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Variant: NM_000152.5(GAA):c.871C>T (p.Leu291Phe)

Version: 1.0

CA8815079

956209 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: eba501a5-9784-427b-9832-ea88a774417b
Approved on: 2021/10/26
Published on: 2021/10/26

HGVS expressions

NM_000152.5(GAA):c.871C>T (p.Leu291Phe)
NM_000152.5:c.871C>T
NC_000017.11:g.80107812C>T
CM000679.2:g.80107812C>T
NC_000017.10:g.78081611C>T
CM000679.1:g.78081611C>T
NC_000017.9:g.75696206C>T
NG_009822.1:g.11257C>T
ENST00000570803.6:c.871C>T
ENST00000572080.2:c.871C>T
ENST00000577106.6:c.871C>T
ENST00000302262.8:c.871C>T
ENST00000302262.7:c.871C>T
ENST00000390015.7:c.871C>T
NM_000152.3:c.871C>T
NM_001079803.1:c.871C>T
NM_001079804.1:c.871C>T
NM_000152.4:c.871C>T
NM_001079803.2:c.871C>T
NM_001079804.2:c.871C>T
NM_001079803.3:c.871C>T
NM_001079804.3:c.871C>T

Pathogenic

Met criteria codes 6

PP4_Moderate PM3_Strong PP3 PS3_Moderate PM5 PM2_Supporting

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.871C>T variant in GAA is a missense variant predicted to cause substitution of leucine by phenylalanine at amino acid 291 (p.Leu291Phe). Five patients with Pompe disease and this variant have been reported, four with characteristics specific for Pompe disease including published laboratory values showing deficient GAA activity and/or on enzyme replacement therapy and/or with documented symptoms consistent with infantile onset Pompe disease (PMID 25526786, 30737479, 31086307, 32849613) (PP4_Moderate). Four of these patients are compound heterozygous for the variant and a pathogenic variant in GAA, phase unknown, including c.716delT (PMID 32849613; 0.5 points), c.1798C>T (p.Arg600Cys)(PMID 26253708; 0.5 points), c.2238G>C (p.Trp746Cys)(PMID 25526786; 0.5 points), and c.2481+102_2646+31del (PMID 31086307; 0.5 points). One patient who is homozygous for the variant, due to uniparental disomy, has also been reported (PMID 30737479; 0.5 points). Total 2.5 points (PM3_Strong). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006378 in the African population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). When expressed in COS cells, this variant had <5% wild type GAA activity and showed evidence of abnormal synthesis and processing on Western blot (PMID 22644586) (PS3_Moderate). The computational predictor REVEL gives a score of 0.701 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Two other missense changes, c.872T>C (p.Leu291Pro) and c.872T>A (p.Leu291His), at the same amino acid residue have been reported; c.872T>C (p.Leu291Pro) has been classified as pathogenic based on the specifications of the ClinGen LSD VCEP (CAID: CA401363854)(PM5). The data for this variant, c.871C>T (p.Leu291Phe, will be used in the assessment of p.Leu291His and is not included here to avoid circular logic. There is a ClinVar entry for this variant (Variation ID 956209; 1 star review status) with two submitters 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 met, as specified by the ClinGen LSD VCEP (Specifications Version 2.0): PM5, PP3, PS3_Moderate, PM3_Strong, PM2_Supporting, PP4_Moderate. (Classification approved by the ClinGen LSD VCEP - Oct. 19, 2021).

Met criteria codes

PP4_Moderate ✔	Four patients with Pompe disease and this variant have been reported with characteristics specific for Pompe disease including published laboratory values showing deficient GAA activity and/or on enzyme replacement therapy and/or with documented symptoms consistent with infantile onset Pompe disease (PMID 25526786, 30737479, 31086307, 32849613) (PP4_Moderate).
PM3_Strong ✔	Four patients with Pompe disease have been reported who are compound heterozygous for the variant and a pathogenic variant in GAA, phase unknown, including c.716delT (PMID 32849613; 0.5 points), c.1798C>T (p.Arg600Cys)(PMID 26253708; 0.5 points), c.2238G>C (p.Trp746Cys)(PMID 25526786; 0.5 points), and c.2481+102_2646+31del (PMID 31086307; 0.5 points). One patient who is homozygous for the variant, due to uniparental disomy, has also been reported (PMID 30737479; 0.5 points). Total 2.5 points (PM3_Strong).
PP3 ✔	The computational predictor REVEL gives a score of 0.701 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
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 <5% GAA activity in cells and <2% in medium, and evidence of abnormal synthesis and processing on Western blot (PS3_Moderate).
PM5 ✔	Two other missense changes, c.872T>C (p.Leu291Pro) and c.872T>A (p.Leu291His), at the same amino acid residue have been reported; c.872T>C (p.Leu291Pro) has been classified as pathogenic based on the specifications of the ClinGen LSD VCEP (CAID: CA401363854)(PM5). The data for this variant, c.871C>T (p.Leu291Phe, will be used in the assessment of p.Leu291His and is not included here to avoid circular logic.
PM2_Supporting ✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006378 in the African population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Curation History

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