

Variant: NM_000152.5(GAA):c.1905C>A (p.Asn635Lys)

Version: 1.0

CA401369859 [↗](#)

632823 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: e38ce100-2ea4-442a-a85d-b69dbf037f86

Approved on: 2023/11/21

Published on: 2023/12/7

HGVS expressions

NM_000152.5(GAA):c.1905C>A (p.Asn635Lys)

NM_000152.5:c.1905C>A

NC_000017.11:g.80112892C>A

CM000679.2:g.80112892C>A

NC_000017.10:g.78086691C>A

CM000679.1:g.78086691C>A

NC_000017.9:g.75701286C>A

NG_009822.1:g.16337C>A

ENST00000570803.6:c.1905C>A

ENST00000572080.2:c.*43C>A

ENST00000577106.6:c.1905C>A

ENST00000302262.8:c.1905C>A

ENST00000302262.7:c.1905C>A

ENST00000390015.7:c.1905C>A

ENST00000570716.1:n.345C>A

ENST00000572080.1:c.324C>A

ENST00000572803.1:n.519C>A

NM_000152.3:c.1905C>A

NM_001079803.1:c.1905C>A

NM_001079804.1:c.1905C>A

NM_000152.4:c.1905C>A

NM_001079803.2:c.1905C>A

NM_001079804.2:c.1905C>A

NM_001079803.3:c.1905C>A

NM_001079804.3:c.1905C>A

Likely Pathogenic

Met criteria codes 4

PM3_Strong

PS3_Moderate

PP4

PM2_Supporting

Not Met criteria codes 3

BP4

PP3

PM5

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.1905C>A variant in GAA is predicted to result in the substitution of asparagine by lysine at amino acid 635 (p.Asn635Lys). The variant has been identified in four probands from Brazil, three of whom were diagnosed with infantile onset Pompe disease (IOPD), with symptoms that included hypotonia, cardiomegaly, and respiratory distress, and death in the first year of life. The fourth patient has late onset Pompe disease (LOPD). No GAA activity was available for any of these individuals (PMID: 19588081) (PP4). Two of these patients have been reported to be compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP; c.2501_2502delCA (p.Thr834Argfs48Ter) in a patient with IOPD, and c.-32-3C>A in a patient with LOPD. The phase was not confirmed. A further two patients are homozygous for the variant (PMID: 19588081)(PM3_Strong). This variant results in 0% GAA activity in cells and 0.1% GAA activity in medium and is abnormally synthesized and processed when expressed in COS-7 or HEK293T cells, and was classified as Class B ("potentially less severe") by Kroos et al, 2012 (PMID: 22644586) (PS3_Moderate). The computational predictor REVEL gives a score of 0.61 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function. The highest population minor allele frequency in gnomAD v4.0. is 0.00002522 (1/39644 alleles) in the East Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). Another missense variant at the same amino acid position, c.1903A>G (p.Asn635Asp), has been reported in individuals with Pompe disease (PMID: 37087815, Clinical diagnostic laboratory). The evidence from c.1905C>A (p.Asn635Lys) will be used to support the classification of c.1903A>G (p.Asn635Asp) and is not included here to avoid circular logic. There is a ClinVar entry for this variant (Variation ID: 632823). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: PM3, PS3_Moderate, PP4, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases VCEP on November 21, 2023)

Met criteria codes

PM3_Strong			Two patients have been reported to be compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP, c.2501_2502delCA (p.Thr834Argfs48Ter) or c.-32-3C>A. The phase is not confirmed (2 x 0.5). A further two probands are homozygous for the variant (PMID: 19588081) (2 x 0.5). Total 2 points (PM3_Strong).
PS3_Moderate			This variant results in 0% GAA activity in cells and 0.1% GAA activity in medium and is abnormally synthesized and processed when expressed in COS-7 or HEK293T cells, and was classified as Class B ("potentially less severe") by Kroos et al, 2012 (PMID: 22644586) (PS3_Moderate)
PP4			The variant has been identified in 4 probands from Brazil, three of whom were diagnosed with infantile onset Pompe disease, with symptoms that included hypotonia, cardiomegaly, and respiratory distress, and death in the first year of life. The fourth patient has late onset Pompe disease. No GAA activity was available for any of these individuals (PMID: 19588081) (PP4).
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.0. is 0.00002522 (1/39644 alleles) in the East Asian 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 0.61 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 0.61 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function.
PM5			Another missense variant at the same amino acid position, c.1903A>G (p.Asn635Asp), has been reported in individuals with Pompe disease (PMID: 37087815, Clinical diagnostic laboratory). The evidence from c.1905C>A (p.Asn635Lys) will be used to support the classification of c.1903A>G (p.Asn635Asp) and is not included here to avoid circular logic.

Curation History 

Showing 1 to 1 of 1 rows

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.