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Variant: NM_000152.5(GAA):c.2314T>C (p.Trp772Arg)

Version: 1.0

CA401324918

552527 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: d12db192-4cfa-484f-a916-6198e1d22564
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HGVS expressions

NM_000152.5(GAA):c.2314T>C (p.Trp772Arg)
NM_000152.5:c.2314T>C
NC_000017.11:g.80117092T>C
CM000679.2:g.80117092T>C
NC_000017.10:g.78090891T>C
CM000679.1:g.78090891T>C
NC_000017.9:g.75705486T>C
NG_009822.1:g.20537T>C
ENST00000570803.6:c.2314T>C
ENST00000572080.2:c.*452T>C
ENST00000577106.6:c.2314T>C
ENST00000302262.8:c.2314T>C
ENST00000302262.7:c.2314T>C
ENST00000390015.7:c.2314T>C
ENST00000573556.1:n.267T>C
NM_000152.3:c.2314T>C
NM_001079803.1:c.2314T>C
NM_001079804.1:c.2314T>C
NM_000152.4:c.2314T>C
NM_001079803.2:c.2314T>C
NM_001079804.2:c.2314T>C
NM_001079803.3:c.2314T>C
NM_001079804.3:c.2314T>C

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PP4 PS3_Moderate PM3_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.2314T>C variant in GAA is a missense variant predicted to cause substitution of Tryptophan by Arginine at amino acid 772 (p.Trp772Arg). This variant has been detected in at least 1 individual with Pompe disease that was compound heterozygous for the variant and a pathogenic variant (PMID: 31619483, 18757064) (PM3_Supporting). At least 1 patient with this variant had documented GAA deficiency in leukocytes or fibroblasts was noted to have deficient GAA activity but results were not provided and was reported to be eligible for enzyme replacement therapy for Pompe disease (PMID: 31619483, 18757064) (PP4). This variant is absent in gnomAD v2.1.1 (PM2_Supporting). Expression of the variant in COS cells resulted in 5% wild type GAA activity and evidence of abnormal GAA synthesis and processing leading the variant to be described as Class B (“potentially less severe”), indicating that this variant may impact protein function (PMID: 18425781) (PS3_Moderate). The computational predictor REVEL gives a score of 0.93 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: 552527; 1 star review status) with 1 submitter classifying the variant as a VUS. In summary, this variant meets the criteria to be classified as Likely Pathogenic for Pompe disease. ACMG/AMP criteria met, based on the specification of the ClinGen LSD VCEP: PS3_Moderate, PM2_Supporting, PP3, PP4, PM3_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.93 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PP4	✔	At least 1 patient with this variant had documented GAA deficiency in leukocytes or fibroblasts was noted to have deficient GAA activity but results were not provided and was reported to be eligible for enzyme replacement therapy for Pompe disease (PMID: 31619483, 18757064) 1.5 points were awarded towards PP4 (PP4).
PS3_Moderate	✔	Expression of the variant in COS cells resulted in 5% wild type GAA activity and evidence of abnormal GAA synthesis and processing leading the variant to be described as Class B (“potentially less severe”), indicating that this variant may impact protein function (PMID: 18425781) (PS3_Moderate).
PM3_Supporting	✔	This variant has been detected in at least 1 individual with Pompe disease that was compound heterozygous for the variant and a pathogenic variant (PMID: 31619483, 18757064). 0.5 points were applied towards PM3 (PM3_Supporting).

Not Met criteria codes

PM5	✖	Another missense variant c.2316G>T (p.Trp772Cys) in the same codon has been reported in a patient with Pompe disease (ClinVar ID: 392862). However, this variant has not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen LSD VCEP and was not used in the curation of this variant to avoid circular logic (PM5 not met).

Curation History

Showing 1 to 1 of 1 rows

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