

Variant: *NM_001204.7(BMPR2):c.2656C>T (p.Arg886Cys)*

Version: 1.0

CA2061559 [↗](#)

458626 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: f559bee5-7640-4263-99c6-7feea7742bdb

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HGVS expressions

NM_001204.7:c.2656C>T

NM_001204.7(BMPR2):c.2656C>T (p.Arg886Cys)

NC_000002.12:g.202556321C>T

CM000664.2:g.202556321C>T

NC_000002.11:g.203421044C>T

CM000664.1:g.203421044C>T

NC_000002.10:g.203129289C>T

NG_009363.1:g.184995C>T

ENST00000374580.10:c.2656C>T

ENST00000638587.1:c.2587C>T

ENST00000374574.2:c.1587-3375C>T

ENST00000374580.8:c.2656C>T

NM_001204.6:c.2656C>T

Likely Benign

Met criteria codes 1

BS1

Not Met criteria codes 7

PM2

PM1

BS2

PS4

BP4

BA1

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 BMPR2 c.2656C>T variant is a missense variant predicted to cause an arginine to cysteine substitution at amino acid position 886. The highest population minor allele frequency in gnomAD v.2.1.1 controls is 0.1130% (11/9738 alleles) in the African/African American population. The population evidence available meets the threshold for BS1 ($\geq 0.1\%$), but not for BA1 ($> 5\%$) or PM2 ($< 0.01\%$) as defined by the ClinGen Pulmonary Hypertension VCEP (PH-VCEP). Computational evidence for pathogenicity as evaluated by REVEL generated a score of 0.485 indicating that neither BP4 or PP3 were met since the threshold specified by the PH-VCEP is < 0.25 and > 0.75 , respectively. The

amino acid substitution occurs in the c-terminal domain, which is not a well-established functional domain, so PM1 was not met. Criteria not evaluated included PP1, PM6, and PS2 due to the absence of segregation data. BS3 and PS3 were not evaluated due to the lack of functional data for this variant. In summary, the variant meets the criteria to be classified as likely benign (LB) for pulmonary arterial hypertension based on the ACMG/AMP criteria applied, as specified by the ClinGen Pulmonary Hypertension VCEP: BS1 (VCEP specification version 1.1, 1/18/2024).

Met criteria codes

BS1			AF of variant on gnomAD v2.1.1 is 0.1130%, which meets the threshold of $\geq 0.1\%$ defined by the pulmonary hypertension expert panel.
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Not Met criteria codes

PM2			AF of variant on gnomAD v2.1.1 is 0.1130%, which is a higher than the threshold of $< 0.01\%$ defined by the pulmonary hypertension expert panel.
PM1			Variant is predicted to cause a substitution of an Arginine residue for a Cysteine in position 886 in the BMPR2 protein. This change occurs in the C-terminal domain, which is not a well established functional domain.
BS2			No homozygotes observed on gnomAD v2.1.1
PS4			There is one submission on ClinVar but PM2 is not met. Based on the BMPR2-specific guidelines developed by the pulmonary hypertension expert panel, PM2 must be met to apply the PS4 criterion.
BP4			REVEL score is 0.485, which is higher than the < 0.25 cut-off defined by the pulmonary hypertension expert panel.
BA1			AF of variant on gnomAD v2.1.1 is 0.1130%, which is lower than the threshold of $> 5\%$ defined by the pulmonary hypertension expert panel.
PP3			REVEL score is 0.485, which is lower than the > 0.75 cut-off defined by the pulmonary hypertension expert panel.

Curation History



 

 

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