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Variant: NM_001079804.3:c.444C>G

Version: 1.3

CA401361416

1327503 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: e52579bd-73f1-4105-a1db-7265b9bf9b8b
Approved on: 2021/12/2
Published on: 2022/11/29

HGVS expressions

NM_001079804.3:c.444C>G
NC_000017.11:g.80105030C>G
CM000679.2:g.80105030C>G
NC_000017.10:g.78078829C>G
CM000679.1:g.78078829C>G
NC_000017.9:g.75693424C>G
NG_009822.1:g.8475C>G
ENST00000570803.6:c.444C>G
ENST00000572080.2:c.444C>G
ENST00000577106.6:c.444C>G
ENST00000302262.8:c.444C>G
ENST00000302262.7:c.444C>G
ENST00000390015.7:c.444C>G
ENST00000570803.5:c.444C>G
ENST00000577106.5:c.444C>G
NM_000152.3:c.444C>G
NM_001079803.1:c.444C>G
NM_001079804.1:c.444C>G
NM_000152.4:c.444C>G
NM_001079803.2:c.444C>G
NM_001079804.2:c.444C>G
NM_000152.5:c.444C>G
NM_001079803.3:c.444C>G

Pathogenic

Met criteria codes 3

PP4 PVS1 PM2_Supporting

Not Met criteria codes 1

PM3

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.444C>G (p.Tyr148Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 2/20, 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, has been reported who responded to enzyme replacement therapy and had muscle histology consistent with Pompe disease (PMID 25093132)(PP4). This patient is compound heterozygous, phase unknown, for the variant and c.2238G>C (p.Trp746Cys). The allelic data for this patient will be used in the assessment of p.Trp746Cys and is not included here to avoid circular logic. The c.444C>G (p.Tyr148Ter) variant is absent in gnomAD v2.1.1 (PM2_Supporting). There is no ClinVar entry for this variant. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. ACMG/AMP criteria met, as specified by the ClinGen LSD VCEP (Specification Version 2.0): PVS1, PP4, PM2_Supporting (Approved by the ClinGen LSD VCEP - Oct. 19th, 2021)

Met criteria codes

PP4	✔	One patient, with late onset Pompe disease, has been reported who responded to enzyme replacement therapy and had muscle histology consistent with Pompe disease (PMID 25093132)(PP4).
PVS1	✔	The NM_000152.5:c.444C>G (p.Tyr148Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 2/20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PM2_Supporting	✔	This variant is absent in gnomAD v2.1.1 (PM2_Supporting).

Not Met criteria codes

PM3	✖	One patient with Pompe disease has been reported with this variant. This patient is compound heterozygous, phase unknown, for the variant and c.2238G>C (p.Trp746Cys). The allelic data for this patient will be used in the assessment of p.Trp746Cys and is not included here to avoid circular logic.

Curation History

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