

Variant: *NM_000152.5(GAA):c.1802C>T (p.Ser601Leu)*

Version: 1.0

CA274982 [↗](#)

194154 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 8b322e84-d5bb-4038-bce4-875136c7e6cd

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HGVS expressions

NM_000152.5(GAA):c.1802C>T (p.Ser601Leu)

NM_000152.5:c.1802C>T

NC_000017.11:g.80112625C>T

CM000679.2:g.80112625C>T

NC_000017.10:g.78086424C>T

CM000679.1:g.78086424C>T

NC_000017.9:g.75701019C>T

NG_009822.1:g.16070C>T

ENST00000570803.6:c.1802C>T

ENST00000572080.2:c.1802C>T

ENST00000577106.6:c.1802C>T

ENST00000302262.8:c.1802C>T

ENST00000302262.7:c.1802C>T

ENST00000390015.7:c.1802C>T

ENST00000570716.1:n.242C>T

ENST00000572080.1:c.190C>T

ENST00000572803.1:n.416C>T

NM_000152.3:c.1802C>T

NM_001079803.1:c.1802C>T

NM_001079804.1:c.1802C>T

NM_000152.4:c.1802C>T

NM_001079803.2:c.1802C>T

NM_001079804.2:c.1802C>T

NM_001079803.3:c.1802C>T

NM_001079804.3:c.1802C>T

Pathogenic

Met criteria codes 5

PM3_Strong

PS3_Moderate

PP3

PM2_Supporting

PP4_Moderate

Not Met criteria codes 1

PM5

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Lysosomal Diseases VCEP

The NM_000152.5:c. c.1802C>T variant in GAA is a missense variant predicted to cause substitution of serine by leucine at amino acid 601 (p.Ser601Leu). At least eight patients with this variant have been reported to have Pompe disease including three with clinical features consistent with infantile onset Pompe disease and on enzyme replacement therapy (PMID 22538254, 30023291), and one with GAA deficiency reported in the affected range in lymphocytes (PMID 22676651), as well as four patients reported to be diagnosed with the condition (PMID 28394184) (PP4_Moderate). Of note, in one patient, with features of infantile onset Pompe disease and on ERT, the variant was reported to be in cis with pseudodeficiency variants c.1726G>A and c.2065G>A (PMID 22538254). Of these patients, four were compound heterozygous for the variant and a variant that has been classified as pathogenic or likely pathogenic by the ClinGen LSD VCEP (PMID 22676651, 28394184, 30023291) One patient was homozygous for the variant (PMID 30023291) (PM3_Strong). In addition, three patients were compound heterozygous for the variant and a missense variant (PMID 22538254, 28394184). The in trans data from these patients will be used in the assessment of the second variant and is not included here in order to avoid circular logic. The highest population minor allele frequency in gnomAD is 0.00064 in the East Asian population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). Expression of the variant in COS cells resulted in 0.5% wild type GAA activity in cells and medium, and evidence of abnormal GAA synthesis and processing, leading the variant to be described as Class B (“potentially less severe”). This indicates that the variant may impact protein function (PMID: 22644586) (PS3_Moderate). The computational predictor REVEL gives a score of 0.961, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense variant, c.1802C>G (p.Ser601Trp), in the same codon has been reported in patients with Pompe disease (PMID 17056254, 29422078). However, the data for p.Ser601Leu will be used in the assessment of p.Ser601Trp and therefore PM5 is not met here in order to avoid circular logic (PM5 not met). The is a ClinVar entry for this variant (Variation ID: 194154). In summary, this variant meets the criteria to be classified at pathogenic for Pompe disease. ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel (Specification version 2.0): PM3_Strong; PS3_Moderate, PP4_Moderate, PM2_Supporting, PP3. (Classification approved on August 17, 2021)

Met criteria codes

PM3_Strong			Of 8 patients reported with Pompe disease, four were compound heterozygous for te variant and a variant that has been classified as pathogenic or likely pathogenic variant by the ClinGen LSD VCEP including c.2411G>A (p.Trp804Ter)(PMID 28394184; 0.25 points), c.971dupC (PMID 28394184; 0.25 points), c.784G>A (p.Glu262Lys)(PMID 30023291; 0.5 points), and c.-32-13T>G (PMID 22676651; 0.5 points). One patient was homozygous for the variant (PMID 30023291; 0.5 points). Total 2 points (PM3_Strong). In addition, three patients were compound heterozygous for the variant and a missense variant including c.1099T>C (p.Trp367Arg)(PMID 22538254), c.1432G>A (p.Gly478Arg)(PMID 28394184), c.1844G>T (p.Gly615Val)(PMID 28394184). The in trans data from these patients will be used in the assessment of the second variant and is not included here in order to avoid circular logic.
PS3_Moderate			Expression of the variant in COS cells resulted in 0.5% wild type GAA activity in cells and medium, and evidence of abnormal GAA synthesis and processing, leading the variant to be described as Class B (“potentially less severe”). This indicates that the variant may impact protein function (PMID: 22644586) (PS3_Moderate).
PP3			The computational predictor REVEL gives a score of 0.961, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM2_Supporting			The highest population minor allele frequency in gnomAD is 0.00064 in the East Asian population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP4_Moderate			At least 8 patients with this variant have been reported to have Pompe disease including three with clinical features consistent with infantile onset Pompe disease, on enzyme replacement therapy (PMID 22538254, 30023291), and

one with GAA deficiency reported in the affected range in lymphocytes (PMID 22676651), as well as four patients reported to be diagnosed with the condition (PMID 28394184) (PP4_Moderate). Of note, in one patient, with features of infantile onset Pompe disease and on ERT, the variant was reported to be in cis with pseudodeficiency variants c.1726G>A and c.2065G>A (PMID 22538254).

Not Met criteria codes

PM5



Another missense variant, c.1802C>G (p.Ser601Trp), in the same codon has been reported in patients with Pompe disease (PMID 17056254, 29422078). However, the data for p.Ser601Leu will be used in the assessment of p.Ser601Trp and therefore PM5 is not met here in order to avoid circular logic (PM5 not met).

Curation History



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