

Variant: *NM_001204.7(BMPR2):c.354T>G (p.Cys118Trp)*

Version: 1.0

CA278075 [↗](#)

8799 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 82e7b757-e5df-4ae4-b47e-2d132ddd21cf

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HGVS expressions

NM_001204.7:c.354T>G

NM_001204.7(BMPR2):c.354T>G (p.Cys118Trp)

NC_000002.12:g.202467625T>G

CM000664.2:g.202467625T>G

NC_000002.11:g.203332348T>G

CM000664.1:g.203332348T>G

NC_000002.10:g.203040593T>G

NG_009363.1:g.96299T>G

ENST00000374580.10:c.354T>G

ENST00000638587.1:c.285T>G

ENST00000374574.2:c.354T>G

ENST00000374580.8:c.354T>G

ENST00000479069.1:n.261T>G

NM_001204.6:c.354T>G

Pathogenic

Met criteria codes **7**

PM5_Supporting PS3 PS4

PM1_Strong PP1 PP3

PM2_Supporting

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 BMPR2 c.354T>C variant is a missense variant predicted to cause a cysteine to tryptophan substitution at amino acid position 118 (p.Cys118Trp). The variant is absent from gnomAD exomes v.2.1.1 controls and gnomAD genomes v3.0 (PM2_supporting). More than 4 unrelated pulmonary arterial hypertension probands were identified with this variant (PMID: 10973254, PMID: 32255665, PMID: 33007923, and PMID: 31727138) (PS4). In one multigenerational family, the variant segregated with PAH in at least 3 family members (PMID:

10973254) (PP1). BMPR2 p.Cys118Trp is located within the conserved extracellular domain and is a Cys residue critical for protein function (PMID: 9886286, PMID: 12221115, PMID: 12045205, PMID: 16429395) (PM1_strong). Several well-controlled in vitro functional assays provided variant-specific evidence of protein loss of function (PMID: 25688877, PMID: 12221115, and PMID: 32255665) (PS3). In silico prediction (REVEL =0.9279) is consistent with a pathogenic effect for this variant (PP3). Additionally, another variant in the same codon, BMPR2 (NM_001204.7):c.353G>A:(p.Cys118Tyr), was classified as likely pathogenic (PM5_supporting). In summary, the 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: PS3, PS4, PM1_strong, PM2_supporting, PM5_supporting, PP3, PP1 (VCEP specification version v 1.1, 1/18/2024).

Met criteria codes

PM5_Supporting			Another variant in the same codon, BMPR2 (NM_001204.7):c.353G>A:(p.Cys118Tyr), was classified as likely pathogenic (PM5_supporting).
PS3			Several well-controlled in vitro functional assays provided variant- specific evidence of protein loss of function (PMID: 25688877, PMID: 12221115, and PMID: 32255665) (PS3).
PS4			More than 4 unrelated pulmonary arterial hypertension probands were identified with this variant (PMID: 10973254, PMID: 32255665, PMID: 33007923, and PMID: 31727138) (PS4).
PM1_Strong			BMPR2 p.Cys118Trp is located within the conserved extracellular domain and is a Cys residue critical for protein function (PMID: 9886286, PMID: 12221115, PMID: 12045205, PMID: 16429395) (PM1_strong).
PP1			In one multigenerational family, the variant segregated with PAH in at least 3 family members (PMID: 10973254) (PP1).
PP3			In silico prediction (REVEL =0.9279) is consistent with a pathogenic effect for this variant (PP3).
PM2_Supporting			The variant is absent from gnomAD genomes v3.0 and gnomAD exomes v.2.1.1 (PM2_supporting)

Curation History



 

 

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