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Variant: NM_000152.5(GAA):c.2012T>G (p.Met671Arg)

Version: 1.0

CA220392

92469 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 384ff8fd-657f-4bd5-9cf8-babc202b3a10
Approved on: 2026/4/24
Published on: 2026/5/14

HGVS expressions

NM_000152.5(GAA):c.2012T>G (p.Met671Arg)
NM_000152.5:c.2012T>G
NC_000017.11:g.80112999T>G
CM000679.2:g.80112999T>G
NC_000017.10:g.78086798T>G
CM000679.1:g.78086798T>G
NC_000017.9:g.75701393T>G
NG_009822.1:g.16444T>G
ENST00000570803.6:c.2012T>G
ENST00000572080.2:c.*150T>G
ENST00000577106.6:c.2012T>G
ENST00000302262.8:c.2012T>G
ENST00000302262.7:c.2012T>G
ENST00000390015.7:c.2012T>G
ENST00000570716.1:n.452T>G
ENST00000572080.1:c.431T>G
NM_000152.3:c.2012T>G
NM_001079803.1:c.2012T>G
NM_001079804.1:c.2012T>G
NM_000152.4:c.2012T>G
NM_001079803.2:c.2012T>G
NM_001079804.2:c.2012T>G
NM_001079803.3:c.2012T>G
NM_001079804.3:c.2012T>G

Likely Pathogenic

Met criteria codes 5

PP4_Moderate PP3 PM3_Supporting PM2_Supporting PS3_Supporting

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.2012T>G variant in GAA is a missense variant predicted to cause substitution of methionine by arginine at amino acid 671 (p.Met671Arg). At least one patient with this variant had documented GAA deficiency with <1% of the normal mean control level of GAA activity in cultured fibroblasts, was diagnosed with infantile onset of Pompe disease, and was reported to be on enzyme replacement therapy for Pompe disease (PMID: 29122469, 16860134). (PP4_Moderate). This patient is compound heterozygous for the variant and a variant that meets the criteria to be classified as pathogenic for Pompe disease by the ClinGen LD VCEP (c.2189+459_3405del, p.Glu730_Cys952del), the phase was unconfirmed (PMID: 29122469) (PM3_Supporting). This variant is absent in gnomAD v4.1.0. (PM2_Supporting). Expression of the variant in COS cells resulted in <2% wild-type GAA activity, indicating that this variant may impact protein function (PMID: 19862843) (PS3_Supporting). The computational predictor REVEL gives a score of 0.864, which is above the threshold of 0.7, evidence that correlates with impact on GAA function (PP3). Three other missense variants in the same codon have been reported in patients with Pompe disease: (c.2012T>C, p.Met671Thr; ClinVar Variation ID: 855859), (c.2012T>A, p.Met671Lys; PMID: 26310554), and (c.2011A>G, p.Met671Val; PMID: 40225932). However, these variants have not yet been classified by the ClinGen Lysosomal Diseases VCEP (PM5 not met). There is a ClinVar entry for this variant (Variation ID: 92469). In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specification Version 2.0): PP4_Moderate, PP3, PS3_Supporting, PM2_Supporting, PM3_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on April 24, 2026)

Met criteria codes

PP4_Moderate	✔	At least one patient with this variant had documented GAA deficiency with <1% of the normal mean control level of GAA activity in cultured fibroblasts, was diagnosed with infantile onset of Pompe disease, and was reported to be on enzyme replacement therapy for Pompe disease (PMID: 29122469, 16860134). (PP4_Moderate).
PP3	✔	The computational predictor REVEL gives a score of 0.864 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM3_Supporting	✔	This variant has been detected in an individual with Pompe disease, who was compound heterozygous for the variant and a variant that meets the criteria to be classified as pathogenic by the ClinGen LD VCEP (c.2189+459_3405del, p.Glu730_Cys952del); the phase is unconfirmed (PMID: 29122469). 0.5 points (PM3_Supporting).
PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0. (PM2_Supporting).
PS3_Supporting	✔	Expression of the variant in COS cells resulted in <2% wild-type GAA activity, indicating that this variant may impact protein function (PMID: 19862843) (PS3_Supporting).

Not Met criteria codes

PM5	✖	Three other missense variants in the same codon have been reported in patients with Pompe disease - c.2012T>C (p.Met671Thr) (ClinVar Variation ID, 855859) c.2012T>A (p.Met671Lys) (PMID: 26310554), and c.2011A>G

p.Met671Val (PMID: 40225932). However, these variants have not yet been classified as pathogenic or likely pathogenic by the ClinGen Lysosomal Diseases VCEP (PM5 not met).

Curation History

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