

Variant: NM_000152.5(GAA):c.2161G>T (p.Glu721Ter)

Version: 1.0

CA401370611 [↗](#)

1322967 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 92b3734a-000b-447b-b3ef-cc2a57896376

Approved on: 2025/11/9

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HGVS expressions

NM_000152.5(GAA):c.2161G>T (p.Glu721Ter)

NM_000152.5:c.2161G>T

NC_000017.11:g.80113338G>T

CM000679.2:g.80113338G>T

NC_000017.10:g.78087137G>T

CM000679.1:g.78087137G>T

NC_000017.9:g.75701732G>T

NG_009822.1:g.16783G>T

ENST00000570803.6:c.2161G>T

ENST00000572080.2:c.*299G>T

ENST00000577106.6:c.2161G>T

ENST00000302262.8:c.2161G>T

ENST00000302262.7:c.2161G>T

ENST00000390015.7:c.2161G>T

ENST00000572080.1:c.580G>T

NM_000152.3:c.2161G>T

NM_001079803.1:c.2161G>T

NM_001079804.1:c.2161G>T

NM_000152.4:c.2161G>T

NM_001079803.2:c.2161G>T

NM_001079804.2:c.2161G>T

NM_001079803.3:c.2161G>T

NM_001079804.3:c.2161G>T

Pathogenic

Met criteria codes **4**

PM2_Supporting

PVS1

PP4_Moderate

PM3_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**

Lysosomal Diseases VCEP

The NM_000152.5:c.2161G>T (p.Glu721Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 15/20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). At least 2 patients diagnosed with late-onset Pompe disease (LOPD) have been reported with this variant. One patient had documented GAA deficiency with <10% of normal mean control level of GAA activity in lymphocytes and the other patient had GAA activity in the affected range in dried blood spot (PMIDs: 25526786, 35071497) (PP4_Moderate). Of those individuals, one was compound heterozygous for the variant and a pathogenic variant (c.1561G>A (p.Glu521Lys), PMID: 25526786), phase unconfirmed; and one was compound heterozygous for the variant and a variant not yet evaluated by the ClinGen Lysosomal Diseases VCEP (c.1409A>G (p.Asn470Ser), PMID: 35071497). (PM3_Supporting). This variant is absent in gnomAD v4.1.0. (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 1322967). In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PVS1, PM2_Supporting, PM3_Supporting, PP4_Moderate. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on November 9, 2025).

Met criteria codes

PM2_Supporting		This variant is absent in gnomAD v4.1.0. (PM2_Supporting).
PVS1	 	The NM_000152.5:c.2161G>T (p.Glu721Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 15/20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PP4_Moderate	 	At least 2 patients diagnosed with LOPD have been reported with this variant. One patient had documented GAA deficiency with <10% of normal mean control level of GAA activity in lymphocytes and the other patient had activity in the affected range in dried blood spot (PMIDs: 25526786, 35071497) (PP4_Moderate).
PM3_Supporting	 	This variant has been detected in at least 2 individuals with LOPD. Of those individuals, one was compound heterozygous for the variant and a pathogenic variant (c.1561G>A (p.Glu521Lys), PMID: 25526786), phase unconfirmed (0.5 points); and one was compound heterozygous for the variant and a variant not yet evaluated by the ClinGen Lysosomal Diseases VCEP (c.1409A>G (p.Asn470Ser), PMID: 35071497). (PM3_Supporting).

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