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_001079804.3:c.1385T>C

Version: 2.0

CA401366477

1693548 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 66d16a76-468c-4150-9cd8-53ea0bb39512
Approved on: 2025/6/17
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HGVS expressions

NM_001079804.3:c.1385T>C
NC_000017.11:g.80110003T>C
CM000679.2:g.80110003T>C
NC_000017.10:g.78083802T>C
CM000679.1:g.78083802T>C
NC_000017.9:g.75698397T>C
NG_009822.1:g.13448T>C
ENST00000570803.6:c.1385T>C
ENST00000572080.2:c.1385T>C
ENST00000577106.6:c.1385T>C
ENST00000302262.8:c.1385T>C
ENST00000302262.7:c.1385T>C
ENST00000390015.7:c.1385T>C
NM_000152.3:c.1385T>C
NM_001079803.1:c.1385T>C
NM_001079804.1:c.1385T>C
NM_000152.4:c.1385T>C
NM_001079803.2:c.1385T>C
NM_001079804.2:c.1385T>C
NM_000152.5:c.1385T>C
NM_001079803.3:c.1385T>C

Likely Pathogenic

Met criteria codes 4

PP3 PS3_Moderate PP4_Moderate PM2_Supporting

Not Met criteria codes 2

PM3 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.1385T>C variant in GAA is a missense variant predicted to cause substitution of leucine by proline at amino acid 462 (p.Leu462Pro). The highest population minor allele frequency in gnomAD v4.1.0. is 8.5e-7 (1/1179884 alleles) in the Non-Finnish European population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). The variant has been reported in an 8 month old male with clinical features consistent with infantile onset Pompe disease and documentation of deficient GAA activity (PMID: 25612604) (PP4_Moderate). This patient is compound heterozygous for the variant and another missense variant that has been classified as likely pathogenic by the ClinGen LD VCEP (PMID: 25612604). Expression of the variant in HEK293 cells (methodology: PMID 36246652) resulted in no GAA activity relative to wild type. Western blot revealed only a precursor (110 kDa) band, evidence of abnormal GAA synthesis and processing (data unpublished) (PS3_moderate). The computational predictor REVEL gives a score of 0.951 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). There is a ClinVar entry for this variant (Variation ID: 1693548, 3 star review status) with 2 submitters as VUS (1 submitter) or pathogenic (1 submitter). 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 2.0.0): PM2_supporting, PP4_moderate, PP3, PS3_moderate (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on June 17, 2025)

Met criteria codes

PP3	✔	The computational predictor REVEL gives a score of 0.951 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PS3_Moderate	✔	This variant has been expressed in a HEK293 cell-based assay (see PMID 36246652 for methodology) and resulted in no residual enzyme activity relative to wild type. Western blot shows a 110kDa band only suggesting insufficient processing of GAA to the mature form (data unpublished).
PP4_Moderate	✔	The patient is reported to have infantile onset Pompe disease and has 2.0 nmol/h/mgP (reference range 62.3–301.7 nmol/h/mgP) detected in a GAA activity assay of a dried blood spot, meeting PP4 (PMID: 25612604).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 8.5e-7 (1/1179884 alleles) in the Non-Finnish European 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

PM3	✖	One patient with Pompe disease is compound heterozygous for the variant and c.1669A>T (p.Ile557Phe); phase unknown. c.1669A>T (p.Ile557Phe) is classified as likley pathogenic by the ClinGen LSD VCEP (0.25 points). Therefore, this evidence is insufficient to support PM3.
PM5	✖	No other variants at this amino acid have been identified in the literature in patients with Pompe disease.

Curation History

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