

Variant: *NM_000518.5(HBB):c.52A>T (p.Lys18Ter)*

Version: 2.0

CA125257 [↗](#)

15401 (ClinVar) [↗](#)

Gene: HBB ([HGNC:3043](#))

Condition: beta-thalassemia HBB/LCRB ([MONDO:0013517](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 14de9b76-177f-4f8c-bda7-7739c9143b2e

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HGVS expressions

NM_000518.5(HBB):c.52A>T (p.Lys18Ter)

NM_000518.5:c.52A>T

NC_000011.10:g.5226970T>A

CM000673.2:g.5226970T>A

NC_000011.9:g.5248200T>A

CM000673.1:g.5248200T>A

NC_000011.8:g.5204776T>A

NG_000007.3:g.70646A>T

NG_059281.1:g.5102A>T

ENST00000647020.1:c.52A>T

ENST00000335295.4:c.52A>T

ENST00000380315.2:c.52A>T

ENST00000485743.1:n.103A>T

ENST00000633227.1:c.52A>T

NM_000518.4:c.52A>T

Pathogenic

Met criteria codes **5**

PM2_Supporting

PVS1_Strong

PM3_Very Strong

PS4

PP1_Moderate

Not Met criteria codes **1**

PS3

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

The c.52A>T (p.Lys18*) variant in HBB is a nonsense variant predicted to cause loss of function of the protein [PVS1_S; PMID: 68654]. The variant has been reported to segregate with beta thalassemia intermedia in 3 affected family members from 3 families. The total number of unaffected segregations is 1, giving a total LOD score of 1.93 [PP1_M; PMID: 31579136; 26029792; 88735]. This variant has been

detected in 5 individuals with beta thalassemia. Of those individuals, 3 were compound heterozygous for the variant and a pathogenic variant, confirmed in trans by family testing, and 2 individuals were homozygous for the variant. Total PM3 points are 4.0 [PM3_VS; PMID: 88735; 31579136; 26029792; 31037981; 11168520]. This variant has been reported in 3 unrelated individuals displaying a hematological phenotype consistent with beta-thalassemia trait with reduced MCV (<79 fl) and MCH (<27 pg) and increased HbA2 (>3.5%), giving a total score of 4.5 [PS4; PMID: 31579136; 11168520; 26029792]. The minor allele frequency in gnomAD v4.1 is 0.00001177 (19/1614014 alleles), which is lower than 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 beta-thalassemia HBB/LCRB (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): PVS1_S, PM3_VS, PP1_M, PS4, PM2_P

Met criteria codes

PM2_Supporting			The minor allele frequency in gnomAD v4.1 is 0.00001177 (19/1614014 alleles), which is lower than the ClinGen Hemoglobinopathy VCEP threshold <0.0001 for PM2_Supporting, and therefore meets this criterion
PVS1_Strong			The c.52A>T (p.Lys18*) variant in HBB is a nonsense variant predicted to cause loss of function of the protein.
PM3_Very Strong			This variant has been detected in 5 individuals with beta thalassemia. Of those individuals, 3 were compound heterozygous for the variant and a pathogenic variant and were confirmed in trans by family testing (3*1.0 point), and 2 individuals were homozygous for the variant (2*0.5 points). Total PM3 points are 4.0 [PMID: 88735, 31579136, 26029792, 31037981, 11168520]
PS4			This variant has been reported in 3 probands with reduced MCV (<79 fl), and MCH (<27 pg); increased HbA2 (>3.5%). Total score is 4.5 [PMID 31579136; 11168520; 26029792].
PP1_Moderate			The variant has been reported to segregate with disease in 3 affected family members from 3 families. The total number of unaffected segregations is 1: Family 1: proband with beta thalassemia intermedia is compound heterozygous (poly A(A>G) and CD17(A>T); father is carrier of poly A(A>G); mother and brother are carriers of CD17(A>T) [PMID 31579136] Family 2: proband with beta thalassemia intermedia is compound heterozygous CD17 A>T and -31 A>G [HBB:c.-81A>G] ; mother is carrier of -31 A>G [HBB:c.-81A>G] [PMID 26029792] Family 3: homozygous proband, no family testing [PMID: 88735] The LOD score is 1.93.

Not Met criteria codes

PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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Curation History 

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