

Variant: *NM_000152.5(GAA):c.2300del (p.Phe767fs)*

Version: 1.0

CA658795282 [↗](#)

555341 (ClinVar) [↗](#)

Gene: GAA ([HGNC:2548](#))

Condition: glycogen storage disease II ([MONDO:0009290](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 0d148acd-7a1a-420b-bd83-5a7c85fa4034

Approved on: 2021/8/27

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HGVS expressions

NM_000152.5:c.2300del

NM_000152.5(GAA):c.2300del (p.Phe767fs)

NC_000017.11:g.80117078del

CM000679.2:g.80117078del

NC_000017.10:g.78090877del

CM000679.1:g.78090877del

NC_000017.9:g.75705472del

NG_009822.1:g.20523del

ENST00000570803.6:c.2300del

ENST00000572080.2:c.*438del

ENST00000577106.6:c.2300del

ENST00000302262.8:c.2300del

ENST00000302262.7:c.2300del

ENST00000390015.7:c.2300del

ENST00000572080.1:c.719del

ENST00000573556.1:n.253del

NM_000152.3:c.2300del

NM_001079803.1:c.2300del

NM_001079804.1:c.2300del

NM_000152.4:c.2300del

NM_001079803.2:c.2300del

NM_001079804.2:c.2300del

NM_001079803.3:c.2300del

NM_001079804.3:c.2300del

Pathogenic

Met criteria codes **4**

PM3_Supporting

PP4_Moderate

PM2_Supporting

PVS1

Evidence Links **0**

Expert Panel

Lysosomal Diseases VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.2300del (p.Phe767SerfsTer14) variant in GAA is a frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 17/20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism. Western blot of protein from the cultured skin fibroblasts of a patient with this variant showed no GAA cross-reactive material i.e. CRIM-negative (PMID: 22252923), supporting that c.2300del is a loss of function variant (PVS1). This patient has <1% normal GAA activity in skin fibroblasts (PP4_Moderate) and is homozygous for the variant (PMID: 22252923, personal communication) (PM3_Supporting). A patient with Pompe disease who is heterozygous for the variant has been reported but further details are unavailable and the second variant was not reported (PMID: 18425781). The variant is absent in gnomAD v2.1.1 (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 555341; 1 star review status) with one submitter classifying the variant as pathogenic and one as likely pathogenic. In summary, this variant meets the criteria to be classified as pathogenic for Pompe disease. GAA-specific ACMG/AMP criteria met, based on the specifications of the ClinGen LSD VCEP (Specifications Version 2.0): PVS1, PP4_Moderate, PM2_Supporting, PM3_Supporting.

Met criteria codes

PM3_Supporting			One patient has been reported who is homozygous for the variant (PMID 22252923, personal communication). 0.5 points, PM3_Supporting.
PP4_Moderate			One patient has been reported with <1% normal GAA activity in skin fibroblasts (PMID 22252923; personal communication) meeting the ClinGen LSD VCEP's specifications for PP4_Moderate. Another patient with the variant has been reported but the GAA activity and second variant were not given (PMID 18425781).
PM2_Supporting			This variant is absent in gnomAD v2.1.1 (PM2_Supporting).
PVS1			The NM_000152.5: c.2300del (p.Phe767SerfsTer14) variant in GAA is a frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 17/20, leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism. Western blot of protein from the cultured skin fibroblasts of a patient with this variant showed no GAA cross-reactive material i.e. CRIM-negative (PMID: 22252923), supporting that c.2300del is a loss of function variant (PVS1).

Curation History



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