

Variant: *NM_000152.5(GAA):c.1309C>T (p.Arg437Cys)*

Version: 1.0

CA274356 [↗](#)

189082 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 0dbf1624-9409-4543-ab0b-0d66118a2e88

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HGVS expressions

NM_000152.5:c.1309C>T

NM_000152.5(GAA):c.1309C>T (p.Arg437Cys)

NC_000017.11:g.80108811C>T

CM000679.2:g.80108811C>T

NC_000017.10:g.78082610C>T

CM000679.1:g.78082610C>T

NC_000017.9:g.75697205C>T

NG_009822.1:g.12256C>T

ENST00000570803.6:c.1309C>T

ENST00000572080.2:c.1309C>T

ENST00000577106.6:c.1309C>T

ENST00000302262.8:c.1309C>T

ENST00000302262.7:c.1309C>T

ENST00000390015.7:c.1309C>T

NM_000152.3:c.1309C>T

NM_001079803.1:c.1309C>T

NM_001079804.1:c.1309C>T

NM_000152.4:c.1309C>T

NM_001079803.2:c.1309C>T

NM_001079804.2:c.1309C>T

NM_001079803.3:c.1309C>T

NM_001079804.3:c.1309C>T

Pathogenic

Met criteria codes 5

PM2_Supporting

PS3_Supporting

PM3_Very Strong

PP3

PP4_Moderate

Not Met criteria codes 1

PM5

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*

[↗](#) **PDF**

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Lysosomal Diseases VCEP

The NM_000152.5:c.1309C>T variant in GAA is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 437 (p.Arg437Cys). This variant has been reported in at least 16 East Asian individuals with late onset Pompe disease (PMID: 34356580) including 11 individuals with documented laboratory values reporting GAA activity <10% normal in muscle or skin fibroblasts or in the affected range in a clinically validated dried blood spot assay and/or histological features consistent with Pompe disease in muscle, and/or on enzyme replacement therapy for Pompe disease (PMID 22521436, 29786057, 27692865, 30360039)(PP4_Moderate). Ten individuals are reported to be compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LSD VCEP including one confirmed in trans, c.1082C>T (p.Pro361Leu) (PMID: 12601120), and 9 phase unknown, c.796C>T (p.Pro266Ser) (PMID: 25526786), c.1082C>T (p.Pro361Leu) (PMID: 27692865), c.1316T>A (p.Met439Lys) (PMID: 25388776), c.1822C>T (p.Arg608Ter) (PMID: 30360039), c.1978C>T (p.Arg600Cys) (PMID: 29124014, 3 probands), c.2238G>C (p.Trp746Cys) (PMID: 27692865), c.2297A>G (p.Tyr766Cys) (PMID: 29124014) (PM3_VeryStrong). The variant has also been reported in compound heterozygosity with c.1544T>A (p.Met515Lys) (PMID: 24190153), c.1562A>T (p.Glu521Val) (PMID: 29786057), c.1857C>G (p.Ser619Arg) (PMID: 291240140, c.2051C>A (p.Pro684Gln) (PMID: 29451150), c.2177C>G (p.Pro726Arg) (PMID: 29124014), and c.2297A>C (p.Tyr766Ser) (PMID: 22521436). The allelic data from these patients will be used in the classification of the second variant and is not included here in order to avoid circular logic. Additional patients have also been reported but the data was not included because the cDNA sequences of the variants was not included (PMID: 18495398, 21471980, 21704464). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00009 (2/21914 alleles) in the African population, which is lower than the ClinGen LSD VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). Expression of the variant in Ad5-SV40 immortalized human GAA-deficient fibroblast cells showed no detectable GAA enzyme activity, and another study showed abnormal synthesis and processing of GAA when the variant was expressed in COS cells, indicating that this variant may impact protein function (PMID: 12601120, 19862843)(PS3_Supporting). The computational predictor REVEL gives a score of 0.782, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). A novel variant at the same amino acid position, c.1310G>A (p.Arg437His) has been reported in a patient with Pompe disease (PMID: 25681614) but has not yet been classified as pathogenic or likely pathogenic by the ClinGen LSD VCEP and, therefore, PM5 is not applied. There is a ClinVar entry for this variant (Variation ID: 189082, 2 star review status) with 6 submitters classifying the variant as pathogenic and two as likely pathogenic). 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 LSD VCEP (Specifications Version 2.0): PM3_VeryStrong, PP4_Moderate, PP3, PS3_Supporting, PM2_Supporting.

Met criteria codes

PM2_Supporting	✓	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00009 (2/21914 alleles) in the African population, which is lower than the ClinGen LSD VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PS3_Supporting	 ✓	<div>Expression of the variant in Ad5-SV40 immortalized human GAA-deficient fibroblast cells showed no detectable GAA enzyme activity, and another study showed abnormal synthesis and processing of GAA when the variant was expressed in COS cells, indicating that this variant may impact protein function (PMID: 12601120, 19862843) (PS3_Supporting).</div> <div>Expression of the variant in COS cells showed that this variant results in >2% wild-type GAA activity (specific level of activity was not provided) and is abnormally synthesized and/or processed when expressed in COS-7 cells (see Supplementa Figure S1 which shows approximately 20% production of total GAA and about 20% 76kD active GAA when compared to wild type). PubMed:19862843 </div>
PM3_Very Strong	 ✓	Ten individuals are reported to be compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LSD VCEP including one confirmed in trans, c.1082C>T (p.Pro361Leu) (PMID: 12601120; 1 point), and 9 phase unknown, c.796C>T (p.Pro266Ser) (PMID: 25526786; 0.5 points), c.1082C>T

(p.Pro361Leu) (PMID: 27692865; 0.5 points), c.1316T>A (p.Met439Lys) (PMID: 25388776, 0.5 points), c.1822C>T (p.Arg608Ter) (PMID: 30360039; 0.5 points), c.1978C>T (p.Arg600Cys) (PMID: 29124014, 3 probands, max 2 x 0.5 points), c.2238G>C (p.Trp746Cys) (PMID: 27692865), c.2297A>G (p.Tyr766Cys) (PMID: 29124014, 0.5 points) (>4 points total, PM3_VeryStrong). The variant has also been reported in compound heterozygosity with c.1544T>A (p.Met515Lys) (PMID: 24190153), c.1562A>T (p.Glu521Val) (PMID: 29786057), c.1857C>G (p.Ser619Arg) (PMID: 291240140, c.2051C>A (p.Pro684Gln) (PMID: 29451150), c.2177C>G (p.Pro726Arg) (PMID: 29124014), and c.2297A>C (p.Tyr766Ser) (PMID: 22521436). The allelic data from these patients will be used in the classification of the second variant and is not included here in order to avoid circular logic. Additional patients have also been reported but the data was not included because the cDNA sequences of the variants was not included (PMID: 18495398, 21471980, 21704464).

PP3			The computational predictor REVEL gives a score of 0.782, which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PP4_Moderate			This variant has been reported in at least 16 East Asian individuals with late onset Pompe disease (PMID: 34356580) in at least 16 individuals including 11 individuals with documented laboratory values reporting GAA activity <10% normal in muscle or skin fibroblasts or in the affected range in a clinically validated dried blood spot assay and/or histological features consistent with Pompe disease in muscle, and/or on enzyme replacement therapy for Pompe disease (PMID 22521436, 29786057, 27692865, 30360039)(PP4_Moderate).

Not Met criteria codes

PM5			A novel variant at the same amino acid position, c.1310G>A (p.Arg437His) has been reported in a patient with Pompe disease (PMID: 25681614) but has not yet been classified as pathogenic or likely pathogenic by the ClinGen LSD VCEP and, therefore, PM5 is not applied.
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Curation History

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