for c.1352C>G (p.Pro451Arg) and an intronic variant, c.1438-7_1438-5delTGT (PMID 29149851). No GAA activity was provided for the patient. This variant was also identified in a cohort of patients with autism spectrum disorder in compound heterozygosity with a second GAA variant, c.277G>A (p.Ala93Thr) (PMID: 37492102). This second variant has been reported in ClinVar as a variant of uncertain significance. However, this individual is not reported to be diagnosed with Pompe disease and no GAA activity is provided. Therefore, this criterion is not met.

