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.953T>A (p.Met318Lys)

Version: 1.1

CA401364275

558700 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 43b12b81-6721-43db-a765-e1404dbfc75d
Approved on: 2026/9/1
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HGVS expressions

NM_000152.5(GAA):c.953T>A (p.Met318Lys)
NM_000152.5:c.953T>A
NC_000017.11:g.80107894T>A
CM000679.2:g.80107894T>A
NC_000017.10:g.78081693T>A
CM000679.1:g.78081693T>A
NC_000017.9:g.75696288T>A
NG_009822.1:g.11339T>A
ENST00000570803.6:c.953T>A
ENST00000572080.2:c.953T>A
ENST00000577106.6:c.953T>A
ENST00000302262.8:c.953T>A
ENST00000302262.7:c.953T>A
ENST00000390015.7:c.953T>A
NM_000152.3:c.953T>A
NM_001079803.1:c.953T>A
NM_001079804.1:c.953T>A
NM_000152.4:c.953T>A
NM_001079803.2:c.953T>A
NM_001079804.2:c.953T>A
NM_001079803.3:c.953T>A
NM_001079804.3:c.953T>A

Likely Pathogenic

Met criteria codes 6

PS3_Moderate PP4_Moderate PM2_Supporting PM3 PM5 PP3

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 2.0*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.953T>A variant in GAA is a missense variant predicted to cause substitution of methionine by lysine at amino acid 318 (p.Met318Lys). At least 3 patients with this variant were diagnosed with Pompe disease and had documented laboratory values showing GAA deficiency with in dried blood spot, or <1% GAA activity in fibroblasts (PMID: 18425781, 21484825, 36237614) (PP4_Moderate). Of those individuals, one was compound heterozygous for the variant and another variant in GAA that has been classified by the ClinGen LD VCEP as pathogenic for Pompe disease, c.1822C>T (p.Arg608Ter); the phase is unknown (PMID 21484825) (0.5 pt), and two patients, assumed to be unrelated, are homozygous for the variant (2 x 0.5 pt). Total 1.5 pts (PM3). This variant is absent from gnomAD v4.1.0. (PM2_Supporting). Expression of the variant in COS cells resulted in 3.2% wild type GAA activity and evidence of abnormal GAA synthesis and processing, leading the variant to be described as Class B (“potentially less severe”), indicating that this variant may impact protein function (PMID 22644586)(PS3_Moderate). The computational predictor REVEL gives a score of 0.926 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense variant at the same amino acid position, c.953T>C (p.Met318Thr) (ClinVar Variation ID: 4021) has been classified as pathogenic by the ClinGen LD VCEP (PM5). There is a ClinVar entry for this variant (Variation ID: 558700). In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease based on the GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PM3, PS3_Moderate, PP4_Moderate, PP3, PM2_Supporting (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on September 1, 2026)

Met criteria codes

PS3_Moderate	✔	Expression of the variant in COS cells resulted in 3.2% wild type GAA activity and evidence of abnormal GAA synthesis and processing, leading the variant to be described as Class B (“potentially less severe”), indicating that this variant may impact protein function (PMID 22644586)(PS3_Moderate).
PP4_Moderate	✔	At least 3 patients with this variant were diagnosed with Pompe disease and had documented laboratory values showing GAA deficiency with in dried blood spot, or <1% GAA activity in fibroblasts (PMID: 18425781, 21484825, 36237614) (PP4_Moderate).
PM2_Supporting	✔	This variant is absent in gnomAD v4.1.0. (PM2_Supporting).
PM3	✔	This variant has been detected in at least 3 individuals with Pompe disease. Of those individuals, one was compound heterozygous for the variant and another variant in GAA that has been classified by the ClinGen LD VCEP as pathogenic for Pompe disease, c.1822C>T (p.Arg608Ter); the phase is unknown (PMID 21484825) (0.5 pt), and two patients, assumed to be unrelated, are homozygous for the variant (2 x 0.5 pt). Total 1.5 pts (PM3).
PM5	✔	Another missense variant at the same amino acid position, c.953T>C (p.Met318Thr) (ClinVar Variation ID: 4021) has been classified as pathogenic by the ClinGen LD VCEP (PM5).
PP3	✔	The computational predictor REVEL gives a score of 0.926 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). SpliceAI predicts that the variant will have no impact on splicing.

Curation History

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