

Variant: *NM_000152.5(GAA):c.1880C>T (p.Ser627Phe)*

Version: 1.0

CA294896504 [↗](#)

597382 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 61f976ce-4a2b-4853-84a7-195a243610c2

Approved on: 2025/6/3

Published on: 2025/9/16

HGVS expressions

NM_000152.5:c.1880C>T

NM_000152.5(GAA):c.1880C>T (p.Ser627Phe)

NC_000017.11:g.80112703C>T

CM000679.2:g.80112703C>T

NC_000017.10:g.78086502C>T

CM000679.1:g.78086502C>T

NC_000017.9:g.75701097C>T

NG_009822.1:g.16148C>T

ENST00000570803.6:c.1880C>T

ENST00000572080.2:c.1880C>T

ENST00000577106.6:c.1880C>T

ENST00000302262.8:c.1880C>T

ENST00000302262.7:c.1880C>T

ENST00000390015.7:c.1880C>T

ENST00000570716.1:n.320C>T

ENST00000572080.1:c.268C>T

ENST00000572803.1:n.494C>T

NM_000152.3:c.1880C>T

NM_001079803.1:c.1880C>T

NM_001079804.1:c.1880C>T

NM_000152.4:c.1880C>T

NM_001079803.2:c.1880C>T

NM_001079804.2:c.1880C>T

NM_001079803.3:c.1880C>T

NM_001079804.3:c.1880C>T

Pathogenic

Met criteria codes **5**

PP4_Moderate

PM3_Strong

PS3_Moderate

PP3

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**

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1880C>T variant in GAA is a missense variant predicted to result in substitution of serine by phenylalanine at amino acid 627 (p.Ser627Phe). This variant has been reported in at least three individuals with features consistent with Pompe disease, documented with deficient GAA activity- one within <10% of normal mean in leukocytes (PMID: 29044175) and two individuals with GAA activity below reference range in muscle (PMID:28763149) (PP4_Moderate). Two of these individuals are compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP, phase known, including c.525delT (ClinVar # VCV000004033.83) (1 points) , c.-32-13T>G (ClinVar # VCV000004027.118) (PMID 28763149) (1 points) (Total 2 points, PM3_strong). In addition, both individuals are heterozygous for c.1642G>T(p.Val548Phe) (ClinVar # VCV000597381.2), which has been classified as likely benign by the ClinGen LD VCEP. In addition, a patient with infantile onset Pompe disease is documented with c.1880C>T (p.Ser627Phe), but no second variant was reported (PMID:29044175). Expression of the variant in HEK293 cells demonstrated loss of GAA activity, and the western blot showed only the 110kDa precursor band suggesting abnormal GAA processing () (PS3_moderate). The computational predictor REVEL gives a score of 0.802 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). The variant is absent in gnomAD v4.1.0.(PM2_Supporting). There is a ClinVar entry for this variant (Variant ID:597382). In summary, this variant meets the criteria to be classified as Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PM3_strong, PS3_moderate, PP4_moderate, PM2_supporting, PP3. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel, June 3, 2025).

Met criteria codes

PP4_Moderate			At least three individuals with this variant had documented GAA deficiency- one within <10%of normal mean in leukocytes (PMID: 29044175) and two individuals with GAA activity below reference range in muscle (PMID:28763149), sufficient to meet the ClinGen LSD VCEP’s specifications for PP4_moderate
PM3_Strong			This variant has been reported in at least three individuals with features consistent with Pompe disease. Two are compound heterozygous for the variant and a variant in GAA classified as Pathogenic by the ClinGen LSD VCEP, phase known, including c.525delT (ClinVar # VCV000004033.83) (2 points) , c.-32-13T>G (ClinVar # VCV000004027.118) (PMID 28763149) (2 points). One infantile patient is documented only with the variant. No second variant reported (PMID:29044175)
PS3_Moderate			Expression of the variant in HEK293 cells resulted in loss of GAA activity and western blot showing only the 110kDa band, suggesting abnormal GAA processing (unpublished data from the laboratory that published PMID: 36246652).
PP3			The computational predictor REVEL gives a score of 0.802 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3) .
PM2_Supporting			This variant is absent in gnomAD v4.1.0. (PM2_supporting)

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