## Phylogeny

• Member of the Tyrosine-Kinase-Like (TKL) group, TGF-β receptor type-II subfamily of the human kinome (trumpp2023characterizationoffibrodysplasia pages 21-22).  
• Paralogs ACVR2A and BMPR2 form a closely related receptor cluster within the type-II branch (hart2020mutationalanalysisof pages 2-3).  
• Orthologs are conserved from vertebrates (Mus musculus, Rattus norvegicus, Danio rerio, Xenopus spp.) to invertebrates (Drosophila melanogaster, Caenorhabditis elegans), demonstrating deep metazoan conservation (vishnu2019molecularcharacterizationand pages 5-6, wodziński2019doestheexpression pages 8-8).

## Reaction Catalyzed

ATP + [protein] → ADP + [protein]-O-Ser/Thr-phosphate (han2007crystalstructureof pages 1-2).

## Cofactor Requirements

Requires Mg²⁺, evidenced by Mg-ADP coordinated in the catalytic cleft of homologous type-II receptor structures (chaikuad2019structuralconsequencesof pages 5-8).

## Substrate Specificity

• Phosphorylates Ser/Thr residues within the GS domain of associated type-I receptors; an independent linear consensus motif has not been defined (sako2010characterizationofthe pages 1-2).  
• ACVR2B was not profiled in the recent kinome-wide substrate atlas, therefore intrinsic peptide specificity remains undetermined (Johnson atlas not available in provided context).

## Structure

Domain organisation  
– Signal peptide 1–24 (vishnu2019molecularcharacterizationand pages 5-6).  
– Extracellular ligand-binding domain 27–117 adopting a three-finger toxin fold; key ligand contacts Tyr60, Val73, Trp78, Leu79, Phe82, Val99, Phe101 (vishnu2019molecularcharacterizationand pages 7-9, chu2022typeiibmp pages 12-13).  
– Single transmembrane helix 138–160 (vishnu2019molecularcharacterizationand pages 5-6).  
– Intracellular serine/threonine kinase domain 190–479 (han2007crystalstructureof pages 1-2).

3D structural features (PDB 2QLU)  
• Canonical bilobal fold with VAIK Lys217 (ATP anchoring), HRD catalytic triad and DFG motif at the activation segment start (han2007crystalstructureof pages 1-2).  
• Gatekeeper Thr265 and supporting Phe247 generate a hydrophobic back pocket that shapes inhibitor selectivity (han2007crystalstructureof pages 1-2).  
• Absent Lys-Glu (β3–αC) salt bridge yet the unphosphorylated activation loop assumes an active-like conformation stabilized by three conserved prolines, contrasting with the longer, flexible loop of BMPR2 (han2007crystalstructureof pages 1-2, chaikuad2019structuralconsequencesof pages 5-8).  
• Extracellular domain engages growth factors through a conserved hydrophobic hotspot shared with ACVR2A and BMPR2 (chu2022typeiibmp pages 12-13).

## Regulation

• Type-II kinase is constitutively active; activation-loop phosphorylation is dispensable for activity (chaikuad2019structuralconsequencesof pages 5-8).  
• Ligand binding drives heterotetramer formation with type-I receptors, enabling phosphorylation of their GS domains (sako2010characterizationofthe pages 1-2).  
• N-linked glycosylation of the extracellular domain is not required for high-affinity ligand binding (sako2010characterizationofthe pages 1-2).  
• SMURF2-mediated ubiquitination of activin receptor complexes targets the receptors for degradation, attenuating signalling (unknownauthors2012activinreceptorsin pages 200-205).  
• ACVR2B forms distinct homo-oligomers compared with ACVR2A; these stoichiometries modulate aberrant activation of the ALK2-R206H mutant implicated in FOP (szilagyi2024theactivationof pages 26-26).  
• Soluble ACVR2B-Fc sequesters circulating ligands, lowers basal SMAD2 phosphorylation and alters downstream responses (goh2017activinreceptortype pages 16-19).

## Function

Expression  
• High expression in skeletal muscle; markedly lower levels in osteoblasts and osteocytes (goh2017activinreceptortype pages 3-5, goh2017activinreceptortype pages 16-19).  
• Transcripts detected in neurogenic zones, vasculature and developing muscle of medaka, supporting conserved roles in neural and muscular tissues (trumpp2023characterizationoffibrodysplasia pages 13-14).

Ligands and signalling partners  
• Binds activin A/B, myostatin (GDF-8), GDF-11, BMP-2 and BMP-7 with variable affinity (sako2010characterizationofthe pages 1-2).  
• Recruits type-I partners ACVR1 (ALK2), ACVR1B (ALK4) and ACVR1C (ALK7) to propagate signals (valer2019acvr1functionin pages 1-4).  
• Activin/GDF binding activates SMAD2/3; BMP ligands redirect signalling to SMAD1/5/8 (sako2010characterizationofthe pages 1-2).

Physiological roles  
• Negative regulator of skeletal muscle mass; ACVR2B-Fc treatment enlarges gastrocnemius, tibialis anterior and quadriceps muscles in mice (goh2017activinreceptortype pages 16-19).  
• Ligand trapping by ACVR2B-Fc nearly triples trabecular bone volume, indicating indirect anabolic effects on bone (goh2017activinreceptortype pages 16-19).  
• Participates in activin-dependent hyperactivation of ALK2-R206H in fibrodysplasia ossificans progressiva (valer2019acvr1functionin pages 1-4).

## Inhibitors

• ACVR2B-Fc (ACE-031): soluble extracellular domain–IgG1 fusion that sequesters myostatin/activins, improves survival and muscle mass in cachectic models and increases bone mass (nissinen2018treatingcachexiausing pages 15-16, goh2017activinreceptortype pages 16-19).

## Other Comments

• Distinct receptor stoichiometry with ACVR2A versus ACVR2B governs pathogenic ALK2-R206H signalling in FOP, positioning ACVR2B as a modifier of disease severity (szilagyi2024theactivationof pages 26-26).

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