

Variant: *NM_000152.5(GAA):c.1556T>C (p.Met519Thr)*

Version: 1.0

CA274402 [↗](#)

189124 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: f4330a30-6672-4c82-87de-66870f00f6d2

Approved on: 2024/5/7

Published on: 2024/5/8

HGVS expressions

NM_000152.5(GAA):c.1556T>C (p.Met519Thr)

NM_000152.5:c.1556T>C

NC_000017.11:g.80110945T>C

CM000679.2:g.80110945T>C

NC_000017.10:g.78084744T>C

CM000679.1:g.78084744T>C

NC_000017.9:g.75699339T>C

NG_009822.1:g.14390T>C

ENST00000570803.6:c.1556T>C

ENST00000572080.2:c.1556T>C

ENST00000577106.6:c.1556T>C

ENST00000302262.8:c.1556T>C

ENST00000302262.7:c.1556T>C

ENST00000390015.7:c.1556T>C

NM_000152.3:c.1556T>C

NM_001079803.1:c.1556T>C

NM_001079804.1:c.1556T>C

NM_000152.4:c.1556T>C

NM_001079803.2:c.1556T>C

NM_001079804.2:c.1556T>C

NM_001079803.3:c.1556T>C

NM_001079804.3:c.1556T>C

Pathogenic

Met criteria codes **6**

PP4_Moderate

PM3_Strong

PP3

PS3_Moderate

PM1

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**

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

Lysosomal Diseases VCEP

The NM_000152.5:c.1556T>C variant in GAA is a missense variant predicted to cause substitution of methionine by threonine at amino acid 519 (p.Met519Thr). This variant has been detected in at least 4 individuals with Pompe disease. Of those individuals, 3 were compound heterozygous for the variant and a variant that has been classified as pathogenic by the ClinGen LD VCEP, phase unconfirmed, either c.525del (ClinVar Variation ID: 4033, SCV001443331.1) (PMID: 14695532), c.1441T>C (p.Trp481Arg) (ClinVar Variation ID: 189007, SCV004227917.1) (PMID: 31086307), or c.[752C>T;761C>T] (p.[Ser251Leu;Ser254Leu] (ClinVar Variation ID 325781/325782) (Clinical laboratory data); One individual was homozygous for the variant (PMID: 33741225) (PM3_Strong). At least 1 patient with this variant had documented GAA deficiency with <10% of normal mean control level of GAA activity in dried blood spot (PMID: 33741225) and 2 patients were reported to have symptoms consistent with infantile onset Pompe disease (PMID: 14695532) (PP4_Moderate). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003 (1/30616 alleles) in the South Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.983 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Expression of the variant in COS-7 resulted in <2% wild type GAA activity with western blot data showing decreased level of mature protein, indicating that this variant may impact protein function (PMIDs: 19862843, 14695532) (PS3_Moderate). This variant alters amino acid M519, a residue that crystallography studies have shown to be important in the active site of GAA, and therefore has been defined as a critical residue by the ClinGen Lysosomal Diseases VCEP (<https://www.biorxiv.org/content/10.1101/212837v1.full.pdf>, PMID: 29061980) (PM1). There is a ClinVar entry for this variant (Variation ID: 189124). In summary, this variant meets the criteria to be classified as Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on the specification of the ClinGen Lysosomal Diseases VCEP (Specifications Version 2.0): PM3_strong, PP4_moderate, PM1, PS3_moderate, PP3, PM2_supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on May 7, 2024)

Met criteria codes

PP4_Moderate			At least 1 patient with this variant had documented GAA deficiency with <10% of normal mean control level of GAA activity in dried blood spot (PMID: 33741225) and 2 patients were reported to have IOPD (PMID: 14695532) (PP4_Moderate).
PM3_Strong			This variant has been detected in at least 5 individuals with Pompe disease. Of those individuals, 3 were compound heterozygous for the variant and a variant that has been classified as pathogenic by the ClinGen LD VCEP, phase unconfirmed, either c.525del (ClinVar Variation ID: 4033, SCV001443331.1) (PMID: 14695532), c.1441T>C (p.Trp481Arg) (ClinVar Variation ID: 189007, SCV004227917.1) (PMID: 31086307), or c.[752C>T;761C>T] (p.[Ser251Leu;Ser254Leu] (ClinVar Variation ID 325781/325782) (Clinical laboratory data), 3 x 0.5 points. One individual was homozygous for the variant (0.5 point, PMID: 33741225). Total 2 points (PM3_Strong).
PP3			The computational predictor REVEL gives a score of 0.983 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PS3_Moderate			Expression of the variant in COS-7 resulted in <2% wild type GAA activity with western blot data showing reduction in level of mature protein, indicating that this variant may impact protein function (PMIDs: 19862843, 14695532) (PS3_Moderate).
PM1			This variant alters amino acid M519, a residue that crystallography studies have shown to be important in the active site of GAA, and therefore has been defined as a critical residue by the ClinGen Lysosomal Diseases VCEP (https://www.biorxiv.org/content/10.1101/212837v1.full.pdf , PMID: 29061980) (PM1).

PM2_Supporting

✓

The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003 (1/30616 alleles) in the South Asian population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

Curation History 

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.