

Variant: NM_000152.5(GAA):c.841C>T (p.Arg281Trp)

Version: 1.1

CA8815025 [↗](#)

283894 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 6a43fe2d-1dea-4a99-bb53-737388ab566c

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HGVS expressions

NM_000152.5:c.841C>T

NM_000152.5(GAA):c.841C>T (p.Arg281Trp)

NC_000017.11:g.80107705C>T

CM000679.2:g.80107705C>T

NC_000017.10:g.78081504C>T

CM000679.1:g.78081504C>T

NC_000017.9:g.75696099C>T

NG_009822.1:g.111150C>T

ENST00000570803.6:c.841C>T

ENST00000572080.2:c.841C>T

ENST00000577106.6:c.841C>T

ENST00000302262.8:c.841C>T

ENST00000302262.7:c.841C>T

ENST00000390015.7:c.841C>T

ENST00000570803.5:c.841C>T

NM_000152.3:c.841C>T

NM_001079803.1:c.841C>T

NM_001079804.1:c.841C>T

NM_000152.4:c.841C>T

NM_001079803.2:c.841C>T

NM_001079804.2:c.841C>T

NM_001079803.3:c.841C>T

NM_001079804.3:c.841C>T

Likely Pathogenic

Met criteria codes **4**

PP3

PP4_Moderate

PM3_Strong

PM2_Supporting

Not Met criteria codes **2**

PS3

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

Lysosomal Diseases VCEP

The NM_000152.5:c.841C>T variant in GAA is predicted to result in the substitution of arginine by tryptophan at amino acid 281 (p.Arg281Trp). This variant has been reported in four individuals with features consistent with Pompe disease and documented GAA activity (PMID: 36299500, clinical diagnostic laboratory - pseudodeficiency variants were ruled out) and another individual with features consistent with infantile onset Pompe disease on enzyme replacement therapy but GAA activity not provided (PMID: 31086307). In addition, the variant was reported in an infant identified on newborn screen (PMID: 33202836), as well as in five individuals reported to have later-onset disease (PMID: 22081099, 33073009) (PP4_Moderate). Four patients are reported to be compound heterozygous for the variant and a pathogenic variant in GAA, including c.172C>T (p.Gln58Ter) (PMID: 36299500, phase unknown) (ClinVar Variation ID: 188903; SCV001371756.1), c.2481+102_2646+31del (clinical diagnostic laboratory; phase unknown) (ClinVar Variation ID: 657307), c.2161delG (clinical diagnostic laboratory; confirmed in trans) (ClinVar Variation ID: 932900, SCV001371755.1), and c.-32-13T>G (PMID: 33202836; phase unknown) (ClinVar Variation ID: 4027) (PM3_Strong). The score for the in silico meta-predictor REVEL, 0.786, suggests that the variant is deleterious, meeting PP3. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00041 (European non-Finnish), meeting PM2_Supporting. To our knowledge, the results of functional studies are not available. There is a ClinVar entry for this variant (Variation ID: 283894). This variant meets the criteria to be classified as likely pathogenic for Pompe disease. The classification was first approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 5, 2019. Since then, the data for this variant have been re-evaluated - no new data were identified. The classification of likely pathogenic was reapproved on April 8, 2024. GAA-specific ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PM3_Strong, PP4_Moderate, PP3, PM2_Supporting.

Met criteria codes

PP3			The computational predictor REVEL gives a score of 0.786 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). SpliceAI predicts that the variant has no impact on splicing.
PP4_Moderate			This variant has been reported in four individuals with features consistent with Pompe disease and documented GAA activity (PMID: 36299500, clinical diagnostic laboratory - pseudodeficiency variants were ruled out) and another individual with features consistent with infantile onset Pompe disease on enzyme replacement therapy but GAA activity not provided (PMID: 31086307). In addition, the variant was reported in an infant identified on newborn screen (PMID: 33202836), as well as in five individuals reported to have later-onset disease (PMID: 22081099, 33073009) (PP4_Moderate).
PM3_Strong			Four patients are reported to be compound heterozygous for the variant and a pathogenic variant in GAA, including c.172C>T (p.Gln58Ter) (PMID: 36299500, phase unknown, 0.5 points) (ClinVar Variation ID: 188903; SCV001371756.1), c.2481+102_2646+31del (clinical diagnostic laboratory; phase unknown, 0.5 points) (ClinVar Variation ID: 657307), c.2161delG (clinical diagnostic laboratory; confirmed in trans; 1 point) (ClinVar Variation ID: 932900, SCV001371755.1), and c.-32-13T>G (PMID: 33202836; phase unknown, 0.5 points) (ClinVar Variation ID: 4027). The variant has been reported in additional individuals where PM3 does not apply (PMID 2208109, 23430949, 31086307). 2.5 points were given, meeting PM3_Strong.
PM2_Supporting			The highest population minor allele frequency in gnomAD v2.1.1 is 0.00041 (51/125884 alleles) in the European non-Finnish population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

Not Met criteria codes

PS3

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No published functional studies, in which the variant was expressed in a heterologous cell type, were identified.

PM5

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Another variant at the same amino acid position has been reported in a patient with Pompe disease, c.842G>C p.(Arg281Pro) (PMID: 36245745). This data will be used in the classification of c.842G>C p.(Arg281Pro) and is not included here to avoid circular logic.

Curation History [↗](#)

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