

Variant: NM_000152.5(GAA):c.1316T>A (p.Met439Lys)

Version: 1.0

CA8815258 [↗](#)

371305 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: aecc4442-0d8c-4bbd-a5ce-42bee4bda6e9

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HGVS expressions

NM_000152.5:c.1316T>A

NM_000152.5(GAA):c.1316T>A (p.Met439Lys)

NC_000017.11:g.80108818T>A

CM000679.2:g.80108818T>A

NC_000017.10:g.78082617T>A

CM000679.1:g.78082617T>A

NC_000017.9:g.75697212T>A

NG_009822.1:g.12263T>A

ENST00000570803.6:c.1316T>A

ENST00000572080.2:c.1316T>A

ENST00000577106.6:c.1316T>A

ENST00000302262.8:c.1316T>A

ENST00000302262.7:c.1316T>A

ENST00000390015.7:c.1316T>A

NM_000152.3:c.1316T>A

NM_001079803.1:c.1316T>A

NM_001079804.1:c.1316T>A

NM_000152.4:c.1316T>A

NM_001079803.2:c.1316T>A

NM_001079804.2:c.1316T>A

NM_001079803.3:c.1316T>A

NM_001079804.3:c.1316T>A

Pathogenic

Met criteria codes **5**

PM2_Supporting

PP4_Moderate

PM3_Very Strong

PS3_Moderate

PP3

Not Met criteria codes **2**

PS1

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.1316T>A variant in GAA is a missense variant predicted to cause substitution of methionine by lysine at amino acid 439 (p.Met439Lys). At least 14 patients have been reported with this variant and features consistent with Pompe disease. This includes 7 patients with documented laboratory values showing deficiency of GAA activity, below the reference range for normal activity in leukocytes (PMIDs: 17092519, 21940687, 23884227, 25388776, 28433475, 30360039), some of whom are also reported to have histological features of Pompe disease in muscle (PMID: 20202878, 30894207), and/or documented features of infantile onset Pompe disease including muscle weakness and cardiomyopathy (PMID: 33344388) and/or on enzyme replacement therapy (PMID: 30894207, 31193175) (PP4_Moderate). Note that pseudodeficiency variants, (p.Gly576Ser and p.Glu689Lys) were confirmed to be absent in at least one of these cases (PMID 28433475). Of these patients, 7 are compound heterozygous for the variant and a variant classified as pathogenic or likely pathogenic by the ClinGen LSD VCEP including c.1798C>T (p.Arg600Cys) (PMID: 20202878; phase unknown, 0.5 points), c.2238G>C (p.Trp746Cys) (PMID: 30894207, confirmed in trans, 1 point) (PMID: 25388776, unknown phase, 0.5 points), c.546G>T (PMID: 28433475, unknown phase, 0.5 points), c.2407_2413del (p.Gln803Ter) (PMID: 23884227, unknown phase, 0.5 points), and c.1579_1580del (p.Arg527GlyfsTer3) (PMID: 30360039, phase unknown, 0.5 points), and c.1225dup (PMID: 29869463; phase unknown, 0.25 points); and one patient is homozygous (PMID: 29124014) (0.5 points). Total 4.25 points (PM3_VeryStrong). Additional patients have been reported who are compound heterozygous for the variant and c.796C>T (p.Pro266Ser) (PMID: 17092519, 29044175, 31850350), c.1225dup (PMID: 29869463), and c.1309C>T (p.Arg437Cys) (PMID: 25388776) but the allelic data from these patients will be used in the assessment of the second variant and is not included here to avoid circular logic. Additional data was not included due to uncertainty about the nomenclature of the second variant (PMIDs: 20202878, 21940687). The highest population minor allele frequency in gnomAD is 0.00038 (6/15644 alleles) in the East Asian population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion. When expressed in COS cells the variant has <2% normal activity and does not show mature GAA protein on western blot (PMID 19862843) (PM3_Moderate). The computational predictor REVEL gives a score of 0.784 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). There is a ClinVar entry for this variant (Variation ID: 371305, 2 star review status) with 3 submitters classifying the variant as pathogenic and 4 as likely pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG-AMP criteria met, as specified by the ClinGen LSD VCEP (Specifications version 2): PM3_VeryStrong, PP4_Moderate, PS3_Moderate, PP3, PM2_Supporting. Classification approved by the ClinGen LSD VCEP on May 16, 2022.

Met criteria codes

PM2_Supporting	✓	The highest population minor allele frequency in gnomAD is 0.00038 (6/15644 alleles) in the East Asian population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion.
PP4_Moderate	 ✓	At least 14 patients have been reported with this variant and features consistent with Pompe disease. This includes 7 patients with documented laboratory values showing deficiency of GAA activity, below the reference range for normal activity in leukocytes (PMIDs: 17092519, 21940687, 23884227, 25388776, 28433475, 30360039), some of whom are also reported to have histological features of Pompe disease in muscle (PMID: 20202878, 30894207), and/or documented features of infantile onset Pompe disease including muscle weakness and cardiomyopathy (PMID: 33344388) and/or on enzyme replacement therapy (PMID: 30894207, 31193175) (PP4_Moderate). Note that pseudodeficiency variants, (p.Gly576Ser and p.Glu689Lys) were confirmed to be absent in at least one of these cases (PMID 28433475).
PM3_Very Strong	 ✓	At least 14 patients have been reported with this variant and features consistent with Pompe disease. Of these patients 7 are compound heterozygous for the variant and a variant classified as pathogenic or by the ClinGen LSD VCEP including c.1798C>T (p.Arg600Cys) (PMID: 20202878; phase unknown, 0.5 points), c.2238G>C (p.Trp746Cys) (PMID: 30894207, confirmed in trans, 1 point) (PMID: 25388776, unknown phase, 0.5 points), c.546G>T (PMID: 28433475, unknown phase, 0.5 points), c.2407_2413del (p.Gln803Ter) (PMID: 23884227, unknown phase, 0.5 points), c.1579_1580del (p.Arg527GlyfsTer3) (PMID: 30360039, phase unknown, 0.5 points) and c.1582_1583del (p.Gly528LeufsTer2) (PMID: 21940687; 0.5 points) and one patient is homozygous (PMID: 29124014) (0.5 points).

Total 4.5 points (PM3_VeryStrong). Additional patients have been reported who are compound heterozygous for the variant and c.796C>T (p.Pro266Ser) (PMID: 17092519, 29044175, 31850350), c.1225dup (PMID: 29869463), and c.1309C>T (p.Arg437Cys) (PMID: 25388776) but the allelic data from these patients will be used in the assessment of the second variant and is not included here to avoid circular logic. Additional data was not included due to uncertainty about the nomenclature (PMIDs: 20202878, 21940687).

PS3_Moderate			When expressed in COS cells the variant has <2% normal activity and does not show mature GAA protein on western blot (PM3_Moderate) (PMID 19862843)
PP3			The computational predictor REVEL gives a score of 0.784 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).

Not Met criteria codes

PS1			The p.Met439Lys amino acid change has not been reported with another nucleotide change in ClinVar, HGMD Pro, LOVD or pompevariantdatabase.nl.
PM5			No other missense changes at amino acid residue 439 have been described in ClinVar, HGMD Pro, LOVD or pompevariantdatabase.nl.

Curation History

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