

Variant: NM_000152.5(GAA):c.1124G>T (p.Arg375Leu)

Version: 2.0

CA8815178 [↗](#)

283230 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: ea5eeffe-15f9-49be-9b02-6863bf2ea91b

Approved on: 2025/12/16

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HGVS expressions

NM_000152.5(GAA):c.1124G>T (p.Arg375Leu)

NM_000152.5:c.1124G>T

NM_000152.5(GAA):c.1124G>T

NC_000017.11:g.80108537G>T

CM000679.2:g.80108537G>T

NC_000017.10:g.78082336G>T

CM000679.1:g.78082336G>T

NC_000017.9:g.75696931G>T

NG_009822.1:g.11982G>T

ENST00000570803.6:c.1124G>T

ENST00000572080.2:c.1124G>T

ENST00000577106.6:c.1124G>T

ENST00000302262.8:c.1124G>T

ENST00000302262.7:c.1124G>T

ENST00000390015.7:c.1124G>T

NM_000152.3:c.1124G>T

NM_001079803.1:c.1124G>T

NM_001079804.1:c.1124G>T

NM_000152.4:c.1124G>T

NM_001079803.2:c.1124G>T

NM_001079804.2:c.1124G>T

NM_001079803.3:c.1124G>T

NM_001079804.3:c.1124G>T

Pathogenic

Met criteria codes **5**

PM3_Strong

PS3_Moderate

PP3

PM2_Supporting

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.1124G>T (p. Arg375Leu) variant in GAA is a missense variant predicted to cause substitution of arginine by leucine at amino acid 375. Multiple patients with late onset Pompe disease from Italy, compound heterozygous for the c.-32-13T>G) have been reported with documented GAA activity in the affected range, and on ERT (PMID: 22081099, 24158270. All of these individuals are compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic for Pompe disease, c.-32-13T>G, including a proband and 3 siblings (max 2 x 0.5 points), phase unconfirmed (PMID: 22081099, 24158270, 29880332, 33807278). Patients with infantile onset Pompe disease have been reported who are compound heterozygous for the variant and c.784G>A (p.Glu262Lys), pathogenic based on classification by the ClinGen LD VCEP and confirmed in trans (1 point) (PMID: 18429042), or c.2261dupC (p.V755SfsTer41), pathogenic based on classification by the LD VCEP, phase unknown, 0.5 points (PMID: 34565280, 34606154). In addition, at least one patient is homozygous for the variant (0.5 point) (PMID: 18429042, 2818289). Finally, a Chinese patient is compound heterozygous for the variant (maternally inherited) and c.2853G>A (p.Trp951Ter) (VUS based on classification by the LD VCEP) (paternally inherited) (PMID: 39213226), Total 3 points (PM3_Strong, PP4_Moderate). The highest population minor allele frequency in gnomAD v4.1.0. is 0.00000254 (3/1179898 alleles) in the European (non-Finnish) population, which is lower than the ClinGen LD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). When expressed in HEK293 cells, the variant results in about 1% WT GAA activity and reduced GAA protein on Western blot (PMID: 28182897), Similarly, expression of the variant in an Ad5-SV40 immortalized human GAA deficient fibroblast cell line demonstrated 0.3% of WT GAA activity and virtually no detectable GAA protein on western blot (PMID: 18429042) (PS3_moderate). The computational predictor REVEL gives a score of 0.976 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense variant c.1124G>A (p. Arg375His) in the same codon has been reported in two patients from Asia with Pompe disease (PMID: 21757382, 21484825). However this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen LD VCEP. In addition, the LD VCEP has classified another variant in the same codon, c.1123C>T (p.Arg375Cys), as a variant of uncertain significance (PM5 not met). There is ClinVar entry for the variant (Variation ID: 283230). In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease, based on the GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel (Specifications Version 2.0): PM3_strong, PS3_Moderate, PP4_Moderate; PS3_supporting, PP3 PM2_Supporting. (Classification approved by the ClinGen Lysosomal Storage Disorders Variant Curation Expert Panel, December 16, 2025)

Met criteria codes

PM3_Strong



Multiple patients with late onset Pompe disease have been reported in studies from Italy, who are compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic for Pompe disease, c.-32-13T>G, including a proband and 3 siblings (max 2 x 0.5 points), phase unconfirmed (PMID: 22081099, 24158270, 29880332, 33807278). Patients with infantile onset Pompe disease have been reported who are compound heterozygous for the variant and c.784G>A (p.Glu262Lys), pathogenic based on classification by the ClinGen LD VCEP and confirmed in trans (1 point) (PMID: 18429042), or c.2261dupC (p.V755SfsTer41), pathogenic based on classification by the LD VCEP, phase unknown, 0.5 points (PMID: 34565280, 34606154). In addition, at least one patient is homozygous for the variant (0.5 point) (PMID: 18429042, 2818289). Finally, a Chinese patient is compound heterozygous for the variant (maternally inherited) and c.2853G>A (p.Trp951Ter) (VUS based on classification by the LD VCEP) (paternally inherited) (PMID: 39213226), Total 3 points.

PS3_Moderate



When expressed in HEK293 cells, the variant results in about 1% WT GAA activity and reduced GAA protein on Western blot (PMID: 28182897), Similarly, expression of the variant in an Ad5-SV40 immortalized human GAA deficient fibroblast cell line demonstrated 0.3% of WT GAA activity and virtually no detectable GAA protein on western blot (PMID: 18429042) (PS3_moderate).

PP3



The computational predictor REVEL gives a score of 0.976 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3)

PM2_Supporting



The highest population minor allele frequency in gnomAD v4.1.0. is 0.00000254 (3/1179898 alleles) in the European (non-Finnish) population, which is lower than the ClinGen LD VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

PP4_Moderate



One late-onset Pompe patient from Italy with GAA genotype [c.-32-13T>G/c.1124G>T (p.Arg375Leu)] documented leukocyte GAA residual activity as 21.98% and muscle GAA activity to be 5.95% (PMID: 24158270). Two late onset Pompe patients from Italy on ERT, confirmed diagnosis with reduced GAA activity below 35% of controls in skeletal muscle, leukocytes or fibroblasts (PMID: 22081099). Two severe infantile Pompe cases, diagnosed based on clinical data including mycardiopathy and severe hypotonia and confirmed by reduced GAA activity in different tissues of fibroblasts and/ or blood samples (PMID: 18429042).

Not Met criteria codes

PM5



Another missense variant c.1124G>A (p. Arg375His) in the same codon has been reported in two patients from Asia with Pompe disease (PMID: 21757382, 21484825). However this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen LD VCEP. In addition, the LD VCEP has classified another variant in the same codon, c.1123C>T (p.Arg375Cys), as a variant of uncertain significance.

Curation History

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