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# *Variant: NM_000152.5(GAA):c.1134C>G (p.Tyr378Ter)*

Version: 2.0

*CA401365023*

*595469 (ClinVar)*

**Gene**: GAA (HGNC:2548)
**Condition**: glycogen storage disease II (MONDO:0009290)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** e2643a0a-ade5-4d0e-be57-7f62b573760d
**Approved on**: 2023/7/3
**Published on**: 2023/9/5

## *HGVS expressions*

**NM_000152.5:c.1134C>G**
**NM_000152.5(GAA):c.1134C>G (p.Tyr378Ter)**
NC_000017.11:g.80108547C>G
CM000679.2:g.80108547C>G
NC_000017.10:g.78082346C>G
CM000679.1:g.78082346C>G
NC_000017.9:g.75696941C>G
NG_009822.1:g.11992C>G
ENST00000570803.6:c.1134C>G
ENST00000572080.2:c.1134C>G
ENST00000577106.6:c.1134C>G
ENST00000302262.8:c.1134C>G
ENST00000302262.7:c.1134C>G
ENST00000390015.7:c.1134C>G
NM_000152.3:c.1134C>G
NM_001079803.1:c.1134C>G
NM_001079804.1:c.1134C>G
NM_000152.4:c.1134C>G
NM_001079803.2:c.1134C>G
NM_001079804.2:c.1134C>G
NM_001079803.3:c.1134C>G
NM_001079804.3:c.1134C>G

**Pathogenic**

**Met criteria codes** 4

PVS1 PP4 PM3_Supporting PM2_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.1134C>G (p.Tyr378Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 7/20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). Two patients with this variant have been reported with Pompe disease, both treated with enzyme replacement therapy (PMID: 29181627, 31392188) (PP4). One of these individuals is compound heterozygous for the variant and a pathogenic variant in GAA, c.-32-13T>G (PMID: 31392188). The second patient is compound heterozygous for the variant and c.1478C>T (p.Pro493Leu) (PMID: 29181627); the allelic data for this patient will be used in the classification of p.Pro493Leu and was not included here to avoid circular logic (PM3_Supporting). This variant was absent in gnomAD v2.1.1 (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 595469). 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: PVS1, PP4, PM2_Supporting, PM3_Supporting. (Classification approved by the ClinGen Lysosomal Diseases VCEP, July 3, 2023)**

**Met criteria codes**

| | | |
|---|---|---|
| **PVS1** | ✔ | The NM_000152.5:c.1134C>G (p.Tyr378Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 7/20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). |
| **PP4** | ✔ | Two patients with this variant have been reported with Pompe disease, both treated with enzyme replacement therapy (PMID: 29181627, 31392188) (PP4). |
| **PM3_Supporting** | ✔ | Two patients with this variant have been reported with Pompe disease. One of these individuals is compound heterozygous for the variant and a pathogenic variant in GAA, c.-32-13T>G, phase unknown (PMID: 31392188) (0.5 points).. The second patient is compound heterozygous for the variant and c.1478C>T (p.Pro493Leu) (PMID: 29181627); the allelic data for this patient will be used in the classification of p.Pro493Leu and was not included here to avoid circular logic. Total points for PM3 = 0.5 (PM3_Supporting). |
| **PM2_Supporting** | ✔ | This variant is absent in gnomAD v2.1.1. |

Curation History

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