

Variant: NM_000152.5(GAA):c.1634C>T (p.Pro545Leu)

Version: 1.0

CA116616 [↗](#)

4032 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: c467b406-b738-4e17-a927-19cdd7ba29d8

Approved on: 2026/4/7

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HGVS expressions

NM_000152.5(GAA):c.1634C>T (p.Pro545Leu)

NM_000152.5:c.1634C>T

NC_000017.11:g.80111023C>T

CM000679.2:g.80111023C>T

NC_000017.10:g.78084822C>T

CM000679.1:g.78084822C>T

NC_000017.9:g.75699417C>T

NG_009822.1:g.14468C>T

ENST00000570803.6:c.1634C>T

ENST00000572080.2:c.1634C>T

ENST00000577106.6:c.1634C>T

ENST00000302262.8:c.1634C>T

ENST00000302262.7:c.1634C>T

ENST00000390015.7:c.1634C>T

ENST00000572080.1:c.22C>T

NM_000152.3:c.1634C>T

NM_001079803.1:c.1634C>T

NM_001079804.1:c.1634C>T

NM_000152.4:c.1634C>T

NM_001079803.2:c.1634C>T

NM_001079804.2:c.1634C>T

NM_001079803.3:c.1634C>T

NM_001079804.3:c.1634C>T

Pathogenic

Met criteria codes 5

PM2_Supporting

PS3_Supporting

PM3_Very Strong

PP3

PP4_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**

Lysosomal Diseases VCEP

The NM_000152.5:c.1634C>T variant in GAA is predicted to result in the missense substitution of proline by leucine at amino acid 545 (p.Pro545Leu). This variant has been reported in at least 11 individuals with late-onset Pompe disease; onset typically in childhood to adolescence. Of those patients, 6 were compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the LD VCEP, phase unknown, including c.525del (PMID: 7881422, 19084399, 29556838; 0.5 points), c.2481+102_2646+31del (PMID: 20817528, 23304582, 27189384; two patients, 2 x 0.5 points), c.1935C>A (p.Asp645Glu) (PMID: 27183828, 27692865, two patients, 2 x 0.5 points), and c.2662G>T (p.Glu888Ter) (PMID: 25526786, 0.5 points). Another patient was compound heterozygous for c.1725C>A (p.Tyr575Ter), classified as pathogenic by the LD VCEP and confirmed in trans (PMID: 19472353), 1 point). One patient was homozygous for the variant (PMID: 7881422, 0.5 points). Total 4.5 points (PM3_VeryStrong). In addition, three more patients were compound heterozygous for the variant and another missense variant - c.796C>T (p.Pro266Ser) (PMID: 39010129), c.1364A>T (p.Tyr455Phe) (PMID: 14695532), or c.1993G>A (p.Gly665Arg) (PMID: 25526786). The allelic data from these patients will be used in the classification of the second variant and was not included here to avoid circular logic. Additional cases were reported but were not included due to insufficient evidence for affected status and/or the presence of additional variants, or second variant not reported (PMID: 7881422, 36105079, 39213226). At least 5 of these individuals have been reported with symptoms consistent with Pompe disease and laboratory values showing GAA activity <10% normal in lymphocytes/leukocytes/muscle samples/<30% normal in cultured fibroblasts/ in the affected range in a clinically validated dried blood spot assay (PMIDs 19472353, 20817528, 23304582, 25526786), and at least two were on enzyme replacement therapy (PMID: 27692865, 27183828 (PP4_Moderate). In several studies in which the variant has been expressed in cultured cells, the activity was <10% (PMIDs 7881422, 14695532, 19862843). In addition, when the variant was expressed in COS cells, an abnormal processing pattern compared to wild type was observed on Western blot; most of the protein was in the 110kD precursor form, with little 95kD or 76kD (active) protein (PMID: 14695532) (PS3_Supporting). The computational predictor REVEL gives a score of 0.838 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). The highest continental population minor allele frequency in a continental population in gnomAD v4.1.0. is 0.0000025 in the European non-Finnish; in the Finnish population, the MAF is 0.0002. The MAF in all populations is lower than the ClinGen LD VCEP's threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). Another variant at the same amino acid position, c.1633C>T (p.Pro545Ser) (ClinVar Variation ID: 1062425) has been reported. The classification of p.Pro545Leu will be used to support the classification of p.Pro545Ser; therefore, PM5 was not applied here to avoid circular logic. There is a ClinVar entry for this variant (Variation ID: 4032). In summary, this variant meets the criteria to be classified as Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PM3_VeryStrong, PP4_Moderate, PP3, PS3_Supporting, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on April 7, 2026).

Met criteria codes

PM2_Supporting	✓	The highest continental population minor allele frequency in a continental population in gnomAD v4.1.0. is 0.0000025 in the European non-Finnish; in the Finnish population, the MAF is 0.0002. The MAF in all populations is lower than the ClinGen LD VCEP's threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PS3_Supporting	 ✓	In several studies in which the variant has been expressed in cultured cells, the activity was <10% (PMIDs 7881422, 14695532, 19862843). In addition, when the variant was expressed in COS cells, an abnormal processing pattern compared to wild type was observed on Western blot; most of the protein was in the 110kD precursor form, with little 95kD or 76kD (active) protein (PMID: 14695532).
PM3_Very Strong	 ✓	Six patients were compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the LD VCEP, phase unknown, including c.525del (PMID: 7881422, 19084399, 29556838; 0.5 points), c.2481+102_2646+31del (PMID: 20817528, 23304582, 27189384; two patients, 2 x 0.5 points), c.1935C>A (p.Asp645Glu) (PMID: 27183828, 27692865, two patients, 2 x 0.5 points), and c.2662G>T (p.Glu888Ter) (PMID:

25526786, 0.5 points). Another patient was compound heterozygous for c.1725C>A (p.Tyr575Ter), classified as pathogenic by the LD VCEP and confirmed in trans (PMID: 19472353), 1 point). One patient was homozygous for the variant (PMID: 7881422, 0.5 points). Total 4.5 points (PM3_VeryStrong). In addition, three more patients were compound heterozygous for the variant and another missense variant - c.796C>T (p.Pro266Ser) (PMID: 39010129), c.1364A>T (p.Tyr455Phe) (PMID: 14695532), or c.1993G>A (p.Gly665Arg) (PMID: 25526786). The allelic data from these patients will be used in the classification of the second variant and was not included here to avoid circular logic. Additional cases were reported but were not included due to insufficient evidence for affected status and/or the presence of additional variants, or second variant not reported (PMID: 7881422, 36105079, 39213226).

PP3			The computational predictor REVEL gives a score of 0.838 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). SpliceAI predicts that the variant has no impact on splicing (all scores <0.01).
PP4_Moderate			At least 5 individuals have been reported with this variant, symptoms consistent with Pompe disease and GAA activity <10% normal in lymphocytes/leukocytes/muscle samples/<30% normal in cultured fibroblasts/ in the affected range in a clinically validated dried blood spot assay (PMIDs 19472353, 20817528, 23304582, 25526786), or on enzyme replacement therapy (PMID: 27692865, 27183828) (PP4_Moderate).

Not Met criteria codes

PM5			Another variant at the same amino acid position, c.1633C>T (p.Pro545Ser) (ClinVar Variation ID: 1062425) has been reported. The classification of p.Pro545Leu will be used to support the classification of p.Pro545Ser; therefore, PM5 was not applied here to avoid circular logic.
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Curation History

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