## Phylogeny

Activin receptor type IIB (ACVR2B) is a member of the Tyrosine-Kinase-Like (TKL) group, TGF-β receptor type-II subfamily of the human kinome (Trumpp et al., 2023). Vertebrate paralogs ACVR2A and BMPR2 form a closely related cluster within the type-II branch (Hart et al., 2020). Orthologs are conserved from vertebrates (e.g., Mus musculus, Danio rerio) to invertebrates (Drosophila melanogaster, Caenorhabditis elegans), indicating deep metazoan conservation (Vishnu et al., 2019; Wodziński, 2019).

## Reaction Catalyzed

ATP + [protein] → ADP + [protein]-O-Ser/Thr-phosphate (Han et al., 2007).

## Cofactor Requirements

Requires Mg²⁺, as shown by Mg-ADP coordination in homologous type-II receptor structures (Chaikuad et al., 2019).

## Substrate Specificity

• Phosphorylates Ser/Thr residues within the GS domain of cognate type-I receptors; no independent linear consensus motif has been defined (Sako et al., 2010).  
• Intrinsic peptide specificity remains undetermined because ACVR2B was not included in recent kinome-wide substrate profiling.

## Structure

Signal peptide (1–24) → extracellular three-finger toxin–fold ligand-binding domain (27–117) → single transmembrane helix (138–160) → intracellular serine/threonine kinase domain (190–479) (Vishnu et al., 2019; Han et al., 2007).  
Crystal structure (PDB 2QLU) shows a canonical bilobal kinase fold with VAIK Lys217, HRD catalytic triad, DFG motif, gatekeeper Thr265, and a hydrophobic back pocket shaped by Phe247 (Han et al., 2007). The activation loop adopts an active-like conformation despite absence of the Lys-Glu (β3–αC) salt bridge, a feature stabilized by three conserved prolines and shorter than that of BMPR2 (Han et al., 2007; Chaikuad et al., 2019). The extracellular domain engages ligands through a conserved hydrophobic hotspot common to ACVR2A and BMPR2 (Chu et al., 2022).

## Regulation

• Kinase is constitutively active; activation-loop phosphorylation is not required (Chaikuad et al., 2019).  
• Ligand binding promotes heterotetramer formation with type-I receptors, enabling GS-domain phosphorylation (Sako et al., 2010).  
• N-linked glycosylation of the extracellular domain is dispensable for high-affinity ligand binding (Sako et al., 2010).  
• SMURF2-mediated ubiquitination targets receptor complexes for degradation, dampening signalling (Unknown Authors, 2012).  
• ACVR2B forms distinct homo-oligomers relative to ACVR2A; these stoichiometries modulate aberrant activation of the ALK2-R206H mutant implicated in fibrodysplasia ossificans progressiva (Szilágyi et al., 2024).  
• Soluble ACVR2B-Fc sequesters circulating ligands, lowering basal SMAD2 phosphorylation and altering downstream responses (Goh et al., 2017).

## Function

Expression – Highly expressed in skeletal muscle; lower levels in osteoblasts and osteocytes (Goh et al., 2017). Transcripts are present in neurogenic zones, vasculature, and developing muscle of medaka, suggesting conserved neural and muscular roles (Trumpp et al., 2023).

Ligands & partners – Binds activin A/B, myostatin (GDF-8), GDF-11, BMP-2 and BMP-7 with variable affinity (Sako et al., 2010). Recruits type-I receptors ACVR1 (ALK2), ACVR1B (ALK4) and ACVR1C (ALK7) (Valer et al., 2019). Activin/GDF engagement activates SMAD2/3, whereas BMP ligands redirect signalling to SMAD1/5/8 (Sako et al., 2010).

Physiological roles – Acts as a negative regulator of skeletal muscle mass; ACVR2B-Fc treatment enlarges multiple hind-limb muscles in mice and nearly triples trabecular bone volume, indicating indirect anabolic effects on bone (Goh et al., 2017). Contributes to activin-dependent hyperactivation of ALK2-R206H in fibrodysplasia ossificans progressiva (Valer et al., 2019).

## Inhibitors

ACVR2B-Fc (ACE-031): soluble extracellular domain–IgG1 fusion that traps myostatin/activins, improves survival and muscle mass in cachectic models, and increases bone mass (Nissinen et al., 2018; Goh et al., 2017).

## Other Comments

Distinct ACVR2B versus ACVR2A receptor stoichiometry influences ALK2-R206H signalling and may modify fibrodysplasia ossificans progressiva severity (Szilágyi et al., 2024).

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