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Variant: NM_000152.4(GAA):c.241C>T (p.Gln81Ter)

Version: 1.0

CA401360518

557360 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: dfb7b388-cfc0-4e2d-a8c4-5c1e4844c6ea
Approved on: 2020/6/15
Published on: 2020/11/11

HGVS expressions

NM_000152.4:c.241C>T
NM_000152.4(GAA):c.241C>T (p.Gln81Ter)
NC_000017.11:g.80104827C>T
CM000679.2:g.80104827C>T
NC_000017.10:g.78078626C>T
CM000679.1:g.78078626C>T
NC_000017.9:g.75693221C>T
NG_009822.1:g.8272C>T
ENST00000570803.6:c.241C>T
ENST00000572080.2:c.241C>T
ENST00000577106.6:c.241C>T
ENST00000302262.8:c.241C>T
ENST00000302262.7:c.241C>T
ENST00000390015.7:c.241C>T
ENST00000570803.5:c.241C>T
ENST00000577106.5:c.241C>T
NM_000152.3:c.241C>T
NM_001079803.1:c.241C>T
NM_001079804.1:c.241C>T
NM_001079803.2:c.241C>T
NM_001079804.2:c.241C>T
NM_000152.5:c.241C>T
NM_001079803.3:c.241C>T
NM_001079804.3:c.241C>T

Pathogenic

Met criteria codes 3

PP4 PM2 PVS1

Not Met criteria codes 1

PM3

Evidence Links 1

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.281C>T (p.Gln81Ter), is a nonsense variant which is predicted to cause nonsense mediated decay and lack of gene product, meeting PVS1. The variant is absent in gnomAD v2.1.1, meeting PM2. Three siblings, all with low residual GAA activity meeting PP4, were reported to be compound heterozygous for the variant and a pathogenic missense change, c.2238G>C (p.Trp746Cys) (PMID 25526786). However, the intrans data was used in the assessment of p.Trp746Cys and was not included here in order to avoid a circular argument. There is a ClinVar entry for this variant (Variation ID: 557360, 1 star review status) with one submitter classifying the variant as likely pathogenic. In summary, meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, based on the specifications of the ClinGen LSD VCEP: PVS1, PM2, PP4.

Met criteria codes

PP4	✔	Three siblings with this variant have residual GAA activity in lymphocytes <10% of the normal mean (PMID 25526786). Note that in some other studies, c.2238G>C (p.Trp746Cys) has been found in cis with the pseudodeficiency variant, p.Gly576Ser. This pseudodeficiency variant was not reported in this study and hence PP4 is met. PubMed:25526786
PM2	✔	This variant is absent in gnomAD v2.1.1.
PVS1	✔	This is a nonsense variant which is predicted to cause nonsense mediated decay resulting in no gene product, meeting PVS1.

Not Met criteria codes

PM3	✖	Three siblings, each meeting PP4, were reported to be compound heterozygous for c.281C>T (p.Gln81Ter) and c.2238G>C (p.Trp746Cys) (PMID 25526786). The in trans data has been included in the assessment of p.Trp746Cys and is not included here in order to avoid a circular argument. Therefore, PM3 is not currently met, based on the available data.

Curation History

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