## Phylogeny

BMPR2 belongs to the Tyrosine Kinase-Like (TKL) group, TGF-β/BMP type II receptor subfamily of the human kinome (Chaikuad et al., 2019). Orthologues are detected in mouse (Bmpr2), rat (Bmpr2), zebrafish (bmpr2a/b), fly (wishful-thinking) and nematode (daf-4), underscoring deep evolutionary conservation (Gómez-Puerto et al., 2019; Hiepen et al., 2019; Iwasa et al., 2023). Within vertebrates the receptor clusters with paralogous type II receptors ACVR2A and ACVR2B, which share similar extracellular and kinase architectures (Chu et al., 2022).

## Reaction Catalyzed

ATP + [type I BMP receptor]-Ser/Thr ⇌ ADP + [type I BMP receptor]-O-Ser/Thr-P (Agnew et al., 2021; Chaikuad et al., 2019).

## Cofactor Requirements

Mg²⁺ is required for catalysis; the crystal structure of the kinase domain was solved in complex with Mg-ADP (Chaikuad et al., 2019).

## Substrate Specificity

BMPR2 phosphorylates serine/threonine residues within the glycine-rich GS domain of partner type I receptors (Agnew et al., 2021). A definitive peptide consensus motif has not been assigned (Iwasa et al., 2023).

## Structure

The full-length receptor contains:  
(i) an extracellular ligand-binding domain (exons 2–3) that engages BMP9/10 and activin B (Guo et al., 2022; Chu et al., 2022);  
(ii) a single-pass transmembrane helix (exon 4) (Machado et al., 2006);  
(iii) an intracellular bilobal kinase domain (residues 189–517) solved at 2.35 Å in an active conformation with Mg-ADP (PDB 3G2F) (Chaikuad et al., 2019);  
(iv) an extended C-terminal tail (residues 518–1038) that binds LIMK1 and Tctex-1 and modulates endocytosis and SMAD signalling (Gipson et al., 2020).

Catalytic features include the Lys230(β3)–Glu243(αC) ion pair, HRD catalytic triad (~His-Arg-Asp330), DFG motif, a complete hydrophobic spine and a partially disordered activation loop containing a six-residue insertion; absence of a GS domain underlies constitutive kinase activity (Chaikuad et al., 2019). C-lobe surfaces mediate heterodimerization with ALK2 in signalling tetramers (Agnew et al., 2021). An AlphaFold model (AF-Q13873-F1) agrees with available structural data (Gómez-Puerto et al., 2019).

## Regulation

Multiple post-translational modifications modulate activity: incompletely mapped Ser/Thr phosphorylations within the kinase domain and tail (Gipson et al., 2020), PRMT1-mediated arginine methylation that delays SMAD activation (Gipson et al., 2020), Smurf1-dependent ubiquitination and SUMOylation that influence receptor stability (Gómez-Puerto et al., 2019). Full-length BMPR2 undergoes clathrin-mediated endocytosis, whereas a tail-truncated splice isoform shows enhanced SMAD signalling (Gipson et al., 2020). FKBP12 binds the GS domain of partner type I receptors and prevents their phosphorylation until ligand engagement (Agnew et al., 2021).

## Function

BMPR2 is highly expressed in vascular endothelial cells, pulmonary artery smooth-muscle cells, lung parenchyma and bone-related tissues (Gómez-Puerto et al., 2019; Guo et al., 2022; Wang et al., 2023). Ligand binding (BMP2/4/7/9/10, GDF6, activin A/B) promotes assembly of a tetrameric complex (two type II + two type I receptors); BMPR2 then phosphorylates ALK1 or ALK2 GS domains (Chu et al., 2022; Agnew et al., 2021).

Canonical output: phosphorylation of SMAD1/5/8, association with SMAD4 and transcriptional regulation (Machado et al., 2006; Newman et al., 2001).  
Non-canonical outputs: activation of p38 MAPK, ERK1/2, JNK, AKT and RHOA/RAC1, particularly in mutant contexts (Rudarakanchana et al., 2002; Johnson et al., 2012; Wang et al., 2023).

Documented interactors include SMAD1/5/8, ALK1/ALK2, FKBP12, LIMK1, Tctex-1, Endoglin, β-Arrestin2, SRC and Smurf1 (Gipson et al., 2020; Gómez-Puerto et al., 2019; Johnson et al., 2012).

## Inhibitors

None selective for BMPR2 have been reported. Available BMP-pathway inhibitors target type I receptors and do not show BMPR2 activity (Gipson et al., 2020; Gómez-Puerto et al., 2019; Iwasa et al., 2023).

## Other Comments

Heterozygous loss-of-function BMPR2 variants account for ~53–96 % of heritable and ~25 % of idiopathic pulmonary arterial hypertension (Gipson et al., 2020). Over 400 pathogenic mutations are catalogued. Core-destabilising missense variants (e.g., S301P, A313P, C347R/Y, C420R/Y, C483R, R491W) disrupt the kinase C-lobe, whereas surface substitutions (e.g., R303H, A490V, C496Y, E503D) are less severe (Chaikuad et al., 2019). Extracellular cysteine substitutions impair trafficking and trigger constitutive p38 MAPK activation (Rudarakanchana et al., 2002). The truncating tail mutation R899X elicits cytoskeletal defects via aberrant Rac1 signalling (Johnson et al., 2012). Disease penetrance is incomplete and shows female bias (Machado et al., 2006).

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