

Variant: *NM_001204.7(BMPR2):c.1040G>A (p.Cys347Tyr)*

Version: 1.0

CA278077 [↗](#)

8800 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 6561fc46-fe70-46c8-873d-74e73f68e6f1

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HGVS expressions

NM_001204.7:c.1040G>A

NM_001204.7(BMPR2):c.1040G>A (p.Cys347Tyr)

NC_000002.12:g.202530866G>A

CM000664.2:g.202530866G>A

NC_000002.11:g.203395589G>A

CM000664.1:g.203395589G>A

NC_000002.10:g.203103834G>A

NG_009363.1:g.159540G>A

ENST00000374580.10:c.1040G>A

ENST00000638587.1:c.971G>A

ENST00000374574.2:c.1040G>A

ENST00000374580.8:c.1040G>A

NM_001204.6:c.1040G>A

Likely Pathogenic

Met criteria codes 5

PM5_Supporting

PS3_Supporting

PS4

PP3

PM2_Supporting

Not Met criteria codes 6

BS1

PS1

BP4

BP1

BA1

PP2

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 NM_001204.7(BMPR2) c.1040A>C variant is a missense variant predicted to cause substitution of cysteine by tyrosine at amino acid 347 (p.Cys347Tyr). This variant is absent from gnomAD v2.1.1 and v3.1.2 controls (PM2_supporting). The computational predictor REVEL gives a score of 0.939, which is above the thresholds predicting a damaging impact on BMPR2 function (PP3). A different change affecting the same amino acid (c.1039T>C p.(Cys347Arg); PMID: 26387786) has been reported as likely pathogenic (PM5_supporting). Cytoplasmatic retention assay demonstrates impaired signaling with subcellular localization in HeLa cells showing retainment in endoplasmatic

reticulum, not significantly different to empty plasmid. However, this analysis lacks validation controls (PMID: 12045205; PS3_supporting). This variant has been reported in 5 probands meeting pulmonary arterial hypertension criteria (PS4 ; PMIDs 10973254; 26645265; 29631995; 31727138). In summary, this 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: PM2_supporting, PS4, PP3, PM5_supporting, PS3_supporting (VCEP specifications version 1.1, 1/18/2024).

Met criteria codes

PM5_Supporting			PMID: 26387786: described c.1039T>C p.(Cys347Arg) as (likely) pathogenic
PS3_Supporting			PMID: 12045205: Subcellular localization in HeLa cells: retainment in endoplasmatic reticulum & Binding to BMP4 corresponds to an empty plasmid. Cytoplasmatic retention assay. PS3 was downgraded to supporting due to a lack of validation controls.
PS4			PMID: 10973254: 1 HPAH family (n=2 but only 1 counted). No information regarding de novo PMID: 26645265: 1 proband with IPAH PMID: 29631995: 2 HPAH unrelated probands Zhu et al. 2019 (PMID: 31727138): 1 IPAH Total of 5 probands. PS4 applicable
PP3			CADD 27.9; REVEL: 0.939 REVEL score is 0.939 so it meets the threshold to be classified as deleterious (REVEL >=0.75)
PM2_Supporting			This variant is absent from gnomAD controls (v2.1.1 and v3.1.2)

Not Met criteria codes

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline



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