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Variant: NM_000152.5(GAA):c.2407C>T (p.Gln803Ter)

Version: 2.0

CA401325116

552368 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: d1d938e4-80ad-43b8-8248-df989788eb58
Approved on: 2023/7/3
Published on: 2023/9/5

HGVS expressions

NM_000152.5(GAA):c.2407C>T (p.Gln803Ter)
NM_000152.5:c.2407C>T
NC_000017.11:g.80117675C>T
CM000679.2:g.80117675C>T
NC_000017.10:g.78091474C>T
CM000679.1:g.78091474C>T
NC_000017.9:g.75706069C>T
NG_009822.1:g.21120C>T
ENST00000570803.6:c.2407C>T
ENST00000572080.2:c.*545C>T
ENST00000577106.6:c.2407C>T
ENST00000302262.8:c.2407C>T
ENST00000302262.7:c.2407C>T
ENST00000390015.7:c.2407C>T
ENST00000573556.1:n.360C>T
NM_000152.3:c.2407C>T
NM_001079803.1:c.2407C>T
NM_001079804.1:c.2407C>T
NM_000152.4:c.2407C>T
NM_001079803.2:c.2407C>T
NM_001079804.2:c.2407C>T
NM_001079803.3:c.2407C>T
NM_001079804.3:c.2407C>T

Pathogenic

Met criteria codes 4

PP4 PM2 PVS1 PM3_Supporting

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.2407C>T (p.Gln803Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 17 (out of 20 exons), leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). One patient with late onset Pompe disease with this variant and treated by enzyme replacement therapy has been reported (PP4). This individual is compound heterozygous for the variant and "IVS 0-45T>G" (assumed to be c.-32-13T>G), a pathogenic variant in GAA, phase unknown (PMID: 26572913) (PM3_Supporting). Two additional patients have been reported to be compound heterozygous for p.Gln803Ter but the cDNA change provided is incorrect and thus this data was not included (PMID: 21940687). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00001 (1/111412 alleles) in the European-Non-Finnish population, which is lower than the ClinGen Lysosomal Diseases VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion. There is a ClinVar entry for this variant (Variation ID: 552368). In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases VCEP (Specifications Version 2.0): PVS1, PP4, PM2_Supporting, PM3_Supporting. (Classification approved by the ClinGen Lysosomal Diseases VCEP, July 3, 2023)

Met criteria codes

PP4	✔	One patient with late onset Pompe disease with this variant and trated by enzyme replacement therapy has been reported (PP4). Two additional patients have been reported to be compound heterozygous for p.Gln803Ter but the cDNA chnage provided is incorrect and thus this data was not included (PMID: 21940687).
PM2	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00001 (1/111412 alleles) in the European-Non-Finnish population, which is lower than the ClinGen Lysosomal Diseases VCEP threshold (<0.001) for PM2_Supporting, meeting this criterion.
PVS1	✔	The NM_000152.5:c.2407C>T (p.Gln803Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 17/20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PM3_Supporting	✔	One patient is compound heterozygous for the variant and "IVS 0-45T>G" (assumed to be c.-32-13T>G), a pathogenic variant in GAA; phase unknown (PMID: 26572913). 0.5 points (PM3_Supporting).

Curation History

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