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Variant: NM_000152.5(GAA):c.1099T>C (p.Trp367Arg)

Version: 2.0

CA401364951

555820 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: a0f9a098-81cb-4711-86b3-a13348379fda
Approved on: 2026/9/1
Published on: 2026/9/1

HGVS expressions

NM_000152.5(GAA):c.1099T>C (p.Trp367Arg)
NM_000152.5:c.1099T>C
NC_000017.11:g.80108512T>C
CM000679.2:g.80108512T>C
NC_000017.10:g.78082311T>C
CM000679.1:g.78082311T>C
NC_000017.9:g.75696906T>C
NG_009822.1:g.11957T>C
ENST00000570803.6:c.1099T>C
ENST00000572080.2:c.1099T>C
ENST00000577106.6:c.1099T>C
ENST00000302262.8:c.1099T>C
ENST00000302262.7:c.1099T>C
ENST00000390015.7:c.1099T>C
NM_000152.3:c.1099T>C
NM_001079803.1:c.1099T>C
NM_001079804.1:c.1099T>C
NM_000152.4:c.1099T>C
NM_001079803.2:c.1099T>C
NM_001079804.2:c.1099T>C
NM_001079803.3:c.1099T>C
NM_001079804.3:c.1099T>C

Pathogenic

Met criteria codes 5

PP3 PP4_Moderate PM3_Strong PM2_Supporting PS3_Supporting

Not Met criteria codes 4

PS1 PM1 PM5 PVS1

Evidence Links 1

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.1099T>C variant in GAA is a missense variant resulting in the substitution of tryptophan by arginine at amino acid 367 (p.Trp367Arg). This variant has been reported in at least 4 patients with a diagnosis of infantile onset Pompe disease (IOPD) presenting with symptoms including cardiomegaly and hypotonia, documented deficient GAA activity and/or on enzyme replacement therapy (PMID: 17056254, 22658377, 23787031, 25139343, 31510962); it was also reported in one patient with late-onset Pompe disease (LOPD) (PMID: 22958975) (PP4_Moderate). Three patients were reported to be compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP. In these patients, the second variant was either c.-32-13T>G (phase unconfirmed, 0.5 pt) (PMID: 22958975), c.1802C>T (p.Ser601Leu) (confirmed in trans, 1 pt) (PMID: 22658377, 23401069, 23787031, 25139343, 29122469, 31904026) or c.1942G>A (p.Gly648Ser) (confirmed in trans, 1 pt) PMID: 31510962). One patient was reported to be homozygous for the variant (PMID: 17056254). An additional patient was compound heterozygous for the variant and c.625T>C (p.Tyr209His), phase unconfirmed (PMID: 40952111). The allelic data from this patient will be used in the classification of c.625T>C (p.Tyr209His) and is not included here to avoid circular logic. Total points: 3 (PM3_Strong). The highest population minor allele frequency in gnomAD v4.1.0 is 8.5e-7 (1/1179976 alleles) in the European (non-Finnish) 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 COS-7 cells resulted in <2% wild type GAA activity without mature processed GAA protein on immunoblots, indicating a negative impact on GAA function (PMID: 19862843) (PS3_Supporting). The computational meta-predictor REVEL has a score of 0.944 for the variant, which is above the threshold of 0.7, indicating a negative impact on GAA function (PP3). Another missense variant, c.1099T>G (p.Trp367Gly), in the same codon has been reported in a patient with LOPD (PMID: 29124014). However, the data for p.Trp367Arg will be used in the assessment of p.Trp367Gly and therefore PM5 is not met here in order to avoid circular argument. There is a ClinVar entry for this variant (Variation ID: 555820). Given the multiple reports of patients with features specific for Pompe disease and multiple lines of evidence, including high REVEL score and availability of functional data, the VCEP elected to elevate the classification from Likely Pathogenic to Pathogenic. In summary, this variant was classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): PM3_Strong, PP4_Moderate, PP3, PS3_Supporting, PM2_Supporting (classification modified to pathogenic). (Classification approved by the ClinGen ClinGen Lysosomal Diseases Variant Curation Expert Panel, on September 1, 2026).

Met criteria codes

PP3	✔	The computational meta-predictor REVEL gives a score of 0.944, which is above the threshold of 0.7, indicating a deleterious impact to GAA function (PP3).
PP4_Moderate	✔	This variant has been reported in at least 4 patients with a diagnosis of infantile onset Pompe disease (IOPD) presenting with symptoms including cardiomegaly and hypotonia, documented deficient GAA activity and/or on enzyme replacement therapy (PMID: 17056254, 22658377, 23787031, 25139343, 31510962); it was also reported in one patient with late-onset Pompe disease (LOPD) (PMID: 22958975) (PP4_Moderate).
PM3_Strong	✔	Three patients were reported to be compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP. In these patients, the second variant was either c.-32-13T>G (phase unconfirmed, 0.5 pt) (PMID: 22958975), c.1802C>T (p.Ser601Leu) (confirmed in trans, 1 pt) (PMID: 22658377, 23401069, 23787031, 25139343, 29122469, 31904026) or c.1942G>A (p.Gly648Ser) (confirmed in trans, 1 pt) PMID: 31510962). One patient was reported to be homozygous for the variant (PMID: 17056254). An additional patient was compound heterozygous for the variant and c.625T>C (p.Tyr209His), phase unconfirmed (PMID: 40952111). The allelic data from this patient will be used in the classification of c.625T>C (p.Tyr209His) and is not included here to avoid circular logic. Total points: 3 (PM3_Strong).

PM2_Supporting		✔	The highest population minor allele frequency in gnomAD v4.1.0 is 8.5e-7 (1/1179976 alleles) in the European (non-Finnish) population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PS3_Supporting	ℹ	✔	Expression of the variant in COS-7 cells resulted in <2% wild type GAA activity without mature processed GAA protein on immunoblots, indicating that the variant may impact protein function (Flanagan et al, 2009, PMID: 19862843) (PS3_Supporting). Expression of the variant in COS-7 cells resulted in <2% wild type GAA activity (Table 3). Data compiled from two or more independent transfections for each variant. Variants listed in the table are in bold if mature GAA species were present on Western blot. This variant is not in bold implying no mature GAA protein. However, Western blots were not shown. PubMed:19862843

Not Met criteria codes

PS1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	ℹ	✖	Not in the ClinGen LSD VCEP specified critical amino acid residues in GAA.
PM5	ℹ	✖	Another missense variant, c.1099T>G (p.Trp367Gly), in the same codon has been reported in a patients with late-onset Pompe disease (Fukuhara et al, 2017, PMID: 29124014). However, the data for p.Trp367Arg will be used in the assessment of p.Trp367Gly and therefore PM5 is not met here in order to avoid circular logic (PM5 not met).
PVS1	ℹ	✖	NA to this missense variant

Curation History

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