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.854C>G (p.Pro285Arg)

Version: 1.3

CA358045

225114 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: fdbef722-4167-4550-b57b-0d4d751a35b3
Approved on: 2025/7/18
Published on: 2025/8/5

HGVS expressions

NM_000152.5(GAA):c.854C>G (p.Pro285Arg)
NM_000152.5:c.854C>G
NC_000017.11:g.80107718C>G
CM000679.2:g.80107718C>G
NC_000017.10:g.78081517C>G
CM000679.1:g.78081517C>G
NC_000017.9:g.75696112C>G
NG_009822.1:g.11163C>G
ENST00000570803.6:c.854C>G
ENST00000572080.2:c.854C>G
ENST00000577106.6:c.854C>G
ENST00000302262.8:c.854C>G
ENST00000302262.7:c.854C>G
ENST00000390015.7:c.854C>G
ENST00000570803.5:c.854C>G
NM_000152.3:c.854C>G
NM_001079803.1:c.854C>G
NM_001079804.1:c.854C>G
NM_000152.4:c.854C>G
NM_001079803.2:c.854C>G
NM_001079804.2:c.854C>G
NM_001079803.3:c.854C>G
NM_001079804.3:c.854C>G

Likely Pathogenic

Met criteria codes 6

PM3_Supporting PS3_Moderate PP4_Moderate PM2_Supporting PM5_Supporting PP3

Not Met criteria codes 1

PS1

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.854C>G variant in GAA is a missense variant predicted to cause substitution of proline by arginine at amino acid 285 (p.Pro285Arg). The highest population minor allele frequency in gnomAD v4.0.1 is 0.000001784 (1/ 1120816 alleles) in the European non-finish population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). At least two probands with symptoms consistent with infantile-onset-Pompe disease have been reported with this variant, both with documented deficiency of GAA activity (PMID: 28196920, 19862843). One proband had juvenile-onset (after 1 year of age) (PMID: 14695532) (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.1655T>C (p.Leu552Pro) (ClinVar Variation ID: 279811); phase unconfirmed (PMID: 12213618, 14695532). Another individual is compound heterozygous for the variant and c.2303C>T (Pro768Leu) (PMID: 28196920). The allelic data from this patient will be used toward the classification of p.Pro768Leu and is not included here to avoid circular logic. Additional reports of this variant identified in newborn screening (PMID: 28196920, 12213618, 14695532, 19862843). Total 0.5 points (PM3_Supporting). Expression of the variant in COS cell type resulted in 2-10% (~ 5%) of wild-type GAA activity and evidence of abnormal GAA synthesis and processing (PMID: 19862843, 14695532, 19862843). The variant was described as Class C ("less severe"), indicating that this variant may impact protein function (PMID: 14695532) (PS3_Moderate). The computational predictor REVEL gives a score of 0.883, which is above the threshold of 0.7, evidence that correlates with impact on GAA function (PP3). Another missense variant (c.853C>T, p.Pro285Ser) (PMID: 18425781, 21484825, 21550241; ClinVar Variation ID 281052) in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (PM5_Supporting). There is a ClinVar entry for this variant (Variation ID: 526532; 2-star review status) with four submitters classifying the variant as pathogenic, and one as likely pathogenic. 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 VCEP (Specifications Version 2.0): PP4_Moderate, PM3_Supporting, PS3_Moderate, PM5_Supporting, PP3, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on July 18, 2025)

Met criteria codes

PM3_Supporting	✔	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.1655T>C (p.Leu552Pro) (ClinVar Variation ID: 279811); phase unconfirmed (PMID: 12213618, 14695532). Another individual is compound heterozygous for the variant and c.2303C>T (Pro768Leu). The allelic data from this patient will be used toward the classification of p.Pro768Leu and is not included here to avoid circular logic. The variant has also been identified in asymptomatic infants by newborn screening (PMID: 28196920, 12213618, 14695532, 19862843). Total 0.5 points (PM3_Supporting).
PS3_Moderate	✔	Expression of the variant in COS cell type resulted in 2-10% (~ 5%) of wild-type GAA activity, and evidence of abnormal GAA synthesis and processing (PMID: 19862843, 14695532, 19862843). The variant was described as Class C ("less severe"), indicating that this variant may impact protein function (PMID: 14695532) (PS3_Moderate).
PP4_Moderate	✔	At least two probands with symptoms consistent with infantile-onset-Pompe disease have been reported with this variant, two with documented deficiency of GAA activity (PMID: 28196920, 19862843) (PP4_Moderate). One proband had juvenile-onset of Pompe (after 1 year of age) (PMID: 14695532).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.0.1 is 0.000001784 (1/ 1120816 alleles) in the European non-finish population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting criterion PM2_Supporting.

PM5_Supporting		✔	Another missense variant (c.853C>T, p.Pro285Ser) (PMID: 18425781, 21484825, 21550241; ClinVar Variation ID 281052) in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (PM5_Supporting).
PP3		✔	The computational predictor REVEL gives a score of 0.883 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

Not Met criteria codes

PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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