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Variant: NM_000517.6(HBA2):c.179G>A (p.Gly60Asp)

Version: 1.0

CA276414731

439112 (ClinVar)

Gene: HBA2 (HGNC:3040)
Condition: HBA2-related alpha thalassemia spectrum (MONDO:0100562)
Inheritance Mode: Autosomal recessive inheritance
UUID: 2f48c5f4-68d9-47cc-957b-e806dfa20731
Approved on: 2026/4/8
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HGVS expressions

NM_000517.6(HBA2):c.179G>A (p.Gly60Asp)
NM_000517.6:c.179G>A
NC_000016.10:g.173208G>A
CM000678.2:g.173208G>A
NC_000016.9:g.223207G>A
CM000678.1:g.223207G>A
NC_000016.8:g.163207G>A
NG_000006.1:g.34071G>A
NG_059186.1:g.1558G>A
NG_059271.1:g.5362G>A
ENST00000251595.11:c.179G>A
ENST00000251595.10:c.179G>A
ENST00000397806.1:c.83G>A
ENST00000482565.1:n.315G>A
ENST00000484216.1:n.148G>A
NM_000517.4:c.179G>A

Pathogenic

Met criteria codes 6

PP1_Strong PS4_Supporting PM3_Very Strong PS1_Moderate PM2_Supporting PP3

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 HBA2 Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Hemoglobinopathy VCEP

This is a missense variant in the HBA2 gene (NM_000517.6(HBA2):c.179G>A; p.Gly60Asp). The variant has been identified in 12 individuals with clinically significant α-thalassemia and in one individual with HbH disease. All affected individuals were compound heterozygotes for

this variant and a known pathogenic variant (Hb Constant Spring; VCV000015624.66), with the two variants confirmed to be in trans through family studies and DNA analysis. Based on this evidence, a total of 13 PM3 points were assigned, meeting criteria for PM3_VS (PMID: 27271331; 24829075). Segregation analysis showed co-segregation of the variant with α-thalassemia associated with the -α3.7 deletion in two affected family members, and with HbH disease associated with the --SEA deletion in one affected family member. Three unaffected segregations were observed, yielding a LOD score of 2.18, supporting PP1_S (PMID: 24829075). The variant has also been reported in five unrelated individuals with low mean corpuscular volume (MCV) and low mean corpuscular hemoglobin (MCH), and in two unrelated individuals with low MCV, low MCH, and normal red blood cell counts. This enrichment corresponds to a total score of 1.15, supporting PS4_P (PMID: 20642338; 24351118; 24829075). The minor allele frequency in gnomAD v4.1 is 8.741e-7 (1/1143980), which is below the ClinGen Hemoglobinopathy VCEP threshold (<0.0001) for PM2_Supporting, meeting this criterion (PM2_P). In silico prediction using REVEL yields a score of 0.867, exceeding the established threshold of 0.8 and supporting a deleterious effect on HBA2 function (PP3). Notably, the same amino acid change (p.Gly60Asp) resulting from the identical nucleotide substitution (c.179G>A) is classified as pathogenic in HBA1 for α-thalassemia (ClinVar: VCV000015849, two-star review status), supporting PS1_M. In summary, this variant meets criteria for a pathogenic classification for HBA2-related alpha thalassemia spectrum (MONDO:0100562) with autosomal recessive inheritance, based on ACMG/AMP guidelines as specified by the ClinGen Hemoglobinopathy VCEP (specification version 1.0.0): PM3_VS, PP1_S, PS1_M, PS4_P, PP3, PM2_P

Met criteria codes

PP1_Strong ✔	The variant has been reported to segregate with alpha thalassemia in 2 affected members (αp.Gly60Aspα/-α3.7) and with HbH (αp.Gly60Aspα/--SEA) in one affected member from one family. The total number of unaffected segregations (did not inherit Hb Adana) is 3. The LOD score is 2.18 (PMID: 24829075). PMID: 24829075 Three affected individuals o Two probands: low (MCV=76.7, MCH=24.7, HbA2=2.0; MCV=75.4, MCH=24.0, HbA2=2.1), Clinically pale, splenomegaly, history of anemia, intermittent jaundice, seldom blood transfusion. o Phenotype more severe than parent carriers: in trans with a3.7del (/-a3.7) o One stillborn hydropic fetus: in trans with SEAdel Three unaffected: did not inherit Hb Adana.
PS4_Supporting ✔	This variant has been reported in 5 unrelated probands meeting low MCV and low MCH, and in 2 unrelated probands meeting low MCV, low MCH and normal red blood cell counts (RBC). Total score is 1.15 (PMID:20642338; PMID: 24351118; PMID: 24829075). PMID:20642338 Family 1: 1-1 (MCV=75.3; MCH=25.8) 1-2 (MCH=63.5; MCH=21.3) => 0.15x2 = 0.3 Family 2: 1-1 (MCV=75.8; MCH=25.2) => 0.15x1 = 0.15 Family 3: 1-1 (MCV=75.3; MCH=24.1) 1-2 (MCH=71.4; MCH=23.4) => 0.15x2 = 0.3 PMID: 24351118 Mother: Low (MCV=68.8; MCH=23.4), normal RBC (5.04x10^12/L) => 0.2 PMID: 24829075 Family 1: Dad: Low (MCV=74.3; MCH=23.6), normal RBC (5.21), anemic (Hb: 12.3gd/L) => 0.2
PM3_Very Strong ✔	This variant has been detected in 12 individuals with alpha thalassemia and in 1 individual with HbH. All individuals were compound heterozygous for the variant (Hb Adana) and a pathogenic variant (Hb CS), and were confirmed in trans by family testing and by DNA studies. Total PM3 points are 13 (PMID:27271331; PMID: 24829075; ClinVar SCVs: 15624; Hemoglobin VCEP). PMID:27271331 - Eleven (11) cases (P2-P12) with severe α-thalassemia (chronic hemolytic anemia, transfusion dependent, hepatosplenomegaly, conjugated bilirubin, jaundice) - In trans with Hb constant spring (αCSα) - CS interpreted as pathogenic based on VCEP classification - CS excluded from “PM3 requiring PM2_P” to be met PMID: 24829075 - Family A: Two (2) affected individuals (anemia, hepatosplenomegaly, MCV=84.6, MCH=25.6, HbA2=2.3; MCV=75.6, MCH=23.4. HbA2=2.3) - In trans with Hb constant spring (αCSα)
PS1_Moderate ✔	The same amino acid change p.Gly60Asp, resulting from the same nucleotide change c.179G>A [ClinVar: 15849] is classified as pathogenic in HBA1 for Alpha thalassemia with a 2 star review status by ClinVar.
PM2_Supporting ✔	The minor allele frequency in gnomAD v4.1 is 8.741e-7 (1/1143980) alleles, which is lower than the ClinGen Hemoglobinopathy VCEP threshold <0.0001 for PM2_Supporting, and therefore meets this criterion [PM2_P].

PP3	✔	The computational predictor REVEL gives a score of 0.867, which is above the threshold of 0.8, evidence that correlates with impact to HBA2 function.

Not Met criteria codes

PM5	✖	Another missense variant c.178G>C, p.(Gly60Arg) in the same codon has been reported in a patient with alpha thalassemia (ClinVar ID: 15688). However, this variant has not yet met the criteria to be classified as pathogenic with a 2-star review status by ClinVar.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000517.6(HBA2):c.179G>A (p.Gly6…	Pathogenic	HBA2-Related Alpha Thalassemia Spectrum	2026-04-08	1.0	ClinGen Hemoglobinopathy Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for HBA2 Version 1.0.0	HBA2

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