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_000152.5(GAA):c.1927G>A (p.Gly643Arg)

Version: 1.0

CA116596

4023 (ClinVar)

Gene: GAA
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: c9c050ca-36c2-4f8f-8ced-4770e7d71fee
Approved on: 2024/6/6
Published on: 2024/6/6

HGVS expressions

NM_000152.5:c.1927G>A
NM_000152.5(GAA):c.1927G>A (p.Gly643Arg)
NM_000152.5(GAA):c.1927G>A
NC_000017.11:g.80112914G>A
CM000679.2:g.80112914G>A
NC_000017.10:g.78086713G>A
CM000679.1:g.78086713G>A
NC_000017.9:g.75701308G>A
NG_009822.1:g.16359G>A
ENST00000570803.6:c.1927G>A
ENST00000572080.2:c.*65G>A
ENST00000577106.6:c.1927G>A
ENST00000302262.8:c.1927G>A
ENST00000302262.7:c.1927G>A
ENST00000390015.7:c.1927G>A
ENST00000570716.1:n.367G>A
ENST00000572080.1:c.346G>A
ENST00000572803.1:n.541G>A
NM_000152.3:c.1927G>A
NM_001079803.1:c.1927G>A
NM_001079804.1:c.1927G>A
NM_000152.4:c.1927G>A
NM_001079803.2:c.1927G>A
NM_001079804.2:c.1927G>A
NM_001079803.3:c.1927G>A
NM_001079804.3:c.1927G>A

Pathogenic

Met criteria codes 5

PM3_Very Strong | PP4_Moderate | PS3_Moderate | PP3 | PM2_Supporting

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.1927G>A variant in GAA is predicted to result in the substitution of glycine by arginine at amino acid 643 (p.Gly643Arg). Numerous individuals have been reported with this variant and specific features of Pompe disease including GAA activity <10% normal in lymphocytes/leukocytes/muscle samples/<30% normal in cultured fibroblasts/ in the affected range in a clinically validated dried blood spot assay; patients with specific features of infantile onset Pompe disease (including cardiac features and hypotonia_, and on enzyme replacement therapy (PMIDs: 8401535, 17723315, 23430912, 23609349 24158270, 25783438, 26349193, 26497565) (PP4_Moderate). The variant has been reported in patients with Pompe disease who are compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP. In these cases, the second variant includes c.-32-13T>G (ClinVar Variation ID: 4027) (at least 10 cases; maximum 2 x 0.5 points; PMID: 16917947, 18607768, 20308911, 23609349, 24158270, 25396301, 25783438, 27862019, 30155607), c.525delT (ClinVar Variation ID: 4033, SCV001443331.1 (2 cases, 2 x 0.5 points) (PMID: 18429042, 23430912), c.1064T>C (p.Leu355Pro) (ClinVar Variation ID: 284093, SCV001371747.2) (0.5 points, PMID: 18429042), c.236_246del (p.Pro79fsTer) (ClinVar Variation ID: 371302, SCV001443298.1 (0.5 points, PMID: 19588081), and c.2662G>T (p.Glu888Ter) (ClinVar Variation ID: 578595, SCV001371767.1 (0.5 points, PMID: 28394184). First cousins have been reported who are compound heterozygous for the variant (inherited from their heterozygous mothers who are sisters) and another pathogenic variant in GAA variant; c.1655T>C (p.Leu552Pro) (ClinVar Variation ID: 279811, SCV001371750.2) in one individual, and "deletion of exon 18" in the other individual (PMID: 26349193). In each case, the second variant was shown to be inherited from the father. Although the genotypes are different, only one case will be counted from this family, as they are related (1 point, pathogenic variant confirmed in trans). At least 2 cases are homozygous for the variant (max 2 x 0.5 points, PMID: 18429042, 24002816, 26497565, 30023291). Additional cases are compound heterozygous for the variant and either c.2040G>A (PMID: 17723315) or c.2173C>T (p.Arg725Trp) (PMID: 8401535). The in trans data for these patients was used in the classification of the other variant as is not included here to avoid circular logic. Finally, the variant is reported in other cases and publications without sufficient evidence to apply PM3 (PMID:9521422, 17915575, 19862843, 22081099, 29880332) Additional cases may be available in the literature but PM3 is already applied at very strong (>5 points) (PM3_VeryStrong). The highest population minor allele frequency (MAF) in gnomAD v2.1.1 is 0.00003667 (4/109080 alleles) in the European non-Finnish population. In gnomAD v4.1, the MAF is 0.00003224 (40/1178798 alleles) in the European non-Finnish population. Both are lower than the ClinGen LD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). The activity of this variant, when expressed in COS cells, has been analyzed in several studies (PMIDs: 8401535, 9521422, 19862843) and varies from <2%-6% with 4MUG and ~3% wild type activity in cells with glycogen. Pulse chase analysis showed that the protein is abnormally processed, with most of the protein remaining as precursor (PMID: 8401535) (PS3_Moderate). The computational predictor REVEL gives a score of 0.976 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). There is a ClinVar entry for this variant (Variation ID: 4023). 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 VCEP: PM3_VeryStrong, PS3_Moderate, PP4_Moderate, PP3, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on June 6, 2024)

Met criteria codes

PM3_Very Strong	✔	The variant has been reported in patients with Pompe disease who are compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP. In these cases, the second variant includes c.-32-13T>G (ClinVar Variation ID: 4027) (at least 10 cases; maximum 2 x 0.5 points; PMID: 16917947, 18607768, 20308911, 23609349, 24158270, 25396301, 25783438, 27862019, 30155607), c.525delT (ClinVar Variation ID: 4033, SCV001443331.1 (2 cases, 2 x 0.5 points) (PMID: 18429042, 23430912), c.1064T>C (p.Leu355Pro) (ClinVar Variation ID: 284093, SCV001371747.2) (0.5 points, PMID: 18429042), c.236_246del (p.Pro79fsTer) (ClinVar Variation ID: 371302, SCV001443298.1 (0.5 points, PMID: 19588081), and c.2662G>T (p.Glu888Ter) (ClinVar Variation ID: 578595, SCV001371767.1 (0.5 points, PMID: 28394184). First cousins have been

reported who are compound heterozygous for the variant (inherited from their heterozygous mothers who are sisters) and another pathogenic variant in GAA variant; c.1655T>C (p.Leu552Pro) (ClinVar Variation ID: 279811, SCV001371750.2) in one individual, and "deletion of exon 18" in the other individual (PMID: 26349193). In each case, the second variant was shown to be inherited from the father. Although the genotypes are different, only one case will be counted from this family, as they are related (1 point, pathogenic variant confirmed in trans). At least 2 cases are homozygous for the variant (max 2 x 0.5 points, PMID: 18429042, 24002816, 26497565, 30023291). Additional cases are compound heterozygous for the variant and either c.2040G>A (PMID: 17723315) or c.2173C>T (p.Arg725Trp) (PMID: 8401535). The in trans data for these patients was used in the classification of the other variant as is not included here to avoid circular logic. Finally, the variant is reported in other cases and publications without sufficient evidence to apply PM3 (PMID:9521422, 17915575, 19862843, 22081099, 29880332) Additional cases may be available in the literature but PM3 is already applied at very strong (>5 points).

PP4_Moderate	✔	Numerous individuals have been reported with this variant and specific features of Pompe disease including GAA activity <10% normal in lymphocytes/leukocytes/muscle samples/<30% normal in cultured fibroblasts/ in the affected range in a clinically validated dried blood spot assay; patients with specific features of infantile onset Pompe disease (including cardiac features and hypotonia_, and on enzyme replacement therapy (PMIDs: 8401535, 17723315, 23430912, 23609349 24158270, 25783438, 26349193, 26497565) (PP4_Moderate).
PS3_Moderate	✔	The activity of this variant, when expressed in COS cells, has been analyzed in several studies (PMIDs: 8401535, 9521422, 19862843) and varies from <2%-6% with 4MUG and ~3% wild type activity in cells with glycogen. Pulse chase analysis showed that the protein is abnormally processed, with most of the protein remaining as precursor (PMID: 8401535) (PS3_Moderate).
PP3	✔	The computational predictor REVEL gives a score of 0.976 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM2_Supporting	✔	The highest population minor allele frequency (MAF) in gnomAD v2.1.1 is 0.00003667 (4/109080 alleles) in the European non-Finnish population. In gnomAD v4.1, the MAF is 0.00003224 (40/1178798 alleles) in the European non-Finnish population. Both are lower than the ClinGen LD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting)

Curation History

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