

Variant: NM_000152.5(GAA):c.1402A>T (p.Ile468Phe)

Version: 1.0

CA10605170 [↗](#)

285589 (ClinVar) [↗](#)

Gene: GAA ([HGNC:2548](#))

Condition: glycogen storage disease II ([MONDO:0009290](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: fe77d260-b9c5-48d1-945c-40012c36cf71

Approved on: 2023/12/19

Published on: 2023/12/22

HGVS expressions

NM_000152.5(GAA):c.1402A>T (p.Ile468Phe)

NM_000152.5:c.1402A>T

NC_000017.11:g.80110020A>T

CM000679.2:g.80110020A>T

NC_000017.10:g.78083819A>T

CM000679.1:g.78083819A>T

NC_000017.9:g.75698414A>T

NG_009822.1:g.13465A>T

ENST00000570803.6:c.1402A>T

ENST00000572080.2:c.1402A>T

ENST00000577106.6:c.1402A>T

ENST00000302262.8:c.1402A>T

ENST00000302262.7:c.1402A>T

ENST00000390015.7:c.1402A>T

NM_000152.3:c.1402A>T

NM_001079803.1:c.1402A>T

NM_001079804.1:c.1402A>T

NM_000152.4:c.1402A>T

NM_001079803.2:c.1402A>T

NM_001079804.2:c.1402A>T

NM_001079803.3:c.1402A>T

NM_001079804.3:c.1402A>T

Likely Pathogenic

Met criteria codes **4**

PP3

PM3

PM2_Supporting

PP4_Moderate

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**

Lysosomal Diseases VCEP

The NM_000152.5:c.1402A>T variant in GAA is a missense variant predicted to cause substitution of isoleucine by phenylalanine at amino acid 468 (p.Ile468Phe). This variant has been identified in at least four unrelated individuals described as having Pompe disease, including two patients with LOPD receiving ERT (PMID: 37701327, 25037089). One of these patients has documented deficiency of GAA in DBS. One individual is part of a cohort of patients with LOPD receiving ERT, although GAA enzyme is not reported (PMID: 37701327). This meets criteria for PP4_moderate. This variant has been reported in compound heterozygosity (phase unknown) in three unrelated patients with the common splice site variant c.-32-13T>G, meeting criteria for PM3. It has also been reported in one individual with confirmed deficient GAA in DBS, muscle, and skin fibroblast with no second variant reported on sequencing or deletion/duplication analysis (PMID: 25037089). The highest population minor allele frequency in gnomAD v4.0.0 is 0.00002 (1/59986 alleles) in the Admixed American population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.747, which meets the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). There is a ClinVar entry for this variant (Variation ID: 269826), 1-star review status) with 9 submitters classifying the variant as likely pathogenic (1) and uncertain significance (8). In summary, this variant meets the criteria to be classified as likely 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): PP4_moderate, PM3, PM2_supporting, PP3. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on December 19, 2023).

Met criteria codes

PP3			The computational predictor REVEL gives a score of 0.747, which meets the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM3			This variant has been reported in compound heterozygosity in three unrelated patients with the common splice site variant c.-32-13T>G. Phase is unknown. This meets criteria for PM3.
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.0.0 is 0.00002 (1/59986 alleles) in the Admixed American population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PP4_Moderate			This variant has been identified in at least four unrelated individuals described as having Pompe disease, including two patients with LOPD receiving ERT (PMID: 37701327, 25037089). One of these patients has documented deficiency of GAA in DBS. One individual is part of a cohort of patients with LOPD receiving ERT, although GAA enzyme is not reported (PMID: 37701327). This meets criteria for PP4_moderate.

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