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Variant: NM_000518.5(HBB):c.82G>T (p.Ala28Ser)

Version: 1.0

CA124983

15239 (ClinVar)

Gene: HBB (HGNC:3043)
Condition: beta-thalassemia HBB/LCRB (MONDO:0013517)
Inheritance Mode: Autosomal recessive inheritance
UUID: 23a1f723-f975-46ee-b42a-01ececf77079
Approved on: 2026/4/7
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HGVS expressions

NM_000518.5:c.82G>T
NM_000518.5(HBB):c.82G>T (p.Ala28Ser)
NC_000011.10:g.5226940C>A
CM000673.2:g.5226940C>A
NC_000011.9:g.5248170C>A
CM000673.1:g.5248170C>A
NC_000011.8:g.5204746C>A
NG_000007.3:g.70676G>T
NG_059281.1:g.5132G>T
ENST00000647020.1:c.82G>T
ENST00000335295.4:c.82G>T
ENST00000380315.2:c.82G>T
ENST00000485743.1:n.133G>T
ENST00000633227.1:c.76+6G>T
NM_000518.4:c.82G>T

Pathogenic

Met criteria codes 6

PM3 PP1_Strong PP3 PM2_Supporting PS4_Moderate PS3_Supporting

Not Met criteria codes 1

PM5

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.82G>T (p.Ala28Ser) variant is located in the HBB gene. This variant has been reported in 12 unrelated individuals displaying a hematological phenotype consistent with beta thalassemia trait (reduced MCV and MCH with normal or increased RBC count), giving a total score of 2.15 [PS4_M; PMID: 7104238; 3955238; The Hemoglobinopathies Laboratory, Department of Human and Clinical Genetics,

Leiden University Medical Center; Department of Medical Genetics, National and Kapodistrian University of Athens]. This variant has been reported to segregate with a beta-thalassemia intermedia phenotype in 8 affected family members from 4 families. The total number of unaffected segregations is 8 with a LOD score of 5.81 [PP1_S; PMID:7104238; 3955238; 25332589; 30777047; 17949282]. It was detected in combination with a pathogenic variant in one affected individual, confirmed in trans by DNA studies, and found in a homozygous state in another, both presenting with a beta-thalassemia intermedia phenotype. Total PM3 points are 1.5 [PM3; PMID:3955238; 25332589; Variation ID: 15438]. Hemoglobin biosynthesis assay showed a change in biosynthetic ratio of globins in a heterozygous sample (β/α ratio 0.45-0.55), indicating that this variant impacts protein function. In addition, in vitro splicing assay showed that this variant leads to abnormal RNA processing by creating/utilizing a cryptic splice site in exon 1 of HBB [PS3_P; PMID:6733281; 7104238; 7173395]. The computational predictor SpliceAI gives a Δ score of 0.79 for donor gain in exon 3, which is above the VCEP threshold >0.3, predicting that this variant may affect splicing by disrupting the donor splice site of intron 3 in HBB [PP3]. The minor allele frequency in gnomAD v4.1 is 0.000002479 (4/1613406) 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 (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): PP1_S, PS4_M, PM3, PM2_P, PP3, PS3_P.

Met criteria codes

PM3	✔	This variant has been detected in 2 individuals with a beta-thalassemia intermedia phenotype. Of those individuals, 1 was compound heterozygous for the variant and a pathogenic variant (β0 IVSII-I G>C), confirmed in trans by family testing and DNA studies, and the other was homozygous for the variant. Total PM3 points: 1.5 [PMID:3955238, PMID:25332589; VCV000015438.38].
PP1_Strong	✔	The variant has been reported to segregate with [beta thalassemia] in [8] affected family members from [4] families. The total number of unaffected segregations is [8]. The LOD score is [5.81] [PMIDs:7104238; 3955238; 25332589; 30777047;17949282]
PP3	✔	The computational predictor SpliceAI gives a Δ score of 0.79 for donor gain in exon 3, which is above threshold >0.3, predicting that the variant may affect splicing by disrupting the donor splice site of intron 3 in HBB.
PM2_Supporting	✔	The minor allele frequency in gnomAD v4.1 is 0.000002479 (4/1613406) alleles, which is lower than the ClinGen Hemoglobinopathy VCEP threshold <0.0001 for PM2_Supporting, and therefore meets this criterion.
PS4_Moderate	✔	This variant has been reported in [12] unrelated probands meeting [beta thalassemia trait]. Total score is 2.15 [PMID: 7104238, PMID:3955238 and internal lab contributors].
PS3_Supporting	✔	Globin biosynthesis showed an β/α ratio to be between 0.45-0.55 indicating that this variant impacts protein function [PMID: 7104238 and PMID:7173395]. [In vitro spicing assay] demonstrated that the variant impacts splicing by [creating a cryptic donor region of exon 1] [PMID:6733281].

Not Met criteria codes

PM5	✖	Two different missense variants [c.83C>T (p.Ala28Val); c.83C>A (p.Ala28Asp)] in the same codon have been reported in patients with haemoglobinopathy [VCV000015184.2; VCV000015386.3]. However, these variants have not yet met the criteria to be classified as pathogenic by the ClinGen Hemoglobinopathy VCEP/(or) with a 2-star review status by ClinVar.

Curation History

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