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Variant: NM_000152.5(GAA):c.1437G>C (p.Lys479Asn)

Version: 1.0

CA401366671

3241647 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: f20ccaba-4a3b-4f55-967f-a305a89a929a
Approved on: 2024/9/17
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HGVS expressions

NM_000152.5(GAA):c.1437G>C (p.Lys479Asn)
NM_000152.5:c.1437G>C
NC_000017.11:g.80110055G>C
CM000679.2:g.80110055G>C
NC_000017.10:g.78083854G>C
CM000679.1:g.78083854G>C
NC_000017.9:g.75698449G>C
NG_009822.1:g.13500G>C
ENST00000570803.6:c.1437G>C
ENST00000572080.2:c.1437G>C
ENST00000577106.6:c.1437G>C
ENST00000302262.8:c.1437G>C
ENST00000302262.7:c.1437G>C
ENST00000390015.7:c.1437G>C
NM_000152.3:c.1437G>C
NM_001079803.1:c.1437G>C
NM_001079804.1:c.1437G>C
NM_000152.4:c.1437G>C
NM_001079803.2:c.1437G>C
NM_001079804.2:c.1437G>C
NM_001079803.3:c.1437G>C
NM_001079804.3:c.1437G>C

Likely Pathogenic

Met criteria codes 4

PP3 PM3 PP4_Moderate PM2_Supporting

Not Met criteria codes 1

PS1

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**

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1437G>C (p.Lys479Asn) variant in GAA alters the last nucleotide of exon 9. The computational predictor SpliceAI predicts that this variant may impact splicing (score for loss of the intron 10 donor splice site = 0.37; possible donor gain 175 bp downstream) (PP3). The computational predictor REVEL gives a score of 0.608 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function. Three probands have been reported with the variant, all with infantile onset Pompe disease and documented values showing GAA activity in the affected range. One of the patients was on enzyme replacement therapy (PMID: 18458862, 31510962, 32711049) (PP4_Moderate). Two probands are compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP, c.1935C>A (p.Asp645Glu) (ClinVar Variation ID: 4029; SCV002032138.1) (PMID: 18458862, 32711049, 2 x 0.5 points) (PM3). Another proband is compound heterozygous for the variant, confirmed in trans with c.1327-2A>G (PMID: 31510962). The allelic data from this patient will be used in the assessment of the splicing variant and is not included here to avoid circular logic. The variant is absent in gnomAD v2.1.1. and v4.1.0. (PM2_Supporting). Other variants of the same splice region have been reported in patients with Pompe disease including c.1437+1G>A (likely pathogenic based on classification by the ClinGen LD VCEP); and c.1437+2T>C (pathogenic based on classification by the ClinGen LD VCEP). However, the SpliceAI score for donor loss is lower than for these other variants, and therefore PS1 was not applied at any strength (see Table 2, PMID: 37352859). There is a ClinVar entry for the variant (Variation ID: 3241647). In summary, this variant meets the criteria to be classified as likely pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications version 2.0): PM3, PP4_Moderate, PP3, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on September 17, 2024)

Met criteria codes

PP3	✔	The NM_000152.5:c.1437G>C (p.Lys479Asn) variant in GAA alters the last nucleotide of exon 9. The computational predictor SpliceAI predicts that this variant may impact splicing (score for loss of the intron10 donor splice site = 0.37; possible donor gain 175 bp downstream) (PP3). The computational predictor REVEL gives a score of 0.608 which is neither above nor below the thresholds predicting a damaging (>0.7) or benign (<0.5) impact on GAA function.
PM3	✔	Two probands are compound heterozygous for the variant and another variant in GAA that has been clasified as pathogenic by the ClinGen LD VCEP, c.1935C>A (p.Asp645Glu) (ClinVar Variation ID: 4029; SCV002032138.1) (PMID: 18458862, 32711049, 2 x 0.5 points). Another proband is compound heterozygous for the variant, confirmed in trans with c.1327-2A>G (PMID: 31510962). The allelic data from the patient will be used in the assessment of the splicing variant and is not included here to avoid circular logic. Total 1 point (PM3).
PP4_Moderate	✔	Three probands have been reported with the variant, all with infantile onset Pompe disease and documented values showing GAA activity in the affected range. One of the patients was on enzyme replacement therapy (PMID: 18458862, 31510962, 32711049) (PP4_Moderate).
PM2_Supporting	✔	The variant is absent in gnomAD v2.1.1. and v4.1.0. (PM2_Supporting).

Not Met criteria codes

PS1	✖	Other variants of the same splice region have been reported in patients with Pompe disease including c.1437+1G>A (likely pathogenic based on classification by the ClinGen LD VCEP); and c.1437+2T>C (pathogenic based on classification by the ClinGen LD VCEP). However, the SpliceAI score for donor loss is lower than for these other variants, and therefore PS1 was not applied at any strength (see Table 2, PMID: 37352859).

Curation History

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