

Variant: *NM_001204.7(BMPR2):c.1042G>A (p.Val348Ile)*

Version: 1.0

CA2061283 [↗](#)

333642 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 82599d46-7d29-49db-b201-a5da48a2deb3

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HGVS expressions

NM_001204.7(BMPR2):c.1042G>A (p.Val348Ile)

NM_001204.7:c.1042G>A

NC_000002.12:g.202530868G>A

CM000664.2:g.202530868G>A

NC_000002.11:g.203395591G>A

CM000664.1:g.203395591G>A

NC_000002.10:g.203103836G>A

NG_009363.1:g.159542G>A

ENST00000374580.10:c.1042G>A

ENST00000638587.1:c.973G>A

ENST00000374574.2:c.1042G>A

ENST00000374580.8:c.1042G>A

NM_001204.6:c.1042G>A

Likely Benign

Met criteria codes **2**

PS3_Supporting

BS1

Not Met criteria codes **10**

PS1

PS4

BP4

BP1

PP2

PP3

PM1

PM5

BA1

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 NM_001204.7(BMPR2) c.1042G>A variant is a missense variant predicted to cause a valine to isoleucine substitution at amino acid 348 (p.Val348Ile). The highest population minor allele frequency in gnomAD v2.1.1 controls is 0.88% (62/7044) alleles in the “Other” East Asian population, which is higher than the ClinGen Pulmonary Hypertension VCEP threshold >0.1% for BS1, and therefore meets this criterion (BS1). PP3 was not met. The computational predictor REVEL gives a score of 0.744 which is below the threshold of >0.75 for pathogenicity. Densitometry analysis indicated a modest reduction in p-SMAD levels but this was not consolidated by additional experimental analysis

(PS3_supporting). In summary the 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, PS3_supporting (VCEP specification version 1.1, 1/18/2024).

Met criteria codes

PS3_Supporting			Densitometry analysis showed a modest reduction of p-SMAD expression (PMID: 36675162) but this was not confirmed by an independent assay, therefore PS3 is downgraded to supporting.
			Functional assessment by densitometry analysis demonstrates p-SMAD levels are moderately diminished in cells transfected with p.V348I, in relation to nonsyndromic oligodontia PubMed:36675162 
BS1			East Asian "Other" control population frequency: 0.88% (62/7044) --> >0.1% cut-off for BS1 for PAH

Not Met criteria codes

PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			REVEL score =0.744 --> not ≤0.75
BP1			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
PP3			REVEL score 0.744 --> not ≥0.75 as cut-off for BMPR2 variants in PAH
PM1			Variant is located in the kinase domain but the mutated residue is not a critical amino acid as determined by evolutionary conservation and structural analysis
PM5			no missense at same amino acid reported as (likely) pathogenic
BA1			No gnomAD control population frequency with at least 1000 individuals >1%
PM2			Variant present in the control population of gnomAD v2.1.1 at a frequency higher than the 0.01% cut-off for PM2 for PAH.



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