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Variant: NM_001079804.3:c.2456G>C

Version: 2.0

CA401325305

1693550 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: b9e5a45b-ca59-4eae-888f-d21b7f925693
Approved on: 2026/7/7
Published on: 2026/7/21

HGVS expressions

NM_001079804.3:c.2456G>C
NC_000017.11:g.80117724G>C
CM000679.2:g.80117724G>C
NC_000017.10:g.78091523G>C
CM000679.1:g.78091523G>C
NC_000017.9:g.75706118G>C
NG_009822.1:g.21169G>C
ENST00000570803.6:c.2456G>C
ENST00000572080.2:c.*594G>C
ENST00000577106.6:c.2456G>C
ENST00000302262.8:c.2456G>C
ENST00000302262.7:c.2456G>C
ENST00000390015.7:c.2456G>C
ENST00000573556.1:n.409G>C
NM_000152.3:c.2456G>C
NM_001079803.1:c.2456G>C
NM_001079804.1:c.2456G>C
NM_000152.4:c.2456G>C
NM_001079803.2:c.2456G>C
NM_001079804.2:c.2456G>C
NM_000152.5:c.2456G>C
NM_001079803.3:c.2456G>C

Pathogenic

Met criteria codes 5

PP3 PM3_Strong PS3_Moderate PP4_Moderate PM2_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 2.0*
PDF
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.2456G>C variant in GAA is a missense variant predicted to cause substitution of arginine by proline at amino acid 819 (p.Arg819Pro). At least four individuals with this variant have been reported to have a diagnosis of infantile-onset Pompe disease (IOPD) with either documented GAA deficiency in the affected range in dried blood spot, muscle, or cultured skin fibroblasts (PMIDs: 22252923, 41695778, Duke University Molecular Diagnostics Laboratory) or were reported to be on enzyme replacement therapy for Pompe disease (PMID: 30214072) (PP4_Moderate). Of those individuals, one was compound heterozygous for the variant and a variant classified as pathogenic by the ClinGen Lysosomal Diseases VCEP, c.1210G>A (p.Asp404Asn), confirmed in trans by parental testing (Duke University Molecular Diagnostics Laboratory). Three individuals were homozygous for the variant (PMIDs: 22252923, 30214072, 41695778) (PM3_Strong). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001101 (1/90848 alleles) in the South Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). Additionally, expression of the variant in COS or HEK293T cells resulted in 0.4% GAA activity in cells and 2.0% in medium, 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, c.2455C>T (p.Arg819Trp) (ClinVar Variation ID: 456402), in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP. However, the classification of this variant will be used to support the classification of c.2455C>T (p.Arg819Trp), so PM5 will not be applied here in order to avoid circular logic (PM5 not met). In summary, this variant meets the criteria to be classified as 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): PS3_Moderate, PM2_Supporting, PM3_Strong, PP3, PP4_Moderate. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on July 7, 2026).

Met criteria codes

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).
PM3_Strong	✔	This variant has been detected in at least four individuals with Pompe disease. Of those individuals, one was compound heterozygous for the variant and a variant classified as pathogenic by the ClinGen Lysosomal Diseases VCEP, c.1210G>A (p.Asp404Asn), confirmed in trans by parental testing (1.0 point) (Duke University Molecular Diagnostics Laboratory). Three individuals were homozygous for the variant (1.0 point) (PMIDs: 22252923, 30214072, 41695778) (total of 2.0 points) (PM3_Strong).
PS3_Moderate	✔	Expression of the variant in COS cells resulted in 0.4% GAA activity in cells and 2.0% in medium, 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 four individuals with this variant have been reported to have a diagnosis of infantile-onset Pompe disease (IOPD) with either documented GAA deficiency in the affected range in dried blood spot, muscle, or cultured skin fibroblasts (PMIDs: 22252923, 41695778, Duke University Molecular Diagnostics Laboratory) or were reported to be on enzyme replacement therapy for Pompe disease (PMID: 30214072) (PP4_Moderate).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001101 (1/90848 alleles) in the South Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

Not Met criteria codes

PM5		✖	Another missense variant, c.2455C>T (p.Arg819Trp) (ClinVar Variation ID: 456402), in the same codon has been classified as likely pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP. However, the classification of this variant will be used to support the classification of c.2455C>T (p.Arg819Trp), so PM5 will not be applied here in order to avoid circular logic (PM5 not met).

Curation History

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