

Variant: *NM_001204.7(BMPR2):c.1258T>C (p.Cys420Arg)*

Version: 1.0

CA350341977 [↗](#)

425906 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: aba17240-a290-4993-a1d0-06b357ca31eb

Approved on: 2025/1/22

Published on: 2025/1/22

HGVS expressions

NM_001204.7:c.1258T>C

NM_001204.7(BMPR2):c.1258T>C (p.Cys420Arg)

NC_000002.12:g.202532714T>C

CM000664.2:g.202532714T>C

NC_000002.11:g.203397437T>C

CM000664.1:g.203397437T>C

NC_000002.10:g.203105682T>C

NG_009363.1:g.161388T>C

ENST00000374580.10:c.1258T>C

ENST00000638587.1:c.1189T>C

ENST00000374574.2:c.1258T>C

ENST00000374580.8:c.1258T>C

NM_001204.6:c.1258T>C

Pathogenic

Met criteria codes 5

PM1_Supporting

PS3

PS4

PP3

PM2_Supporting

Not Met criteria codes 4

BA1

BS1

BS3

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 1.1.0

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

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

Evidence submitted by expert panel

Pulmonary Hypertension VCEP

BMPR2 c.1258T>C is a missense variant predicted to cause substitution of cysteine to arginine at amino acid position 420 (p.Cys420Arg). This variant resides within the catalytic kinase domain but is not a known critical residue (PM1_moderate met). The variant is absent in gnomAD databases, meeting PM2_supporting criterion (BA1 and BS1 not met). The REVEL score of 0.934 meets PP3_supporting criteria (≥ 0.75) (BP4 not met). Functional studies indicated subcellular mislocalization of the mutant protein (PMID: 25688877) and decreased receptor-mediated signaling (PMID: 12045205) (PS3 met). At least five unrelated probands have been reported in the literature (PMID:

11115378, 21801371, 27587546, 32634488, 32966279), meeting the PS4 threshold of >4 probands. Alternative missense variants have been reported in the same location but these variants are pending expert panel curation and PM5 is not scored at this time. In summary, this 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: PS4_strong, PS3_strong, PM1_moderate, PM2_supporting, PP3 (VCEP specification version 1.1.0, 1/18/2024).

Met criteria codes

PM1_Supporting			Variant is present in the catalytic kinase domain but is not a known critical residue.
PS3			Fluorescent imaging studies indicate that the expressed protein is mislocalized to the endoplasmic reticulum and cytoplasm, based on overlapping signal with ER markers endoglin and calnexin (PMID: 25688877). Additionally, p.Cys420Arg mutant protein produces a lower response to BMP4 ligand in a luciferase reporter assay (PMID: 12045205). The assays contained both positive and negative controls.
PS4			At least five unrelated probands have been reported in the literature (PMID: 11115378, 21801371, 27587546, 32634488, 32966279), meeting the threshold of >4 probands.
PP3			The REVEL score of 0.934 meets the threshold for PP3 (>=0.75) but not BP4 (<=0.25).
PM2_Supporting			Variant is absent from gnomAD v2.1.1 controls and v4.1.0.

Not Met criteria codes

BA1			Variant is absent from gnomAD v2.1.1 controls and v4.1.0.
BS1			Variant is absent from gnomAD v2.1.1 controls and v4.1.0.
BS3			Fluorescent imaging studies indicate that the expressed protein is mislocalized to the endoplasmic reticulum and cytoplasm, based on overlapping signal with ER markers endoglin and calnexin (PMID: 25688877). Additionally, p.Cys420Arg mutant protein produces a lower response to BMP4 ligand in a luciferase reporter assay (PMID: 12045205). The assays contained both positive and negative controls.
BP4			The REVEL score of 0.934 meets the threshold for PP3 (>=0.75) but not BP4 (<=0.25).

Curation History 

Showing 1 to 1 of 1 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.