The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

# *Variant: NM_000517.6(HBA2):c.*94A>G*

Version: 1.0

*CA16602272*

*375749 (ClinVar)*

**Gene**: HBA2 (HGNC:3040)
**Condition**: HBA2-related alpha thalassemia spectrum (MONDO:0100562)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 5e4e4c17-b303-41d3-abc1-5f33b6d7c972
**Approved on**: Tue, 17 Nov 2026 00:00:00 +0000
**Published on**: Tue, 17 Nov 2026 00:00:00 +0000

## *HGVS expressions*

**NM_000517.6:c.*94A>G**
**NM_000517.6(HBA2):c.*94A>G**
NC_000016.10:g.173694A>G
CM000678.2:g.173694A>G
NC_000016.9:g.223693A>G
CM000678.1:g.223693A>G
NC_000016.8:g.163693A>G
NG_000006.1:g.34557A>G
NG_059186.1:g.2044A>G
NG_059271.1:g.5848A>G
ENST00000251595.11:c.*94A>G
ENST00000251595.10:c.*94A>G
ENST00000397806.1:c.*94A>G
NM_000517.4:c.*94A>G

**Pathogenic**

**Met criteria codes** 7

PP3 PP1_Strong PM2_Supporting PS3_Supporting PM1 PM3_Strong PS4

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*
**Criteria Specification Approval History**
**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***Hemoglobinopathy VCEP***

**The c.*94A>G variant is located in the HBA2 gene. This variant has been reported in 25 unrelated individuals displaying an hematological phenotype consistent with alpha thalassemia trait (low MCV and MCH) giving a total score 4.4 [PS4; PMID:128162; Blood Disorder Genetics & Thalassemia Department, CING; Thalassemia and rare inherited anemias Unit, AOU San Luigi Gonzaga University Hospital; Department of Medical Genetics, National and Kapodistrian University of Athens; Molecular Pathology Laboratory, Reference Haematology, King’s College**

**Hospital]. The variant has been reported to segregate with HbH disease in 8 affected family members from 5 families. It has also been reported to segregate with a rare form of HbH hydrops fetalis syndrome. The total number of unaffected segregations is 0, resulting in a LOD score of 5.42 [PP1_Strong; PMID:7701914,1281602, 12028055]. The c.*94A>G variant was identified in two compound heterozygous individuals, both confirmed in trans by parental testing: one with HbH hydrops fetalis syndrome carrying the --MED ($\alpha^0$-thalassemia) deletion [PMIDs: 12028055] and another carrying the established pathogenic α(-5nt) variant [ClinVar ID: 375746; PMID: 7701914]. An additional compound heterozygous case involving the --MED deletion was reported in a six-year-old child with severe HbH disease, for whom parental confirmation of phase was not documented [PMID: 12358934]. Additionally, 7 individuals with HbH disease were reported to be homozygous for the variant, contributing the maximum permitted cumulative score of 1 point [PMID: 1281602]. The total PM3 score is 3.5 [PM3_Strong]. The variant is located within the polyadenylation signal (AATAAA) of HBA2, a region defined as a mutational hotspot and critical functional domain by the ClinGen Hemoglobinopathy VCEP [PM1]. In vivo cell-based assays showed a 15% reduction in mRNA levels associated with the c.*94A>G variant, while in vitro studies demonstrated that transcription failed to terminate in the absence of active 3′-end processing, supporting an impact on transcriptional termination [PS3_P; PMID:3024968 and 6646217]. The computational predictor CADD (PHRED score 12.77; VCEP threshold >12) suggests that this variant impacts HBA2 function [PP3]. The minor allele frequency in gnomAD v4.1.2 is 0.000009787 (15/1532660) which is lower that the ClinGen Hemoglobinopathy VCEP threshold (<0.0001) for PM2_Supporting, and therefore meets this criterion [PM2_P]. In summary, this variant meets the criteria to be classified as pathogenic 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): PP1_S, PS4, PM3_S, PM1, PM2_P, PP3, PS3_P.**

**Met criteria codes**

| | | |
|---|---|---|
| **PP3** | ✔ | The computational predictor CADD (PHRED score 12.77; VCEP threshold > 12) suggests that this variant impacts HBA2 function [PP3]. |
| **PP1_Strong** | ✔ | The variant has been reported to segregate with HbH disease in 8 affected family members from 5 families. This variant has also been reported to segregate with a rare form of HbH or Hb H hydrops fetalis syndrome. The total number of unaffected segregations is 0, resulting in a LOD score of 6.01 [PP1_Strong; PMID:7701914,1281602, 12028055 and 12358934]. |
| **PM2_Supporting** | ✔ | The minor allele frequency in gnomAD v4.1.1 is 0.000009787 (15/1532660) which is lower that the ClinGen Hemoglobinopathy VCEP threshold (<0.0001) for PM2_Supporting, and therefore meets this criterion [PM2_P]. |
| **PS3_Supporting** | ✔ | In vivo cell based assays showed that the mRNA produced when the c.*94A>G is present is reduced by 15% and furthermore in vitro studies showed that transcription failed to terminate without active 3' end processing indicating that this variant impacts transcriptional termination [PMID:3024968 and 6646217] [PS3_P]. |
| **PM1** | ✔ | This variant (NM_000517.6:HBA2:c.*94A>G) resides in a region, Poly(A) signals:AATAA, of HbA2 that is defined as a mutational hotspot and critical functional domain by the ClinGen Hemoglobinopathy VCEP [PM1]. |
| **PM3_Strong** | ✔ | This variant has been detected in 3 individuals with HbH disease. Of these, 1 was compound heterozygous for the variant and a pathogenic variant [ClinVar ID:375746], which was confirmed to be in trans by parental testing. In addition, 2 individuals were homozygous for the variant. Furthermore, 1 case with Hb H hydrops fetalis syndrome was compound heterozygote for the variant and the --MED($\alpha^0$-thalassemia deletion). The total PM3 score is 3, meeting the threshold for PM3_Strong [PMIDs:7701914, 1281602 and 12028055]. |
| **PS4** | ✔ | This variant has been reported in 25 unrelated individuals displaying an hematological phenotype consistent with alpha thalassemia trait. The cumulative score is 4.4, meeting the threshold for PS4_Strong [PMID:128162, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, AOU San Luigi Gonzaga University Hospital and Department of Medical Genetics, National and Kapodistrian University of Athens, Molecular Pathology Laboratory, Reference Haematology, King’s College Hospital] |

## Curation History

Showing 1 to 1 of 1 rows

| See Report | Preferred Variant Title | Classification | Condition | Published Date | Version | Criteria Specification | Gene |
|---|---|---|---|---|---|---|---|
| View | NM_000517.6(HBA2):c.*94A>G | Pathogenic | HBA2-Related Alpha Thalassemia Spectrum | 2026-11-17 | 1.0 | ClinGen Hemoglobinopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for HBA2 Version 1.0 | HBA2 |

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.