

Variant: NM_000152.5(GAA):c.2105G>T (p.Arg702Leu)

Version: 1.0

CA220396 [↗](#)

92472 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: 3e7bd67d-b563-4ca2-a3cb-daf3018e5942

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HGVS expressions

NM_000152.5:c.2105G>T

NM_000152.5(GAA):c.2105G>T (p.Arg702Leu)

NC_000017.11:g.80113282G>T

CM000679.2:g.80113282G>T

NC_000017.10:g.78087081G>T

CM000679.1:g.78087081G>T

NC_000017.9:g.75701676G>T

NG_009822.1:g.16727G>T

ENST00000570803.6:c.2105G>T

ENST00000572080.2:c.*243G>T

ENST00000577106.6:c.2105G>T

ENST00000302262.8:c.2105G>T

ENST00000302262.7:c.2105G>T

ENST00000390015.7:c.2105G>T

ENST00000572080.1:c.524G>T

NM_000152.3:c.2105G>T

NM_001079803.1:c.2105G>T

NM_001079804.1:c.2105G>T

NM_000152.4:c.2105G>T

NM_001079803.2:c.2105G>T

NM_001079804.2:c.2105G>T

NM_001079803.3:c.2105G>T

NM_001079804.3:c.2105G>T

Pathogenic

Met criteria codes **5**

PM2_Supporting

PS3_Moderate

PP3

PP4_Moderate

PM3_Strong

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.2105G>T variant in GAA is a missense variant predicted to cause substitution of arginine by leucine at amino acid 702 (p.Arg702Leu). It has been reported in at least two unrelated patients with infantile-onset Pompe disease with documented GAA deficiency and receiving enzyme replacement therapy, and in one patient identified via newborn screening with deficient confirmatory enzyme in blood and clinical symptoms (Clinical diagnostic laboratory) described as having late-onset Pompe disease, meeting criteria for PP4_moderate (PMID: 26497565, 27344650, 26167453). Of those individuals, a proband and full sibling were compound heterozygous for the variant and variant that has been classified as pathogenic by the ClinGen LD VCEP, c.2512C>T (p.Gln838Ter) (ClinVar Variation ID: Variation ID: 92479, SCV001371718.1), confirmed in trans by parental testing (PMID: 26167453) (1 point). Another patient was compound heterozygous for the variant and variant classified as pathogenic by the ClinGen LD VCEP, c.1798C>T (p.Arg600Cys) (Variation ID: 640911; SCV002032136.1), phase unknown (PMID: 26497565, 27344650). The variant has also been reported in trans with a pathogenic variant (c.-32-13T>G; ClinVar Variation ID: 4027) in one individual identified on newborn screening with deficient confirmatory GAA and clinical symptoms with deficient confirmatory GAA in DBS (Clinical diagnostic laboratory) (PM3_Strong). It has also been reported in one individual with a positive newborn screen for Pompe disease and deficient confirmatory GAA activity, but no reported phenotype (PMID: 33202836). It is absent from large population databases (gnomAD v2.1.1.) meeting PM2_Supporting. Expression of the variant in COS-7 and HEK293T cells resulted in 0.4% GAA activity in cells and 1.3% in medium and evidence of abnormal GAA synthesis and processing - leading the variant to be classified as Class B (“potentially less severe”), indicating that this variant may impact protein function (PMID:22644586), meeting PS3_moderate. The computational predictor REVEL gives a score of 0.972 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3). There is a ClinVar entry for this variant (Variation ID: 92472). In summary, this variant meets the criteria to be classified as pathogenic 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): (PM3_strong, PP4_moderate, PS3_moderate, PM2_supporting, PP3). (Classification approved by the ClinGen Lysosomal Diseases Variant Curation Expert Panel on March 5, 2024).

Met criteria codes

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 0.00001339 (1/7466 alleles) in the African/African-American population, which is lower than the ClinGen Lysosomal Diseases VCEP’s threshold for PM2_Supporting (<0.001), meeting this criterion (PM2_Supporting).
PS3_Moderate		Expression of the variant in COS-7 or HEK293T cells resulted in 0.4% GAA activity in cells and 1.3% in medium and evidence of abnormal GAA synthesis and processing, leading the variant to be classified as Class B (“potentially less severe”), indicating that this variant may impact protein function (PMID:22644586). (PS3_moderate).
PP3		The computational predictor REVEL gives a score of 0.972 which is above the threshold of 0.7, evidence that correlates with impact to GAA function (PP3).
PP4_Moderate		One patient with IOPD receiving enzyme replacement therapy (PMID: 26497565) has been reported with this variant and GAA activity <10% of normal in leukocytes (PP4_moderate). Two siblings with IOPD have been described (PMID: 22252923, 26167453) with CRIM-positive IOPD and receiving enzyme replacement therapy. This variant has been reported in a patient identified via newborn screening who developed clinical features and described as having LOPD (unpublished). This variant has been reported in one individual identified on newborn with deficient confirmatory GAA enzyme in DBS but no reported phenotype (PMID: 33202836).
PM3_Strong		

This variant has been detected in at least three individuals with IOPD. Of those individuals, two full siblings were compound heterozygous for the variant and variant that has been classified as pathogenic by the ClinGen LD VCEP, c.2512C>T (p.Gln838Ter) (ClinVar Variation ID: Variation ID: 92479, SCV001371718.1), confirmed in trans by parental testing (PMID: 26167453) (1 point). Another patient was compound heterozygous for the variant and variant classified as pathogenic by the ClinGen LD VCEP, c.1798C>T (p.Arg600Cys) (Variation ID: 640911; SCV002032136.1), phase unknown (PMID: 26497565, 27344650). The variant has also been reported in trans with a pathogenic variant (c.-32-13T>G; ClinVar Variation ID: 4027) in one individual identified on newborn screening with deficient confirmatory GAA and clinical symptoms with deficient confirmatory GAA in DBS (Clinical diagnostic laboratory) (1 point). Total 2.5 points (PM3_Strong).

Curation History

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