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Variant: NM_000517.6(HBA2):c.377T>G (p.Leu126Arg)

Version: 1.0

CA125658

15690 (ClinVar)

Gene: HBA2 (HGNC:3040)
Condition: HBA2-related alpha thalassemia spectrum (MONDO:0100562)
Inheritance Mode: Autosomal recessive inheritance
UUID: 1e6dcef7-360e-4f30-ab5c-a3383e00a026
Approved on: 2026/4/8
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HGVS expressions

NM_000517.6:c.377T>G
NM_000517.6(HBA2):c.377T>G (p.Leu126Arg)
NC_000016.10:g.173548T>G
CM000678.2:g.173548T>G
NC_000016.9:g.223547T>G
CM000678.1:g.223547T>G
NC_000016.8:g.163547T>G
NG_000006.1:g.34411T>G
NG_059186.1:g.1898T>G
NG_059271.1:g.5702T>G
ENST00000251595.11:c.377T>G
ENST00000251595.10:c.377T>G
ENST00000397806.1:c.281T>G
ENST00000482565.1:n.513T>G
NM_000517.4:c.377T>G

Likely Pathogenic

Met criteria codes 4

PS4_Moderate PP3 PM3 PM2_Supporting

Not Met criteria codes 4

PP1 PM1 PM5 BP4

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.377T>G variant in HBA2 is a missense variant predicted to cause substitution of leucine by arginine at amino acid 125 (p.Leu126Arg). This variant has been reported in at least 8 unrelated individuals with an α-thalassaemia trait phenotype (low MCV and MCH with normal/increased RBC count) [PS4_M; PMID:15921163;23368878; The Hemoglobinopathies Laboratory, Department of

Human and Clinical Genetics, Leiden University Medical Center; Molecular Genetics Laboratory, Hamilton Regional Laboratory Medicine Program, Hamilton Health Sciences]. It has also been detected in two homozygous individuals with moderate anemia, microcytosis and hypochromia, with one requiring transfusion therapy. Total PM3 points are 1 [PM3; PMID: 21077766; Molecular Genetics Laboratory, Hamilton Regional Laboratory Medicine Program, Hamilton Health Sciences]. The computational predictor REVEL (score 0.843; VCEP threshold >0.8) suggests that this variant impacts HBA2 function [PP3]. There is no detection of abnormal Hb protein and globin chain by electrophoretic techniques (e.g., IEF, electrophoresis on citrate agar and ion exchange HPLC) and reversed-phase HPLC, respectively, while the isopropanol precipitation test for Hb stability is negative. The minor allele frequency in gnomAD v4.1 is 0.0000031 (5/1607758 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 a likely pathogenic variant for recessive HBA2-related alpha thalassemia spectrum (MONDO:0100562) based on the ACMG/AMP criteria applied, as specified by the ClinGen Hemoglobinopathy VCEP (specification version 1.0.0): PS4_M, PM3, PP3, PM2_P.

Met criteria codes

PS4_Moderate	✔	This variant has been reported in at least 8 unrelated probands with an α-thalassaemia trait phenotype meeting reduced red cell indices (MCV <79 fl, MCH <27 pg) with normal/increased red blood cell count. Total points 1.6 [PMID:15921163; PMID:23368878; Internal lab collaborators].
PP3	✔	The computational predictor REVEL gives a score of 0.843, which is above the threshold of 0.8, evidence that correlates with impact to HBA2 function.
PM3	✔	This variant has been detected in 2 individuals with an α-thalassaemia diagnosis. Both were homozygous for the variant. Total PM3 points are 1. [PMID: 21077766; internal laboratory data].
PM2_Supporting	✔	The minor allele frequency in gnomAD v4.1 is 0.0000031 (5/1607758 alleles), which is lower than the ClinGen Hemoglobinopathy VCEP threshold (<0.0001) for PM2_Supporting, and therefore meets this criterion

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Not Met criteria codes

PP1	✖	The variant has been reported to segregate with a more severe phenotype compared to both variants in isolation in 1 affected family member from 1 family. The total number of unaffected segregations is 0. The LOD score is 0.6 [internal laboratory data]
PM1	✖	This variant does not reside within a region of HBA2 that is defined as a mutational hotspot and/or critical functional domain by the ClinGen Hemoglobinopathy VCEP. According to literature, residue α125 is located in helix H and is critical for the α1β1 contact. Replacement of the non-polar Leu residue by the positively charged Arg residue changes the α1β1 contact and, therefore, the dimer formation is impaired.
PM5	✖	2 different missense variants [NM_000517.6(HBA2):c.377T>A (p.Leu126Gln), no-star P in ClinVar; NM_000517.6(HBA2):c.377T>C (p.Leu126Pro), one-star P in ClinVar] in the same codon have been reported in patients with alpha thalassemia [VCV000869221.1; VCV000015630.3]. However, these variants have not yet met the criteria to be classified as pathogenic or likely pathogenic by the ClinGen Hemoglobinopathy VCEP/(or) with a 2 star review status by ClinVar.
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

Showing 1 to 1 of 1 rows

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