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Variant: NM_000152.5(GAA):c.172C>T (p.Gln58Ter)

Version: 1.0

CA274104

188903 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 754c7592-35d5-41bd-83e3-3babcec0b5d8
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HGVS expressions

NM_000152.5(GAA):c.172C>T (p.Gln58Ter)
NM_000152.5:c.172C>T
NC_000017.11:g.80104758C>T
CM000679.2:g.80104758C>T
NC_000017.10:g.78078557C>T
CM000679.1:g.78078557C>T
NC_000017.9:g.75693152C>T
NG_009822.1:g.8203C>T
ENST00000570803.6:c.172C>T
ENST00000572080.2:c.172C>T
ENST00000577106.6:c.172C>T
ENST00000302262.8:c.172C>T
ENST00000302262.7:c.172C>T
ENST00000390015.7:c.172C>T
ENST00000570803.5:c.172C>T
ENST00000577106.5:c.172C>T
NM_000152.3:c.172C>T
NM_001079803.1:c.172C>T
NM_001079804.1:c.172C>T
NM_000152.4:c.172C>T
NM_001079803.2:c.172C>T
NM_001079804.2:c.172C>T
NM_001079803.3:c.172C>T
NM_001079804.3:c.172C>T

Pathogenic

Met criteria codes 4

PM2 PM3 PP4_Moderate PVS1

Evidence Links 2

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.172C>T (p.Gln58Ter), is a nonsense variant, predicted to result in nonsense-mediated decay and lack of gene product, meeting PVS1. The variant is not in gnomAD v2.1.1, meeting PM2. This variant was found in compound heterozygosity with a pathogenic variant in two patients who meet the ClinGen LSD VCEP's PP4 specifications; one with c.525delT, confirmed in trans (PMID 10377006), and the other with c.841C>T (p.Arg281Trp), identified in a clinical diagnostic laboratory. This data meets PM3. Of note, pseudodeficiency variants are absent in the latter patient, allowing PP4_Moderate to be applied. Additional patients have been reported but were not included because the residual GAA activity was not provided and therefore PP4 cannot be assessed (PMID 20817528). There is a ClinVar entry for this variant (Variation ID: 188903, 1 star review status) with one submitter classifying the variant as likely pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: PVS1, PM2, PM3, PP4_Moderate.

Met criteria codes

PM2	✔	This variant is not in gnomAD v2.1.1.
PM3	✔	This variant was found in compound heterozygosity with a pathogenic variant, c.525delT, in a patient with Pompe disease who also meets the ClinGen LSD VCEP's PP4 specifications (PMID 10377006). The variants were confirmed to be in trans. 1 point was given towards PM3, meeting PM3. The variant was also identified in a clinical laboratory in a compound heterozygote with c.841C>T (p.Arg281Trp). In trans data from this patient was used in the classification of p.Arg281Trp and is not included here in order to avoid a circular argument. An additional two individuals who are compound heterozygous for the variant and c.-32-13T>G have been reported but are not included because the residual GAA activity was not provided and therefore PP4 cannot be assessed (PMID 20817528). PubMed:20817528
PP4_Moderate	✔	This variant has been identified in two individuals meeting PP4 specifications. One individual, reported in the literature, has <1% residual GAA activity in fibroblasts (PMID 10377006). The other individual was identified in a clinical diagnostic laboratory and had GAA activity in the affected range on dried blood spot. Pseudodeficiency variants were absent in this individual, allowing PP4_Moderate to be applied. PubMed:10377006
PVS1	✔	This is a nonsense variant which is predicted to cause nonsense mediated decay resulting in lack of gene product. Therefore, PVS1 can be applied.

Curation History

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