

Variant: NM_000152.5(GAA):c.1903A>G (p.Asn635Asp)

Version: 1.0

CA401369854 [↗](#)

1348299 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 9ca28db3-48b9-4706-80db-f4d8c9b1f50e

Approved on: 2023/12/20

Published on: 2023/12/22

HGVS expressions

NM_000152.5(GAA):c.1903A>G (p.Asn635Asp)

NM_000152.5:c.1903A>G

NC_000017.11:g.80112890A>G

CM000679.2:g.80112890A>G

NC_000017.10:g.78086689A>G

CM000679.1:g.78086689A>G

NC_000017.9:g.75701284A>G

NG_009822.1:g.16335A>G

ENST00000570803.6:c.1903A>G

ENST00000572080.2:c.*41A>G

ENST00000577106.6:c.1903A>G

ENST00000302262.8:c.1903A>G

ENST00000302262.7:c.1903A>G

ENST00000390015.7:c.1903A>G

ENST00000570716.1:n.343A>G

ENST00000572080.1:c.322A>G

ENST00000572803.1:n.517A>G

NM_000152.3:c.1903A>G

NM_001079803.1:c.1903A>G

NM_001079804.1:c.1903A>G

NM_000152.4:c.1903A>G

NM_001079803.2:c.1903A>G

NM_001079804.2:c.1903A>G

NM_001079803.3:c.1903A>G

NM_001079804.3:c.1903A>G

Likely Pathogenic

Met criteria codes 4

PP4_Moderate

PM3

PM5_Supporting

PM2_Supporting

Not Met criteria codes 2

BP4

PP3

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.1903A>G variant in GAA is predicted to result in a missense substitution from asparagine to aspartate at amino acid 635 (p.Asn635Asp). The variant has been identified in at least 3 probands, all identified by positive newborn screen, with confirmatory GAA activity in dried blood spot of 1.0, 1.3, and 1.34 pmol/punch/hour (affected range <3.88); pseudodeficiency variants are confirmed to be absent (Clinical Diagnostic Laboratory, PMID: 37087815) (PP4_Moderate). Each of these individuals is compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP, either c.2238G>C (p.Trp746Cys), c.2560C>T (p.Arg854Ter), and c.-32-13T>G; phase not confirmed (Clinical diagnostic laboratory) (PM3). The highest population minor allele frequency in gnomAD v4.0. is 0.000003602 (4/1110350 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 0.518 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function. Another missense variant at the same amino acid position, c.1905C>A (p.Asn635Lys), has been reported in four Brazilian probands with Pompe disease (PMID: 19588081) and has been classified as likely pathogenic by the ClinGen LD VCEP (PM5_Supporting). There is a ClinVar entry for this variant (Variation ID: 1348299). In summary, this variant meets the criteria to e classified as likely pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PM3, PP4_Moderate, PM2_Supporting, PM5_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 20, 2023).

Met criteria codes

PP4_Moderate			The variant has been identified in at least 3 probands, all identified by positive newborn screen, with confirmatory GAA activity in dried blood spot of 1.0, 1.3, and 1.34 pmol/punch/hour (affected range <3.88). A fourth patient has borderline GAA activity of 4.0 pmol/punch/hour; pseudodeficiency variants are confirmed to be absent in all four patients (Clinical Diagnostic Laboratory, PMID: 37087815) (PP4_Moderate).
PM3			Thee patients with confirmed deficient GAA activity in dried blood spots, are compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP, either c.2238G>C (p.Trp746Cys), c.2560C>T (p.Arg854Ter), and c.-32-13T>G; phase not confirmed (Clinical diagnostic Laboratory). 3 x 0.5 points. A fourth patient, with borderline GAA activity is compound heterozygous for the variant and c.841C>T (p.Arg281Trp), which has been classified as laikley pathogenic by the ClinGen LD VCEP; this patient was not ncluded because the GAA activity, although low, was above the affected range.
PM5_Supporting			Another missense variant at the same amino acid position, c.1905C>A (p.Asn635Lys), has been reported in four Brazilian probands with Pompe disease (PMID: 19588081) and has been classified as likely pathogenic by the ClinGen LD VCEP (PM5_Supporting).
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.0. is 0.000003602 (4/1110350 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).

Not Met criteria codes

BP4			The computational predictor REVEL gives a score of 0.518 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function.
PP3			The computational predictor REVEL gives a score of 0.518 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function.

Curation History 		
<div><div></div><div></div><div></div></div>		
Showing 1 to 1 of 1 rows		
<div></div>		

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.