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_000152.5(GAA):c.796C>T (p.Pro266Ser)

Version: 1.2

CA401363495

556117 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2b5077ea-d72a-4564-a83c-2aea98c3b4a8
Approved on: 2026/7/10
Published on: 2026/7/21

HGVS expressions

NM_000152.5(GAA):c.796C>T (p.Pro266Ser)
NM_000152.5:c.796C>T
NC_000017.11:g.80107660C>T
CM000679.2:g.80107660C>T
NC_000017.10:g.78081459C>T
CM000679.1:g.78081459C>T
NC_000017.9:g.75696054C>T
NG_009822.1:g.11105C>T
ENST00000570803.6:c.796C>T
ENST00000572080.2:c.796C>T
ENST00000577106.6:c.796C>T
ENST00000302262.8:c.796C>T
ENST00000302262.7:c.796C>T
ENST00000390015.7:c.796C>T
ENST00000570803.5:c.796C>T
NM_000152.3:c.796C>T
NM_001079803.1:c.796C>T
NM_001079804.1:c.796C>T
NM_000152.4:c.796C>T
NM_001079803.2:c.796C>T
NM_001079804.2:c.796C>T
NM_001079803.3:c.796C>T
NM_001079804.3:c.796C>T

Likely Pathogenic

Met criteria codes 5

PP4_Moderate BP4 PM3_Strong PM2_Supporting PS3_Supporting

Not Met criteria codes 3

PM5 PS1 PP3

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.796C>T variant in GAA is a missense variant predicted to cause substitution of proline by serine at amino acid 266 (p.Pro266Ser). At least seven patients with this variant and features consistent with Pompe disease have been reported. This includes 2 patients with documented laboratory values showing deficient GAA activity (<10% normal or below reference range in leukocytes) (PMID: 17092519, 29124014) (PP4_Moderate). These patients are all compound heterozygous for the variant and another variant in GAA classified as pathogenic or likely pathogenic by the ClinGen LD VCEP, phase unknown, including c.1309C>T (p.Arg437Cys) (PMID: 25526786), c.1316T>A (p.Met439Lys) (PMID: 17092519, 31193175,), c.1935C>A (p.Asp645Glu) (PMID: 28394184) (ClinVar# SCV002032138.1), c.546G>T (PMID: 29124014) (ClinVar# SCV002032139.1), and c.1602_1605delinsAGG (p.Asn535GlyfsTer43) (PMID: 28394184) (PM3_Strong). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001333 (1/70356 alleles) in the African/African American population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). This variant resulted in 14-18% wild type GAA activity, in two different studies, when expressed in COS cells. (PMID: 18425781, 19862843). Western blot revealed presence of the active 76kDa GAA band, but at a much lower level than wild type (PMID: 19862843). Additional variants at this amino acid positions have been reported (c.797C>T (p.Pro266Leu); c.796C>A (p.Pro266Thr) (PMID: 29451150); these variants have not been classified as pathogenic or likely pathogenic by the ClinGen LD VCEP. The score from the in silico metapredictor REVEL is 0.476 (BP4), which is a single piece of conflicting evidence in comparison with the evidence for pathogenicity. There is a ClinVar entry for this variant (Variation ID:556117, 2 star review status) with two submitters classifying the variant as pathogenic and one as likely pathogenic. In summary, based on the overall evidence, this variant meets the criteria to be classified as likely pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LD VCEP (Specifications Version 2.0.0): PM3_Strong, PP4_Moderate, PS3_Supporting, PM2_Supporting, BP4. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on July 10, 2026)

Met criteria codes

PP4_Moderate	✔	At least seven patients with this variant and features consistent with Pompe disease have been reported. This includes 2 patients with documented values showing deficient GAA activity (<10% normal or below reference range in leukocytes) (PMID: 17092519, 29124014) (PP4_Moderate).
BP4	✔	REVEL score = 0.476 which is lower than the LD VCEP threshold for BP4 (<0.5), and therefore meets this criterion.
PM3_Strong	✔	Seven patients with features consistent with Pompe disease are compound heterozygous for the variant and a variant in GAA classified as pathogenic or likely pathogenic by the ClinGen LD VCEP, phase unknown, including c.1309C>T (p.Arg437Cys) (PMID: 25526786; 0.5 points), c.1316T>A (p.Met439Lys) (PMID: 17092519, 31193175, 2 x 0.5 points), c.1935C>A (p.Asp645Glu) (PMID: 28394184) (ClinVar# SCV002032138.1) (0.5 points), c.546G>T (PMID: 29124014) (ClinVar# SCV002032139.1) (2 x 0.5 points), and c.1602_1605delinsAGG (p.Asn535GlyfsTer43) (PMID: 28394184) (0.25 points). Total 3.25 points (PM3_Strong).
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1.0. is 0.00001333 (1/70356 alleles) in the African/African American population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PS3_Supporting	✔	This variant resulted in 14-18% wild type GAA activity, in two different studies, when expressed in COS cells. (PMID: 18425781, 19862843). Western blot revealed presence of the active 76kDa GAA band, but at a much lower level than wild type (PMID: 19862843).

Not Met criteria codes

PM5	✖	

A missense change (p.Pro266Leu, c.797C>T) at the same amino acid residue has been reported by ClinVar. Another missense change (p.Pro266Thr, c.796C>A) at the same amino acid residue is reported in literature. These variants have not been classified as pathogenic or likely pathogenic by the ClinGen LD VCEP. Therefore, PM5 is not met.

PS1	ℹ	✖	The p.Pro266Ser amino acid change has not been reported with another nucleotide change in ClinVar, HGMD Pro, LOVD or pompevariantdatabase.nl.
PP3	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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