## Phylogeny

ACVR2A belongs to the STRK group of the TGF-β receptor family within the human kinome and clusters with the type-II receptors ACVR2B and BMPR2, forming a branch distinct from TGFβR2 and AMHR2 (Manning et al., 2002; Hart et al., 2020). Orthologs are conserved across vertebrates, including Mus musculus Acvr2a, Gallus gallus ActRIIB and multiple teleost duplicates (e.g., gilthead sea-bream saAcvr2b-1/-2a/-2b; medaka olaAcvr2ab/ba/bb) that illustrate lineage-specific expansion (Funkenstein et al., 2012; Trumpp et al., 2023). Invertebrate homologues such as Drosophila punt and Caenorhabditis daf-4 retain the ancestral architecture, albeit with shorter kinase domains (Unknown Authors, 2002).

## Reaction Catalyzed

ATP + [type-I receptor]-Ser/Thr ⇌ ADP + [type-I receptor]-O-phospho-Ser/Thr (Lee et al., 2006).

## Cofactor Requirements

Mg²⁺ is required for catalysis, consistent with other STRK family kinases (Manning et al., 2002).

## Substrate Specificity

High-throughput peptide profiling did not define a consensus motif for ACVR2A (Johnson et al., 2023). Biochemical data show that the kinase phosphorylates Ser/Thr residues within the glycine-serine (GS) regulatory segment of partner type-I receptors during trans-activation (Lee et al., 2006).

## Structure

The mature receptor contains an N-terminal signal peptide (1–24), an extracellular β-sandwich ligand-binding domain (25–116), a single-pass transmembrane helix (~138–160) and a C-terminal Ser/Thr kinase domain (190–479) (Vishnu et al., 2019). Extracellular structures bound to activin A (PDB: 5NH3, 1REW) display a rigid seven-strand β-sheet core, an aromatic hydrophobic triad and an extended β2–β3 loop (61–66) that confer receptor specificity (Chu et al., 2022). The isolated kinase domain (PDB: 3Q4T) shows the canonical bilobal fold with Lys219 (VAIK), His334-Asp336 (HRD) and Asp354-Phe355-Gly356 (DFG) aligned along the hydrophobic spine; the activation loop contacts the catalytic loop and αC helix to orient substrates (Unknown Authors, 2023). Several solvent-exposed Asn residues constitute predicted N-glycosylation sites analogous to those validated in BMPR2 (Lowery et al., 2014).

## Regulation

N-linked glycosylation enhances ligand affinity and cell-surface delivery (Lowery et al., 2014). Ligand binding promotes assembly of a (ACVR2A)\_2:(type-I)\_2 complex that enables trans-phosphorylation of the type-I GS domain and subsequent SMAD activation (Goh et al., 2017). Activin A can also form a non-signalling ACVR1–ACVR2A complex that sequesters receptors from canonical pathways (Aykul et al., 2020). In cells expressing the pathogenic ALK2-R206H mutant, ACVR2A homodimerization becomes ligand-dependent and modulates aberrant SMAD1/5/8 signalling (Szilágyi et al., 2024).

## Function

Transcript analyses show highest ACVR2A expression in placenta, endometrium, vascular endothelium, skeletal muscle and differentiating osteoblasts (Yang et al., 2025).  
• Bone: ACVR2A signalling limits osteoblast differentiation and bone formation; the soluble receptor ectodomain (ACVR2A-Fc) relieves this inhibition and increases trabecular and cortical bone mass (Goh et al., 2017).  
• Placenta/trophoblasts: Together with ALK4, ACVR2A activates the SMAD1/5-SMAD4-TCF7/c-JUN axis to promote invasion and spiral-artery remodelling (Yang et al., 2025).  
• Skeletal muscle: Binding of myostatin and activins represses mTOR-dependent protein synthesis and satellite-cell proliferation (Hulmi et al., 2021).  
Downstream pathways include canonical SMAD2/3 and non-SMAD cascades (PI3K, p38 MAPK, RhoA). Partner type-I receptors are ALK4, ALK2 and ALK3, with FKBP12 acting as a constitutive repressor on their GS domains (Szilágyi et al., 2024).

## Inhibitors

High-affinity ligand traps ACVR2A-Fc and ACVR2B-Fc increase bone and muscle mass in vivo (Goh et al., 2017). Clinical-stage agents—ACE-011 (sotatercept), luspatercept and the neutralizing antibody bimagrumab—target ACVR2A or its ligands to treat osteoporosis, anaemia and cachexia (Lodberg et al., 2021).

## Other Comments

Frameshift and truncating ACVR2A mutations are common in microsatellite-unstable colorectal carcinoma and correlate with larger primary tumours (Wodzinski et al., 2019). Reduced placental ACVR2A contributes to pre-eclampsia (Yang et al., 2025). Interaction with ALK2-R206H links ACVR2A to fibrodysplasia ossificans progressiva pathogenesis (Szilágyi et al., 2024).

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