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Variant: NM_000152.5(GAA):c.1645G>A (p.Gly549Arg)

Version: 1.0

CA401368765

2202283 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: c42af56d-6852-48ef-86d3-a78234c654dc
Approved on: 2026/6/2
Published on: 2026/7/6

HGVS expressions

NM_000152.5:c.1645G>A
NM_000152.5(GAA):c.1645G>A (p.Gly549Arg)
NC_000017.11:g.80111991G>A
CM000679.2:g.80111991G>A
NC_000017.10:g.78085790G>A
CM000679.1:g.78085790G>A
NC_000017.9:g.75700385G>A
NG_009822.1:g.15436G>A
ENST00000570803.6:c.1645G>A
ENST00000572080.2:c.1645G>A
ENST00000577106.6:c.1645G>A
ENST00000302262.8:c.1645G>A
ENST00000302262.7:c.1645G>A
ENST00000390015.7:c.1645G>A
ENST00000572080.1:c.33G>A
ENST00000572803.1:n.259G>A
NM_000152.3:c.1645G>A
NM_001079803.1:c.1645G>A
NM_001079804.1:c.1645G>A
NM_000152.4:c.1645G>A
NM_001079803.2:c.1645G>A
NM_001079804.2:c.1645G>A
NM_001079803.3:c.1645G>A
NM_001079804.3:c.1645G>A

Likely Pathogenic

Met criteria codes 5

PS3_Supporting PS1_Moderate PM2_Supporting PP3 PP4

Not Met criteria codes 1

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
Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1645G>A variant in GAA is a missense variant predicted to cause substitution of glycine by arginine at amino acid 549 (p.Gly549Arg). This variant is absent in gnomAD v4.1.1 (PM2_Supporting). This variant has been reported in two probands diagnosed with Pompe disease. The first proband, diagnosed with juvenile-onset Pompe disease, was reported to have deficient GAA activity but values were not provided. This individual was reported to be compound heterozygous for this variant and an unidentified variant (PMID: 14695532). The second proband, diagnosed with infantile-onset Pompe disease, was also reported to have deficient GAA activity levels but values were not provided. This individual was reported to be compound heterozygous for this variant and an unidentified variant (PMID: 40225932) (PP4, PM3_Not Met). Expression of the variant in COS cells resulted in 13.0% wild-type GAA activity, 3.0% wild-type GAA activity in medium, and 18.6% glycogen compared to wild-type cells. Additionally, an aberrant pattern of processing was observed via Western blot, indicating the variant may impact protein synthesis (PMID: 14695532) (PS3_Supporting). The computational predictor REVEL gives a score of 0.878 which is above the threshold predicting a damaging impact on GAA function (>0.7) (PP3). The same amino acid change (p.Gly549Arg), resulting from a different nucleotide change (c.1645G>C; ClinVar Variation ID 3769497), is classified as likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (Accession: SCV006333385.1) (PS1_Moderate). There is a ClinVar entry for this variant (Variation ID: 2202283). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Lysosomal Diseases VCEP (Specifications Version 2.0.0): PM2_Supporting, PP3, PS1_Moderate, PS3_Supporting, PP4. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel, June 2, 2026).

Met criteria codes

PS3_Supporting	✔	Expression of the variant in COS cells resulted in 13.0% wild-type GAA activity, 3.0% wild-type GAA activity in medium, and 18.6% glycogen of wild-type cells. Western blot analysis showed an aberrant pattern of processing (referred to as type C) and described as having a mild effect. PS3_Supporting.
PS1_Moderate	✔	The same amino acid change (p.Gly549Arg), resulting from a different nucleotide change (c.1645G>C; ClinVar Variation ID 3769497), is classified as likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (Accession: SCV006333385.1). PS1_Moderate.
PM2_Supporting	✔	This variant is absent in gnomAD v4.1.1. (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.878 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PP4	✔	At least two patients with this were noted to have deficient GAA activity but results were not provided. One individual with confirmed IOPD showed GAA enzyme activity levels below the cutoff via DBS testing (cutoff = 2.0 umol/L/h), but values not provided (PMID: 40225932). A second individual with with juvenile-onset Pompe disease (onset after first year, but before adulthood, and prolonged survival) was noted to have deficient GAA activity but values were not provided (PMID: 14695532). PP4_Met.

Not Met criteria codes

PM3		✖	This variant has been detected in two individuals with Pompe disease. Of those individuals, both were compound heterozygous for the variant and a second variant which was not identified. None of these were confirmed in trans (PMID: 14695532, 40225932). Zero individuals were homozygous for this variant. Zero points. PM3_Not met.

Curation History

Showing 1 to 1 of 1 rows

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