

Variant: *NM_000518.5(HBB):c.114G>A (p.Trp38Ter)*

Version: 1.0

CA125265 [↗](#)

15405 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal recessive inheritance

UUID: db77be2b-6a3a-4e5c-89bd-64d4b22f558f

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HGVS expressions

NM_000518.5:c.114G>A

NM_000518.5(HBB):c.114G>A (p.Trp38Ter)

NC_000011.10:g.5226778C>T

CM000673.2:g.5226778C>T

NC_000011.9:g.5248008C>T

CM000673.1:g.5248008C>T

NC_000011.8:g.5204584C>T

NG_000007.3:g.70838G>A

NG_059281.1:g.5294G>A

ENST00000647020.1:c.114G>A

ENST00000335295.4:c.114G>A

ENST00000380315.2:c.114G>A

ENST00000475226.1:n.46G>A

ENST00000485743.1:n.165G>A

ENST00000633227.1:c.98G>A

NM_000518.4:c.114G>A

Pathogenic

Met criteria codes **5**

PP1

PM3

PS4_Supporting

PVS1

PM2_Supporting

Not Met criteria codes **3**

PP3

BA1

BS1

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.114G>A (p.Trp38Ter) variant in HBB results in a premature termination codon predicted to cause truncated or absent HBB protein, which is a commonly known mechanism for disease. This is reflected in the 0% HbA detected by HPLC analysis and Hb electrophoresis in

homozygous patients [PVS1; PMID: 24385817; 22385009]. This variant was reported in five unrelated individuals displaying a hematological phenotype consistent with β -thalassemia trait (reduced MCV and MCH) with a total score of 0.75 [PS4_P; PMID: 23510507; 22385009; 24385817; The Hemoglobinopathies Laboratory, Department of Human and Clinical Genetics, Leiden University Medical Center]. It has been detected in two individuals with a β -thalassemia intermedia phenotype, one who received transfusion therapy. Of those individuals, one was compound heterozygous for the variant and a pathogenic variant (c.93-1G>C) and was confirmed in trans by DNA studies, and the other was homozygous for the variant. Total PM3 points are 1.5 [PM3; PMID: 23510507; 24385817; Variation ID: 439166]. The variant has been reported to segregate with β -thalassemia (an intermediate or transfusion-dependent condition) in two affected family members from two families. The total number of unaffected segregations is one, giving a LOD score of 1.33 [PP1; PMID: 23510507; 3006832]. The minor allele frequency in gnomAD v4.1 is 0.000001239 (2/1614108 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 autosomal recessive beta thalassemia (MONDO:0013517) based on the ACMG/AMP criteria applied, as specified by the ClinGen Hemoglobinopathy VCEP (specification version 1.0.0): PVS1, PM3, PS4_P, PP1, PM2_P.

Met criteria codes

PP1			The variant has been reported to segregate with disease in [2] affected family members from [2] families. (For recessive haemoglobinopathies - The total number of unaffected segregations is [1]). The LOD score is [1.33]. [PMID:23510507, PMID:3006832]
PM3			This variant has been detected in 2 individuals with β -thalassemia. Of those individuals, 1 was compound heterozygous for the variant and a pathogenic variant (c.93-1G>C) and was confirmed in trans by family testing and DNA studies, and the other was homozygous for the variant. Total PM3 points are 1.5 [PMID: 23510507; 24385817].
PS4_Supporting			This variant has been reported in 5 unrelated probands meeting low MCV (<79 fL), low MCH (<27 pg) and increased HbA2 (>3.5%). Total score is 0.75 [PMID: 24385817, PMID:22385009, PMID:23510507; Internal lab collaborator].
PVS1			The c.14G>A(p.Trp38Ter) variant in [NM_000518.5(HBB)] is a nonsense variant predicted to cause loss of function of the protein.
PM2_Supporting			The minor allele frequency in gnomAD v4.1 is 0.000001239 (2/1614108 alleles), which is lower than the ClinGen Hemoglobinopathy VCEP threshold <0.0001 for PM2_Supporting, and therefore meets this criterion [PM2_P].

Not Met criteria codes

PP3			The computational predictor CADD gives a PHRED score of 42, which is above threshold >12, evidence that correlates with impact to HBB function. Cannot be applied with PVS1.
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

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