

Variant: *NM_001204.7(BMPR2):c.1156G>C (p.Glu386Gln)*

Version: 1.0

CA350341737 [↗](#)

425884 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: fca75eb6-75d0-4f6b-bd07-4a1884c342a7

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HGVS expressions

NM_001204.7:c.1156G>C

NM_001204.7(BMPR2):c.1156G>C (p.Glu386Gln)

NC_000002.12:g.202532612G>C

CM000664.2:g.202532612G>C

NC_000002.11:g.203397335G>C

CM000664.1:g.203397335G>C

NC_000002.10:g.203105580G>C

NG_009363.1:g.161286G>C

ENST00000374580.10:c.1156G>C

ENST00000638587.1:c.1087G>C

ENST00000374574.2:c.1156G>C

ENST00000374580.8:c.1156G>C

NM_001204.6:c.1156G>C

Likely Pathogenic

Met criteria codes **4**

PP3

PM2_Supporting

PM1_Strong

PM5_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.1156G>C variant is a missense variant predicted to cause a glutamic acid to glutamine substitution at amino acid position 386. The variant is absent from the gnomAD v2.1.1 control and v4.1.0 populations (PM2_supporting). Only one patient with the variant has been reported (PMID: 26387786), and therefore, PS4 is not met. Glu386Gln is located in the catalytic kinase domain and is known to be an indispensable residue (PM1_strong). Other likely pathogenic missense variants causing a different amino acid change at the same residue have been reported, including Glu386Lys, Glu386Ala, Glu386Val, and Glu386Gly (PM5_supporting). Computational evidence for

pathogenicity included a REVEL score of 0.961, which meets the threshold of >0.75 defined by the ClinGen Pulmonary Hypertension VCEP, and AlphaMissense 0.9837 (PP3 met but not BP4). Criteria not evaluated included PP1, PM6, and PS2 due to the absence of segregation evidence. Similarly, functional data is unavailable for this variant, so BS3 and PS3 were not evaluated. In summary, this variant meets the criteria to be classified as likely pathogenic (LP) for pulmonary arterial hypertension based on the ACMG/AMP criteria applied, as specified by the ClinGen Pulmonary Hypertension VCEP: PM1_strong, PM2_supporting, PM5_supporting, and PP3 (VCEP specification version 1.1, 1/18/2024).

Met criteria codes

PP3			REVEL score is 0.961, which meets the ClinGen Pulmonary Hypertension VCEP cut-off of >0.75.
PM2_Supporting			The variant is absent from the gnomAD v2.1.1 controls and v4.1.0 populations. This criterion is applied at the supporting level, based on the specifications of the ClinGen Pulmonary Hypertension VCEP.
PM1_Strong			The variant is predicted to change a Glutamic Acid residue for a Glutamine in position 386. This change occurs in the Kinase Domain and changes an invariant residue. Therefore, we upgrade this criterion to a strong level.
PM5_Supporting			There are 4 additional missense changes reported in ClinVar that have been classified as pathogenic, including p.Glu386Lys, p.Glu386Val, p.Glu386Gly, and p.Glu386Ala. Since it is likely that no adapted ACMG guidelines were used for the classification of these variants, we take a conservative approach and apply this criterion at the supporting level.

Curation History



 

 

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