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Variant: NM_000518.5(HBB):c.92+5G>C

Version: 2.0

CA125310

15447 (ClinVar)

Gene: HBB (HGNC:3043)
Condition: beta-thalassemia HBB/LCRB (MONDO:0013517)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2466639d-2e77-42b7-9452-ce584ef83a72
Approved on: 2026/4/30
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HGVS expressions

NM_000518.5:c.92+5G>C
NM_000518.5(HBB):c.92+5G>C
NC_000011.10:g.5226925C>G
CM000673.2:g.5226925C>G
NC_000011.9:g.5248155C>G
CM000673.1:g.5248155C>G
NC_000011.8:g.5204731C>G
NG_000007.3:g.70691G>C
NG_059281.1:g.5147G>C
ENST00000647020.1:c.92+5G>C
ENST00000335295.4:c.92+5G>C
ENST00000380315.2:c.92+5G>C
ENST00000485743.1:n.143+5G>C
ENST00000633227.1:c.76+21G>C
NM_000518.4:c.92+5G>C

Pathogenic

Met criteria codes 5

PM3 PP1_Strong PS3_Supporting PS4 PP3

Not Met criteria codes 7

PM2 PM1 PM5 BA1 BS1 BP7 PVS1

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.92+5G>C variant in HBB is an intronic variant lying in the 5’ splice site consensus sequence. This variant has been reported in 4 unrelated individuals displaying a hematological phenotype consistent with β-thalassemia trait (low MCV (<79 fL), low MCH (<27 pg) and increased HbA2 (>3.5%)), giving a total score of 6 (PS4; PMID: 27690257; 23425159; 26291970; 29651865). This variant was found to co-

segregate with beta-thalassemia (e.g., anemia, transfusion requirements and/or hepatosplenomegaly) in 4 affected individuals from different families. There were two unaffected segregations from the same family, giving a LOD score of 2.66 (PP1_S; PMID: 27690257; 2342515926291970; 29651865). This variant has been detected in two homozygous individuals with transfusion-dependent thalassemia, giving a score of 1 (PM3; PMID: 27690257; 23425159). The computational predictor SpliceAI predicts that this variant may affect splicing by disrupting the donor splice site of intron I of HBB (Δ score 0.81; VCEP threshold >0.3) (PP3). Transfection of cell cultures with constructs bearing the cloned mutant gene showed that this variant significantly reduces HBB gene expression (low RNA levels) and impacts splicing by producing both the normal and three abnormally spliced RNA products (PS3_P; PMID: 6188062). The highest population minor allele frequency in gnomAD v4.1 is 0.004481 (442/91042 alleles) in South Asian, exceeding the ClinGen Hemoglobinopathy VCEP BS1 threshold (≥0.001). However, this variant is on the VCEP exclusion list for BA1/BS1; therefore, these criteria were not applied. In summary, this variant meets 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): PS4, PP1_S, PM3,PP3, PS3_P.

Met criteria codes

PM3	✔	This variant has been detected in 2 individuals with transfusion-dependent thalassaemia. Both were homozygous for the variant. Total PM3 points: 1 [PMID: 27690257; PMID: 23425159].
PP1_Strong	✔	The variant has been reported to segregate with disease in 4 affected family members from 4 families. The total number of unaffected segregations is 2. The LOD score is 2.66
PS3_Supporting	✔	Transfection of cell cultures with constructs bearing the cloned mutant gene showed that this variant significantly reduces HBB gene expression (low RNA levels) and impacts splicing by producing both the normal and three abnormally spliced RNA products [PMID: 6188062].
PS4	✔	This variant has been reported in 4 unrelated probands meeting low MCV (<79 fL), low MCH (<27 pg) and increased HbA2 (>3.5%). Total score is 6 [PMID: 27690257; PMID: 23425159; PMID: 26291970; PMID: 29651865].
PP3	✔	The computational predictor SpliceAI gives a Δ score of 0.81 for donor loss, which is above threshold >0.3, predicting that the variant may affect splicing by disrupting the donor splice site of intron I of HBB.

Not Met criteria codes

PM2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	Found in the 5' splice site consensus sequence. This variant does not reside within a region of HBB that is defined as a mutational hotspot and/or critical functional domain by the ClinGen Hemoglobinopathy VCEP.
PM5	✖	Two different variants [c.92+5G>T; c.92+5G>A] [VCV000015448.17; VCV000015449.15] in the same base site have been classified as pathogenic for β-thalassemia with a 2-star review status by ClinVar. Splicing predictor SpliceAI predicts a splicing impact for both variants c.92+5G>T: Splice AI Δ score 0.73 for donor loss c.92+5G>A: Splice AI Δ score 0.76 for donor loss
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS1	ℹ	✖	The highest population minor allele frequency in gnomAD v4.1 is 0.004481 (442/91042 alleles) in South Asian, exceeding the ClinGen Hemoglobinopathy VCEP BS1 threshold (≥0.001). However, this variant is on the VCEP exclusion list for BA1/BS1; therefore, these criteria were not applied.
BP7	ℹ	✖	This is an intron variant [SO:0001627], not a synonymous (silent) variant as defined by the criterion.
PVS1	ℹ	✖	This is an intron variant [SO:0001627], not a null variant as defined by the criterion.

Curation History

Showing 1 to 2 of 2 rows

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