

Variant: *NM_000152.5(GAA):c.1832G>A (p.Gly611Asp)*

Version: 1.0

CA16041897 [↗](#)

371226 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 2e25b3bd-5daa-4239-8291-b76ed3fe954a

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HGVS expressions

NM_000152.5:c.1832G>A

NM_000152.5(GAA):c.1832G>A (p.Gly611Asp)

NC_000017.11:g.80112655G>A

CM000679.2:g.80112655G>A

NC_000017.10:g.78086454G>A

CM000679.1:g.78086454G>A

NC_000017.9:g.75701049G>A

NG_009822.1:g.16100G>A

ENST00000570803.6:c.1832G>A

ENST00000572080.2:c.1832G>A

ENST00000577106.6:c.1832G>A

ENST00000302262.8:c.1832G>A

ENST00000302262.7:c.1832G>A

ENST00000390015.7:c.1832G>A

ENST00000570716.1:n.272G>A

ENST00000572080.1:c.220G>A

ENST00000572803.1:n.446G>A

NM_000152.3:c.1832G>A

NM_001079803.1:c.1832G>A

NM_001079804.1:c.1832G>A

NM_000152.4:c.1832G>A

NM_001079803.2:c.1832G>A

NM_001079804.2:c.1832G>A

NM_001079803.3:c.1832G>A

NM_001079804.3:c.1832G>A

Likely Pathogenic

Met criteria codes 4

PP4_Moderate PP3 PM3

PM2_Supporting

Not Met criteria codes 2

PM5 PS3

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP [↗](#)

Criteria Specification Information **!**

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

Lysosomal Diseases VCEP

The NM_000152.5:c.1832G>A variant in GAA is a missense variant predicted to cause substitution of glycine by aspartate at amino acid 611 (p.Gly611Asp). Four patients with a diagnosis of Pompe disease and this variant have been reported including two with documented features of infantile onset Pompe disease and laboratory values showing deficient GAA activity <1% in skin fibroblasts (PMID: 22252923) or in the affected range in dried blood spot assay (PMID: 25681614), and another reported with features consistent with infantile onset Pompe disease and deficient GAA activity but the laboratory value was not provided (PMID: 24269976). Finally, a patient with deficient GAA activity (level not known) was identified in clinical laboratory data (PP4_Moderate). Of the reported patients, three are compound heterozygous for the variant and a variant classified as pathogenic or likely pathogenic by the ClinGen LSD VCEP including c.2501_2502delCA, (pathogenic, presumed in trans, clinical laboratory data), c.1848dupC (clinical laboratory data) (pathogenic, phase unknown), and c.1843G>A (p.Gly615Arg) (PMID: 24269976) (likely pathogenic, phase unknown), and one patient is homozygous (PMID: 25681614). Another patient is compound heterozygous for the variant and c.1570A>T (p.Asn524Tyr). However, the allelic data from this patient with be used in the assessment of p.Asn524Tyr and is not included here to avoid circular logic. (PM3_Strong). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.821 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense variant [c.1831G>A, p.Gly611Ser] (ClinVar variation ID: 935199) in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen LSD VCEP. However, the data from c.1832 (p.Gly611Asp) was used in the classification of p.Gly611Ser, and therefore the data is not ncluded here to avoid circular logic. There is a ClinVar entry for this variant (Variation ID: 371226, 1 star review status) with 2 submitters classifying the variant as Likely Pathogenic and 1 submitter classifying the variant as a Variant of Uncertain Significance. In summary, this variant meets the criteria to be classified as Likely Pathogenic for Pompe disease based on the 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.

Met criteria codes

PP4_Moderate			Four patients with a diagnosis of Pompe disease and this variant have been reported including two with documented features of infantile onset Pompe disease and laboratory values showing deficient GAA activity <1% in skin fibroblasts (PMID: 22252923) or in the affected range in dried blood spot assay (PMID: 25681614), and another reported with features consistent with infantile onset Pompe disease and deficient GAA activity but the laboratory value was not provided (PMID: 24269976). Finally, a patient with deficient GAA activity (level not known) was identified in clinical laboratory data. (PP4_Moderate).
PP3			The computational predictor REVEL gives a score of 0.821 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM3			Of the reported patients, three are compound heterozygous for the variant and a variant classified as pathogenic or likely pathogenic by the ClinGen LSD VCEP including c.2501_2502delCA, (pathogenic, presumed in trans, clinical laboratory data, 1 point), c.1848dupC (clinical laboratory data) (pathogenic, phase unknown, 0.5 points), and c.1843G>A (p.Gly615Arg) (PMID: 24269976) (likely pathogenic, phase unknown, 0.25 points), and one patient is homozygous (PMID: 25681614) (0.5 points). Another patient is compound heterozygous for the variant and c.1570A>T (p.Asn524Tyr). However, the allelic data from this patient with be used in the assessment of p.Asn524Tyr and is not included here to avoid circular logic. Total points for PM3 =2.25 (PM3_Strong).
PM2_Supporting			This variant is absent from gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

