

Variant: *NM_001204.7(BMPR2):c.251G>A (p.Cys84Tyr)*

Version: 1.0

CA350399510 [↗](#)

812796 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 4db4a74b-0bdd-48e9-9e2a-3e8c5939e77c

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HGVS expressions

NM_001204.7:c.251G>A

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NC_000002.12:g.202467522G>A

CM000664.2:g.202467522G>A

NC_000002.11:g.203332245G>A

CM000664.1:g.203332245G>A

NC_000002.10:g.203040490G>A

NG_009363.1:g.96196G>A

ENST00000374580.10:c.251G>A

ENST00000638587.1:c.182G>A

ENST00000374574.2:c.251G>A

ENST00000374580.8:c.251G>A

ENST00000479069.1:n.158G>A

NM_001204.6:c.251G>A

Pathogenic

Met criteria codes 5

PS4_Moderate

PP3

PM5

PM2_Supporting

PM1_Strong

Not Met criteria codes 3

BA1

PP2

BP1

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

NM_001204.7 (BMPR2):c.251G>A (p.Cys84Tyr) The BMPR2 c.251G>A variant is a missense variant predicted to cause a cysteine to tyrosine substitution at amino acid 84 (p.Cys84Tyr). The variant is absent from gnomAD controls v.2.1.1 and gnomAD v4.0.0 (PM2_supporting). Four unrelated pulmonary arterial hypertension probands were identified with this variant (PMID: 31727138, PMID: 29650961 and 2 identified in the internal ClinGen Pulmonary Hypertension VCEP database) (PS4_moderate). BMPR2 p.Cys84Tyr is located within the conserved

extracellular domain and is a Cys residue critical for protein function (PMID: 16429395, PMID: 9886286) (PM1_strong). A different amino acid change at the same position (p.Cys84Phe) was classified as pathogenic (PMID: 21737554, PMID: 28507310) (PM5). Two more amino acid changes, p.Cys84Arg and p.Cys84Gly, were reported to be pathogenic (PMID: 19555857). In silico prediction (REVEL =0.951) 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: PM2_sup, PS4_mod, PM1_strong, PM5, PP3 (VCEP specification version 1.1, 1/18/2024).

Met criteria codes

PS4_Moderate			4 PAH patients (>3 and <5 to be scored moderate) n=1 Zhu et al. 2019 (Genome Med 11:69, PMID: 31727138) n=1 Gräf et al. 2018 (Nat Com 9:1416, PMID: 29650961) n=2 in ClinGen PH VCEP internal database
PP3			REVEL Score = 0.951 (>=0.75 met)
PM5			p.Cys84Phe: Liu et al. 2012 (ERJ 39:3 PubmedID: 21737554): 1x IPAH incl. functional characterization in Pousada et al. 2017 (Sci Rep 7:1 PMID: 28507310): Retention of BMPR2 in the cytoplasm p.Cys84Arg & p.Cys84Gly reported as pathogenic by Machado et al. 2009 (JACC 54:1 PMID: 19555857)
PM2_Supporting			not found in GnomAD controls (v.2.1.1)
PM1_Strong			Crucial cysteine residue located in extracellular domain and demonstrated to be critical. 1. Greenwald et al 1999. (Nat Struct Biol 6:18–22. PMID: 9886286) 2. Machado et al. 2006 (Hum Mutat. 2006 ;27(2):121-32. PMID: 16429395)

Not Met criteria codes

BA1			is not found at high frequency
PP2			NA
BP1			NA

Curation History



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