

Variant: *NM_000517.6(HBA2):c.313T>C (p.Cys105Arg)*

Version: 1.0

CA393994398 [↗](#)

804215 (ClinVar) [↗](#)

Gene: HBA2 ([HGNC:3040](#))

Condition: HBA2-related alpha thalassemia spectrum ([MONDO:0100562](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 9d526273-4423-4e22-9774-67d254958d67

Approved on: 2026/4/8

Published on: 2026/4/8

HGVS expressions

NM_000517.6:c.313T>C

NM_000517.6(HBA2):c.313T>C (p.Cys105Arg)

NC_000016.10:g.173484T>C

CM000678.2:g.173484T>C

NC_000016.9:g.223483T>C

CM000678.1:g.223483T>C

NC_000016.8:g.163483T>C

NG_000006.1:g.34347T>C

NG_059186.1:g.1834T>C

NG_059271.1:g.5638T>C

ENST00000251595.11:c.313T>C

ENST00000251595.10:c.313T>C

ENST00000397806.1:c.217T>C

ENST00000482565.1:n.449T>C

NM_000517.4:c.313T>C

Likely Pathogenic

Met criteria codes **4**

PM3

PM5

PS4_Supporting

PM2_Supporting

Not Met criteria codes **3**

PP3

PM1

BP4

Evidence Links **0**

Expert Panel

Hemoglobinopathy VCEP [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** ClinGen Hemoglobinopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for HBA2 Version 1.0.0

[↗](#) **Criteria Specification Approval History**

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

Evidence submitted by expert panel

Hemoglobinopathy VCEP

The NM_000517.6(HBA2):c.313T>C variant in HBA2 is a missense variant predicted to cause substitution of cysteine by arginine at amino acid 104 (p.Cys105Arg). This variant has been reported in 5 individuals displaying a hematological phenotype consistent with α -thalassemia trait (reduced MCV and MCH excluding iron deficiency), giving a score of 0.9 [PS4_P; PMID: 23181747]. It has been detected in

2 homozygous individuals presenting with mild-to-moderate anemia with microcytic hypochromic red cell indices. Total PM3 points is 1 [PM3; Department of Clinical Hematology, Hospitais da Universidade de Coimbra]. Another missense variant [c.314G>A (p.Cys105Tyr); VCV000015656.4] in the same codon is considered to have valid evidence for pathogenicity by the VCEP [PMID: 36453528] and has been classified as pathogenic/likely pathogenic for alpha-thalassemia/HbH disease with a 2-star review status by ClinVar [PM5]. The minor allele frequency in gnomAD v4.1 is 6.226e-7 (1/1606102), which is lower than the ClinGen Hemoglobinopathy VCEP threshold <0.0001 for PM2_Supporting, and therefore meets this criterion. In summary, this variant meets the criteria to be classified as a likely pathogenic variant for HBA2-related alpha thalassemia spectrum (MONDO:0100562) in an autosomal recessive manner based on the ACMG/AMP criteria applied, as specified by the ClinGen Hemoglobinopathy VCEP (specification version 1.0.0): PM3, PM5, PM2_P, PS4_P.

Met criteria codes

PM3			This variant has been detected in 2 homozygous individuals presenting with mild-to-moderate anemia with microcytic hypochromic red cell indices. Total PM3 points is 1 [Internal lab collaborators].
PM5			Another missense variant [c.314G>A (p.Cys105Tyr)] [VCV000015656.4] in the same codon is considered to have valid evidence for pathogenicity by the VCEP and has been classified as pathogenic/likely pathogenic for alpha-thalassaemia/HbH disease with a 2-star review status by ClinVar.
PS4_Supporting			This variant has been reported in 3 individuals with α-thalassaemia trait phenotype meeting low MCV and MCH with normal/increased RBC count, excluding iron deficiency. Total score is 0.9 [PMID: 23181747].
PM2_Supporting			The minor allele frequency in gnomAD v4.1 is 6.226e-7 (1/1606102), which is lower than the ClinGen Hemoglobinopathy VCEP threshold <0.0001 for PM2_Supporting, and therefore meets this criterion.

Not Met criteria codes

PP3			The computational predictor REVEL gives a score of 0.713, which is neither above nor below the thresholds predicting a damaging [>0.8] or benign [<0.7] impact on HBA2 function.
PM1			This HBA2 variant resides in a region (p.Cys105Arg) of the G11 helix, which is involved in α1β1 interactions and binding to the α Hb stabilizing protein (AHSP), but is not defined as a mutational hotspot and/or critical functional domain by the ClinGen Hemoglobinopathy VCEP.
BP4			The computational predictor REVEL gives a score of 0.713, which is neither above nor below the thresholds predicting a damaging [>0.8] or benign [<0.7] impact on HBA2 function.

Curation History 

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