

Variant: NM_000152.5(GAA):c.510C>T (p.Asp170=)

Version: 1.0

CA8814885 [↗](#)

280956 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: c1895578-2558-42af-9ccd-f9bfdd774803

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HGVS expressions

NM_000152.5(GAA):c.510C>T (p.Asp170=)

NM_000152.5:c.510C>T

NC_000017.11:g.80105096C>T

CM000679.2:g.80105096C>T

NC_000017.10:g.78078895C>T

CM000679.1:g.78078895C>T

NC_000017.9:g.75693490C>T

NG_009822.1:g.8541C>T

ENST00000570803.6:c.510C>T

ENST00000572080.2:c.510C>T

ENST00000577106.6:c.510C>T

ENST00000302262.8:c.510C>T

ENST00000302262.7:c.510C>T

ENST00000390015.7:c.510C>T

ENST00000570803.5:c.510C>T

ENST00000577106.5:c.510C>T

NM_000152.3:c.510C>T

NM_001079803.1:c.510C>T

NM_001079804.1:c.510C>T

NM_000152.4:c.510C>T

NM_001079803.2:c.510C>T

NM_001079804.2:c.510C>T

NM_001079803.3:c.510C>T

NM_001079804.3:c.510C>T

Uncertain Significance

Met criteria codes **3**

BP4

BP7

PM2_Supporting

Not Met criteria codes **3**

PM3

PS3

PP4

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

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.510C>T variant in GAA is a synonymous (silent) variant (p.Asp170=) that is not predicted to impact splicing (BP7, BP4). This variant has been detected in at least 14 individuals with Pompe disease (PMIDs 14695532, 30564623, 30922962, 34405923). However, in all but one individual it was found to co-occur with two additional GAA variants. Additionally, studies have shown that c.510C>T frequently occurs in cis with the c.-32-13T>G variant (pathogenic by the ClinGen Lysosomal Disease VCEP) and is associated with an earlier age of onset and lower GAA enzyme activity in fibroblasts compared to individuals with c.-32-13T>G that do not carry c.510C>T (PMIDs 30922962, 34405923). RT-PCR from patients with c.510C>T and c.-32-13T>G and minigene assays demonstrate that c.510C>T modulates the aberrant splicing caused by c.-32-13T>G, but does not have a significant impact on splicing when it occurs in isolation (PMID 30922962). The highest population minor allele frequency in gnomAD v2.1.1. is 0.00008925 (11/123248 alleles) in the European (non-Finnish) population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting). There is a ClinVar entry for this variant (Variation ID: 280956). While it is uncertain if c.510C>T is causative of disease, there is evidence suggesting that this variant acts as a negative modifying factor when it occurs in cis with c.-32-13T>G. Therefore, this variant is classified as a variant of unknown significance for Pompe disease based on the ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): BP4, BP7, PM2_Supporting. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on March 19, 2024).

Met criteria codes

BP4			The computational splicing predictor SpliceAI gives a score of 0.01 for acceptor loss suggesting that the variant has no impact on splicing (BP4).
BP7			The NM_000152.5:c.510C>T (p.Asp170=) variant is a synonymous (silent) variant that is not predicted by SpliceAI to impact splicing. In addition, it occurs at a nucleotide that is not conserved as shown by PhyloP (BP7).
PM2_Supporting			The highest population minor allele frequency in gnomAD v2.1.1. is 0.00008925 (11/123248 alleles) in the European (non-Finnish) population, which is lower than the ClinGen Lysosomal Diseases VCEP's threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).

Not Met criteria codes

PM3			This variant has been detected in at least 14 individuals with Pompe disease (14695532, 30564623, 30922962, 34405923). However, in all but one individual, it was found to co-occur with two additional GAA variants. This variant is known to frequently occur in cis with c.-32-13T>G and therefore PM3 is not met.
PS3			RT-PCR from patients with c.510C>T and c.-32-13T>G and minigene assays demonstrate that c.510C>T modulates the aberrant splicing caused by c.-32-13T>G, but does not have a significant impact on splicing when it occurs in isolation (PMID 30922962). Therefore, PS3 was not applied.
PP4			This variant has been detected in at least 14 individuals with Pompe disease (PMIDs 14695532, 30564623, 30922962, 34405923). However, in all but one individual, it was found to co-occur with two other GAA variants.

Therefore, PP4 was not applied. However, findings suggest that c.510C>T is associated with an earlier age of onset and lower enzyme activity when combined with c.-32-13T>G (PMID 34405923).

Curation History [↗](#)

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