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Variant: NM_000152.5(GAA):c.1961C>A (p.Ser654Ter)

Version: 1.2

CA16043014

372968 (ClinVar)

Gene: GAA (HGNC:2548)
Condition: glycogen storage disease II (MONDO:0009290)
Inheritance Mode: Autosomal recessive inheritance
UUID: 1c44650b-cb84-4ebf-98b5-8d7696e6a2f6
Approved on: 2026/4/9
Published on: 2026/4/9

HGVS expressions

NM_000152.5:c.1961C>A
NM_000152.5(GAA):c.1961C>A (p.Ser654Ter)
NC_000017.11:g.80112948C>A
CM000679.2:g.80112948C>A
NC_000017.10:g.78086747C>A
CM000679.1:g.78086747C>A
NC_000017.9:g.75701342C>A
NG_009822.1:g.16393C>A
ENST00000570803.6:c.1961C>A
ENST00000572080.2:c.*99C>A
ENST00000577106.6:c.1961C>A
ENST00000302262.8:c.1961C>A
ENST00000302262.7:c.1961C>A
ENST00000390015.7:c.1961C>A
ENST00000570716.1:n.401C>A
ENST00000572080.1:c.380C>A
ENST00000572803.1:n.575C>A
NM_000152.3:c.1961C>A
NM_001079803.1:c.1961C>A
NM_001079804.1:c.1961C>A
NM_000152.4:c.1961C>A
NM_001079803.2:c.1961C>A
NM_001079804.2:c.1961C>A
NM_001079803.3:c.1961C>A
NM_001079804.3:c.1961C>A

Likely Pathogenic

Met criteria codes 2

PVS1 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.1961C>A (p.Ser654Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 14 out of a total of 20 exons, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1). The variant is absent in gnomAD v4.1.0. (PM2_Supporting). To our knowledge, this variant has not been reported in the literature in any individual with Pompe disease. However, there is a ClinVar entry for this variant (Variation ID 372968), and a different variant resulting in a stop codon at the same position, c.1961C>G (p.Ser654Ter), has been reported (PMID: 31342611). The classification of this variant has been upgraded from Variant of Uncertain Significance to Likely Pathogenic based on the recommendations of the ClinGen Sequence Variant Interpretation Working Group, that a variant meeting PVS1 and PM2_Supporting is classified as Likely Pathogenic (https://clinicalgenome.org/site/assets/files/5182/pm2_-_svi_recommendation_-_approved_sept2020.pdf). In summary, this variant meets the criteria to be classified as Likely Pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen Lysosomal Diseases VCEP (Specifications Version 2.0): PVS1, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases VCEP, April 9, 2026).

Met criteria codes

PVS1	✔	The NM_000152.5:c.1961C>A (p.Ser654Ter) variant in GAA is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 14 out of a total of 20 exons, 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 v4.1.0. (PM2_Supporting)

Curation History

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