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.1725C>A (p.Tyr575Ter)

Version: 1.0

CA8815439

972744 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: d6f03a6d-cb71-4d51-bda0-19713f955a46
Approved on: 2025/10/14
Published on: 2025/12/2

HGVS expressions

NM_000152.5:c.1725C>A
NM_000152.5(GAA):c.1725C>A (p.Tyr575Ter)
NC_000017.11:g.80112071C>A
CM000679.2:g.80112071C>A
NC_000017.10:g.78085870C>A
CM000679.1:g.78085870C>A
NC_000017.9:g.75700465C>A
NG_009822.1:g.15516C>A
ENST00000570803.6:c.1725C>A
ENST00000572080.2:c.1725C>A
ENST00000577106.6:c.1725C>A
ENST00000302262.8:c.1725C>A
ENST00000302262.7:c.1725C>A
ENST00000390015.7:c.1725C>A
ENST00000572080.1:c.113C>A
ENST00000572803.1:n.339C>A
NM_000152.3:c.1725C>A
NM_001079803.1:c.1725C>A
NM_001079804.1:c.1725C>A
NM_000152.4:c.1725C>A
NM_001079803.2:c.1725C>A
NM_001079804.2:c.1725C>A
NM_001079803.3:c.1725C>A
NM_001079804.3:c.1725C>A

Pathogenic

Met criteria codes 3

PP4_Moderate PVS1 PM2_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

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1725C>A (p.Tyr575Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 12/20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). At least one patient with this variant has been reported with late onset Pompe disease and <10% GAA normal GAA activity in leukocytes and is compound heterozygous with c.1634C>T (p.Pro545Leu) (PMID 19472353) (PP4_Moderate). The highest population minor allele frequency in gnomAD v4.1.0. is 0.0001720 (11/63956 alleles) in the European (Finnish) population (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 972744, 2 star review status) with 2 submitters classifying the variant as Pathogenic. 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, PP4_Moderate, PM2_Supporting. Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on October 24, 2025)

Met criteria codes

PP4_Moderate	✔	At least 1 patient(s) with this variant had documented GAA deficiency with <10% of normal mean control level of GAA activity in leukocytes, lymphocytes, muscle samples (PP4_Moderate).
PVS1	✔	The NM_000152.5:c.1725C>A (p.Tyr575Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 12/20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.0001720 (11/63956 alleles) in the European (Finnish) population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

Curation History

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