

Variant: *NM_000152.5(GAA):c.482_483del (p.Pro161fs)*

Version: 1.0

CA8814879 [↗](#)

596146 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 38310e9d-9be4-498f-9717-df269b61d625

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HGVS expressions

NM_000152.5(GAA):c.482_483del (p.Pro161fs)

NM_000152.5:c.482_483del

NC_000017.11:g.80105068_80105069del

CM000679.2:g.80105068_80105069del

NC_000017.10:g.78078867_78078868del

CM000679.1:g.78078867_78078868del

NC_000017.9:g.75693462_75693463del

NG_009822.1:g.8513_8514del

ENST00000570803.6:c.482_483del

ENST00000572080.2:c.482_483del

ENST00000577106.6:c.482_483del

ENST00000302262.8:c.482_483del

ENST00000302262.7:c.482_483del

ENST00000390015.7:c.482_483del

ENST00000570803.5:c.482_483del

ENST00000577106.5:c.482_483del

NM_000152.3:c.482_483del

NM_001079803.1:c.482_483del

NM_001079804.1:c.482_483del

NM_000152.4:c.482_483del

NM_001079803.2:c.482_483del

NM_001079804.2:c.482_483del

NM_001079803.3:c.482_483del

NM_001079804.3:c.482_483del

Pathogenic

Met criteria codes **4**

PVS1 PP4 PM2 PM3

Evidence Links **8**

Expert Panel

[Lysosomal Diseases VCEP](#) [↗](#)

Criteria Specification Information **!**

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

Evidence submitted by expert panel

Lysosomal Diseases VCEP

This variant, c.482_483del (p.Pro161GlnfsTer15), is a frameshift variant that is predicted to result in a premature termination codon, nonsense mediated decay, and lack of gene product, meeting PVS1. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00001836 in the European non-Finnish population, meeting PM2. Five individuals have been reported with Pompe disease who meet the ClinGen LSD VCEP's specifications for PP4. Of these individuals, three are compound heterozygous for c.-32-13T>G (PMID 9196050, 26873529), one is compound heterozygous for c.-32-3C>A (PMID 21550241; a patient with a similar description is reported in PMIDs 30155607, 21803581), and the second variant was unidentified in the remaining patient (PMID 9196050). The phase of the variants is unknown in these cases. The in trans data for the patient who is compound heterozygous for c.-32-3C>A will be used in the assessment of that variant and was not included here in order to avoid a circular argument. Therefore, PM3_Supporting is met. Additional patients have been reported but were not included because the residual GAA activity was not provided (and therefore PP4 cannot be assessed) or full HGVS nomenclature was not provided (PMIDs 11071489, 28648663, 32248831). There is a ClinVar entry for this variant (Variation ID: 596146, 1 star review status) with one submitter classifying the variant as pathogenic. 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 LSD VCEP: PVS1, PM2, PM3_Supporting, PP4.

Met criteria codes

PVS1			This is a frameshift variant which is predicted to result in a premature termination codon, nonsense mediated decay, and lack gene product, meeting PVS1.
PP4			Five individuals have been reported with either GAA activity in cultured skin fibroblasts <30% normal, and/or activity in leukocytes below the control range of the laboratory (PMIDs 9196050, 21550241, 26873529), meeting PP4. Another individual with "P 161 ->Shift" has also been reported, but information is not available to confirm that this is the same variant (PMID 11071489).

PubMed:21803581 

PM2			The highest population minor allele frequency in gnomAD v2.1.1 is 0.00001836 in the European non-Finnish population, which is lower than the ClinGen LSD VCEP threshold (<0.001) for PM2, meeting this criterion.
PM3			Four individuals have been reported with Pompe disease who meet the ClinGen LSD VCEP's specifications for PP4. Of these individuals, two are compound heterozygous for c.-32-13T>G (PMID 9196050; 0.5 points given for PM3), and one is compound heterozygous for c.-32-3C>A (PMID 21550241, probably the same patient is also reported in PMIDs 30155607, 21803581). The phase is unknown in these cases. The in trans data for the latter patient, who is compound heterozygous for c.-32-3C>A, will be used in the assessment of that variant and was not included here in order to avoid a circular argument. Therefore, a total of 0.5 points was given, meeting PM3_Supporting. Additional patients have been reported but were not included because the residual GAA activity was not provided (and therefore PP4 cannot be assessed) or full HGVS nomenclature was not provided (PMIDs 11071489, 28648663, 32248831).

PubMed:11071489 

PubMed:26873529 

PubMed:30155607 

PubMed:9196050 

PubMed:28648663 

PubMed:32248831 

PubMed:21550241 

Curation History [↗](#)











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