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Variant: NM_001079804.3:c.1456G>C

Version: 1.0

CA401366835

2675751 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: bf54daf7-e8bb-4dd2-8d7f-6c4a20a667a5
Approved on: 2026/4/6
Published on: 2026/5/14

HGVS expressions

NM_001079804.3:c.1456G>C
NC_000017.11:g.80110745G>C
CM000679.2:g.80110745G>C
NC_000017.10:g.78084544G>C
CM000679.1:g.78084544G>C
NC_000017.9:g.75699139G>C
NG_009822.1:g.14190G>C
ENST00000570803.6:c.1456G>C
ENST00000572080.2:c.1456G>C
ENST00000577106.6:c.1456G>C
ENST00000302262.8:c.1456G>C
ENST00000302262.7:c.1456G>C
ENST00000390015.7:c.1456G>C
NM_000152.3:c.1456G>C
NM_001079803.1:c.1456G>C
NM_001079804.1:c.1456G>C
NM_000152.4:c.1456G>C
NM_001079803.2:c.1456G>C
NM_001079804.2:c.1456G>C
NM_000152.5:c.1456G>C
NM_001079803.3:c.1456G>C

Likely Pathogenic

Met criteria codes 5

PP3 PM3 PP4_Moderate PM2_Supporting PS3_Moderate

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.1456G>C variant in GAA is a missense variant predicted to cause substitution of alanine by proline at amino acid 486 (p.Ala486Pro). At least four individuals with this variant have been reported to have a diagnosis of Pompe disease. One individual was reported to have clinical features consistent with infantile-onset Pompe disease (IOPD), was on enzyme replacement therapy for Pompe disease, and was homozygous for this variant (PMIDs: 25626711, 27927596) (PP4_Moderate). Three individuals were reported to have late-onset Pompe disease (LOPD), but the reported information did not meet criteria for PP4. All three individuals with a diagnosis of LOPD were compound heterozygous for the variant and c.-32-13T>G, which is classified as pathogenic by the ClinGen LD VCEP, phase unconfirmed (PMIDs: 19588081, 26350092, 40714860) (PM3). The highest population minor allele frequency in gnomAD v4.1.0. is 0.000001695 (2/1180014 alleles) in the European (non-Finnish) population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). Expression of the variant in COS-7 or HEK293 cells resulted in 0% wild type GAA activity in cells and 3.0% in medium and evidence of abnormal GAA synthesis and processing on Western blot, leading the variant to be described as Class B ("potentially less severe"), indicating that this variant may impact protein function (PMID: 22644586) (PS3_Moderate). Additionally, the computational predictor REVEL gives a score of 0.765, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Three other missense variants in the same codon (c.1456G>A (p.Ala486Thr), c.1456G>T (p.Ala486Ser), and c.1457C>T (p.Ala486Val)) have been reported in ClinVar. However, these variants have not yet been evaluated by the ClinGen Lysosomal Diseases VCEP (PM5 not met). 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): PS3_Moderate, PM2_Supporting, PM3, PP3, PP4_Moderate. (Classififcation approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on April 6, 2026)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.765, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM3	✔	This variant has been detected in at least four individuals diagnosed with Pompe disease. Of those individuals, three were compound heterozygous for the variant and c.-32-13T>G, which is classified as pathogenic by the ClinGen LD VCEP, phase unconfirmed (PMIDs: 19588081, 26350092, 40714860) (1.0 point). One individual was homozygous for the variant (PMIDs: 25626711, 27927596) (0.5 points) (total of 1.5 points, PM3).
PP4_Moderate	✔	At least four individuals with this variant have been reported to have a diagnosis of Pompe disease. One individual was reported to have clinical features consistent with infantile-onset Pompe disease and was on enzyme replacement therapy for Pompe disease (PMIDs: 25626711, 27927596). Three individuals were reported to have late-onset Pompe disease, but the reported information did not meet criteria for PP4 (PMIDs: 19588081, 26350092, 40714860) (PP4_Moderate).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.000001695 (2/1180014 alleles) in the European (non-Finnish) population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PS3_Moderate	✔	Expression of the variant in COS-7 or HEK293 cells resulted in 0% wild type GAA activity in cells and 3.0% in medium, and evidence of abnormal GAA synthesis and processing on Western blot, leading the variant to be described as Class B ("potentially less severe"), indicating that this variant may impact protein function (PMID: 22644586) (PS3_Moderate).

Not Met criteria codes

PM5 ✖ Three other missense variants in the same codon (c.1456G>A (p.Ala486Thr), c.1456G>T (p.Ala486Ser), and c.1457C>T (p.Ala486Val)) have been reported in ClinVar. However, these variants have not yet been evaluated by the ClinGen Lysosomal Diseases VCEP (PM5 not met).

Curation History

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