The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000152.4(GAA):c.1942G>A (p.Gly648Ser)

Version: 1.1

CA274102

188902 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2485e980-b2ce-432e-871f-861aec685091
Approved on: 2023/7/3
Published on: 2023/9/5

HGVS expressions

NM_000152.4(GAA):c.1942G>A (p.Gly648Ser)
NM_000152.4:c.1942G>A
NC_000017.11:g.80112929G>A
CM000679.2:g.80112929G>A
NC_000017.10:g.78086728G>A
CM000679.1:g.78086728G>A
NC_000017.9:g.75701323G>A
NG_009822.1:g.16374G>A
ENST00000570803.6:c.1942G>A
ENST00000572080.2:c.*80G>A
ENST00000577106.6:c.1942G>A
ENST00000302262.8:c.1942G>A
ENST00000302262.7:c.1942G>A
ENST00000390015.7:c.1942G>A
ENST00000570716.1:n.382G>A
ENST00000572080.1:c.361G>A
ENST00000572803.1:n.556G>A
NM_000152.3:c.1942G>A
NM_001079803.1:c.1942G>A
NM_001079804.1:c.1942G>A
NM_001079803.2:c.1942G>A
NM_001079804.2:c.1942G>A
NM_000152.5:c.1942G>A
NM_001079803.3:c.1942G>A
NM_001079804.3:c.1942G>A

Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PS3_Supporting PP4_Moderate PM3_Very Strong

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.1942G>A (p.Gly648Ser) variant in GAA is a missense variant with a highest population minor allele frequency in gnomAD v2.1.1 of 0.00034 (10/29720 alleles) in the S. Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). At least 18 patients with a diagnosis of Pompe disease have been reported with this variant including those with documented deficient GAA activity and/or symptoms consistent with infantile onset Pompe disease and/or on enzyme replacment therapy (PMIDs 9535769, 17573812, 26497565, 29422078, 30214072, 31510962) (PP4_Moderate). In a study of the Maroon population of French Guiana, 9 out of 15 probands with "enzymatically confirmed" infantile onset Pompe disease were compound heterozygous for c.1942G>A (p.Gly648Ser) and c.2560C>T (p.Arg854Ter), a variant which has been classified as pathogenic by the ClinGen LD VCEP. The two variants are assumed to be in trans based on the high carrier frequency of both variants in that population. The carrier frequency of c.1942G>A (p.Gly648Ser) was 1 in 47 (9/425 women tested) (PMID: 29637184). Patients have also been reported who are compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP including c.2214G>A (p.Trp768Ter) (PMID: 26575883) and c.-32-13T>G (2 patients, PMIDs: 17643989, 25455803, 27193587). In addition, at least 3 patients are homozygous for the variant (PMID: 26497565, 29122469, 29889338, 30214072) (PM3_VeryStrong). Patients compound heterozygous for the variant and c.1076-22T>G (17643989, 25455803), c.2646+2T>A (PMID: 29422078), and c.1099T>C (p.Trp367Arg) (PMID: 31510962) have also been reported. However, the in trans data from these patients will be used in the assessment of the second variant and was not included here in order to avoid circular logic. When expressed in SV40_immortalized GAA deficient fibroblasts, the enzyme activity was "negligible" (PMID: 9535769), and when expressed in COS cells, the variant resulted in <2% wild type GAA activity (PMID: 19862843) (PS3_Supporting). The score for the REVEL meta-predictor, 0.98, also supports that the variant has a deleterious impact on GAA function (PP3). Another amino acid substitution at the same position has been reported in at least one individual with Pompe disease c.1943G>A (p.Gly648Asp) (PMIDs 22644586, 23146291, 23843830) (note that this data will be used in the classification of p.Gly648Asp and was not used here in order to avoid a circular argument). There is a ClinVar entry for this variant (Variation ID: 188902). In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Diseases VCEP (Specifications Version 2.0): PM3_VeryStrong, PP4_Moderate, PP3, PS3_Supporting, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases VCEP, July 3, 2023)

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00034 (10/29720 alleles) in the S. Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PP3	✔	REVEL (in silico meta predictor for missense changes) score = 0.98 which is higher than the LSD VCEP threshold for PP3, and therefore meets this criterion.
PS3_Supporting	✔	When expressed in SV40_immortalized GAA deficient fibroblasts, the enzyme activity was "negligible" (PMID 9535769), and when expressed in COS cells, the variant resulted in <2% wild type GAA activity (PMID 19862843) (PS3_Supporting)
PP4_Moderate	✔	At least 18 probands with this variant and a diagnosis of Pompe disease have been reported. This includes individuals with documented deficient GAA activity <10% normal in lymphocytes, leukocytes, or muscle samples, or <30% normal in cultured fibroblasts, or in the affected range in a clinically validated assay have been reported (PMIDs 9535769, 17573812, 26497565, 29422078, 30214072, 31510962), patients reported to be on ERT (PMID: 26497565, 29422078, 31510962). (PP4_Moderate).

PM3_Very Strong		✔	At least 12 probands are compound heterozygous for the variant and a variant that has been classified as pathogenic for Pompe disease. This includes 9 probands and two siblings from the Maroon population in French Guiana who are compound heterozygous for c.1942G>A (p.Gly648Ser) and c.2560C>T (p.Arg854Ter), all assumed to be in trans based on the carrier frequency for both of these variants in that population; approximately 1 in 47 for c.1942G>A (p.Gly648Ser) and 1 in 71 for c.2560C>T (p.Arg854Ter) (PMID: 29637184) (2 points). Patients have also been reported who are compound heterozygous for (c.2214G>A (p.Trp768Ter) (PMID: 26575883) (0.5 points) and c.-32-13T>G (2 patients, PMIDs: 17643989, 25455803, 27193587), phase unknown (2 x 0.5 points). In addition, at least 3 patients are homozygous for the variant (PMID: 26497565, 29122469, 29889338, 30214072) (1 point). Patients compound heterozygous for the variant and c.1076-22T>G (17643989, 25455803), c.2646+2T>A (PMID: 29422078), and c.1099T>C (p.Trp367Arg) (PMID: 31510962) have also been reported. However, the in trans data from these patients will be used in the assessment of the second variant and was not included here in order to avoid circular logic. Total points for PM3 = 4.5 points (PM3_VeryStrong).

Not Met criteria codes

PM5		✖	Another amino acid substitution at the same position has been reported, c.1943G>A (p.Gly648Asp) (PMIDs 22644586, 23146291, 23843830) (note that this data will be used in the classification of p.Gly648Asp and was not used here in order to avoid a circular argument).

Curation History

Showing 1 to 2 of 2 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.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.