

Variant: NM_000152.5(GAA):c.1920T>G (p.Pro640=)

Version: 1.0

CA8815546 [↗](#)

255358 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 9d48e112-7668-4bd7-bd5b-12c256c5bf4e

Approved on: 2024/5/7

Published on: 2024/12/17

HGVS expressions

NM_000152.5:c.1920T>G

NM_000152.5(GAA):c.1920T>G (p.Pro640=)

NC_000017.11:g.80112907T>G

CM000679.2:g.80112907T>G

NC_000017.10:g.78086706T>G

CM000679.1:g.78086706T>G

NC_000017.9:g.75701301T>G

NG_009822.1:g.16352T>G

ENST00000570803.6:c.1920T>G

ENST00000572080.2:c.*58T>G

ENST00000577106.6:c.1920T>G

ENST00000302262.8:c.1920T>G

ENST00000302262.7:c.1920T>G

ENST00000390015.7:c.1920T>G

ENST00000570716.1:n.360T>G

ENST00000572080.1:c.339T>G

ENST00000572803.1:n.534T>G

NM_000152.3:c.1920T>G

NM_001079803.1:c.1920T>G

NM_001079804.1:c.1920T>G

NM_000152.4:c.1920T>G

NM_001079803.2:c.1920T>G

NM_001079804.2:c.1920T>G

NM_001079803.3:c.1920T>G

NM_001079804.3:c.1920T>G

Likely Benign

Met criteria codes **2**

BP4 BP7

Not Met criteria codes **2**

PP4 PM2

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

Evidence submitted by expert panel

Lysosomal Diseases VCEP

The NM_000152.5:c.1920T>G variant in GAA is a synonymous (silent) variant that does not change the encoded amino acid (p.Pro640=) and is not predicted to impact splicing. This variant has not been reported as disease-causing in an individual with Pompe disease. It has been described as a polymorphism in a cohort of patients with infantile or juvenile-onset Pompe disease from Taiwan (PMID:18458862). It was also reported in two patients in a European cohort with limb-girdle muscle weakness without a second variant (PMID: 29149851). Thus, there is insufficient data to apply PP4. The highest population minor allele frequency in gnomAD v3.1.2 is [0.001534] (8/5184 alleles) in East Asian population. This is higher than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), and lower than the threshold for BS1 (>0.005). Therefore none of the population data codes are met. This 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 PhyloP100 (-2.182) and PhastCons (0.000) (BP4, BP7). There is a ClinVar entry for this variant (Variation ID: 255358; 1-star review status) with 10 submitters classifying the variant as uncertain significance (4) or likely benign (6). In summary, this variant meets the criteria to be classified as likely benign 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. (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on May 7, 2024).

Met criteria codes

BP4			The computational splicing predictor SpliceAI suggests that the variant has no impact on splicing.
BP7			This 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 PhyloP100 (-2.182) and PhastCons (0.000) (BP7).

Not Met criteria codes

PP4			This variant has not been reported as disease-causing in an individual with Pompe disease. IT has been reported as a polymorphism in a cohort of patients with infantile or juvenile-onset Pompe disease from Taiwan (PMID:18458862). It was also reported in a 2 patients in a European cohort (n=606) with limb-girdle muscle weakness or elevated creatine kinase without a second variant (PMID: 29149851). Thus, there is insufficient data to apply PP4.
PM2			The highest population minor allele frequency in gnomAD v2.1.1 is 0.0009150 (18/19672), and in v3.1.2 it is 0.001534 (8/5184 alleles) in the East Asian population. This is higher than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), and lower than the threshold for BS1 (>0.005). Therefore none of the population data codes are met.

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