

Variant: NM_000152.5(GAA):c.2003A>G (p.Tyr668Cys)

Version: 2.0

CA401370051 [↗](#)

546808 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 42c20a94-2649-4d62-b93a-f945e43c889e

Approved on: 2025/8/8

Published on: 2025/10/28

HGVS expressions

NM_000152.5:c.2003A>G

NM_000152.5(GAA):c.2003A>G (p.Tyr668Cys)

NC_000017.11:g.80112990A>G

CM000679.2:g.80112990A>G

NC_000017.10:g.78086789A>G

CM000679.1:g.78086789A>G

NC_000017.9:g.75701384A>G

NG_009822.1:g.16435A>G

ENST00000570803.6:c.2003A>G

ENST00000572080.2:c.*141A>G

ENST00000577106.6:c.2003A>G

ENST00000302262.8:c.2003A>G

ENST00000302262.7:c.2003A>G

ENST00000390015.7:c.2003A>G

ENST00000570716.1:n.443A>G

ENST00000572080.1:c.422A>G

NM_000152.3:c.2003A>G

NM_001079803.1:c.2003A>G

NM_001079804.1:c.2003A>G

NM_000152.4:c.2003A>G

NM_001079803.2:c.2003A>G

NM_001079804.2:c.2003A>G

NM_001079803.3:c.2003A>G

NM_001079804.3:c.2003A>G

Likely Pathogenic

Met criteria codes **4**

PP4_Moderate

PP3

PM3

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**

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.2003A>G variant in GAA is a missense variant predicted to cause substitution of Tyr by Cys at amino acid 668 (p.Tyr668Cys). This variant was identified in one patient with Pompe disease and documented deficiency of GAA activity whose sibling was identified on newborn screen. The proband was compound heterozygous for the variant and c.-32-13T>G, with the variants confirmed to be in trans (clinical laboratory data) (1 point, PM3; PP4_Moderate). The variant has also been reported in 3 individuals identified by newborn screen, including one individual with low GAA activity in DBS and fibroblast (PMID 31076647, 33073027, 34922579) and 2 individuals (clinical laboratories data) with deficiency of GAA activity. One of these individuals was compound heterozygous for the variant and c.752C>T+c.761C>T and pseudodeficiency variants c.1726G>A and c.2065G>A (PMID 31076647, 33073027, 34922579), another was compound heterozygous for the variant and c.-32-13T>G, and another had no second variant identified. As none of these individuals had symptoms of Pompe disease at the time of report, the data was not included. This variant is absent in gnomAD v4.1.0. (PM2_Supporting). The computational predictor REVEL gives a score of 0.929 which is above the threshold predicting a damaging (>0.7) impact on GAA function (PP3). There is a ClinVar entry for this variant (Variation ID: 546808). 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): PM2_supporting, PP4_Moderate, PM3, PP3. (Classification approved by the ClinGen Lysosomal Diseases VCEP on August 8, 2025)

Met criteria codes

PP4_Moderate			This variant has been reported in one patient with Pompe disease with documented deficiency of GAA activity in dried blood spot (Invitae). The sibling of this patient was identified by newborn screen (no further details) (PP4_Moderate). At least two additional individuals have been identified by newborn screen, but were asymptomatic at the time of report (PMID: 31076647, Revvity).
PP3			The computational predictor REVEL gives a score of 0.929 which is above the threshold predicting a damaging (>0.7) impact on GAA function (PP3).
PM3			One patient was compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic for Pompe disease, c.-32-13T>G (ClinVar Variation ID: 4027); the variants were confirmed to be in trans by parental testing (Invitae) (1 point).
PM2_Supporting			This variant is absent in gnomAD v4.1.0. (PM2_Supporting).

Curation History [↗](#)

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