## Phylogeny

Member of the tyrosine-kinase-like (TKL) branch, TGF-β/BMP type I receptor subgroup. The kinase domain shares 82–85 % identity with ALK1/3/4/5/6/7, consistent with a recent vertebrate duplication (Rooney & Jones, 2021). Canonical orthologs are documented in Homo sapiens, Mus musculus, Gallus gallus, Xenopus laevis and Danio rerio (Katagiri, Tsukamoto, & Kuratani, 2021). A paralogous zebrafish Acvr1l retains BMP-SMAD signalling and is routinely used for functional analyses (Allen et al., 2023).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr ⇄ ADP + H⁺ + [protein]-O-Ser/Thr (Anwar & Yokota, 2023).

## Cofactor Requirements

Activity requires divalent Mg²⁺ or Mn²⁺ ions, as shown in vitro (Investigation of kinase activation in fibrodysplasia ossificans progressiva, 2014).

## Substrate Specificity

Selectively phosphorylates the C-terminal Ser-X-Ser motif of receptor-regulated SMAD1, SMAD5 and SMAD8/9; no broader consensus motif has been defined (Anwar & Yokota, 2023; Sánchez-Duffhues et al., 2020).

## Structure

Signal peptide (1–20), extracellular ligand-binding region (21–123), single transmembrane helix (124–146), GS regulatory loop (178–207) and bilobal kinase domain (208–502) form the typical architecture (Katagiri et al., 2021).  
• Autoinhibited FKBP12-bound structure resolved at 2.7 Å (PDB 3H9R); the unphosphorylated GS loop occludes the catalytic cleft and displaces the αC-helix (Valer et al., 2019).  
• Inhibitor complexes with BLU-782 analogue (PDB 6T8N) and momelotinib (PDB 7NNS) make a hinge H-bond to His286 and preserve a four-water lattice in the ATP pocket (Rooney & Jones, 2021).  
• Active-state modelling shows alignment of the HRD (His286-Arg287-Asp288) and DFG (Asp354-Phe355-Gly356) motifs and completion of the hydrophobic spine upon GS-loop phosphorylation (Agnew et al., 2021).  
• Pathogenic variants R206H (GS loop) and G328V/W/E, R258S (kinase core) cluster at the GS–kinase interface or activation segment, weakening autoinhibition (Anwar & Yokota, 2023; Pacifici & Shore, 2016).

## Regulation

Type II receptors BMPR2, ACVR2A and ACVR2B phosphorylate GS-loop residues Thr189/Ser190/Ser192/Ser194 to initiate activation (Anwar & Yokota, 2023; Allen et al., 2023). FKBP1A binds the unphosphorylated GS loop to maintain basal inactivity; the R206H mutation disrupts this interaction, enabling ligand-independent signalling (Katagiri et al., 2021). Subsequent autophosphorylation within the activation segment stabilises the active conformation and enhances SMAD binding (Agnew et al., 2021). Inhibitory SMAD6/7 recruit SMURF1/2 E3 ligases for ubiquitin-mediated down-regulation, although specific lysine targets on the receptor remain unmapped (Sánchez-Duffhues et al., 2020).

## Function

Widely expressed, with high levels in bone, cartilage, heart, neural and reproductive tissues (Valer et al., 2019). Upstream ligands BMP2, BMP4, BMP7, BMP9 and Activin A bind heterotetrameric complexes with type II receptors to trigger SMAD1/5/8 phosphorylation (Anwar & Yokota, 2023; Valer et al., 2019). The receptor can compete with activin for type II receptors, attenuating TGF-β/activin signals (Rooney & Jones, 2021). It also activates non-canonical p38 MAPK and PI3K/AKT/mTOR pathways, influencing chondrogenesis and osteogenesis (Valer et al., 2019). Complete knockout in mice is embryonic-lethal owing to failed primitive streak formation, highlighting essential developmental roles (Pacifici & Shore, 2016).

## Inhibitors

• Dorsomorphin, IC₅₀ ≈ 109 nM (Rooney & Jones, 2021)  
• LDN-193189, IC₅₀ ≈ 10 nM; suppresses heterotopic ossification in vivo (Katagiri et al., 2021)  
• LDN-212854, sub-100 nM potency, > 100-fold selectivity over ALK5 (Development of a selective inhibitor of the BMP type I receptor kinases, n.d.)  
• Saracatinib, IC₅₀ 6 nM; blocks aberrant SMAD1/5 signalling and prevents heterotopic ossification in FOP models (Williams et al., 2021)  
• Momelotinib, IC₅₀ ≈ 72 nM; CNS-penetrant for DIPG applications (Rooney & Jones, 2021)

## Other Comments

The germ-line R206H mutation (> 95 % of cases) confers neofunctional responsiveness to Activin A and causes fibrodysplasia ossificans progressiva (Anwar & Yokota, 2023; Katagiri et al., 2021). Somatic kinase-domain mutations (G328V/W/E, R258S) drive diffuse intrinsic pontine glioma (Rooney & Jones, 2021). K400E is linked to diffuse idiopathic skeletal hyperostosis, whereas H286N and L343P loss-of-function alleles underlie congenital heart defects (Katagiri et al., 2021).

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