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Variant: NM_000152.5(GAA):c.896T>C (p.Leu299Pro)

Version: 1.0

CA273686

180144 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: f6e2a5b8-6227-4d3b-b770-cadd3638fb54
Approved on: 2022/5/11
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HGVS expressions

NM_000152.5(GAA):c.896T>C (p.Leu299Pro)
NM_000152.5:c.896T>C
NC_000017.11:g.80107837T>C
CM000679.2:g.80107837T>C
NC_000017.10:g.78081636T>C
CM000679.1:g.78081636T>C
NC_000017.9:g.75696231T>C
NG_009822.1:g.11282T>C
ENST00000570803.6:c.896T>C
ENST00000572080.2:c.896T>C
ENST00000577106.6:c.896T>C
ENST00000302262.8:c.896T>C
ENST00000302262.7:c.896T>C
ENST00000390015.7:c.896T>C
NM_000152.3:c.896T>C
NM_001079803.1:c.896T>C
NM_001079804.1:c.896T>C
NM_000152.4:c.896T>C
NM_001079803.2:c.896T>C
NM_001079804.2:c.896T>C
NM_001079803.3:c.896T>C
NM_001079804.3:c.896T>C

Pathogenic

Met criteria codes 5

PM3 PP4_Moderate PS3 PP3 PM2_Supporting

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.896T>C variant in GAA is a missense variant predicted to cause substitution of Leucine by Proline at amino acid 299 (p.Leu299Pro). At least 4 individuals have been reported with this variant and either diagnosis of Pompe disease with ERT treatment or GAA activity <10% normal in lymphocytes/leukocytes/muscle samples/unknown tissue (PMIDs 26622091, 26873529, 25626711,29422078). Another patient was homozygous for this variant and identified by newborn screening for Pompe disease (PMID: 22133539). This meets the criteria for PP4_Moderate. This variant has been detected in at least 7 individuals with Pompe disease or identified by newborn screening for Pompe disease. Of those individuals, 4 were compound heterozygous for the variant and a pathogenic variant, c.-32-13T>G (PMID:18757064, 26622091, 26873529). At least 1 individual was homozygous for the variant (PMID: 22133539,25626711). Criteria for PM3 were met. This variant is absent in gnomAD v2.1.1 (PM2_Supporting). Expression of the variant in COS cells resulted in 0% wild type GAA activity and evidence of abnormal synthesis and processing on Western blots leading the variant to be described as Class B ("potentially less severe", indicating that this variant may impact protein function (PMID:18425781)(PS3). REVEL Score = 0.952 which is higher than the LSD VCEP threshold for PP3 (>0.7) and therefore meets this criterion. There is a ClinVar entry for this variant (Variation ID: 180144, 2 star review status) with 5 submitters classifying the variant as Pathogenic. In summary, this variant meets the criteria to be classified as Pathogenic for Pompe disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Storage Disorders Variant Curation Expert panel (specifications Version 2.0): PS3, PP4_Moderate, PM3, PM2_Supporting, PP3

Met criteria codes

PM3	✔	This variant has been detected in at least 7 individuals with Pompe disease or identified by newborn screening for Pompe disease. Of those individuals, 4 were compound heterozygous for the variant and a pathogenic variant, c.-32-13T>G and 0.5 points were applied toward PM3 (PMID:18757064, 26622091, 26873529) and 1 was compound heterozygous for this variant and a variant that has not yet been evaluated by the ClinGen LSD VCEP, c.742delC (PMID:29422078). At least 1 individual was homozygous for the variant and 0.5 points was applied toward PM3 (PMID: 22133539,25626711) (PM3). Note also: https://dergipark.org.tr/en/download/article-file/206254
PP4_Moderate	✔	At least 4 individuals have been reported with this variant and either diagnosis of Pompe disease with ERT treatment or GAA activity <10% normal in lymphocytes/leukocytes/muscle samples/unknown tissue (PMIDs 26622091, 26873529, 25626711,29422078). Another patient was homozygous for this variant and identified by newborn screening for Pompe disease (PMID: 22133539). This meets the criteria for PP4_Moderate.
PS3	✔	Expression of the variant in COS cells resulted in 0% wild type GAA activity and evidence of abnormal synthesis and processing on Western blots leading the variant to be described as Class B ("potentially less severe", indicating that this variant may impact protein function (PMID:18425781)(PS3).
PP3	✔	REVEL Score = 0.952 which is higher than the LSD VCEP threshold for PP3 (>0.7) and therefore meets this criterion.
PM2_Supporting	✔	This variant is absent in gnomAD.

Not Met criteria codes

PM5	✖	Another variant, c.896T>G (p.Leu299Arg), has been identified in the same codon (ClinVar ID: 4025). PM5 was not applied because this variant meets criteria to be classified as pathogenic without this criteria and to avoid circular logic in the curation of p.Leu299Arg.

Curation History

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