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.1941C>G (p.Cys647Trp)

Version: 1.0

CA8815554

550327 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: a3c3a3a7-7ae4-469a-8ead-80c01b286ac7
Approved on: 2022/11/15
Published on: 2022/11/28

HGVS expressions

NM_000152.5(GAA):c.1941C>G (p.Cys647Trp)
NM_000152.5:c.1941C>G
NC_000017.11:g.80112928C>G
CM000679.2:g.80112928C>G
NC_000017.10:g.78086727C>G
CM000679.1:g.78086727C>G
NC_000017.9:g.75701322C>G
NG_009822.1:g.16373C>G
ENST00000570803.6:c.1941C>G
ENST00000572080.2:c.*79C>G
ENST00000577106.6:c.1941C>G
ENST00000302262.8:c.1941C>G
ENST00000302262.7:c.1941C>G
ENST00000390015.7:c.1941C>G
ENST00000570716.1:n.381C>G
ENST00000572080.1:c.360C>G
ENST00000572803.1:n.555C>G
NM_000152.3:c.1941C>G
NM_001079803.1:c.1941C>G
NM_001079804.1:c.1941C>G
NM_000152.4:c.1941C>G
NM_001079803.2:c.1941C>G
NM_001079804.2:c.1941C>G
NM_001079803.3:c.1941C>G
NM_001079804.3:c.1941C>G

Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PS3_Supporting PP4_Moderate PM3_Very Strong

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.1941C>G variant in GAA is a missense variant that is predicted to result in substitution of cysteine by tryptophan at amino acid 647 (p.Cys647Trp). At least 10 patients with this variant have been reported to have Pompe disease including two with documented laboratory values showing deficiency of GAA, one of whom also had reported symptoms consistent with infantile onset Pompe disease (PMID: 7981676, 9535769, 17723315) (meeting PP4_Moderate), three patients with reported symptoms consistent with infantile onset Pompe disease (PMID: 7981676, 19588081, 22658377, 31510962), one patient on enzyme replacement therapy (PMID: 31086307) (all meeting PP4). Four patients are compound heterozygous for the variant and a variant in GAA that has been classified as pathogenic for Pompe disease including c.-32-13T>G (PMID: 25681614, 31931849; 2 patients), c.2481+110_2646+39del (exon 18 deletion, PMID: 7981676), and c.1655T>C (p.Leu552Pro) (PMID: 19588081), all phase unconfirmed. In another patient, the variant is confirmed in trans with an allele containing two pathogenic variants, c.1456_1468del (p.Ala486fsTer30) (confirmed de novo) and c.2238G>C (p.Trp746Cys) (PMID: 7981676), and two patients are homozygous for the variant (PMID: 9535769, 31510962) (PM3_Very Strong). In addition, two patients are compound heterozygous for the variant and either c.1846G>A (p.Asp616Asn) (PMID: 31086307) or c.1781G>C (p.Arg594Pro) (PMID: 19588081). The allelic data from these patients will be used in the classification of the second variant and is not included here to avoid circular logic. In another patient, no second variant was found (PMID: 25681614). When expressed in GAA-deficient SV40 immortalized fibroblasts, the variant resulted in <1% GAA activity compared to the normal control (PMID: 9535769) (PS3_Supporting).The computational predictor REVEL gives a score of 0.802 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). The highest continental population minor allele frequency in gnomAD v2.1.1 is 0.00002 (3/124712 alleles) in the European non-Finnish population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). Of note, the highest population minor allele frequency in gnomAD v2.1.1 is in the "other" population, 0.00014 (1/7006 alleles) which also meets the PM2_Supporting threshold. There is a ClinVar entry for this variant (Variation ID: 550327). In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG-AMP criteria met, as specified by the ClinGen Lysosomal Storage Disorders VCEP (Specifications Version 2.0): PM3_Very_Strong, PP4_Moderate, PP3, PS3_Supporting, PM2_Supporting. Classification approved by the ClinGen LSD VCEP on Nov. 15, 2022.

Met criteria codes

PM2_Supporting	✔	The highest continental population minor allele frequency in gnomAD v2.1.1 is 0.00002 (3/124712 alleles) in the European non-Finnish population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). Of note, the highest population minor allele frequency in gnomAD v2.1.1 is in the "other" population, 0.00014 (1/7006 alleles) which also meets the PM2_Supporting threshold.
PP3	✔	The computational predictor REVEL gives a score of 0.802 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PS3_Supporting	✔	When expressed in GAA-deficient SV40 immortalized fibroblasts, the variant resulted in <1% GAA activity compared to the normal control (PMID: 9535769) (PS3_Supporting).
PP4_Moderate	✔	At least 10 patients with this variant have been reported to have Pompe disease including two with documented laboratory values showing deficiency of GAA, one of whom also had reported symptoms consistent with infantile onset Pompe disease (PMID: 7981676, 9535769, 17723315) (meeting PP4_Moderate), three patients with reported symptoms consistent with infantile onset Pompe disease (PMID: 7981676, 19588081, 22658377, 31510962), one patient reported to be on enzyme replacement therapy (PMID: 31086307) (all meeting PP4), and three probands

plus one sibling reported to have Pompe disease but with insufficient data provided to apply PP4 (PMIDs: 19588081, 25681614, 31931849).

PM3_Very Strong ✔

Four patients are compound heterozygous for the variant and a variant in GAA that has been classified as pathogenic for Pompe disease including c.-32-13T>G (PMID: 25681614, 31931849; 2 patients, 2 x 0.5 points), c.2481+110_2646+39del (exon 18 deletion, PMID: 7981676, 0.5 points), and c.1655T>C (p.Leu552Pro) (PMID: 19588081, 0.5 points), all phase unconfirmed. In another patient, the variant is confirmed in trans with an allele containing two pathogenic variants, c.1456_1468del (p.Ala486fsTer30) (confirmed de novo) and c.2238G>C (p.Trp746Cys) (PMID: 7981676) (1 point), and two patients are homozygous for the variant (PMID: 9535769, 31510962, 2 x 0.5 points). Total 4 points (PM3_Very Strong). In addition, two patients are compound heterozygous for the variant and either c.1846G>A (p.Asp616Asn) (PMID: 31086307) or c.1781G>C (p.Arg594Pro) (PMID: 19588081). The allelic data from these patients will be used in the classification of the second variant and is not included here to avoid circular logic. In another patient, no second variant was found (PMID: 25681614).

Curation History

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