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Variant: NM_000152.5(GAA):c.1843G>A (p.Gly615Arg)

Version: 2.0

CA273955

188786 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 65500b97-e3f4-4f6a-a495-6a030c5a7eba
Approved on: 2026/3/3
Published on: 2026/3/3

HGVS expressions

NM_000152.5(GAA):c.1843G>A (p.Gly615Arg)
NM_000152.5:c.1843G>A
NC_000017.11:g.80112666G>A
CM000679.2:g.80112666G>A
NC_000017.10:g.78086465G>A
CM000679.1:g.78086465G>A
NC_000017.9:g.75701060G>A
NG_009822.1:g.16111G>A
ENST00000570803.6:c.1843G>A
ENST00000572080.2:c.1843G>A
ENST00000577106.6:c.1843G>A
ENST00000302262.8:c.1843G>A
ENST00000302262.7:c.1843G>A
ENST00000390015.7:c.1843G>A
ENST00000570716.1:n.283G>A
ENST00000572080.1:c.231G>A
ENST00000572803.1:n.457G>A
NM_000152.3:c.1843G>A
NM_001079803.1:c.1843G>A
NM_001079804.1:c.1843G>A
NM_000152.4:c.1843G>A
NM_001079803.2:c.1843G>A
NM_001079804.2:c.1843G>A
NM_001079803.3:c.1843G>A
NM_001079804.3:c.1843G>A

Pathogenic

Met criteria codes 5

PP3 | PM3_Very Strong | PP4_Moderate | PS3_Supporting | PM2_Supporting

Not Met criteria codes 1

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

Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5: c.1843G>A variant in GAA is a missense variant predicted to cause substitution of glycine by arginine at amino acid 615 (p.Gly615Arg). At least 17 patients with a diagnosis of Pompe disease have been reported with this variant. Where data is available, these patients are all of East Asian descent. Most of these patients have been diagnosed with infantile-onset Pompe disease, with documentation of hypertrophic cardiomyopathy and hypotonia, as well as laboratory values showing deficient GAA activity <10% GAA activity in cultured fibroblasts and/or GAA activity in the affected range in leukocytes or dried blood spots (PMIDs: 15366815, 16860134, 18458862, 25037089, 32711049, 37542277 40952111) and on enzyme replacement therapy (PMIDs: 16860134, 25037089) (PP4_Moderate). At least 9 patients are compound heterozygous, phase unknown, for the variant and another variant in GAA that has been classified as pathogenic for Pompe disease by the ClinGen LD VCEP including c.1411_1414del (PMID: 32711049, 40952111; 2 x 0.5 points), c.1935C>A (p.Asp645Glu) (PMID: 18458862, 32711049, 37542277, 4 patients, max 2 x 0.5 points), c.2815_2816delGT (PMID: 37542277, 0.5 points), c.2238G>A (p.Trp746Ter) (PMID: 16860134, 0.5), and c.-32-13T>G (PMID: 18607768, 0.5 points); and one patient is compound heterozygous for a likely pathogenic variant, c.796C > T (p.Pro266Ser) (PMID: 40952111, 0.25 points). At least 2 patients are homozygous for the variant (PMID: 15366815, 25037089, 32711049, max 2 x 0.5). Total for PM3 = 4.75 (PM3_VeryStrong). A further 8 patients are compound heterozygous for the variant and a second variant in GAA (c.1933G>C (p.Asp645His) (PMID: 40952111, n=4); c.625T > C (p.Tyr209His) (PMID: 40952111); c.2563G> C p.(Gly855Arg) (PMID: 40952111); c.1723T > C p.(Tyr575His) (PMID: 40952111), and c.1832G>A (p.Gly611Asp) (PMID: 24269976). The allelic data from these patients will be used in the classification of the second variant and will not be included here to avoid circular logic. Additional patients have been reported in the literature, but the data was not included because the cDNA change for the variant was not provided, or a second GAA variant was not identified (PMIDs: 10338092, 21757382, 40952111). The highest population minor allele frequency in gnomAD v4.1.0. is 0.0001115 (5/44842 alleles) in the East Asian population, which is lower than the ClinGen LD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). When expressed in COS cells, the variant resulted in <2% GAA activity (PMID 19862843) (PS3_Supporting). The computational predictor REVEL gives a score of 0.989 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Two other missense variants have been reported at this amino acid position - c.1844G>T (p.Gly615Val) (ClinVar Variation ID: 1002225), c.1844G>A (p.Gly615Glu) (ClinVar Variation ID: 972758). The classification of p.Gly615Arg will be used to support the classification of these other variants and is not included here to avoid circular logic. There is a ClinVar entry for this variant (Variation ID: 188746. In summary, this variant meets the criteria to be classified as Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PM3_Very Strong, PP4_Moderate, PS3_Supporting, PM2_Supporting, PP3. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on March 3, 2026)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.989 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM3_Very Strong	✔	At least 9 patients are compound heterozygous, phase unknown, for the variant and another variant in GAA that has been classified as pathogenic for Pompe disease by the ClinGen LD VCEP including c.1411_1414del (PMID: 32711049, 40952111; 2 x 0.5 points), c.1935C>A (p.Asp645Glu) (PMID: 18458862, 32711049, 37542277, 4 patients, max 2 x 0.5 points), c.2815_2816delGT (PMID: 37542277, 0.5 points), c.2238G>A (p.Trp746Ter) (PMID: 16860134, 0.5), and c.-32-13T>G (PMID: 18607768, 0.5 points); and one patient is compound heterozygous for a likely pathogenic variant, c.796C > T (p.Pro266Ser) (PMID: 40952111, 0.25 points). At least 2 patients are homozygous for the variant (PMID: 15366815, 25037089, 32711049, max 2 x 0.5). Total for PM3 = 4.75 (PM3_VeryStrong). A further 8 patients are compound heterozygous for the variant and a second variant in GAA (c.1933G>C (p.Asp645His) (PMID: 40952111, n=4); c.625T > C (p.Tyr209His) (PMID: 40952111); c.2563G> C p.(Gly855Arg) (PMID: 40952111); c.1723T>C p.(Tyr575His) (PMID: 40952111), and c.1832G>A (p.Gly611Asp) (PMID:

24269976). The allelic data from these patients will be used in the classification of the second variant and will not be included here to avoid circular logic. Additional patients have been reported in the literature, but the data was not included because the cDNA change for the variant was not provided, or a second GAA variant was not identified (PMIDs: 10338092, 21757382, 40952111). As noted above, total for PM3 = 4.75 points (PM3_VeryStrong).

PP4_Moderate	✔	At least 17 patients with a diagnosis of Pompe disease have been reported with this variant. Where data is available, these patients are all of East Asian descent. Most of these patients have been diagnosed with infantile onset Pompe disease, with documentation of hypertrophic cardiomyopathy and hypotonia, as well as laboratory values showing deficient GAA activity <10% GAA activity in cultured fibroblasts and/or GAA activity in the affected range in leukocytes or dried blood spots (PMIDs: 15366815, 16860134, 18458862, 25037089, 32711049, 37542277 40952111) and on enzyme replacement therapy (PMIDs: 16860134, 25037089) (PP4_Moderate).
PS3_Supporting	✔	When expressed in COS cells, the variant resulted in <2% GAA activity (PMID 19862843).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.0001115 (5/44842 alleles) in the East Asian population, which is lower than the ClinGen LD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Not Met criteria codes

PM5	✖	Two other missense variants have been reported at this amino acid position - c.1844G>T (p.Gly615Val) (ClinVar Variation ID: 1002225), c.1844G>A (p.Gly615Glu) (ClinVar Variation ID: 972758). The classification of p.Gly615Arg will be used to support the classification of these other variants and is not included here to avoid circular logic.

Curation History

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