

Variant: *NM_001204.7(BMPR2):c.2618G>A (p.Arg873Gln)*

Version: 1.2

CA2061553 [↗](#)

425999 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 1b0344d0-aad2-4412-a6e0-ab7c3c719261

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HGVS expressions

NM_001204.7(BMPR2):c.2618G>A (p.Arg873Gln)

NM_001204.7:c.2618G>A

NC_000002.12:g.202556283G>A

CM000664.2:g.202556283G>A

NC_000002.11:g.203421006G>A

CM000664.1:g.203421006G>A

NC_000002.10:g.203129251G>A

NG_009363.1:g.184957G>A

ENST00000374580.10:c.2618G>A

ENST00000638587.1:c.2549G>A

ENST00000374574.2:c.1586+3395G>A

ENST00000374580.8:c.2618G>A

NM_001204.6:c.2618G>A

Benign

Met criteria codes **3**

BS1

BS4

BS3_Supporting

Not Met criteria codes **7**

PS4

BA1

PP3

PM1

PM2

BS2

BP4

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 2.0.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Pulmonary Hypertension VCEP

The c.2618G>A variant (NM_001204.7) in BMPR2 is a missense variant predicted to cause substitution of arginine by glutamine at amino acid 873 (p.Arg873Gln). The highest population minor allele frequency in gnomAD v2.2.1 controls is 0.001595 in Other East Asian, which is higher than the ClinGen Pulmonary Hypertension VCEP threshold (≥ 0.001) for BS1 but great than the threshold for BA1 ($>05\%$) (BS1 met). This variant was reported to not segregate with pulmonary arterial hypertension in one affected family member from one family (BS4; Internal PH VCEP member contribution). In vitro reporter system assay in mouse embryonic endothelial cells showed that the c.2618 G>A

variant activated BRE-Luc (specific reporter gene for Smad1/5 activation) in response to BMP4 treatment in a similar way as the wild-type BMPR2 reporter gene. However the impairment of another function through an alternative signaling pathway of BMPRII could not be excluded (PMID 25429696)(BS3_Supporting). In summary, this variant meets the criteria to be classified as benign for pulmonary arterial hypertension based on the ACMG/AMP criteria applied, as specified by the ClinGen Pulmonary Hypertension VCEP (specification version 2.0, 1/30/2026): BS4, BS1, BS3_Supporting.

Met criteria codes

BS1			The highest population minor allele frequency in gnomAD v2.2.1 is 0.001769 in Other East Asian population, which is higher than the ClinGen Pulmonary Hypertension VCEP threshold (≥ 0.001) for BS1, and therefore meets this criterion (BS1).
BS4			This variant has been reported not to segregate with pulmonary arterial hypertension in one affected family member from one family (BS4; Internal lab contributors).
BS3_Supporting			In vitro reporter system assay in mouse embryonic endothelial cells showed that the c.2618 G>A variant activate BRE-Luc (specific reporter gene for Smad1/5 activation) in response to BMP4 treatment in a similar way as the wild-type BMPR2 reporter gene. However the impairment of another function through an alternative signaling pathway of BMPRII could not be excluded (PMID 25429696)(BS3_Supporting).

Not Met criteria codes

PS4			This variant has been reported in one proband meeting pulmonary arterial hypertension (SCV000576302.1). However, PS4 cannot be applied because gnomAD v2.1.1 frequency is $> 0.01\%$ (PM2_Supporting Not Met).
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			The computational predictor REVEL gives a score] of 0.551, which is neither above nor below the thresholds predicting a damaging or benign impact on BMPR2 function.
PM1			This variant does not reside within a region of BMPR2 that is defined as a mutational hotspot or critical functional domain by the ClinGen Pulmonary Hypertension VCEP.
PM2			The highest population minor allele frequency in gnomAD v2.2.1 is 0.001769 in Other East Asian, which is higher than the ClinGen Pulmonary Hypertension VCEP threshold for PM2 (< 0.0001).
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			The computational predictor REVEL gives a score] of 0.551, which is neither above nor below the thresholds predicting a damaging or benign impact on BMPR2 function.

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