

Variant: *NM_001204.7(BMPR2):c.100T>C (p.Cys34Arg)*

Version: 1.0

CA350399040 [↗](#)

425702 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: e18b79b3-7e9c-473b-a771-5f33b02792cf

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HGVS expressions

NM_001204.7:c.100T>C

NM_001204.7(BMPR2):c.100T>C (p.Cys34Arg)

NC_000002.12:g.202464832T>C

CM000664.2:g.202464832T>C

NC_000002.11:g.203329555T>C

CM000664.1:g.203329555T>C

NC_000002.10:g.203037800T>C

NG_009363.1:g.93506T>C

ENST00000374580.10:c.100T>C

ENST00000638587.1:c.25T>C

ENST00000374574.2:c.100T>C

ENST00000374580.8:c.100T>C

ENST00000479069.1:n.7T>C

NM_001204.6:c.100T>C

Pathogenic

Met criteria codes 6

PS4_Supporting

PM5_Supporting

PM1_Strong

PS3

PP3

PM2_Supporting

Not Met criteria codes 1

PS1

Evidence Links 2

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 NM_001204.7(BMPR2) c.100T>C variant is a missense variant predicted to cause a cysteine to arginine substitution at amino acid position 34 (p.Cys34Arg). The variant is absent from gnomAD v.2.1.1 and v4.1 (PM2_supporting) and has been reported in two unrelated PAH probands (PMID: 29650961) (PS4_supporting). The variant is located within the extracellular ligand-binding domain and p.Cys34 is a critical residue for protein function (PM1_strong). Two additional likely pathogenic variants, c.101G>T (p.Cys34Phe) and c.102T>G

(p.Cys34Trp) have been reported at the same residue (PMID: 27453251, PMID: 30578397) (PM5_supporting). HeLa cells transfected with a BMPR2 p.C34R construct demonstrated that the mutant protein is mislocalized in the cell and does not reach the plasma membrane, with some retention in the ER/Golgi (PMID: 25688877) (PS3). In silico prediction (REVEL = 0.939) is consistent with a pathogenic effect for this variant (PP3). In summary, the variant meets the criteria to be classified as pathogenic for pulmonary arterial hypertension based on the ACMG/AMP criteria applied, as specified by the ClinGen Pulmonary Hypertension VCEP: PS3, PS4_supporting, PM1_strong, PM2_supporting, PM5_supporting, PP3 (VCEP specification version v 1.1, 1/18/2024).

Met criteria codes

PS4_Supporting			Variant has been reported in two unrelated IPAH patients (Graf et al. 2018, PMID: 29650961). PM2 is met
PM5_Supporting			Two missense variants classified as likely pathogenic have been reported at the same amino acid residue
PM1_Strong			Variant is located in the extracellular ligand-binding domain and the mutated residue is critical for correct protein folding, as determined by multiple sequence alignment and X-crystallography studies
p.Cys34 is a highly conserved residue in the ligand-binding domain PubMed:9886286 			
PS3			Cells transfected with the p.C34R variant show a damaging effect on cellular localisation with some ER/Golgi retention (John et al. 2015)
The p.C34R mutant does not localise to the plasma membrane PubMed:25688877 			
PP3			REVEL score is 0.939 so meets the threshold to be classified as deleterious (REVEL >0.75)
PM2_Supporting			Variant allele is absent from gnomAD v2.1.1 and v4.1

Not Met criteria codes

PS1			Same amino acid change has not been reported previously
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Curation History



 

 

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