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Variant: NM_000152.5(GAA):c.853C>T (p.Pro285Ser)

Version: 2.0

CA10603793

281052 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2a535c11-a37f-4ba1-af92-15a1f7e38989
Approved on: 2026/9/1
Published on: 2026/9/1

HGVS expressions

NM_000152.5:c.853C>T
NM_000152.5(GAA):c.853C>T (p.Pro285Ser)
NC_000017.11:g.80107717C>T
CM000679.2:g.80107717C>T
NC_000017.10:g.78081516C>T
CM000679.1:g.78081516C>T
NC_000017.9:g.75696111C>T
NG_009822.1:g.11162C>T
ENST00000570803.6:c.853C>T
ENST00000572080.2:c.853C>T
ENST00000577106.6:c.853C>T
ENST00000302262.8:c.853C>T
ENST00000302262.7:c.853C>T
ENST00000390015.7:c.853C>T
ENST00000570803.5:c.853C>T
NM_000152.3:c.853C>T
NM_001079803.1:c.853C>T
NM_001079804.1:c.853C>T
NM_000152.4:c.853C>T
NM_001079803.2:c.853C>T
NM_001079804.2:c.853C>T
NM_001079803.3:c.853C>T
NM_001079804.3:c.853C>T

Pathogenic

Met criteria codes 5

PP3 PM3_Strong PS3_Moderate PP4_Moderate PM2_Supporting

Not Met criteria codes 1

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 2.0*
PDF
Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.853C>T variant in GAA is a missense variant predicted to cause substitution of proline by serine at amino acid 285 (p.Pro285Ser). At least 4 patients with this variant had symptoms consistent with Pompe disease and documented laboratory values showing deficiency GAA activity; one was also treated with ERT (PMID: 21484825, 21550241, 37087815 (PP4_Moderate). All four patients were reported to be compound heterozygous for the variant and another variant in GAA, phase unconfirmed, that has been classified as pathogenic for Pompe disease by the ClinGen LD VCEP. In these cases, the second variant was either c.2560C>T (p.Arg854Ter) (PMID: 37087815; 2 patients, unrelated based on personal communication with author, 2 x 0.5 points), c.1354_1372del19 (PMID: 21550241, 21803581, 0.5 points), c.2237G>A (p.Trp746Ter) (PMID: 21484825, 0.5 points). Total 2 points (PM3_Strong). An infant who was compound heterozygous for the variant and c.670C>T (p.Arg224Trp) was identified on newborn screen but this data will not be included because no further clinical or laboratory data is available (Revvity). The highest population minor allele frequency in gnomAD v4.1.0 is 0.00013 (3/22640 alleles) in the African / African American population which is lower than the ClinGen LD VCEP's threshold (<0.001) for PM2_Supporting, meeting this criterion. The computational predictor REVEL gives a score of 0.757 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). This variant results in <5% GAA activity when expressed in COS cells, and was classified as Class C ("less severe") by Kroos et al, 2012 (PMID:22644586), meeting the ClinGen LD VCEP criteria for PS3_Supporting. There is a ClinVar entry for this variant (Variation ID: 281052). In summary, this variant meets the criteria to be classified as Pathogenic for Pompe disease based on the GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel (Specifications Version 2.0): PM3_Strong, PP4_moderate, PP3, PM2_supporting, PS3_supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on September 1, 2026)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.757 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM3_Strong	✔	Four patients with symptoms consistent with Pompe disease and documented laboratory values showing deficiency GAA activity have been reported to be compound heterozygous for the variant and another variant in GAA, phase unconfirmed, that has been classified as pathogenic for Pompe disease by the ClinGen LD VCEP. In these cases, the second variant was either c.2560C>T (p.Arg854Ter) (PMID: 37087815; 2 patients, unrelated based on personal communication with author, 2 x 0.5 points), c.1354_1372del19 (PMID: 21550241, 21803581, 0.5 points), c.2237G>A (p.Trp746Ter) (PMID: 21484825, 0.5 points). Total 2 points (PM3_Strong). An infant who was compound heterozygous for the variant and c.670C>T (p.Arg224Trp) was identified on newborn screen but this data will not be included because no further clinical or laboratory data is available (Revvity).
PS3_Moderate	✔	This variant results in <5% GAA activity when expressed in COS cells, and was classified as Class C ("less severe") by Kroos et al, 2012 (PMID:22644586), meeting the ClinGen LD VCEP criteria for PS3_Supporting.
PP4_Moderate	✔	At least 4 patients with this variant had symptoms consistent with Pompe disease and documented laboratory values showing deficiency GAA activity; one was also treated with ERT (PMID: 21484825, 21550241, 37087815 (PP4_Moderate).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is 0.00013 (3/22640 alleles) in the African / African American population which is lower than the ClinGen LD VCEP's threshold (<0.001) for PM2_Supporting, meeting this criterion.

Not Met criteria codes

PM5	✖	

A different missense change, c.854C>G (p.Pro285Arg) (ClinVarID: 225114), occurs at the same residue and has been classified as likely pathogenic for Pompe disease by the LD VCEP. However, as the classification of p.Pro285Ser was used in the classification of p.Pro285Arg, PM5_Supporting was not applied to avoid circularity.

Curation History

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