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_000518.5(HBB):c.-78A>C

Version: 1.0

CA125328

15470 (ClinVar)

Gene: HBB (HGNC:3043)
Condition: beta-thalassemia HBB/LCRB (MONDO:0013517)
Inheritance Mode: Autosomal recessive inheritance
UUID: 16667374-bf76-4afd-a940-8aa7726825fd
Approved on: 2026/4/7
Published on: 2026/4/7

HGVS expressions

NM_000518.5(HBB):c.-78A>C
NC_000011.10:g.5227099T>G
CM000673.2:g.5227099T>G
NC_000011.9:g.5248329T>G
CM000673.1:g.5248329T>G
NC_000011.8:g.5204905T>G
NG_000007.3:g.70517A>C
NG_059281.1:g.4973A>C
ENST00000647020.1:c.-78A>C
ENST00000380315.2:c.-18-60A>C

Pathogenic

Met criteria codes 7

PM2_Supporting | PP3 | PM1 | PM5 | PS3_Supporting | PS4_Very Strong | PM3_Strong

Not Met criteria codes 1

PP1

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 HBB Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hemoglobinopathy VCEP

This variant (NM_000518.5: HBB:c.-78A>C) resides in a region, c.-80 to c.-76 (TATAA box), of HBB that is defined as a mutational hotspot and critical functional domain by the ClinGen Hemoglobinopathy VCEP [PM1]. It has been detected in three individuals with beta thalassemia major. These individuals are compound heterozygous for the variant (c.-78A>C) and a pathogenic variant (c.118C>T; c.36del and c.92+1G>A), confirmed in trans by family testing; total PM3 score is 3 [PM3_S; PMID 19960060; 8619407; Molecular Genetics Laboratory, Hamilton Regional Laboratory Medicine Program, Hamilton Health Sciences; ClinVar IDs: 15402; 15423 and 15436]. It has also been reported in 13 unrelated individuals with low MCV (67-77.8 fl), low MCH (20.5-25.9 pg) and increased HbA2 (4.6-6.3%), and in 2 unrelated individuals with just low MCV (58.1 and 70 fl) and low MCH (18.2 and 23.3 pg); total score is 16.3 [PS4_VS; PMID 19960060; 8619407; Molecular Genetics Laboratory, Hamilton Regional Laboratory Medicine Program, Hamilton Health Sciences; Department of

Medical Genetics, National and Kapodistrian University of Athens; BGI Genomics]. In vitro transcriptional assay and transient expression assay showed 2- to 3-fold decrease in beta globin transcription indicating that this variant impacts protein function [PS3_P; PMID: 2987224]. Kinetic studies showed reduced association rate constant and increase dissociation constant of the TATA binding protein (TBP)/TATA box complex, also indicating that this variant impacts protein function (PMID: 24616209). The computational predictor CADD PHRED score 19.52 (above threshold >12) indicates that this variant impacts HBB function [PP3]. The minor allele frequency in gnomAD v4.1 is 0.000002948 (3/1017550) alleles, which is lower than the ClinGen Hemoglobinopathy VCEP threshold <0.0001 for PM2_Supporting, and therefore meets this criterion [PM2_P]. Another single nucleotide variant c.-78A>G (ClinVar ID: 15471) in the same base position is considered to have valid evidence for pathogenicity by the VCEP (PMID: 36453528) and has been classified as pathogenic for beta thalassemia with a 2-star review status by ClinVar [PM5]. In summary, this variant meets the criteria to be classified as pathogenic for beta thalassemia (MONDO:0013517) in an autosomal recessive manner based on the ACMG/AMP criteria applied, as specified by the ClinGen Hemoglobinopathy VCEP (specification version 1.0.0): PS4_VS, PM3_S, PM5, PM1, PM2_P, PS3_P, PP3.

Met criteria codes

PM2_Supporting	✔	The minor allele frequency in gnomAD v4.1 is 0.000002948 (3/1017550) alleles, which is lower than the ClinGen Hemoglobinopathy VCEP threshold <0.0001 for PM2_Supporting, and therefore meets this criterion [PM2_P].
PP3	✔	The computational predictor CADD gives a PHRED score of 19.52, which is above threshold >12, evidence that correlates with impact to HBB function.
PM1	✔	This variant resides in a region c.-80 to c.-76 (TATAA box), of HBB that is defined as a mutational hotspot and critical functional domain by the ClinGen Hemoglobinopathy VCEP
PM5	✔	Another single nucleotide variant c.-78A>G (ClinVar ID: 15471) in the same base position is considered to have valid evidence for pathogenicity by the VCEP and has been classified as pathogenic for beta thalassemia with a 2-star review status by ClinVar
PS3_Supporting	✔	In vitro transcriptional assay and transient expression assay showed 2- to 3-fold decrease in beta globin transcription indicating that this variant impacts protein function (PMID: 2987224). Kinetic studies showed reduced association rate constant and increase dissociation constant of the TATA binding protein (TBP)/TATA box complex also indicating that this variant impacts protein function (PMID: 24616209)
PS4_Very Strong	✔	This variant has been reported in 13 unrelated individuals with low mcv (67-77.8), low mch (20.5-25.9), and increased HbA2 (4.6-6.3), and in 2 individuals with just low MCV (58.1 and 70) and low MCH (18.2 and 23.3): Total score is 16.3 (PMID 19960060; PMID: 8619407; Internal Lab database) PMID 19960060; PMID: 8619407: 2 individuals with low MCV (69 and 69.9), low MCH (21.8 and 20.5) and increased HbA2 (4.8 and 5): 2x1.5=3 Internal lab database contribution: 11 individuals with low MCV (67-77.8), low MCH (20.5-25.9) and increased HbA2 (4.6-6.3): 11x1.5=16.5=max score is 16 2 individuals with low MCV (58.1 and 70), low MCH (18.2 and 23.3): 2x0.15=0.3
PM3_Strong	✔	This variant has been detected in three individuals with beta thalassemia/major. These individuals are compound heterozygous for the variant (c.78A>C) and pathogenic beta thalassemia and related diseases variants (c.118C>T; c.36del and C.92+1G>A), and were confirmed in trans by family testing. Total PM3 score is 3 (PMID 19960060; PMID: 8619407; internal lab database; ClinVar IDs: 15402; 15423 and 15436) PMID 19960060: In Trans with pathogenic c.118C>T, p.Gln40Ter (CD 39 C>T): Two stars in ClinVar (ID: 15402): exempt from PM2 requirement PMID: 8619407: In Trans with pathogenic c.36del, p.Thr13fs (CD 11 (-T): Two stars in ClinVar (ID: 15423): rare in gnomAD Internal lab database contribution: In trans with pathogenic C.92+1G>A (IVS I-1 G-A): Two stars in ClinVar (ID: 15436): exempt from PM2 requirement.

Not Met criteria codes

PP1	ℹ	✖	The variant has been reported to segregate with disease in 1 affected family member from one family. The total number of unaffected segregations is 0. The LOD score is 0.6 (PMID: 8619407).

Curation History

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.