## Phylogeny

BMPR2 is classified within the Tyrosine Kinase-Like (TKL) group, TGF-β/BMP type II receptor subfamily of the human kinome (chaikuad2019structuralconsequencesof pages 5-8). Orthologs are present in Mus musculus (Bmpr2), Rattus norvegicus (Bmpr2), Danio rerio (bmpr2a/b), Drosophila melanogaster (wishful-thinking) and Caenorhabditis elegans (daf-4), demonstrating deep evolutionary conservation (gomez‐puerto2019bonemorphogeneticprotein pages 27-30, iwasa2023computationalandexperimental pages 17-18, hiepen2019bmpr2actsas pages 43-44). BMPR2 clusters with the paralogous type II receptors ACVR2A and ACVR2B, which share closely related extracellular and kinase architectures (chu2022typeiibmp pages 11-12).

## Reaction Catalyzed

ATP + [type I BMP receptor]-Ser/Thr → ADP + [type I BMP receptor]-O-Ser/Thr-P (agnew2021structuralbasisfor pages 1-2, chaikuad2019structuralconsequencesof pages 5-8).

## Cofactor Requirements

Catalytic activity requires Mg²⁺; the crystal structure of the kinase domain was solved in complex with Mg-ADP (chaikuad2019structuralconsequencesof pages 5-8).

## Substrate Specificity

BMPR2 phosphorylates serine/threonine residues within the glycine-rich GS domain of cognate type I receptors (agnew2021structuralbasisfor pages 1-2). The Johnson et al. 2023 kinome atlas did not assign a definitive consensus motif to BMPR2, indicating that detailed sequence preferences remain unresolved (iwasa2023computationalandexperimental pages 17-18).

## Structure

The receptor comprises: (i) an extracellular ligand-binding domain (exons 2–3) that recognizes BMP9/10 and activin B (guo2022crystalstructuresof pages 1-2, chu2022typeiibmp pages 11-12); (ii) a single-pass transmembrane helix (exon 4) (machado2006mutationsofthe pages 2-3); (iii) an intracellular bilobal kinase domain (residues 189–517) solved at 2.35 Å (PDB 3G2F) in an active conformation with Mg-ADP (chaikuad2019structuralconsequencesof pages 17-26); and (iv) an extended C-terminal tail (residues 518–1038) that binds LIMK1 and Tctex-1 and modulates endocytosis and SMAD signaling (gipson2020structuralperspectiveof pages 12-14). Catalytic hallmarks include the Lys230(β3)–Glu243(αC) salt bridge, an HRD catalytic triad (~His-Arg-Asp330), a DFG motif preceding a partially disordered activation loop with a six-residue insertion, and a complete hydrophobic spine; the receptor lacks a GS domain, explaining its constitutive activity (chaikuad2019structuralconsequencesof pages 5-8, chaikuad2019structuralconsequencesof pages 12-17). C-lobe surfaces mediate heterodimerization with ALK2 in the signaling tetramer (agnew2021structuralbasisfor pages 1-2). A full-length AlphaFold model (AF-Q13873-F1) is congruent with these experimental data (gomez‐puerto2019bonemorphogeneticprotein pages 27-30).

## Regulation

Ser/Thr phosphorylation events across the kinase domain and tail support downstream signaling, though exact sites remain incompletely mapped (gipson2020structuralperspectiveof pages 12-14). PRMT1-mediated arginine methylation slows SMAD activation kinetics (gipson2020structuralperspectiveof pages 12-14). Smurf1 ubiquitinates BMPR2, and SUMOylation further modulates receptor stability, although precise lysine targets and the SUMO E3 ligase are not fully defined (gomez‐puerto2019bonemorphogeneticprotein pages 27-30). Full-length BMPR2 is internalized via clathrin-mediated endocytosis, whereas a splice isoform lacking most of the tail displays enhanced SMAD output (gipson2020structuralperspectiveof pages 12-14). FKBP12 binds the GS domain of partner type I receptors, preventing their phosphorylation until ligand engagement (agnew2021structuralbasisfor pages 1-2).

## Function

BMPR2 is abundantly expressed in vascular endothelial cells, pulmonary artery smooth-muscle cells, lung parenchyma and bone-related tissues (gomez‐puerto2019bonemorphogeneticprotein pages 27-30, guo2022crystalstructuresof pages 1-2, wang2023dysregulatedsmoothmuscle pages 1-3). Upon binding BMP2, BMP4, BMP7, BMP9, BMP10, GDF6 or activin A/B, two type II and two type I receptors assemble; BMPR2 phosphorylates ALK1/ALK2 GS domains to initiate signaling (chu2022typeiibmp pages 9-10, agnew2021structuralbasisfor pages 1-2). Canonical signaling proceeds through SMAD1/5/8 phosphorylation, SMAD4 association and nuclear transcriptional regulation (newman2001mutationinthe pages 3-4, machado2006mutationsofthe pages 2-3). Non-canonical outputs include p38 MAPK, ERK1/2, JNK, AKT and RHOA/RAC1 activation, particularly in mutant settings (rudarakanchana2002functionalanalysisof pages 2-3, johnson2012cytoskeletaldefectsin pages 1-2, wang2023dysregulatedsmoothmuscle pages 1-3). Interactors encompass SMAD1/5/8, ALK1/ALK2, FKBP12, LIMK1, Tctex-1, Endoglin, β-Arrestin2, SRC and Smurf1 (gipson2020structuralperspectiveof pages 12-14, gomez‐puerto2019bonemorphogeneticprotein pages 27-30, johnson2012cytoskeletaldefectsin pages 1-2).

## Inhibitors

None reported to date; available BMP pathway inhibitors target type I receptors and lack BMPR2 selectivity (gipson2020structuralperspectiveof pages 12-14, gomez‐puerto2019bonemorphogeneticprotein pages 27-30, iwasa2023computationalandexperimental pages 17-18).

## Other Comments

Heterozygous loss-of-function variants in BMPR2 account for 53–96 % of heritable and ~25 % of idiopathic pulmonary arterial hypertension (gipson2020structuralperspectiveof pages 12-14). More than 400 pathogenic mutations are catalogued; core-destabilizing missense variants such as S301P, A313P, C347R/Y, C420R/Y, C483R and R491W compromise the C-lobe hydrophobic core, whereas surface substitutions including R303H, A490V, C496Y and E503D have milder effects (chaikuad2019structuralconsequencesof pages 17-26, chaikuad2019structuralconsequencesof pages 8-12). Extracellular cysteine substitutions (e.g., C347Y, C420R, C483R) block surface trafficking and trigger constitutive p38 MAPK activation (rudarakanchana2002functionalanalysisof pages 3-4). The truncating R899X mutation in the tail induces cytoskeletal defects via aberrant Rac1 signaling (johnson2012cytoskeletaldefectsin pages 1-2). Disease penetrance is incomplete and exhibits a female bias (machado2006mutationsofthe pages 12-12).

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