

Variant: NM_000152.5(GAA):c.2105G>C (p.Arg702Pro)

Version: 1.2

CA401370504 [↗](#)

593593 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 553c6303-639d-49e6-b287-9e2b3168adba

Approved on: 2024/3/5

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HGVS expressions

NM_000152.5:c.2105G>C

NM_000152.5(GAA):c.2105G>C (p.Arg702Pro)

NC_000017.11:g.80113282G>C

CM000679.2:g.80113282G>C

NC_000017.10:g.78087081G>C

CM000679.1:g.78087081G>C

NC_000017.9:g.75701676G>C

NG_009822.1:g.16727G>C

ENST00000570803.6:c.2105G>C

ENST00000572080.2:c.*243G>C

ENST00000577106.6:c.2105G>C

ENST00000302262.8:c.2105G>C

ENST00000302262.7:c.2105G>C

ENST00000390015.7:c.2105G>C

ENST00000572080.1:c.524G>C

NM_000152.3:c.2105G>C

NM_001079803.1:c.2105G>C

NM_001079804.1:c.2105G>C

NM_000152.4:c.2105G>C

NM_001079803.2:c.2105G>C

NM_001079804.2:c.2105G>C

NM_001079803.3:c.2105G>C

NM_001079804.3:c.2105G>C

Uncertain Significance

Met criteria codes **4**

PP3

PM5

PM2_Supporting

PM3_Supporting

Not Met criteria codes **1**

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

[↗](#) Criteria Specifications for this VCEP

Lysosomal Diseases VCEP

The NM_000152.5:c.12105G>C variant in GAA is a missense variant predicted to cause substitution of arginine by proline at amino acid 702 (p.Arg702Pro). It has been reported in one individual in national mutation database for the country of Oman (PMID: 26594346). However, no clinical details were provided and thus points can not be applied for PP4. This individual was compound heterozygous for the variant and variant classified as pathogenic by the ClinGen LD VCEP (c.2560C>T, p.Arg854Ter; ClinVar Variation ID: Variation ID: 4034, SCV001371731.1), phase unknown (PMID: 26594346) (PM3_supporting). This variant is absent in gnomAD v2.1.1. (PM2_Supporting). The computational predictor REVEL gives a score of 0.989 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). Another missense variant [c.2105G>T, p.Arg702Leu] in the same codon has been classified as pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (ClinVar Variation ID: Variation ID: 92472) (PM5). There is a ClinVar entry for this variant (Variation ID: 593593). Due to insufficient evidence, this variant is classified as a variant of unknown significance for Pompe disease based on the GAA-specific ACMG/AMP criteria applied, as specified by the ClinGen Lysosomal Diseases Variant Curation Expert Panel (Specifications Version 2.0): (PM5, PM3_supporting, PM2_supporting, PP3). (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on March 5, 2024).

Met criteria codes

PP3			The computational predictor REVEL gives a score of 0.989 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PM5			Another missense variant [c.2105G>T, p.Arg702Leu] in the same codon has been classified as pathogenic for Pompe disease by the ClinGen Lysosomal Diseases VCEP (ClinVar Variation ID: Variation ID: 92472) (PM5)
PM2_Supporting			This variant is absent in gnomAD v2.1.1. (PM2_Supporting). // The highest population minor allele frequency in gnomAD v4.0.0 is 0.0000009 (1/1105906 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).
PM3_Supporting			This variant has been detected in one individual described as having Pompe disease. This individual was compound heterozygous for the variant and a known pathogenic variant (c.2560C>T), phase unknown. (PM3_supporting).

Not Met criteria codes

PP4			There is one reported individual in the literature enrolled in a national mutation database in Oman (PMID: 26594346) described as having Glycogen Storage Disease II. There are no additional clinical details thus we cannot apply PP4.
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