

Variant: NM_000152.5(GAA):c.1669A>T (p.Ile557Phe)

Version: 2.0

CA401368911 [↗](#)

558634 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: ba123cf8-84ca-4dc2-a485-78f138703aa2

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HGVS expressions

NM_000152.5(GAA):c.1669A>T (p.Ile557Phe)

NM_000152.5:c.1669A>T

NC_000017.11:g.80112015A>T

CM000679.2:g.80112015A>T

NC_000017.10:g.78085814A>T

CM000679.1:g.78085814A>T

NC_000017.9:g.75700409A>T

NG_009822.1:g.15460A>T

ENST00000570803.6:c.1669A>T

ENST00000572080.2:c.1669A>T

ENST00000577106.6:c.1669A>T

ENST00000302262.8:c.1669A>T

ENST00000302262.7:c.1669A>T

ENST00000390015.7:c.1669A>T

ENST00000572080.1:c.57A>T

ENST00000572803.1:n.283A>T

NM_000152.3:c.1669A>T

NM_001079803.1:c.1669A>T

NM_001079804.1:c.1669A>T

NM_000152.4:c.1669A>T

NM_001079803.2:c.1669A>T

NM_001079804.2:c.1669A>T

NM_001079803.3:c.1669A>T

NM_001079804.3:c.1669A>T

Pathogenic

Met criteria codes 5

PP4_Moderate

PS3_Moderate

PM5_Supporting

PM3_Very Strong

PM2_Supporting

Not Met criteria codes 2

PP3

BP4

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**

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1669A>T variant in GAA is a missense variant predicted to result in substitution of isoleucine by phenylalanine at amino acid 557 (p.Ile557Phe). The variant has been reported to be in cis, or phase unconfirmed, with c.2132C>G (p.Thr711Arg) in some cases. Excluding those cases, five probands in whom the p.Ile557Phe variant is in compound heterozygosity with a variant other than p.Thr711Arg, have been reported, all with infantile onset Pompe disease. At least one of these patients has documented features of infantile onset Pompe disease and deficient GAA activity (PMID: 36428004, 38162137, Clinical Laboratory) (PP4_Moderate). Five patients with IOPD have been reported who are compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic or likely pathogenic for Pompe disease by the ClinGen LD VCEP. For four of these patients, the second variant was confirmed to be in trans; the second variant was either c.1935C>A (p.Asp645Glu) (P, ClinVar Variation ID: 4029, 1 point) (PMID: 38162137), c.2662G>T (p.Glu888Ter) (P, ClinVar ID Variation ID: 578595, 1 point) (PMID: 38162137), or c.1978C>T (p.Arg660Cys) (P, ClinVar Variation ID: 558604, 1 point) (Duke) or c.1843G>A (p.Gly615Arg) (LP, ClinVar Variation ID: 188786) (PMID: 36428004). Another patient was compound heterozygous for the variant, phase unconfirmed, and c.2237G>A (p.Trp746Ter) (ClinVar Variation ID: 280063, 0.5 points) (PMID: 38162137), Total 4.5 points (PM3_Very_Strong). In addition, a patient with IOPD was compound heterozygous for c.118C>T (p.Arg40Ter) (paternal), and c.[1669A>T; 2132C>G] (p.[Ile557Phe:Thr711Arg]) (maternal). c.118C>T (p.Arg40Ter) (ClinVar Variation ID: 426593) is pathogenic based on classification by the ClinGen LD VCEP, while another is compound heterozygous for c.2799+4 A>G (LP based on classification by the ClinGen LD VCEP), c.2132C>G (p.Thr711Arg), and c.1669A>T (p.Ile557Phe), phase unknown. Due to the presence of three variants, phase unknown, this data was not included. Additional patients are compound heterozygous for the variant and c.1385T>C (p.Leu462Pro) (PMID: 25612604), c.1013A>T (p.Asp338Val) (PMID: 34134972), or c.2132C>G (p.Thr711Arg) (PMID: 23884227, 39010129). The allelic data from these patients will be used for the classification of the second variant and is not included here to avoid circular logic. The highest population minor allele frequency in gnomAD v4.1.0. is 0.00002228 (1/44880 alleles) in the East Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). Expression of the variant in COS7 or HEK293 cells resulted in 2.7% GAA activity in cells and 0.3% in medium, and evidence of abnormal synthesis and processing on Western blot, indicating that this variant may impact protein function (PMID: 22644586) (PS3_Moderate). The computational predictor REVEL gives a score of 0.662 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function. Two other missense variants, c.1669A>G (p.Ile557Val) (ClinVar Variation ID: 856959) and c.1670T>G (p.Ile557Ser) (PMID: 26474166), in the same codon have been reported in patients with Pompe disease; p.Ile557Ser (ClinVar Variation ID: 1693547) has been classified as likely pathogenic for Pompe disease by the ClinGen LD VCEP (PM5_Supporting). There is a ClinVar entry for this variant (Variation ID: 558634). In summary, this variant meets the criteria to be classified as Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0.0): PM3_Very Strong, PS3_Moderate, PP4_Moderate, PM2_Supporting, PM5_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel, December 16, 2025).

Met criteria codes**PP4_Moderate**

The variant has been reported to be in cis with c.2132C>G (p.Thr711Arg) in some cases. Excluding those cases, five probands in whom the p.Ile557Phe variant is in compound heterozygosity with a variant other than p.Thr711Arg, have been reported, all with infantile onset Pompe disease. At least one of these patients has documented features of infantile onset Pompe disease and deficient GAA activity (PMID: 36428004, 38162137, Clinical Laboratory) (PP4_Moderate). Additional patients with IOPD carry p.Ile557Phe, p.Thr711Arg and an additional variant (PMIDs 23884227, 25612604, 39213226). Two additional patients have been reported who were identified by newborn screening and also carry pseudodeficiency variants (PMID 20080426, 31076647).

PS3_Moderate

Expression of the variant in COS7 or HEK293 cells resulted in 2.7% GAA activity in cells and 0.3% in medium, and evidence of abnormal synthesis and processing on Western blot leading the variant to be described as Class B

(“potentially less severe”), and indicating that this variant may impact protein function (PMID 22644586) (PS3_Moderate).

PM5_Supporting			Two other missense variants, c.1669A>G (p.Ile557Val) (ClinVar Variation ID: 856959) and c.1670T>G (p.Ile557Ser) (PMID: 26474166), in the same codon have been reported in patients with Pompe disease. p.Ile557Ser (ClinVar Variation ID: 1693547) has been classified as LP by the ClinGen LD VCEP (PM5_Supporting).
PM3_Very Strong			Five patients with IOPD have been reported who are compound heterozygous fot the variant and another variant in GAA that has been classified as pathogenic or likely pathogenic for Pompe disease by the ClinGen LD VCEP. For four of these patients, the second variant was confirmed to be in trans; the second variant was either c.1935C>A (p.Asp645Glu) (P, ClinVar Variation ID: 4029, 1 point) (PMID: 38162137), c.2662G>T (p.Glu888Ter) (P, ClinVar ID Variation ID: 578595, 1 point) (PMID: 38162137), or c.1978C>T (p.Arg660Cys) (P, ClinVar Variation ID: 558604, 1 point) (Duke) or c.1843G>A (p.Gly615Arg) (LP, ClinVar Variation ID: 188786) (PMID: 36428004). Another patient was compound heterozygous for the variant, phase unconfirmed, and c.2237G>A (p.Trp746Ter) (ClinVar Variation ID: 280063, 0.5 points) (PMID: 38162137), Total 4.5 points (PM3_Very_Strong) In addition, a patient with IOPD was compound heterozygous for c.118C>T (p.Arg40Ter) (paternal), and c.[1669A>T; 2132C>G] (p.[Ile557Phe:Thr711Arg]) (maternal). c.118C>T (p.Arg40Ter) (ClinVar Variation ID: 426593) is pathogenic based on classification by the ClinGen LD VCEP, while another is compound heterozygous for c.2799+4 A>G (LP based on classification by the ClinGen LD VCEP), c.2132C>G (p.Thr711Arg), and c.1669A>T (p.Ile557Phe), phase unknown. Additional patients are compound heterozygous for the variant and c.1385T>C (p.Leu462Pro) (PMID: 25612604), c.1013A>T (p.Asp338Val) (PMID: 34134972), or c.2132C>G (p.Thr711Arg) (PMID: 23884227, 39010129). The allelic data from these patients will be used for the classification of the second variant and is not included here to avoid circular logic. Note that c.2132C>G (p.Thr711Arg) is reported to occur in cis with p.Ile557Phe in some patients. In other patients, both variants have been reported, phase unconfirmed, and the two were reported to be in trans in another family (PMID: 23884227)
PM2_Supporting			The highest population minor allele frequency in gnomAD v4.1.0. is 0.00002228 (1/44880 alleles) in the East 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

PP3			The computational predictor REVEL gives a score of 0.662 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function.
BP4			The computational predictor REVEL gives a score of 0.662 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function.

Curation History 

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