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Variant: NM_000152.5(GAA):c.1802C>G (p.Ser601Trp)

Version: 1.0

CA294896338

501793 (ClinVar)

Gene: GAA
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2ac96484-f834-4db9-b360-bd753d1bf30e
Approved on: 2025/5/20
Published on: 2025/5/20

HGVS expressions

NM_000152.5(GAA):c.1802C>G
NM_000152.5(GAA):c.1802C>G (p.Ser601Trp)
NM_000152.5:c.1802C>G
NC_000017.11:g.80112625C>G
CM000679.2:g.80112625C>G
NC_000017.10:g.78086424C>G
CM000679.1:g.78086424C>G
NC_000017.9:g.75701019C>G
NG_009822.1:g.16070C>G
ENST00000570803.6:c.1802C>G
ENST00000572080.2:c.1802C>G
ENST00000577106.6:c.1802C>G
ENST00000302262.8:c.1802C>G
ENST00000302262.7:c.1802C>G
ENST00000390015.7:c.1802C>G
ENST00000570716.1:n.242C>G
ENST00000572080.1:c.190C>G
ENST00000572803.1:n.416C>G
NM_000152.3:c.1802C>G
NM_001079803.1:c.1802C>G
NM_001079804.1:c.1802C>G
NM_000152.4:c.1802C>G
NM_001079803.2:c.1802C>G
NM_001079804.2:c.1802C>G
NM_001079803.3:c.1802C>G
NM_001079804.3:c.1802C>G

Likely Pathogenic

Met criteria codes 6

PM3 PM5 PS3_Supporting PM2_Supporting PP3 PP4_Moderate

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.1802C>G variant in GAA is a missense variant predicted to cause substitution of serine serine by tryptophan at amino acid 601 (p.Ser601Trp). The highest population minor allele frequency in gnomAD v4.1.0 is 0.0000008475 (1/1179962 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). The computational predictor REVEL gives a score of 0.964 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). When expressed in COS-7 cells, the variant resulted in <2% wild type activity indicating that this variant may impact protein function (PMID: 19862843) (PS3_supporting). Another missense variant (c.1802C>T, p.Ser601Leu) in the same codon has been classified as pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (ClinVar Variation ID: 194154; Accession: SCV002032130.1) (PM5). This variant has been detected in at least 11 individuals with Pompe disease. Of those individuals, 9 were compound heterozygous for the variant and the c.-32-13T>G variant (classified as pathogenic by the ClinGen LD VCEP). One individual was compound heterozygous for the variant and the c.1935C>A (p.Asp645Glu) variant (classified as pathogenic by the ClinGen LD VCEP). One individual was compound heterozygous for the variant and c.2800-1G>C (not classified by the ClinGen LD VCEP). Zero individuals were homozygous for the variant. (PM3). At least 3 patients with this variant had documented GAA deficiency with <10% of normal mean control level of GAA activity in leukocytes, lymphocytes, or muscle samples (PMID: 17056254, 22958975, 24158270) and 2 patients were reported to be on enzyme replacement therapy for Pompe disease (PMID: 22081099, 29422078). This meets the criteria for PP4_moderate. There is a ClinVar entry for this variant (Variation ID: 501793). 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, PM5, PP3, PM2_supporting, PS3_supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on May 20, 2025)

Met criteria codes

PM3	✔	This variant has been detected in at least 11 individuals with Pompe disease. Of those individuals, 9 were compound heterozygous for the variant and the c.-32-13T>G variant (classified as pathogenic by the ClinGen LD VCEP) (1 point). One individual was compound heterozygous for the variant and the c.1935C>A (p.Asp645Glu) variant (classified as pathogenic by the ClinGen LD VCEP) (0.5 points). One individual was compound heterozygous for the variant and c.2800-1G>C (not classified by the ClinGen LD VCEP) (0 points). Zero individuals were homozygous for the variant. (1.5 points total; PM3_met).
PM5	✔	Another missense variant (c.1802C>T, p.Ser601Leu) in the same codon has been classified as pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (ClinVar Variation ID: 194154; Accession: VCV000194154.28) (PM5).
PS3_Supporting	✔	When expressed in COS-7 cells, the variant resulted in <2% wild type activity indicating that this variant may impact protein function (PMID: 19862843) (PS3_supporting).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0 is [0.0000008475] (1/1179962 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).
PP3	✔	

The computational predictor REVEL gives a score of 0.964 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

PP4_Moderate ✔

At least 3 patients with this variant had documented GAA deficiency with <10% of normal mean control level of GAA activity in leukocytes, lymphocytes, or muscle samples (PMID: 17056254, 22958975, 24158270) and 2 patients were reported to be on enzyme replacement therapy for Pompe disease (PMID: 22081099, 29422078). This meets the criteria for PP4_moderate.

Curation History

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