

Variant: *NM_000152.5(GAA):c.281_282del (p.Pro94fs)*

Version: 1.5

CA16041881 [↗](#)

370458 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 9c3f906c-869b-4686-9b9b-c498c12a2e14

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HGVS expressions

NM_000152.5(GAA):c.281_282del (p.Pro94fs)

NM_000152.5:c.281_282del

NC_000017.11:g.80104867_80104868del

CM000679.2:g.80104867_80104868del

NC_000017.10:g.78078666_78078667del

CM000679.1:g.78078666_78078667del

NC_000017.9:g.75693261_75693262del

NG_009822.1:g.8312_8313del

ENST00000570803.6:c.281_282del

ENST00000572080.2:c.281_282del

ENST00000577106.6:c.281_282del

ENST00000302262.8:c.281_282del

ENST00000302262.7:c.281_282del

ENST00000390015.7:c.281_282del

ENST00000570803.5:c.281_282del

ENST00000577106.5:c.281_282del

NM_000152.3:c.281_282del

NM_001079803.1:c.281_282del

NM_001079804.1:c.281_282del

NM_000152.4:c.281_282del

NM_001079803.2:c.281_282del

NM_001079804.2:c.281_282del

NM_001079803.3:c.281_282del

NM_001079804.3:c.281_282del

Likely Pathogenic

Met criteria codes 2

PM2_Supporting

PVS1

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 2.0

[↗](#) PDF

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.281_282del (p.Pro94ArgfsTer51) variant in GAA is a frameshift variant predicted to cause a premature stop codon in exon 2 out of a total of 20 exons, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). At least two possible patients have been reported with this variant, one with cardiomyopathy and/or arrhythmia, but no additional details available (PMID: 35947370), and at least one patient who is asymptomatic, with elevated CK (level unknown), positive family history (PMID: 34020684, 34305788). There is insufficient evidence available to apply PP4. At least 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.-32-13G>T. However, given that the patient is asymptomatic, other than elevated CK (no further details available) (PMID: 34020684, 34305788; possibly the same patient/family member), this data will not be counted for PM3. The highest population minor allele frequency in gnomAD v4.1.0. is 0.00003 (2/60004 alleles) in the Admixed American population, which is lower than the ClinGen LD VCEP's threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 370458). The classification of this variant has been upgraded from Variant of Uncertain Significance to Likely Pathogenic based on the recommendations of the ClinGen Sequence Variant Interpretation Working Group, that a variant meeting PVS1 and PM2_Supporting is classified as Likely Pathogenic (https://clinicalgenome.org/site/assets/files/5182/pm2_-_svi_recommendation_-_approved_sept2020.pdf). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PVS1, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on August 4, 2026)

Met criteria codes

PM2_Supporting		The highest population minor allele frequency in gnomAD v4.1.0. is 0.00003 (2/60004 alleles) in the Admixed American population, which is lower than the ClinGen LD VCEP's threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PVS1		The NM_000152.5:c.281_282del (p.Pro94ArgfsTer51) variant in GAA is a frameshift variant predicted to cause a premature stop codon in exon 2 out of a total of 20 exons, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).

Not Met criteria codes

PP4		At least two possible patients have been reported with this variant, one with cardiomyopathy and/or arrhythmia, but no additional details available (PMID: 35947370), and at least one patient who is asymptomatic, with elevated CK (level unknown), positive family history (PMID: 34020684, 34305788). There is insufficient evidence available to apply PP4.
PM3		At least 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.-32-13G>T. However, given that the patient is asymptomatic, other than elevated CK (no further details available) (PMID: 34020684, 34305788; possibly the same patient/family member), this data will not be counted for PM3.

Curation History	
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