

Variant: *NM_001204.7(BMPR2):c.1509A>C (p.Glu503Asp)*

Version: 2.1

CA16610570 [↗](#)

409828 (ClinVar) [↗](#)

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

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

Inheritance Mode: Autosomal dominant inheritance

UUID: 43fb2d44-b756-4904-9ef4-19f0070db7a5

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HGVS expressions

NM_001204.7(BMPR2):c.1509A>C (p.Glu503Asp)

NM_001204.7:c.1509A>C

NC_000002.12:g.202552811A>C

CM000664.2:g.202552811A>C

NC_000002.11:g.203417534A>C

CM000664.1:g.203417534A>C

NC_000002.10:g.203125779A>C

NG_009363.1:g.181485A>C

ENST00000374580.10:c.1509A>C

ENST00000638587.1:c.1440A>C

ENST00000374574.2:c.1509A>C

ENST00000374580.8:c.1509A>C

NM_001204.6:c.1509A>C

Uncertain Significance

Met criteria codes **1**

PM2

Not Met criteria codes **7**

PS1

BP4

PP3

PM1

PM5

BS1

BS3

Evidence Links **4**

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 2.0.0

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Pulmonary Hypertension VCEP

The NM_001204.7(BMPR2) c.1509A>C variant is a missense variant predicted to cause substitution of glutamate by aspartate at amino acid 503 (p.Glu503Asp). The maximum subpopulation allele frequency in gnomAD v4.1 is 8.474e-7 (1/1180024 alleles, non-Finnish Europeans), below the PH VCEP threshold of 0.01% (PM2 met). The variant REVEL score (0.662) meets the PH VCEP threshold of ≥ 0.644 but the AlphaMissense score (0.2603) and CADD score (17.69) are below the thresholds for pathogenicity (PP3 not met). The variant does not affect protein localization to the plasma membrane (PMID: 25688877) or cell viability (PMID: 30809644). A single luciferase assay

demonstrated comparable canonical transcriptional activity to wild-type (PMID: 18321866). However, the lack of effect on canonical signaling in one assay without replication in an independent assay, did not provide conclusive evidence for non-criticality (BS3 not met). In summary, this variant meets the criteria to be classified as a variant of uncertain significance for pulmonary arterial hypertension based on the ACMG/AMP criteria applied, as specified by the ClinGen Pulmonary Hypertension VCEP: PM2. (VCEP specifications version 2.0, 1/30/2026)

Met criteria codes

PM2	✓	The maximum subpopulation allele frequency in gnomAD v4.1 is 8.474e-7 (1/1180024 alleles, non-Finnish Europeans), below the PH VCEP threshold of 0.01%.
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Not Met criteria codes

PS1		✗	Amino acid change has not been reported previously
BP4		✗	REVEL score is 0.662 so does not meet the threshold to be classified as no impact on gene or gene product (REVEL <0.25).
PP3		✗	The variant REVEL score (0.662) meets the PH VCEP threshold of >=0.644 but the AlphaMissense score (0.2603) and CADD score (17.69) are below the thresholds for pathogenicity.
PM1		✗	Variant is located in the kinase domain but the mutated residue is not a critical amino acid as determined by evolutionary conservation and structural analysis (Hanks and Hunter, 1995; PMID: 7768349). p.E503 is a poorly conserved residue across the eukaryotic protein kinase superfamily PubMed:7768349
PM5		✗	Amino acid residue has not been previously reported as mutated
BS1		✗	Allele frequency is less than 0.1% in gnomAD v2.1.1 controls
BS3		✗	Cells transfected with the p.E503D variant have no damaging effects on cellular localization (PMID: 25688877), transcriptional activity (PMID: 18321866), or cell viability (PMID: 30809644). However, the lack of effect on canonical signaling in one assay without replication in an independent assay, does not provide conclusive evidence for non-criticality. The p.E503D mutant shows normal localisation to the plasma membrane PubMed:25688877 Cells transfected with the p.E503D variant show no detrimental effect on cell viability PubMed:30809644 Transcriptional activity of the p.E503D variant is comparable to wild-type using a luciferase assay PubMed:18321866

