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Variant: NM_000152.5(GAA):c.1781G>C (p.Arg594Pro)

Version: 1.1

CA8815476

289361 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 95270750-a614-4a98-84a6-5dee355863fa
Approved on: 2026/2/18
Published on: 2026/2/18

HGVS expressions

NM_000152.5(GAA):c.1781G>C (p.Arg594Pro)
NM_000152.5:c.1781G>C
NC_000017.11:g.80112604G>C
CM000679.2:g.80112604G>C
NC_000017.10:g.78086403G>C
CM000679.1:g.78086403G>C
NC_000017.9:g.75700998G>C
NG_009822.1:g.16049G>C
ENST00000570803.6:c.1781G>C
ENST00000572080.2:c.1781G>C
ENST00000577106.6:c.1781G>C
ENST00000302262.8:c.1781G>C
ENST00000302262.7:c.1781G>C
ENST00000390015.7:c.1781G>C
ENST00000570716.1:n.221G>C
ENST00000572080.1:c.169G>C
ENST00000572803.1:n.395G>C
NM_000152.3:c.1781G>C
NM_001079803.1:c.1781G>C
NM_001079804.1:c.1781G>C
NM_000152.4:c.1781G>C
NM_001079803.2:c.1781G>C
NM_001079804.2:c.1781G>C
NM_001079803.3:c.1781G>C
NM_001079804.3:c.1781G>C

Likely Pathogenic

Met criteria codes 6

PM2_Supporting PP3 PM3 PM5 PS3_Moderate PP4_Moderate

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.1781G>C variant in GAA is a missense variant predicted to cause substitution of arginine by proline at amino acid 594 (p.Arg594Pro). This variant has been detected in at least 3 probands with Pompe disease (PMID: 34952985, 19588081, 18425781, clinical diagnostic laboratory). Two of these individuals are reported to have clinical features consistent with the condition, and one is reported to be on enzyme replacement therapy, but residual GAA activity was not provided (PMID: 19588081, 34952985). Another patient, identified by a clinical diagnostic laboratory, has deficiency GAA activity in dried blood spot and a brother reported to have Pompe disease (PP4_Moderate). Each of the 3 probands is compound heterozygous, phase unknown, for the variant and another pathogenic variant in GAA, either c.525delT (clinical diagnostic laboratory), c.32-13T>G (PMID: 34952985) or c.1941C>G (p.Cys647Trp) (PMID: 19588081) (PM3). The highest population minor allele frequency in gnomAD v4.1.0 is 8.475e-7 (1/1179952 alleles) in the European (non-Finnish) population, which is lower than the ClinGen LD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). Expression of the variant in COS cells resulted in 1.2% wild type GAA activity leading the variant to be described as Class B ("potentially less severe"), indicating that this variant may impact protein function (PMID: 22644586) (PS3_Moderate). The computational predictor REVEL gives a score of 0.941 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense change (c.1781G>A, p.Arg594His) (ClinVar Variation ID: 972747) at the same amino acid residue has been classified as pathogenic by the ClinGen LD VCEP (PM5). There is a ClinVar entry for this variant (Variation ID: 289361). In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease based on the GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel (Specifications Version 2.0.0): PM3, PM5, PS3_Moderate, PP4_Moderate, PP3, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel on February 18, 2026).

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 8.475e-7 (1/1179952 alleles) in the European (non-Finnish) population, which is lower than the ClinGen LD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.941 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM3	✔	Three patients with Pompe disease are compound heterozygous, phase unknown, for the variant and another pathogenic variant in GAA, either c.525delT (clinical diagnostic laboratory, 0.5 points), c.32-13T>G (PMID: 34952985, 0.5 points), or c.1941C>G (p.Cys647Trp) (PMID: 19588081, 0.5 points). The phase is unknown is all cases. Total 1.5 points (PM3).
PM5	✔	Another missense change (c.1781G>A, p.Arg594His) (ClinVar Variation ID: 972747) at the same amino acid residue has been classified as pathogenic by the ClinGen LD VCEP (PM5). Data from p.Arg594Pro was not used in the classification of Arg594His to avoid a circular logic.
PS3_Moderate	✔	Expression of the variant in COS cells resulted in 1.2% wild type GAA activity leading the variant to be described as Class B ("potentially less severe", indicating that this variant may impact protein function (PMID: 22644586) (PS3_Moderate).

PP4_Moderate		✔	At least 3 probands with this variant and Pompe disease have been identified. Two have clinical features consistent with the condition, and one is reported to be on enzyme replacement therapy, but residual GAA activity was not provided (PMID: 19588081, 34952985). Another patient, identified by a clinical diagnostic laboratory, has deficiency GAA activity in dried blood spot and a brother reported to have Pompe disease (PP4_Moderate).

Curation History

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