

Variant: NM\_000152.5(GAA):c.1820G>A (p.Gly607Asp)

Version: 1.0

CA401369511 [↗](#)

932221 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** 94886669-b25a-4231-b58b-9823fb60a02b

**Approved on:** 2024/4/2

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## HGVS expressions

**NM\_000152.5(GAA):c.1820G>A (p.Gly607Asp)**

**NM\_000152.5:c.1820G>A**

NC\_000017.11:g.80112643G>A

CM000679.2:g.80112643G>A

NC\_000017.10:g.78086442G>A

CM000679.1:g.78086442G>A

NC\_000017.9:g.75701037G>A

NG\_009822.1:g.16088G>A

ENST00000570803.6:c.1820G>A

ENST00000572080.2:c.1820G>A

ENST00000577106.6:c.1820G>A

ENST00000302262.8:c.1820G>A

ENST00000302262.7:c.1820G>A

ENST00000390015.7:c.1820G>A

ENST00000570716.1:n.260G>A

ENST00000572080.1:c.208G>A

ENST00000572803.1:n.434G>A

NM\_000152.3:c.1820G>A

NM\_001079803.1:c.1820G>A

NM\_001079804.1:c.1820G>A

NM\_000152.4:c.1820G>A

NM\_001079803.2:c.1820G>A

NM\_001079804.2:c.1820G>A

NM\_001079803.3:c.1820G>A

NM\_001079804.3:c.1820G>A

Likely Pathogenic

Met criteria codes **5**

PM2\_Supporting

PS3\_Moderate

PP3

PP4\_Moderate

PM3

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.1820G>A variant in GAA is a missense variant predicted to cause substitution of glycine by aspartic acid at amino acid 607 (p.Gly607Asp). Four probands with symptoms consistent with infantile-onset-Pompe disease have been reported with this variant (PMID: 29889338, 33301762, 37087815), three with documented deficiency of GAA activity (PMID: 33301762, 37097815) (PP4\_Moderate). All of these probands are homozygous this variant. This variant is absent in both gnomAD 2.1.1 and 4.0.0 (PM2\_Supporting). Expression of the variant in COS-7 cells resulted 2% wild-type GAA activity in one study (PMID: 14695532) and <2% wild-type GAA activity in a separate study (PMID: 19862843) (PS3\_Moderate). The computational predictor REVEL gives a score of 0.872 which is above the threshold predicting a damaging (>0.7) or benign (<0.5) impact on GAA function. Two other missense variants, c.1819G>T (p.Gly607Cys) (ClinVar Variation ID: 2118057) and c.1819G>A (p.Gly607Ser) (ClinVar Variation ID: 456385), in the same codon have been reported in patients with Pompe disease. However, these variants have not been classified by the ClinGen Lysosomal Diseases VCEP and, therefore, this evidence is not sufficient to meet PM5 at any strength. There is a ClinVar entry for this variant (Variation ID: 932221). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on specifications of the ClinGen Lysosomal Diseases VCEP (Specifications Version 2.0): PM3, PS3\_Moderate, PP4\_Moderate, PM2\_Supporting, PP3). (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on April 2, 2024)

Met criteria codes

|                |  |                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PM2_Supporting |  | This variant is absent in gnomAD v2.1.1 (PM2_Supporting). This variant is absent in gnomAD v4.0.0 (PM2_Supporting).                                                                                                                                                                                                                                                                                          |
| PS3_Moderate   |  | Expression of the variant in COS-7 cells resulted in 2% wild type GAA activity in cells and 0.6% in media, leading the variant to be described as severe, indicating that this variant may impact protein function (wild-type = 100%) (PMID: 14695532). COS-7 cells transfected with mutant GAA showed <2% WT activity, indicating this variant may impact protein function (PMID: 19862843) (PS3_Moderate). |
| PP3            |  | The computational predictor REVEL gives a score of 0.872 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3_Met).                                                                                                                                                                                                                                                |
| PP4_Moderate   |  | This variant has been detected in at least 4 patients reported to have Pompe disease including 3 individuals with reported laboratory values demonstrating deficient GAA activity and 1 for whom GAA activity was not reported (PMID: 29889338, 33301762, 37087815) (PP4_Moderate).                                                                                                                          |
| PM3            |  | This variant has been detected in 4 individuals with Pompe disease, all of which were homozygous for the c.1820G>A (p.Gly607Asp) variant (PMID: 29889338, 33301762, 37087815). (2 x 0.5 points = 1 point (PM3_Met)).                                                                                                                                                                                         |

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