

Variant: *NM\_000517.6(HBA2):c.89T>C (p.Leu30Pro)*

Version: 1.0

CA125593 [↗](#)

15651 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Autosomal recessive inheritance

**UUID:** 29bc99e3-6288-43e4-9650-419a4e857e56

**Approved on:** 2026/4/8

**Published on:** 2026/4/8

### HGVS expressions

**NM\_000517.6(HBA2):c.89T>C (p.Leu30Pro)**

**NM\_000517.6:c.89T>C**

NC\_000016.10:g.173001T>C

CM000678.2:g.173001T>C

NC\_000016.9:g.223000T>C

CM000678.1:g.223000T>C

NC\_000016.8:g.163000T>C

NG\_000006.1:g.33864T>C

NG\_059186.1:g.1351T>C

NG\_059271.1:g.5155T>C

ENST00000251595.11:c.89T>C

ENST00000251595.10:c.89T>C

ENST00000397806.1:c.-2+43T>C

ENST00000482565.1:n.108T>C

ENST00000484216.1:n.58T>C

NM\_000517.4:c.89T>C

**Pathogenic**

Met criteria codes **5**

PP3

PS4\_Moderate

PP1\_Strong

PM2\_Supporting

PM3\_Very Strong

Not Met criteria codes **1**

PM1

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 c.89T>C (p.Leu30Pro) variant in HBA2 is a missense variant with a minor allele frequency of 0.0000022 (1/446,884 alleles) in gnomAD v4.1, which is lower than the ClinGen Hemoglobinopathy VCEP threshold (<0.0001) for PM2\_Supporting and therefore meets this criterion

[PM2\_P]. This variant has been detected in 9 individuals with a severe clinical phenotype characterized by HbH inclusions and requirements for transfusion and splenectomy. Total PM3 points are 8 [PM3\_VS; PMID: 20854116; 29219637; 18473239]. It has also been reported to segregate with HbH disease in 8 affected individuals from 8 families. The number of unaffected segregations is 4, giving a LOD score of 5.32 [PP1\_S; PMID:29219637; 9629496; 8136277; 23094635]. This variant has been reported in 10 unrelated individuals with a hematological phenotype consistent with  $\alpha$ -thalassemia trait (reduced MCV, MCH [7\*0.15=1.05] or reduced MCV and MCH with normal RBC count [3\*0.2=0.6]), giving a total score of 1.65 [PS4\_M; PMID: 29219637; 23094635; 8136277; 9629496]. The computational predictor REVEL (score 0.91; VCEP threshold >0.8) suggests that this variant impacts HBA2 function [PP3]. Overall, this variant is classified as a pathogenic variant for recessive HBA2-related alpha thalassemia spectrum (MONDO:0100562) based on the ACMG/AMP criteria applied, as specified by the ClinGen Hemoglobinopathy VCEP (specification version 1.0.0): PM3\_VS, PP1\_S, PS4\_M, PP3, PM2\_P

Met criteria codes

|                 |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PP3             |    |    | The computational predictor REVEL gives a score of 0.91, which is above the threshold of 0.8, evidence that correlates with impact to HBA2 function.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| PS4_Moderate    |    |    | This variant has been reported in ten unrelated individuals meeting reduced MCV, MCH [7*0.15=1.05] or reduced MCV, MCH and normal RBC count [3*0.2=0.6]. Total score is 1.65 [PMID: 29219637; 23094635; 8136277; 9629496]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| PP1_Strong      |    |    | The variant has been reported to segregate with disease in 8 affected family members from 8 families. The total number of unaffected segregations is 4. The LOD score is 5.32. PMID: 29219637: 2 families with homozygous probands with HbH disease, parents all tested and heterozygous carriers. LOD: 1.2 PMID: 23094635: family B: both parents heterozygous carriers, proband homozygous and 2 siblings are heterozygous carriers and one sibling without the variant. LOD: 0.98 family C: Homozygous proband, family pedigree structure is unclear. LOD: 0.6 PMID: 8136277: 3 Family A: proband with HbH disease comp het: Hb Agrinio-Hb TSaudi, Both parents tested, mother is carrier of Hb Agrinio. LOD: 0.6 Family D: proband with HbH disease comp het: Hb Agrinio-Hb TSaudi, Both parents tested, mother is carrier of Hb Agrinio. One sibling who has 2 normal alleles. LOD: 0.73 Family F: proband with HbH disease comp het: Hb Agrinio-Hb TSaudi, Both parents tested, mother is carrier of Hb Agrinio. LOD: 0.6 PMID: 9629496: 1 homozygous proband with HbH disease, parents tested. LOD: 0.6 |
| PM2_Supporting  |  |  | The minor allele frequency in gnomAD v4.1 is 0.0000022 (1/446884 alleles), which is lower than the ClinGen Hemoglobinopathy VCEP threshold <0.0001 for PM2_Supporting, and therefore meets this criterion [PM2_P].                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| PM3_Very Strong |  |  | This variant has been detected in 9 individuals with severe clinical phenotype characterized by HbH inclusions and need for transfusion and splenectomy. Of those individuals, 7 were compound heterozygous for the variant and a pathogenic variant and were confirmed in trans by family studies, and 2 individuals were homozygous for the variant. Total PM3 points are 8 [PMID: 20854116; 29219637; 18473239]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

Not Met criteria codes

|     |                                                                                     |                                                                                     |                                                                                                                                                                      |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PM1 |  |  | This variant does not reside within a region of HBA2 that is defined as a mutational hotspot and/or critical functional domain by the ClinGen Hemoglobinopathy VCEP. |
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