Phylogeny  
ACVR1B (ALK4) belongs to the receptor serine/threonine kinase (RSTK) group, TGF-β receptor family, activin receptor-like kinase (ALK) subgroup, clustering most closely with ALK2 (ACVR1) and ALK5 (TGFBR1) (Olsen et al., 2020). Verified vertebrate orthologs include human ACVR1B, mouse Acvr1b, chicken ALK4 and zebrafish Acvr1b-like; the β4β5-loop Tyr74 essential for Activin A binding is conserved in all examined vertebrates except zebrafish, and is absent from Drosophila sequences (Goebel et al., 2025).

Reaction Catalyzed  
ATP + [protein]-Ser/Thr → ADP + [protein]-Ser/Thr-P (Olsen et al., 2020).

Cofactor Requirements  
Mg²⁺ is required and is coordinated by the conserved AxK Lys and DLG Asp that bind ATP in the active site (Iwasa et al., 2023).

Substrate Specificity  
ALK4 shows highest activity toward receptor-regulated SMADs (SMAD2/3) that carry a C-terminal SSXS motif. Serine at the 0 position is preferred; serines at −2/−1 and +2 enhance recognition, a consensus shared by other TGF-β/Activin type I receptors (Olsen et al., 2020).

Structure  
The receptor comprises an N-terminal extracellular two-domain β-sandwich, a single-pass transmembrane helix, a GS regulatory loop and a C-terminal bilobal kinase domain (Olsen et al., 2020). Cryo-EM of the ActRIIB:Activin A:ALK4 complex (PDB 7OLY) reveals an extended β4β5-loop; Tyr74 directly contacts Activin A Asp406, rationalising ligand specificity (Goebel et al., 2025). The kinase adopts a canonical active DFG-in conformation with intact regulatory and catalytic hydrophobic spines; key motifs VAIK, HRD and DFG are aligned (Olsen et al., 2020).

Regulation  
Type II receptors ACVR2A/B trans-phosphorylate multiple Ser/Thr residues in the GS loop, relieving autoinhibition and correctly positioning the αC-helix (Olsen et al., 2020; Szilágyi et al., 2022). Subsequent autophosphorylation within the activation segment further stabilises activity (Olsen et al., 2020). Signal termination involves PPM1A-mediated dephosphorylation and SMURF2-dependent ubiquitination (Olsen et al., 2020). The extracellular domain is N-glycosylated, a modification needed for folding and plasma-membrane localisation (Szilágyi et al., 2022).

Function  
Ligand engagement: Activin A first binds ACVR2A/B, which then recruits and phosphorylates ALK4, forming an active heterotetramer (Olsen et al., 2020).  
Downstream signalling: Active ALK4 phosphorylates SMAD2/3, which complex with SMAD4 and enter the nucleus to regulate genes controlling neuronal differentiation, hair-follicle cycling, FSH synthesis, wound repair, extracellular-matrix production and immunomodulation (Olsen et al., 2020).  
Tissue expression: Highest levels are reported in ovary, pituitary and brain; functional receptor is present in human U2OS osteosarcoma cells (Olsen et al., 2020; Szilágyi et al., 2022).  
Pathway crosstalk: Competition between ALK4 and BMP-type I receptors for ACVR2A modulates choice between SMAD2/3 and SMAD1/5/9 pathways (Szilágyi et al., 2022). Extracellular antagonists such as Follistatin and Cerberus sequester Activins and dampen ALK4 activation (Olsen et al., 2020).

Inhibitors  
SB-431542 is an ATP-competitive inhibitor selective for ALK4/5/7 that blocks SMAD2/3 phosphorylation with sub-micromolar potency in cells (Olsen et al., 2020).

Other Comments  
Missense variants (e.g., K232R in the N-lobe, R338Q near the catalytic loop) alter SMAD2/3 activation and have been detected in disease settings, though detailed phenotypic correlations remain limited (Olsen et al., 2020).

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