

Variant: *NM_000152.5(GAA):c.1978C>T (p.Arg660Cys)*

Version: 1.1

CA8815561 [↗](#)

558604 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 55109263-57b6-46d4-879a-dd022f1ae61c

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HGVS expressions

NM_000152.5(GAA):c.1978C>T (p.Arg660Cys)

NM_000152.5:c.1978C>T

NC_000017.11:g.80112965C>T

CM000679.2:g.80112965C>T

NC_000017.10:g.78086764C>T

CM000679.1:g.78086764C>T

NC_000017.9:g.75701359C>T

NG_009822.1:g.16410C>T

ENST00000570803.6:c.1978C>T

ENST00000572080.2:c.*116C>T

ENST00000577106.6:c.1978C>T

ENST00000302262.8:c.1978C>T

ENST00000302262.7:c.1978C>T

ENST00000390015.7:c.1978C>T

ENST00000570716.1:n.418C>T

ENST00000572080.1:c.397C>T

NM_000152.3:c.1978C>T

NM_001079803.1:c.1978C>T

NM_001079804.1:c.1978C>T

NM_000152.4:c.1978C>T

NM_001079803.2:c.1978C>T

NM_001079804.2:c.1978C>T

NM_001079803.3:c.1978C>T

NM_001079804.3:c.1978C>T

Pathogenic

Met criteria codes **6**

PP4_Moderate PS3_Supporting

PM3_Strong PP3 PM5

PM2_Supporting

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.1978C>T variant in GAA is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 660 (p.Arg660Cys). At least 6 patients with clinical features consistent with Pompe disease have been reported with this variant; three with documented laboratory data showing deficiency of GAA in dried blood spot, or lymphocytes and muscle (PMID: 17056254, 31193175, clinical laboratory data), and two reported to have deficient GAA activity and to be on enzyme replacement therapy on enzyme replacement therapy (PMID: 25626711, 29122469, 31904026) (PP4_Moderate). Three of these patients are compound heterozygous, phase unknown, for the variant and a variant classified as pathogenic by the ClinGen LSD VCEP, either c.784G>A (p.Glu262Lys) (PMID 31193175), c.1082C>T (p.Pro361Leu) (clinical laboratory data), or c.546G>T (PMID: 29124014) and another patient is homozygous (PMID: 25626711) (PM3_Strong). An additional two patients are compound heterozygous for the variant and [c.1477C>T; c.2221G>A] ([p.Pro493Ser; p.Asp741Asn]) (PMID: 29122469, 31904026), or c.1397T>G (p.Val466Gly) (PMID: 17056254). The allelic data from the latter 2 patients will be used in the classification of the second variant and is not included here to avoid circular logic. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006 (1/18006 alleles) in the East Asian population, which is lower than the ClinGen LSD VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). When expressed in COS cells, the variant results in <2% normal GAA activity (PMID 19862843) (PS3_Supporting). The computational predictor REVEL gives a score of 0.966 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another variant at this amino acid position, c.1979G>A (p.Arg660His) has been classified as pathogenic by the ClinGen LSD VCEP (PM5). There is a ClinVar entry for this variant (Variation ID: 558604; 2 star review status) with four 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 met, based on the specifications of the ClinGen LSD VCEP (Specifications Version 2.0): PM5, PM3_Strong, PP4_Moderate, PS3_Supporting, PM2_Supporting. (Approved by LSD VCEP on Feb 15, 2022).

Met criteria codes

PP4_Moderate			At least 6 patients with clinical features consistent with Pompe disease have been reported with this variant; three with documented laboratory data showing deficiency of GAA in dried blood spot, or lymphocytes and muscle (PMID: 17056254, 31193175, clinical laboratory data), and two reported to have deficient GAA activity and to be on enzyme replacement therapy on enzyme replacement therapy (PMID: 25626711, 29122469, 31904026) (PP4_Moderate).
PS3_Supporting			When expressed in COS cells, the variant results in <2% normal GAA activity (PMID 19862843) (PS3_Supporting).
PM3_Strong			At least six patients with clinical features consistent with Pompe disease have been reported with this variant. Three of these patients are compound heterozygous, phase unknown, for the variant and a variant classified as pathogenic by the ClinGen LSD VCEP, either c.784G>A (p.Glu262Lys) (PMID 31193175) (0.5 points), c.1082C>T (p.Pro361Leu) (clinical laboratory data) (0.5 points), or c.546G>T (PMID: 29124014) (0.5 points) and another patients is homozygous (PMID: 25626711) (0.5 points). An additional two patients are compound heterozygous for the variant and [c.1477C>T; c.2221G>A] ([p.Pro493Ser; p.Asp741Asn]) (PMID: 29122469, 31904026), or c.1397T>G (p.Val466Gly) (PMID: 17056254). The allelic data from the latter 2 patients will be used in the classification of the second variant and is not included here to avoid circular logic. Total 2 points (PM3_Strong).
PP3			The computational predictor REVEL gives a score of 0.966 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM5			

Another variant at this amino acid position, c.1979G>A (p.Arg660His) has been classified as pathogenic by the ClinGen LSD VCEP (PM5).

PM2_Supporting

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The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006 (1/18006 alleles) in the East Asian population, which is lower than the ClinGen LSD VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

Curation History [↗](#)

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