

Variant: *NM_000517.6(HBA2):c.2del (p.Met1fs)*

Version: 1.0

CA125662 [↗](#)

15692 (ClinVar) [↗](#)

Gene: HBA2 ([HGNC:3040](#))

Condition: HBA2-related alpha thalassemia spectrum ([MONDO:0100562](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 2b0b3327-e61d-4879-b167-b7e7398f3b0c

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HGVS expressions

NM_000517.6(HBA2):c.2del (p.Met1fs)

NM_000517.6:c.2del

NC_000016.10:g.172914del

CM000678.2:g.172914del

NC_000016.9:g.222913del

CM000678.1:g.222913del

NC_000016.8:g.162913del

NG_000006.1:g.33777del

NG_059186.1:g.1264del

NG_059271.1:g.5068del

ENST00000251595.11:c.2del

ENST00000251595.10:c.2del

ENST00000397806.1:c.-46del

ENST00000482565.1:n.21del

NM_000517.4:c.2del

Pathogenic

Met criteria codes 5

PM3_Strong

PP1

PM2_Supporting

PS4_Supporting

PVS1

Not Met criteria codes 2

PS3

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 HBA2 Version 1.0.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Hemoglobinopathy VCEP

The NM_000517.6(HBA2):c.2del, p.(Met1fs), variant is an initiation codon loss predicted to cause loss of function of the protein [PVS1]. It has been reported in 3 individuals displaying a hematological phenotype consistent with α -thalassemia trait (reduced MCV and MCH with normal/increased RBC count), giving a total score of 0.55 [PS4_P; PMID 16116675; 9322079; 28620953]. This variant has been detected in

two individuals with HbH disease. Both were compound heterozygous for the variant and a pathogenic variant (α^0 --SEA) and were confirmed in trans by family testing; total PM3 points are 2 [PM3_S; PMID: 16116675; 9322079]. It has been reported to segregate with HbH disease phenotype in 2 affected family members from 2 families. The total number of unaffected segregations is 1, giving a LOD score of 1.33 [PP1; PMID: 16116675; 9322079]. The minor allele frequency in gnomAD v4.1 is 0.000007432 (2/269118 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 HBA2-related alpha thalassemia spectrum (MONDO:0100562) 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, PM3_S, PP1, PS4_P, PM2_P.

Met criteria codes

PM3_Strong			This variant has been detected in two individuals with HbH disease. Both were compound heterozygous for the variant and a pathogenic variant (α^0 --SEA) and were confirmed in trans by family testing. Total PM3 points are 2. [PMID: 16116675, PMID: 9322079].
PP1			The variant has been reported to segregate with Hb H disease phenotype in 2 affected family members from 2 families. The total number of unaffected segregations is 1. The LOD score is 1.33 [PMID: 16116675, 9322079].
PM2_Supporting			The minor allele frequency in gnomAD v4.1 is 0.000007432 (2/269118) alleles, which is lower than the ClinGen Hemoglobinopathy VCEP threshold <0.0001 for PM2_Supporting, and therefore meets this criterion [PM2_P]
PS4_Supporting			This variant has been reported in 1 proband meeting low MCV (77.5), low MCH (25.0), with normal red blood cell counts (5.03×10^{12}) and normal HbA2 (2.4), in one proband reported to meet α -thalassemia trait phenotype (low MCV: 74.7 and normal HbA2: 2.3), and in one other proband meeting low MCV (75.4) and low MCH (26.2). Total score is 0.55 (PMID 16116675; PMID 9322079, PMID: 28620953) PMID 16116675: Mum ($\alpha\alpha/\alpha c.2delT\alpha$): Low MCV (77.5), MCH (25.0), normal RBC (5.03×10^{12}), normal HbA2 (2.4) => 0.2 PMID 9322079: Mum ($\alpha\alpha/\alpha c.2delT\alpha$): Alpha-thal trait phenotype (stated in paper) Low MCV (74.7), normal Hb (12.2), normal HbA2 (2.3) => 0.2 PMID: 28620953: Two (2) mutation carriers: mean Hb: 12.7 ± 0.1 ; mean MCH: 26.2 ± 0.4 ; mean MCV: 91.2 ± 15.8 At least one of two will have low MCV (MCV: 91.2 ± 15.8 => $91.2 - 15.8 = 75.4$) Hence low MCH (MCH 26.2 ± 0.4), low MCV (75.4) => $0.15 \times 1 = 0.15$
PVS1			The c.2delT, p.(Met1fs) variant in HBA2 is an initiation codon loss predicted to cause loss of function of the protein

Not Met criteria codes

PS3			Hemoglobin electrophoresis showed a change in electrophoretic mobilities (13.6% Hb H=> $\beta 4$ and 5% Hb Bart's => $\gamma 4$), indicating that this variant impacts protein function (PMID 16116675)
PM5			Three (3) different initiation codon loss variants (c.2T>C, p.Met1Thr; c.1delA, p.Met1fs; c.1A>G, p.Met1Val) in the same codon have been reported in patients with alpha thalassemia/HbH disease (ClinVar ID: 15643; 15694; 15645). However, these variants have not yet met the criteria to be classified as pathogenic with a 2-star review status by ClinVar

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