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.1222A>G (p.Met408Val)

Version: 1.1

CA8815236

371235 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: e8e8f441-1f7e-4b2e-8c9f-940203b26cb8
Approved on: 2024/5/6
Published on: 2024/5/8

HGVS expressions

NM_000152.4(GAA):c.1222A>G (p.Met408Val)
NM_000152.4:c.1222A>G
NC_000017.11:g.80108724A>G
CM000679.2:g.80108724A>G
NC_000017.10:g.78082523A>G
CM000679.1:g.78082523A>G
NC_000017.9:g.75697118A>G
NG_009822.1:g.12169A>G
ENST00000570803.6:c.1222A>G
ENST00000572080.2:c.1222A>G
ENST00000577106.6:c.1222A>G
ENST00000302262.8:c.1222A>G
ENST00000302262.7:c.1222A>G
ENST00000390015.7:c.1222A>G
NM_000152.3:c.1222A>G
NM_001079803.1:c.1222A>G
NM_001079804.1:c.1222A>G
NM_001079803.2:c.1222A>G
NM_001079804.2:c.1222A>G
NM_000152.5:c.1222A>G
NM_001079803.3:c.1222A>G
NM_001079804.3:c.1222A>G

Likely Pathogenic

Met criteria codes 4

PM3 PP4_Moderate PM2_Supporting PS3_Supporting

Not Met criteria codes 2

PP3 BP4

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.1222A>G variant in GAA is predicted to result in the substitution of methionine by valine at amino acid 408 (p.Met408Val). Four patients have been reported with this variant; three with infantile onset Pompe disease and documented values showing GAA deficiency, at least two of them treated with enzyme replacement therapy (PMID: 11738358, 26497565, 34995642). Another patient has later onset symptoms with reduction of urine Glc4 on enzyme replacement therapy (PMID: 21687968) (PP4_Moderate). One individual is compound heterozygous for the variant and a variant in GAA that has been classified as pathogenic by the ClinGen Lysosomal Diseases Variant Curation Expert Panel, c.1579del, confirmed in trans (PMID: 34995642) (ClinVar Variation ID: 952947). Another patient is homozygous for the variant (PMID: 26497565). Two patients are compound heterozygous for the variant and either c.1000G>A (p.Gly334Ser) (PMID: 21687968) or c.1408_1410del (PMID: 11738358); the allelic data for these two patients will be used in the classification of the other variant and is not included here to avoid circular logic (PM3). When expressed in COS-7 cells, this variant results in <2% wild type GAA activity (PMID 19862843) (PS3_Supporting). The computational predictor REVEL gives a score of 0.637 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00002 (2/111716 alleles) in the European, non-Finnish population. There is a ClinVar entry for this variant (Variation ID: 371235). In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease. The classification was first approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on May 26, 2020. Since then, the data for this variant have been re-evaluated. The classification of likely pathogenic was reapproved on May 6, 2024. GAA-specific ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PM3, PP4_Moderate, PS3_Supporting, PM2_Supporting.

Met criteria codes

PM3	✔	One individual is compound heterozygous for the variant and a variant in GAA that has been classified as pathogenic by the ClinGen Lysosomal Diseases Variant Curation Expert Panel, c.1579del (PMID: 34995642) (ClinVar Variation ID: 952947), confirmed in trans (1 point). Another patient is homozygous for the variant (0.5 points) (PMID: 26497565). Two patients are compound heterozygous for the variant and either c.1000G>A (p.Gly334Ser) (PMID: 21687968) or c.1408_1410del (PMID: 11738358); the allelic data for these patients will be used in the classification of the other variant and is not included here to avoid circular logic. Total 1.5 points (PM3).
PP4_Moderate	✔	Four patients have been reported with this variant; three with infantile onset Pompe disease and documented GAA deficiency, at least two of them treated with enzyme replacement therapy (PMID: 11738358, 26497565, 34995642). Another patient has later onset symptoms with reduction of urine Glc4 on enzyme replacement therapy (PMID: 21687968) (PP4_Moderate). Another individual, identified by newborn screening, was heterozygous for the variant and homozygous for pseudodeficiency variants (PMID: 20080426).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00002 (2/111716 alleles) in the European, non-Finnish population which is lower than the ClinGen Lysosomal Diseases VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PS3_Supporting	✔	This variant results in <2% GAA activity when expressed in COS-7 cells (PMID: 19862843) (PS3_Supporting).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.637 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function.

BP4		✖	The computational predictor REVEL gives a score of 0.637 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function.

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.