

Variant: *NM_001204.7(BMPR2):c.908G>A (p.Arg303His)*

Version: 1.0

CA2061247 [↗](#)

425842 (ClinVar) [↗](#)

Gene: BMPR2 ([HGNC:659](#))

Condition: pulmonary arterial hypertension ([MONDO:0015924](#))

Inheritance Mode: Autosomal dominant inheritance

UUID: 059df39a-bbb2-4e25-af5a-965bd14ee707

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HGVS expressions

NM_001204.7(BMPR2):c.908G>A (p.Arg303His)

NM_001204.7:c.908G>A

NC_000002.12:g.202520142G>A

CM000664.2:g.202520142G>A

NC_000002.11:g.203384865G>A

CM000664.1:g.203384865G>A

NC_000002.10:g.203093110G>A

NG_009363.1:g.148816G>A

ENST00000374580.10:c.908G>A

ENST00000638587.1:c.839G>A

ENST00000374574.2:c.908G>A

ENST00000374580.8:c.908G>A

NM_001204.6:c.908G>A

Likely Pathogenic

Met criteria codes **2**

PS3 **PM1**

Not Met criteria codes **6**

BA1 **BS1** **BP4** **PS4** **PP3**

PM2

Evidence Links **1**

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.908G>A variant is a missense variant in exon 7 predicted to result in substitution of arginine to histidine at amino acid position 303 (p. Arg303His). The highest population minor allele frequency in gnomAD v2.1.1 (controls) is 0.00043 (1/2334 alleles) in subpopulation “remaining individuals” which exceeds the ClinGen PH VCEP threshold (<0.01%) for PM2 (PM2 not met). Neither BS1 (≥0.1%) nor BA1 (1%) met. The computational predictor REVEL gives a score of 0.497 indicating neither PP3 (≥0.75) nor BP4 (≤0.25) met. SpliceAI algorithm predicts no deleterious effect on acceptor or donor splice site. The variant is located in the kinase domain (PM1 met).

Genetic evidence showed the presence of the variant in only one IPAH patient (PMID:16429395) (PS4 not met). Immunofluorescence staining of Hela cells transfected with an R303H mutant construct showed mislocalization of BMPR2 protein to the endoplasmic reticulum (PMID:25688877) and included positive and negative controls (PS3 met). In summary, the variant meets the criteria to be classified as likely pathogenic for pulmonary arterial hypertension based on the ACMG/AMP criteria applied, as specified by the ClinGen Pulmonary Hypertension VCEP: PS3, PM1 (VCEP specification version 1.1, 1/18/2024).

Met criteria codes

PS3			Immunofluorescence staining of Hela cells transfected with R303H mutant construct showed co-localization of BMPR2 protein with calnexin antibody in endoplasmic reticulum. Quantification of co-localization of BMPR2 R303H mutant with calnexin as compared to wild type was significant (p<= 0.05). Statistically significant co-localization of some other critical BMPR2 cysteine substitution mutants (C34R, C66R, C118W, D485G, A490D, R491W) was also observed. Immunofluorescence staining of Hela cells transfected with R303H mutant construct showed colocalization of BMPR2 protein with calnexin antibody which is an endoplasmic reticulum marker. Quantification of co-localization of BMPR2 wild type and R303H mutant with calnexin by pixel analysis showed that co-localization of the mutant is significant. PubMed:25688877 
PM1			The variant is present in the kinase domain.

Not Met criteria codes

BA1			Minor allele frequency in gnomAD v2.1.1 (controls) in subpopulation “remaining individuals” is 0.00043 which is below our threshold of (1%)
BS1			Minor allele frequency in gnomAD v2.1.1 (controls) in subpopulation “remaining individuals” is 0.00043 which is below our threshold of (>=0.1%)
BP4			REVEL score for this variant is 0.497 which is above our criteria for BP4 (<0.25).
PS4			ClinVar has two entries for pulmonary arterial hypertension - one idiopathic PAH and the other PAH associated with congenital heart disease. The PH VCEP specifications are based on idiopathic and heritable PAH, not associated forms. Thus, PS4 was not met.
PP3			REVEL score for this variant is 0.497 which is below our criteria (>=0.75). Splice AI predicts no impact on splicing.
PM2			Minor allele frequency in gnomAD v2.1.1 (controls) in subpopulation “remaining individuals” is 0.00043 (1/2334 alleles) which is above our threshold of (<0.01%).

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