

Variant: NM_001079804.3:c.872T>C

Version: 1.0

CA401363854 [↗](#)

1327502 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 6f3a7b01-e825-4e59-bd44-f2aaa013e512

Approved on: 2021/12/2

Published on: 2021/12/2

HGVS expressions

NM_001079804.3:c.872T>C
NC_000017.11:g.80107813T>C
CM000679.2:g.80107813T>C
NC_000017.10:g.78081612T>C
CM000679.1:g.78081612T>C
NC_000017.9:g.75696207T>C
NG_009822.1:g.11258T>C
ENST00000570803.6:c.872T>C
ENST00000572080.2:c.872T>C
ENST00000577106.6:c.872T>C
ENST00000302262.8:c.872T>C
ENST00000302262.7:c.872T>C
ENST00000390015.7:c.872T>C
NM_000152.3:c.872T>C
NM_001079803.1:c.872T>C
NM_001079804.1:c.872T>C
NM_000152.4:c.872T>C
NM_001079803.2:c.872T>C
NM_001079804.2:c.872T>C
NM_000152.5:c.872T>C
NM_001079803.3:c.872T>C

Pathogenic

Met criteria codes 5

PM3_Strong PS3_Moderate PP3
PM2_Supporting PP4_Moderate

Not Met criteria codes 1

PM5

Evidence Links 0

Expert Panel

Lysosomal Diseases VCEP [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.872T>C variant in GAA is a missense variant predicted to cause substitution of leucine by proline at amino acid 291 (p.Leu291Pro). At least 5 patients have been reported with this variant and features consistent with Pompe disease, including documented laboratory values showing deficiency GAA activity and/or treated with enzyme replacement therapy, and/or features consistent with infantile onset Pompe disease meeting specifications of the ClinGen LSD VCEP for PP4_Moderate (PMID 17151339, 18458862, 22353292, 22658377, 24243590, 25213570, 31193175). Additional patients have also been reported (PMID 18425781, 18458862, 29095275). Four patients are compound heterozygous for the variant and GAA variant classified as pathogenic by the ClinGen LSD VCEP, phase unknown, including c.1411_1414del (PMID 24243590; ClinVar SCV001443324.1), c.1798C>T (p.Arg600Cys)(PMID 18458862, 22353292, 25213570; 2 patients), and c.1935C>A (p.Asp645Glu)(PMID 29095275), and at least 2 patients are homozygous for the variant (PMID 16857770, 17151339, 18458862, 22658377, 31193175)(PM3_Strong). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). When expressed in COS cells, this variant had 0.7% wild type GAA activity in cells and showed evidence of abnormal synthesis and processing on Western blot (PMID:22644586) (PS3_Moderate). The computational predictor REVEL gives a score of 0.908 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Two other variants have been identified at the same amino acid position, c.871C>T (p.Leu291Phe) and c.872T>A (p.Leu291His). The data from this variant, c.872T>C (p.Leu291Pro), will be used in the classification of p.Leu291Phe and p.Leu291His and is not included here to avoid circular logic. There is no entry for this variant in ClinVar. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, as specified by the ClinGen LSD VCEP (Specifications Version 2.0): PS3_Moderate, PM3_Strong, PM2_Supporting, PP3, PP4_Moderate.

Met criteria codes

PM3_Strong			Four patients with Pompe disease are compound heterozygous for the variant and GAA variant classified as pathogenic by the ClinGen LSD VCEP, phase unknown, including c.1411_1414del (PMID 24243590; ClinVar SCV001443324.1; 0.5 points), c.1798C>T (p.Arg600Cys)(PMID 18458862, 22353292, 25213570; 2 x 0.5 points), and c.1935 C>A (p.Asp645Glu)(PMID 29095275; 0.5 points), and at least 2 patients are homozygous for the variant (PMID 16857770, 17151339, 18458862, 22658377, 31193175; 2 x 0.5 points). Total 3 points (PM3_Strong).
PS3_Moderate			When expressed in COS cells, this variant was classified as Class B ("potentially less severe") by Kroos et al, 2012 (PMID:22644586). This includes 0.7% GAA activity in cells and 1.4% in medium, and evidence of abnormal synthesis and processing on Western blot (PS3_Moderate).
PP3			The computational predictor REVEL gives a score of 0.908 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3)
PM2_Supporting			This variant is absent in gnomAD v2.1.1 (PM2_Supporting).
PP4_Moderate			At least 5 patients have been reported with this variant and features consistent with Pompe disease, including documented laboratory values showing deficiency GAA activity and/or treated with enzyme replacement therapy, and/or features consistent with infantile onset Pompe disease meeting specifications of the ClinGen LSD VCEP for PP4_Moderate (PMID 17151339, 18458862, 22353292, 22658377, 24243590, 25213570, 31193175). Additional patients have also been reported (PMID 18425781, 18458862, 29095275).

Not Met criteria codes

PM5			Two other variants have been identified at the same amino acid position, c.871C>T (p.Leu291Phe) and c.872T>A (p.Leu291His). The data from this variant, c.872T>C (p.Leu291Pro), will be used in the classification of p.Leu291Phe and p.Leu291His and is not included here to avoid circular logic.
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Curation History 

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