

Variant: *NM_001204.7(BMPR2):c.901T>C (p.Ser301Pro)*

Version: 1.0

CA10576586 [↗](#)

228460 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 35456c4e-ef26-4ca0-902b-0d0270033b01

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HGVS expressions

NM_001204.7(BMPR2):c.901T>C (p.Ser301Pro)

NM_001204.7:c.901T>C

NC_000002.12:g.202520135T>C

CM000664.2:g.202520135T>C

NC_000002.11:g.203384858T>C

CM000664.1:g.203384858T>C

NC_000002.10:g.203093103T>C

NG_009363.1:g.148809T>C

ENST00000374580.10:c.901T>C

ENST00000638587.1:c.832T>C

ENST00000374574.2:c.901T>C

ENST00000374580.8:c.901T>C

NM_001204.6:c.901T>C

Pathogenic

Met criteria codes **5**

PM2_Supporting PM1 PS3 PS4

PM6

Not Met criteria codes **5**

BA1 BP4 BS1 BS2 PP3

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 c.901T>C variant (NM_001204.7) in BMPR2 is a missense variant predicted to cause substitution of serine by proline at amino acid 301 (p.Ser301Pro). The variant is absent from gnomAD v2.1.1 and v3.1.2 controls (PM2_supporting). The variant has been identified in 5 probands, meeting the PH VCEP threshold for PS4 (>4 pro bands; PMIDs 16429395, 18356561, 25917481, 29743074, and PH VCEP internal lab contributors). The variant has been identified as a de novo occurrence in one individual with pulmonary arterial hypertension and unconfirmed parental relationships (PM6; PMID 29743074). Immunostaining in Hela cells transfected with a FLAG-tagged c.901C>T BMPR2

expression construct demonstrated impaired subcellular trafficking of BMPRII (PMID: 25688877) and Western-blot analysis of pulmonary artery smooth muscle cells isolated from a patient with the c.901C>T variant showed no BMP4-induced phosphorylation of Smad1/5/8 (PMID: 19324947), indicating an effect on protein function (PS3). This variant resides in a conserved kinase domain (amino acids 203 - 504) but is not defined as a critical residue by the ClinGen PH VCEP (PM1_moderate). 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 (specification version 1.0): PS4, PM6, PM2_Supporting, PS3, PM1_moderate).

Met criteria codes

PM2_Supporting			This variant is absent from gnomAD v2.1.1 and v3.1.2 (PM2_Supporting).
PM1			This variant resides within a region (Kinase domain, amino acids 203 – 504), of BMPR2. However it was only scored for PM1_moderate because the variant was not specified as critical or not critical for protein function as defined by the ClinGen Pulmonary Hypertension VCEP.
PS3			Immunostaining in Hela cells transfected with FLAG-tagged BMPR2 expression construct harboring the c.901C>T variant showed that this variant affect partially the subcellular trafficking of BMPRII (PMID: 25688877). Western-blot analysis using pulmonary artery smooth muscle cells isolated from a patient carrying the c.901C>T variant showed no BMP4-induced phosphorylation of Smad1/5/8 (PMID: 19324947). These results indicate that this variant impacts protein function (PS3).
PS4			This variant has been reported in 5 probands meeting pulmonary arterial hypertension (PS4 ; PMIDs 16429395, 18356561, 25917481, 29743074, Internal lab contributors).
PM6			This variant has been identified as a de novo occurrence with unconfirmed parental relationships in one individual with pulmonary arterial hypertension (PM6; PMID 29743074)

Not Met criteria codes

BA1			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 0.451, which is neither above nor below the thresholds predicting a damaging or benign impact on BMPR2 function.
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			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 0.451, which is neither above nor below the thresholds predicting a damaging or benign impact on BMPR2 function.



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