The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000152.5(GAA):c.343C>T (p.Gln115Ter)

Version: 2.0

CA274228

188996 (ClinVar)

Gene: GAA
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: d382c6c9-a66c-4284-9719-b0cd451e6985
Approved on: 2023/3/7
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HGVS expressions

NM_000152.5:c.343C>T
NM_000152.5(GAA):c.343C>T (p.Gln115Ter)
NM_000152.5(GAA):c.343C>T
NC_000017.11:g.80104929C>T
CM000679.2:g.80104929C>T
NC_000017.10:g.78078728C>T
CM000679.1:g.78078728C>T
NC_000017.9:g.75693323C>T
NG_009822.1:g.8374C>T
ENST00000570803.6:c.343C>T
ENST00000572080.2:c.343C>T
ENST00000577106.6:c.343C>T
ENST00000302262.8:c.343C>T
ENST00000302262.7:c.343C>T
ENST00000390015.7:c.343C>T
ENST00000570803.5:c.343C>T
ENST00000577106.5:c.343C>T
NM_000152.3:c.343C>T
NM_001079803.1:c.343C>T
NM_001079804.1:c.343C>T
NM_000152.4:c.343C>T
NM_001079803.2:c.343C>T
NM_001079804.2:c.343C>T
NM_001079803.3:c.343C>T
NM_001079804.3:c.343C>T

Pathogenic

Met criteria codes 3

PVS1 PM3_Supporting PM2_Supporting

Not Met criteria codes 1

PP4

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(GAA):c.343C>T (p.Gln115Ter) 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). At least three individuals have been reported to have Pompe disease and this variant (PMIDs 17041744, 17616415, 32528171). GAA activity is reduced in the patients for whom it was reported (13-35% normal) but PP4 was not applied because the activity does not meet the strict thresholds specified by the ClinGen LD VCEP. ONe of these individuals is compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP, c.1076-1G>C, phase unknown (PMID: 17616415). Two additional reports describe a child who is compound heterozygous for the variant and p.Pro482Leu (PMID: 17041744, 17616415). The allelic data will be used in the classification of p.Pro482Leu and is not included here to avoid circular logic (PM3_Supporting). There is a ClinVar entry for this variant (Variation ID: 188996). 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 LD VCEP (specifications Version 2.0): PVS1, PM2_Supporting, PM3_Supporting.

Met criteria codes

PVS1	✔	The NM_000152.5(GAA):c.343C>T (p.Gln115Ter) 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).
PM3_Supporting	✔	At least three individuals with symptoms consistent with Pompe disease have been reported with this variant including one who is compound heterozygous for the variant and another variant in GAA that has been classified as pathogenic by the ClinGen LD VCEP, c.1076-1G>C, phase unknown, 0.5 points (PMID: 17616415). Two additional reports (unclear if this is the same patient) describe a child who is compound heterozygous for the variant and p.Pro482Leu (PMID: 17041744, 17616415). The allelic data will be used in the classification of p.Pro482Leu and is not included here to avoid circular logic. (PM3_Supporting).
PM2_Supporting	✔	This variant is absent in gnomAD (PM2_Supporting).

Not Met criteria codes

PP4	✖	At least three individuals have been reported to have Pompe disease and this variant (PMIDs 17041744, 17616415, 32528171). GAA activity is reduced in the patients for whom it was reported (13-35% normal) but does not meet the strict thresholds specified by the ClinGen LD VCEP. Therefore, PP4 is not met.

Curation History

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