

Variant: NM_000152.5(GAA):c.1082C>T (p.Pro361Leu)

Version: 1.0

CA8815163 [↗](#)

403712 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 9f8dfb67-c941-448e-9f21-0942d1c57fab

Approved on: 2022/6/3

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HGVS expressions

NM_000152.5:c.1082C>T

NM_000152.5(GAA):c.1082C>T (p.Pro361Leu)

NC_000017.11:g.80108495C>T

CM000679.2:g.80108495C>T

NC_000017.10:g.78082294C>T

CM000679.1:g.78082294C>T

NC_000017.9:g.75696889C>T

NG_009822.1:g.11940C>T

ENST00000570803.6:c.1082C>T

ENST00000572080.2:c.1082C>T

ENST00000577106.6:c.1082C>T

ENST00000302262.8:c.1082C>T

ENST00000302262.7:c.1082C>T

ENST00000390015.7:c.1082C>T

NM_000152.3:c.1082C>T

NM_001079803.1:c.1082C>T

NM_001079804.1:c.1082C>T

NM_000152.4:c.1082C>T

NM_001079803.2:c.1082C>T

NM_001079804.2:c.1082C>T

NM_001079803.3:c.1082C>T

NM_001079804.3:c.1082C>T

Pathogenic

Met criteria codes 5

PS3_Moderate

PP4_Moderate

PM3_Strong

PM2_Supporting

PP3

Not Met criteria codes 1

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.1082C>T variant in GAA is a missense variant predicted to cause substitution of proline by leucine at amino acid 361 (p.Pro361Leu). This variant has been reported in at least 13 individuals with clinical symptoms consistent with Pompe disease including 6 individuals with documented laboratory values showing deficiency of GAA activity below normal range in leukocytes or <1% activity in fibroblasts or another tissue, many of whom were also reported to be showing improvement on enzyme replacement therapy and/or had specific features reported for infantile onset Pompe disease including cardiomyopathy and motor delay (PMID: 21484825, 25139343, 25526786, 26497565, 27344650, 31439017, 31915562) and another patient with features specific for infantile onset Pompe disease, on enzyme replacement therapy (PMID: 30023291). Pseudodeficiency variants, c.1726G>A and c.2065G>A, were reported to be absent in at least one of these patients (PMID: 25526786) (PP4_Moderate). Of the patients reported with this variant, four are compound heterozygous for the variant and another variant in GAA classified as pathogenic by the ClinGen LSD VCEP including c.784G>A (p.Glu262Lys) (PMID: 31915562; confirmed in trans by parental DNA testing) and c.1933G>A (p.Asp645Asn) (PMID: 26497565, 27344650; phase unknown), c.1935C>A (p.Asp645Glu) (PMID: 31439017; phase unknown), and c.2238G>C (p.Trp746Cys) (PMID: 35123860; phase unknown). In addition, two homozygotes have been reported (PMID: 30023291, 31931849), one of whom was identified by next generation sequencing panel for limb girdle muscle weakness, and not counted due to no report of follow up enzyme studies to confirm diagnosis of Pompe disease (PMID: 31931849) (PM3_Strong). Additional patients have been reported with the variant in compound heterozygosity with another variant including c.503G>C (p.Arg168Pro) (PMID: 25526786), c.953T>C (p.Met318Thr) (PMID: 25139343), c.1309C>T (p.Arg437Cys) (PMID: 12601120, 27692865), c.1432G>A (p.Gly478Arg) (PMID: 25213570), c.1979G>A (p.Arg660His) (PMID: 21484825), and c.1551+1G>C (PMID: 16917947). In these cases, the allelic data will be used in the assessment of the second variant and was not applied to PM3 here in order to avoid circular logic. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006 in the Latino population which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion. When expressed in COS cells and GAA deficient fibroblasts, this variant resulted in <4% wild type GAA activity in three different studies (PMID: 12601120, 19862843, 22644586) and showed evidence of abnormal synthesis and processing on Western blot (PMID: 22644586) (PS3_Moderate). The computational predictor REVEL gives a score of 0.951 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another variant at the same codon, c.1082C>A (p.Pro361Arg) has been reported (PMID: 31076647). The classification of p.Pro163Leu will be used in the assessment of p.Pro361Arg and, therefore, PM5 is not applied here. There is a ClinVar entry for this variant (Variation ID: 403712, 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 applied, as specified by the ClinGen LSD VCEP: PM3_Strong, PS3_Moderate, PP4_Moderate, PP3, PM2_Supporting. Classification approved by the ClinGen LSD VCEP on May 16, 2022.

Met criteria codes

PS3_Moderate			When expressed in COS cells and GAA deficient fibroblasts, this variant resulted in <4% wild type GAA activity in three different studies (PMID: 12601120, 19862843, 22644586) and showed evidence of abnormal synthesis and processing on Western blot (PMID: 22644586) (PS3_Moderate).
PP4_Moderate			This variant has been reported in at least 13 individuals with clinical symptoms consistent with Pompe disease including 6 individuals with documented laboratory values showing deficiency of GAA activity below normal range in leukocytes or <1% activity in fibroblasts or another tissue, many of whom were also reported to be showing improvement on enzyme replacement therapy and/or had specific features reported for infantile onset Pompe disease including cardiomyopathy and motor delay (PMID: 21484825, 25139343, 25526786, 26497565, 27344650, 31439017, 31915562) and another patient with features specific for infantile onset Pompe disease, on enzyme replacement therapy (PMID: 30023291). Pseudodeficiency variants, c.1726G>A and c.2065G>A, were reported to be absent in at least one of these patients (PMID: 25526786) (PP4_Moderate).
PM3_Strong			Of the 13 patients reported with this variant, four are compound heterozygous for the variant and another variant in GAA classified as pathogenic by the ClinGen LSD VCEP including c.784G>A (p.Glu262Lys) (PMID: 31915562;

confirmed in trans by parental DNA testing, 1 point) and c.1933G>A (p.Asp645Asn) (PMID: 26497565, 27344650; phase unknown, 0.5), c.1935C>A (p.Asp645Glu) (PMID: 31439017; phase unknown, 0.5 points), and c.2238G>C (p.Trp746Cys) (PMID: 35123860; phase unknown, 0.5 points). In addition, two homozygotes have been reported (PMID: 30023291, 31931849; 0.5), one of whom was identified by next generation sequencing panel for limb girdle muscle weakness, and not counted due to no report of follow up enzyme studies to confirm diagnosis of Pompe disease (PMID: 31931849). Total 3 points (PM3_Strong). Additional patients have been reported with the variant in compound heterozygosity with another variant including c.503G>C (p.Arg168Pro) (PMID: 25526786), c.953T>C (p.Met318Thr) (PMID: 25139343), c.1309C>T (p.Arg437Cys) (PMID: 12601120, 27692865), c.1432G>A (p.Gly478Arg) (PMID: 25213570), c.1979G>A (p.Arg660His) (PMID: 21484825), and c.1551+1G>C (PMID: 16917947). In these cases, the allelic data will be used in the assessment of the second variant and was not applied to PM3 here in order to avoid circular logic.

PM2_Supporting			The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006 in the Latino population which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion.
PP3			The computational predictor REVEL gives a score of 0.951 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
Not Met criteria codes			
PM5			Another variant at the same codon, c.1082C>A (p.Pro361Arg) has been reported (PMID: 31076647). The classification of p.Pro163Leu will be used in the assessment of p.Pro361Arg and, therefore, PM5 is not applied here.

Curation History



 

 

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