

Variant: NM_001204.7(BMPR2):c.1157A>C (p.Glu386Ala)

Version: 1.0

CA350341739 [↗](#)

425885 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 6159ab1c-d5c5-49eb-905a-68819d908261

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HGVS expressions

NM_001204.7(BMPR2):c.1157A>C (p.Glu386Ala)

NM_001204.7:c.1157A>C

NC_000002.12:g.202532613A>C

CM000664.2:g.202532613A>C

NC_000002.11:g.203397336A>C

CM000664.1:g.203397336A>C

NC_000002.10:g.203105581A>C

NG_009363.1:g.161287A>C

ENST00000374580.10:c.1157A>C

ENST00000638587.1:c.1088A>C

ENST00000374574.2:c.1157A>C

ENST00000374580.8:c.1157A>C

NM_001204.6:c.1157A>C

Likely Pathogenic

Met criteria codes 4

PM5_Supporting

PM1_Strong

PP3

PM2_Supporting

Not Met criteria codes 2

PS1

BP4

Evidence Links 1

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 NM_001204.7(BMPR2):c.1157A>C (p.Glu386Ala) variant is harboured in exon 9 of the BMPR2 gene, encoding the functionally relevant catalytic kinase domain and impacts an amino acid indispensable to kinase structure and function (PM1_strong). The variant has been reported once in an IPAH subject (PMID: 23675998). The variant is absent from gnomAD v2.1.1 (controls) and v4.1.0 (PM2_supporting). The REVEL prediction algorithm score is 0.991, AlphaMissense is 0.9832 indicating pathogenicity (PP3_met). PS2 was not assessed due to lack of paternity data. Functional studies have not been conducted for this variant (PS3 not assessed). Four additional likely pathogenic

variants (p.Glu386Gln, p.Glu386Gly, p.Glu386Lys, p.Glu386Val) have been reported at the same position (PMID: 26387786) (PM5_supporting). In summary, this variant meets the criteria to be classified as likely pathogenic for pulmonary arterial hypertension based on the ACMG/AMP criteria applied, as specified by the ClinGen Pulmonary Hypertension VCEP: PM1_strong, PM2_supporting, PP3, PM5_supporting (VCEP specification version 1.1.0, 1/18/2024).

Met criteria codes

PM5_Supporting			Four additional missense changes affecting the same residue have been reported: p.Glu386Gln, p.Glu386Gly, p.Glu386Lys, p.Glu386Val. All are classified as likely pathogenic, based on the ACMG/AMP criteria applied as specified by the ClinGen pulmonary hypertension VCEP.
PM1_Strong			The p.Glu386 residue is located in the functionally relevant catalytic kinase domain and impacts an amino acid indispensable to kinase structure and function (Agnew et al. 2021). p.Glu386 is indispensable to kinase structure and function. PubMed:34400635 
PP3			REVEL score is 0.991, which meets the threshold for pathogenicity (>0.75). AlphaMissense score is 0.983, indicating likely pathogenicity.
PM2_Supporting			Variant is absent from gnomAD v2.1.1 (controls) and v4.1.0 populations.

Not Met criteria codes

PS1			Same amino acid change has not been previously reported.
BP4			REVEL score is 0.991, which does not meet the threshold for benignity (<0.25).

Curation History



 

 

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