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.1432G>A (p.Gly478Arg)

Version: 1.3

CA8815317

551295 (ClinVar)

Gene: GAA
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: cac360bb-30f4-45c3-9c3b-3dd1b89561db
Approved on: 2024/11/5
Published on: 2024/12/17

HGVS expressions

NM_000152.5(GAA):c.1432G>A (p.Gly478Arg)
NM_000152.5(GAA):c.1432G>A
NM_000152.5:c.1432G>A
NC_000017.11:g.80110050G>A
CM000679.2:g.80110050G>A
NC_000017.10:g.78083849G>A
CM000679.1:g.78083849G>A
NC_000017.9:g.75698444G>A
NG_009822.1:g.13495G>A
ENST00000570803.6:c.1432G>A
ENST00000572080.2:c.1432G>A
ENST00000577106.6:c.1432G>A
ENST00000302262.8:c.1432G>A
ENST00000302262.7:c.1432G>A
ENST00000390015.7:c.1432G>A
NM_000152.3:c.1432G>A
NM_001079803.1:c.1432G>A
NM_001079804.1:c.1432G>A
NM_000152.4:c.1432G>A
NM_001079803.2:c.1432G>A
NM_001079804.2:c.1432G>A
NM_001079803.3:c.1432G>A
NM_001079804.3:c.1432G>A

Pathogenic

Met criteria codes 5

PP4_Moderate PS3_Moderate PP3 PM3_Strong 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.1432G>A variant in GAA is a missense variant predicted to cause substitution of glycine by arginine at amino acid 478 (p.Gly478Arg). At least seven probands with symptoms consistent with infantile-onset-Pompe disease or late-onset Pompe disease with documented deficiency of GAA activity have been reported with this variant (PMIDs 25998610, 25213570, 17616415, 28394184) (PP4_Moderate). Six of these probands are compound heterozygous for the variant and a variant classified as pathogenic by the ClinGen Lysosomal Diseases VCEP; the variants were confirmed in trans by parental testing for one of the patients (PM3_Strong). The highest population minor allele frequency in gnomAD v2.1,1 is 0.00002895 (Latino) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_supporting, meeting this criterion. Expression of the variant in COS7 cells resulted in <2% GAA activity in cells, indicating that this variant may impact protein function (PMID 22253258, 19862843) (PS3_Moderate). The computational predictor REVEL gives a score of 0.954 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: 551295, 2 star review status) with 2 submitters classifying the variant as Likely Pathogenic and 2 submitters classfying the variant as Pathogenic. In summary, this variant meets the criteria to be classified as Pathogenic for Pompe disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert panel (specifications Version 2.0): PM3_Strong, PP4_Moderate, PS3_Moderate, PP3, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on November 5, 2024)

Met criteria codes

PP4_Moderate	✔	At least 7 patient(s) with this variant had documented GAA deficiency with GAA activity in the affected range in muscle, cultured skin fibroblasts, leukocytes, lymphocytes, whole blood or dried blood spot, or were noted to have deficient GAA activity but results were not provided (PP4_Moderate).
PS3_Moderate	✔	Expression of the variant in COS-7 resulted in <2% wild type GAA activity, and the variant was described as Class B (“potentially less severe"), indicating that this variant may impact protein function (PMIDs 22253258, 19862843) (PS3_Moderate).
PP3	✔	REVEL score = 0.954 which is higher than the LSD VCEP threshold for PP3 (>0.75) and therefore meets this criterion.
PM3_Strong	✔	This variant has been detected in at least 7 individuals with Pompe disease. Of those individuals, 6 were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and 1 of those were confirmed in trans by family testing. 2.5 pts, PMIDs 25998610, 25213570, 17616415, 28394184 (PM3_Strong).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD is 0.00002895 (Latino) which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_supporting, meeting this criterion.

Curation History

Showing 1 to 4 of 4 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.