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Variant: NM_000152.5(GAA):c.1841C>T (p.Thr614Met)

Version: 1.1

CA8815496

286469 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: f731f3f2-2282-42e4-adc7-6260b76a51e5
Approved on: 2026/2/19
Published on: 2026/2/20

HGVS expressions

NM_000152.5(GAA):c.1841C>T (p.Thr614Met)
NM_000152.5:c.1841C>T
NC_000017.11:g.80112664C>T
CM000679.2:g.80112664C>T
NC_000017.10:g.78086463C>T
CM000679.1:g.78086463C>T
NC_000017.9:g.75701058C>T
NG_009822.1:g.16109C>T
ENST00000570803.6:c.1841C>T
ENST00000572080.2:c.1841C>T
ENST00000577106.6:c.1841C>T
ENST00000302262.8:c.1841C>T
ENST00000302262.7:c.1841C>T
ENST00000390015.7:c.1841C>T
ENST00000570716.1:n.281C>T
ENST00000572080.1:c.229C>T
ENST00000572803.1:n.455C>T
NM_000152.3:c.1841C>T
NM_001079803.1:c.1841C>T
NM_001079804.1:c.1841C>T
NM_000152.4:c.1841C>T
NM_001079803.2:c.1841C>T
NM_001079804.2:c.1841C>T
NM_001079803.3:c.1841C>T
NM_001079804.3:c.1841C>T

Likely Pathogenic

Met criteria codes 5

PP4_Moderate PP3 PM2_Supporting PM3 PM5

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.1841C>T variant in GAA is a missense variant predicted to cause substitution of threonine by methionine at amino acid 614 (p.Thr614Met). This variant has been reported in at least 5 probands. At least 3 probands with this variant were reported with documented GAA deficiency <10% of normal mean control level of GAA activity in leukocytes (PMID: 33741225, 40639956) (PP4_Moderate). One patient was compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP, c.246C>A (p.Cys82Ter); phase unknown (0.5 points; PMID: 33741225). At least 4 probands were homozygous for the variant (max 2 x 0.5 points, PMID: 33301762, 33741225, 33250842, 4063995, 41111870 (PM3). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00008 (6/74920 alleles) in the African/African-American population, which is lower than the ClinGen LD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). To our knowledge, the results of functional assays have not been reported for this variant. The computational predictor REVEL gives a score of 0.769 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense variant, c.1841C>A (p.Thr614Lys) (ClinVar Variation ID: 167113), in the same codon has been classified as pathogenic for Pompe disease by the ClinGen LD VCEP (PM5). Splicing prediction using Splice AI revealed no expected effects on splicing due to either of these variants. There is a ClinVar entry for this variant (Variation ID: 286469). 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 Diseases Variant Curation Expert Panel (Specifications Version 2.0): PP4_Moderate, PM3, PM5, PP3, PM2_Supporting (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on February 19, 2026)

Met criteria codes

PP4_Moderate	✔	This variant has been reported in at least 5 probands. At least 3 probands with this variant were reported with documented GAA deficiency with <10% of normal mean control level of GAA activity in leukocytes (PMID: 33741225, 40639956) (PP4_Moderate).
PP3	✔	The computational predictor REVEL gives a score of 0.769 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.00008 (6/74920 alleles) in the African/African-American population, which is lower than the ClinGen LD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PM3	✔	One patient was compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP, c.246C>A (p.Cys82Ter); phase unknown (0.5 points; PMID: 33741225). At least 4 probands were homozygous for the variant (max 2 x 0.5 points, PMID: 33301762, 33741225, 33250842, 4063995, 41111870 (PM3).
PM5	✔	Another missense variant, c.1841C>A/p.Thr614Lys (ClinVar Variation ID: 167113), in the same codon has been classified as pathogenic for Pompe disease by the ClinGen LD VCEP (PM5). Splicing prediction using Splice AI revealed no expected effects on splicing due to either of these variants.

Curation History

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