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Variant: NM_001204.7(BMPR2):c.276A>C (p.Gln92His)

Version: 1.0

CA2061080

225305 (ClinVar)

Gene: BMPR2 (HGNC:659)
Condition: pulmonary arterial hypertension (MONDO:0015924)
Inheritance Mode: Autosomal dominant inheritance
UUID: bda06391-0688-4adc-81a7-7f003b26e1c6
Approved on: 2024/11/1
Published on: 2024/11/1

HGVS expressions

NM_001204.7(BMPR2):c.276A>C (p.Gln92His)
NM_001204.7:c.276A>C
NC_000002.12:g.202467547A>C
CM000664.2:g.202467547A>C
NC_000002.11:g.203332270A>C
CM000664.1:g.203332270A>C
NC_000002.10:g.203040515A>C
NG_009363.1:g.96221A>C
ENST00000374580.10:c.276A>C
ENST00000638587.1:c.207A>C
ENST00000374574.2:c.276A>C
ENST00000374580.8:c.276A>C
ENST00000479069.1:n.183A>C
NM_001204.6:c.276A>C

Likely Benign

Met criteria codes 2

BS1 PM1

Not Met criteria codes 7

BS2 BP4 PM2 PS1 PM5 BA1 PP3

Evidence Links 0

Expert Panel

Pulmonary Hypertension VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Pulmonary Hypertension Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for BMPR2 Version 1.1.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Pulmonary Hypertension VCEP

The BMPR2 c.276A>C variant is a missense variant predicted to cause substitution of glutamine to histidine at amino acid position 92 (p.(Gln92His)). The highest population minor allele frequency in gnomAD v2.1.1 (controls) is 0.001589 in the East Asian population (Korean) (BS1 met but not PM2 or BA1). Computational predictor REVEL score is 0.57, which is in between the PH-VCEP specified threshold of ≤0.25 and ≥0.75, so neither PP3 nor BP4 are met. This variant is located in the extracellular domain, critical for ligand binding (PM1 met), but

does not affect a known critical or non-critical amino acid (no up- or downward adjustment for PM1). BS2 was not met due to absence of homozygous individuals (gnomAD v.2.1.1 controls). PS4 was not applied as PM2 was not met. PP1, PS2, PM6 were not met due to the absence of co-segregation data. PS3 and BS3 were not met due to the lack of experimental evidence. Although other variants in the same amino acid been reported, for pulmonary arterial hypertension, the variants were not deemed pathogenic or likely pathogenic by the PH-VCEP (PS1, PM5 not met). In summary, this variant meets the criteria to be classified as likely benign for pulmonary arterial hypertension based on the ACMG/AMP criteria applied, as specified by the ClinGen Pulmonary Hypertension VCEP: BS1, PM1 (VCEP specification version 1.1.0, 1/18/2024).

Met criteria codes

BS1	✔	The highest population minor allele frequency in gnomAD v2.1.1 (controls) is 0.001589 in the East Asian population (Korean) with is higher than the threshold of <0.0001 (BS1 met but not PM2 or BA1).
PM1	✔	This variant is located in the extracellular domain, critical for ligand binding (PM1 met), but does not affect a known critical or non-critical amino acid (no up- or downward adjustment for PM1).

Not Met criteria codes

BS2	✖	BS2 was not met due to absence of homozygous controls (gnomAD v.2.1.1)
BP4	✖	Computational predictor REVEL score is 0.57, which is in between the PH-VCEP specified threshold of ≤0.25 and ≥0.75, so PP3 or BP4 are not met.
PM2	✖	The highest population minor allele frequency in gnomAD v2.1.1 (controls) is 0.001589 in the East Asian population (Korean) with is higher than the threshold of <0.0001 (BS1 met but not PM2 or BA1).
PS1	✖	The alternative variants were not deemed pathogenic or likely pathogenic by the PH-VCEP.
PM5	✖	The alternative variants were not deemed pathogenic or likely pathogenic by the PH-VCEP.
BA1	✖	The highest population minor allele frequency in gnomAD v2.1.1 (controls) is 0.001589 in the East Asian population (Korean) with is higher than the threshold of <0.0001 (BS1 met but not PM2 or BA1).
PP3	✖	Computational predictor REVEL score is 0.57, which is in between the PH-VCEP specified threshold of ≤0.25 and ≥0.75, so PP3 or BP4 are not met.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_001204.7(BMPR2):c.276A>C (p.Gln...	Likely Benign	Pulmonary Arterial Hypertension	2024-11-01	1.0	ClinGen Pulmonary Hypertension Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for BMPR2 Version 1.1.0	BMPR2

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