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_000152.4(GAA):c.2269C>T (p.Gln757Ter)

Version: 1.0

CA294856548

429727 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: b0971d5d-fc3b-4e12-bca3-0beb81e86282
Approved on: 2020/5/5
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HGVS expressions

NM_000152.4:c.2269C>T
NM_000152.4(GAA):c.2269C>T (p.Gln757Ter)
NC_000017.11:g.80117047C>T
CM000679.2:g.80117047C>T
NC_000017.10:g.78090846C>T
CM000679.1:g.78090846C>T
NC_000017.9:g.75705441C>T
NG_009822.1:g.20492C>T
ENST00000570803.6:c.2269C>T
ENST00000572080.2:c.*407C>T
ENST00000577106.6:c.2269C>T
ENST00000302262.8:c.2269C>T
ENST00000302262.7:c.2269C>T
ENST00000390015.7:c.2269C>T
ENST00000572080.1:c.688C>T
ENST00000573556.1:n.222C>T
NM_000152.3:c.2269C>T
NM_001079803.1:c.2269C>T
NM_001079804.1:c.2269C>T
NM_001079803.2:c.2269C>T
NM_001079804.2:c.2269C>T
NM_000152.5:c.2269C>T
NM_001079803.3:c.2269C>T
NM_001079804.3:c.2269C>T

Pathogenic

Met criteria codes 3

PM2 PVS1 PP4

Not Met criteria codes 1

PM3

Evidence Links 3

Expert Panel

Lysosomal Diseases VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.2269C>T (p.Gln757Ter), which results in a premature termination codon, is expected to undergo nonsense medicated decay resulting in absence of gene product, meeting PVS1. The variant is absent in gnomAD v2.1.1, meeting PM2. One patient meeting the ClinGen LSD VCEP's specifications for PP4 and compound heterozygous for this variant and c.925G>A (p.Gly309Arg) in GAA has been reported (PMID 24337590). The phase of the variants was not confirmed. In trans data from this patient was used in the assessment of p.Gly309Arg and was not included here in order to avoid circular logic. Additional cases have been reported but were not included because the residual GAA activity was not provided, and therefore PP4 cannot be assessed (PMIDs 17723315, 29149851). There is a ClinVar entry for this variant (Variation ID: 429727, 2 star review status) with two submitters classifying the variant as pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for GSD Pompe disease. GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen LSD VCEP: PVS1, PM2, PP4.

Met criteria codes

PM2	✔	This variant is not in gnomAD v2.1.1.
PVS1	✔	This variant is predicted to result in a premature stop codon resulting in nonsense mediated decay and lack of gene product, meeting PVS1.
PP4	✔	An individual with infantile onset Pompe disease <10% normal GAA activity in leukocytes was reported, meeting PP4 (PMID 24337590). Patient 10, an individual with late-onset Pompe disease, has 15% normal GAA activity (unspecified tissue). PP4 could not be counted for this patient. PubMed:17723315 The patient, an individual with infantile-onset Pompe disease, has 3% normal GAA activity in leukocytes. The activity in leukocytes (<10% normal) meets the threshold of the ClinGen Storage Disorders VCEP. PubMed:24337590

Not Met criteria codes

PM3	✖	One patient meeting the ClinGen LSD VCEP's specifications for PP4 and compound heterozygous for this variant and c.925G>A (p.Gly309Arg) in GAA has been reported (PMID 24337590). The phase of the variants was not confirmed. In trans data from this patient was used in the assessment of p.Gly309Arg and was not included here in order to avoid circular logic. Patient 10 is a compound heterozygote for p.Gln757Ter and c.-32-13T>G in GAA, a known pathogenic variant. However, the phase of the variants was not confirmed and this patient did not meet PP4 criterion (0 points). PubMed:17723315 Patient is a compound heterozygote for p.Gln757Ter and p.Gly309Arg in GAA, a pathogenic variant. The phase of the variants was not confirmed. This patient meets PP4 criterion. However, p.Gln757Ter was used to calculate PM3 strength for p.Gly309Arg, so 0 points were awarded her to avoid a circular dependency. PubMed:24337590 Patient 7 is a compound heterozygote for p.Gln757Ter and c.-32-13T>G in GAA, a known pathogenic variant. However, the phase of the variants was not confirmed and the patient does not meet PP4 (0 points). PubMed:29149851

Curation History

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