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.169C>T (p.Gln57Ter)

Version: 1.5

CA16041879

370124 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: a9a94504-8171-4e5e-98ae-30d711747395
Approved on: 2023/11/6
Published on: 2024/4/12

HGVS expressions

NM_000152.5(GAA):c.169C>T (p.Gln57Ter)
NM_000152.5:c.169C>T
NC_000017.11:g.80104755C>T
CM000679.2:g.80104755C>T
NC_000017.10:g.78078554C>T
CM000679.1:g.78078554C>T
NC_000017.9:g.75693149C>T
NG_009822.1:g.8200C>T
ENST00000570803.6:c.169C>T
ENST00000572080.2:c.169C>T
ENST00000577106.6:c.169C>T
ENST00000302262.8:c.169C>T
ENST00000302262.7:c.169C>T
ENST00000390015.7:c.169C>T
ENST00000570803.5:c.169C>T
ENST00000577106.5:c.169C>T
NM_000152.3:c.169C>T
NM_001079803.1:c.169C>T
NM_001079804.1:c.169C>T
NM_000152.4:c.169C>T
NM_001079803.2:c.169C>T
NM_001079804.2:c.169C>T
NM_001079803.3:c.169C>T
NM_001079804.3:c.169C>T

Pathogenic

Met criteria codes 3

PM2_Supporting PVS1 PP4_Moderate

Not Met criteria codes 1

PM3

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.169C>T (p.Gln57Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 2 (there are 20 exons in GAA), leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). One individual with symptoms consistent with late-onset Pompe disease and deficient GAA activity in lymphocytes has been reported who is compound heterozygous for the variant and a missense variant, c,655G>A (p.Gly219Arg), in GAA (PMID 29124014) (PP4_Moderate). The allelic data for this patient will be used in the classification of p.Gly219Arg and is not included here to avoid circular logic. This variant is absent in gnomAD v2.1.1. (PM2_Supporting). 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 Variant Curation Expert Panel (Specifications Version 2.0): PVS1, PP4_Moderate, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases VCEP on November 6, 2023).

Met criteria codes

PM2_Supporting	✔	This variant is not in gnomAD v2.1.1.
PVS1	✔	The NM_000152.5:c.169C>T (p.Gln57Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 2 (there are 20 exons in GAA), leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1).
PP4_Moderate	✔	One individual with symptoms consistent with late-onset Pompe disease and <10% GAA activity in lymphocytes (PMID 29124014) (PP4_Moderate).

Not Met criteria codes

PM3	✖	One individual with Pompe disease has been reported who is compound heterozygous for the variant and a missense variant, c,655G>A (p.Gly219Arg), in GAA (PMID 29124014). The allelic data for this patient will be used in the classification of p.Gly219Arg and is not included here to avoid circular logic. PM3 is not met at the current time.

Curation History

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