

Variant: *NM_000152.4(GAA):c.1064T>C (p.Leu355Pro)*

Version: 1.4

CA8815136 [↗](#)

284093 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 7b23f882-c6fd-4d3b-b9ef-d2268a89f53a

Approved on: 2021/9/7

Published on: 2021/9/7

HGVS expressions

NM_000152.4(GAA):c.1064T>C (p.Leu355Pro)

NM_000152.4:c.1064T>C

NC_000017.11:g.80108398T>C

CM000679.2:g.80108398T>C

NC_000017.10:g.78082197T>C

CM000679.1:g.78082197T>C

NC_000017.9:g.75696792T>C

NG_009822.1:g.11843T>C

ENST00000570803.6:c.1064T>C

ENST00000572080.2:c.1064T>C

ENST00000577106.6:c.1064T>C

ENST00000302262.8:c.1064T>C

ENST00000302262.7:c.1064T>C

ENST00000390015.7:c.1064T>C

NM_000152.3:c.1064T>C

NM_001079803.1:c.1064T>C

NM_001079804.1:c.1064T>C

NM_001079803.2:c.1064T>C

NM_001079804.2:c.1064T>C

NM_000152.5:c.1064T>C

NM_001079803.3:c.1064T>C

NM_001079804.3:c.1064T>C

Pathogenic

Met criteria codes 5

PP4_Moderate

PM3_Strong

PP3

PS3_Moderate

PM2_Supporting

Not Met criteria codes 2

PS1

PM5

Evidence Links 0

Expert Panel

[Lysosomal Diseases VCEP](#) [↗](#)

Criteria Specification Information **!**

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

Lysosomal Diseases VCEP

The NM_000152.5:c.1064T>C variant in GAA is a missense variant predicted to cause substitution of leucine to proline at amino acid 355 (p.Leu355Pro). This variant has been reported in over 20 individuals with Pompe disease including at least 9 individuals with documented laboratory values showing GAA deficiency (PP4_Moderate) (PMIDs 14972326, 17213836, 17723315, 17213836, 23632174, 24016645, 30595407)(PP4_Moderate). The variant is homozygous in multiple patients (PMIDs 14972326, 16917947, 17213836, 17573812, 17723315, 18429042, 22658377, 23787031, 24016645, 30023291, 33325062). Three individuals are compound heterozygous for the variant and another variant that has been assessed as pathogenic by the ClinGen LSD VCEP; c.-32-13T>G in two patients (PMIDs 17643989, 21803581), and confirmed in trans with c.670C>T (p.Arg224Trp) in another patient (PMID 23632174; (PM3_Strong). p.Leu355Pro has also been reported in individuals with Pompe disease who are compound heterozygous for c.2041-2A>C (PMID 33325062), c.2303C>G (p.Pro768Arg) (PMID 17027861), c.1210G>A (p.Asp404Asn) (PMID 22658377, 23787031), c.1120T>C (p.Cys374Arg) (PMID 14695532), c.1927G>A (p.Gly643Arg) (PMID 18429042), c.1106T >C (p.Leu369Pro) (PMID 23430493), and c.380G>T (p.Cys127Phe) (PMID 24016645). The in trans data from these patients will be used in the assessment of the other variant and was not included here in order to avoid circular logic. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003 (1/34580) in the Latino 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, this variant results in absent GAA activity, and there is evidence of abnormal synthesis and processing of GAA on Western blot (PMIDs 14695532, 14972326, 19862843) (PS3_Moderate). The computational predictor REVEL gives a score of 0.805 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: 284093, 2 star review status) with four submitters each classifying the variant as 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_Strong, PS3_Moderate, PP4_Moderate, PP3, PM2_Supporting. (Classification approved August 17, 2021)

Met criteria codes

PP4_Moderate			Over 20 individuals with this variant have been reported to have Pompe disease. At least 9 of these individuals have documented values showing GAA deficiency (PP4_Moderate) (PMIDs 14972326, 17213836, 17723315, 17213836, 23632174, 24016645, 30595407). The variant has also been reported in additional patients with Pompe disease (PMIDs 14695532, 16917947, 17027861, 18429042, 17573812, 17643989, 21803581, 22658377, 23787031, 30023291, 33325062).
PM3_Strong			The variant has been reported to be homozygous in multiple patients (1 point) (PMIDs 14972326, 16917947, 17213836, 17573812, 17723315, 18429042, 22658377, 23787031, 24016645, 30023291, 33325062), compound heterozygous with c.-32-13T>G in two patients (PMIDs 17643989, 21803581, 2 X 0.5 points), and confirmed in trans with c.670C>T (p.Arg224Trp) (PMID 23632174; p.Arg224Trp is pathogenic for Pompe disease based on the assessment of the ClinGen LSD VCEP; 1 point). p.Leu355Pro has also been reported in individuals with Pompe disease who are compound heterozygous for c.2041-2A>C (PMID 33325062), c.2303C>G (p.Pro768Arg) (PMID 17027861), c.1210G>A (p.Asp404Asn) (PMID 22658377, 23787031), c.1120T>C (p.Cys374Arg) (PMID 14695532), c.1927G>A (p.Gly643Arg) (PMID 18429042), c.1106T >C (p.Leu369Pro) (PMID 23430493), and c.380G>T (p.Cys127Phe) (PMID 24016645). The in trans data from these patients will be used in the assessment of the other variant and was not included here in order to avoid circular logic. In total, 3 points were given towards PM3, meeting PM3_Strong.
PP3			REVEL (in silico meta predictor for missense changes) score = 0.805 which is higher than the LSD VCEP threshold for PP3, and therefore meets this criterion.
PS3_Moderate			When expressed in COS cells, this variant results in very low (<2% wild type GAA) activity, and there is evidence of abnormal synthesis and processing of GAA on Western blot (PMIDs 14695532, 14972326, 19862843). The meets the specifications for PS3_Moderate.

PM2_Supporting			The highest population minor allele frequency in gnomAD v2.1.1 is 0.00003 (1/34580) in the Latino/Admixed American population, which is lower than the ClinGen LSD VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
Not Met criteria codes			
PS1			No other variants at this codon were identified.
PM5			No other variants at this codon were identified.

Curation History			
Showing 1 to 5 of 5 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.