## Phylogeny

• Tyrosine-kinase-like (TKL) branch; TGF-β/BMP type I receptor subgroup (rooney2021recentadvancesin pages 1-2)  
• Kinase domain shares 82–85 % identity with ALK1/3/4/5/6/7, indicating recent duplication within vertebrates (rooney2021recentadvancesin pages 1-2)  
• Orthologs documented in Homo sapiens, Mus musculus, Gallus gallus, Xenopus laevis, Danio rerio, all retaining canonical domain architecture (katagiri2021accumulatedknowledgeof pages 2-4)  
• Zebrafish paralog Acvr1l exhibits conserved BMP-SMAD signaling and is used for functional studies (allen2023reducedgsdomain pages 4-8)

## Reaction Catalyzed

• ATP + [protein]-Ser/Thr → ADP + [protein]-O-Ser/Thr + H⁺ (anwar2023navigatingthecomplex pages 2-3)

## Cofactor Requirements

• Requires divalent cations (Mg²⁺/Mn²⁺) for phosphotransfer activity as observed in in-vitro kinase assays (unknownauthors2014investigationofkinase pages 188-191)

## Substrate Specificity

• Phosphorylates the C-terminal Ser-X-Ser motif of receptor-regulated SMAD1, SMAD5, and SMAD8/9 (anwar2023navigatingthecomplex pages 2-3)  
• No broader consensus motif has been experimentally defined beyond SMAD tails (sanchezduffhues2020bonemorphogeneticprotein pages 4-5)

## Structure

• Domain map: signal peptide 1-20, extracellular ligand-binding 21-123, transmembrane helix 124-146, GS regulatory loop 178-207, bilobal kinase domain 208-502 (katagiri2021accumulatedknowledgeof pages 2-4)  
• Autoinhibited FKBP12-bound structure resolved at 2.7 Å (PDB 3H9R); unphosphorylated GS loop blocks catalytic cleft and displaces αC-helix (valer2019acvr1functionin pages 1-4)  
• Inhibitor complexes: BLU-782 analogue (PDB 6T8N) and Momelotinib (PDB 7NNS) display hinge H-bond to His286 and conserve a four-water network in the ATP pocket (rooney2021recentadvancesin pages 5-6)  
• Active-state model shows HRD motif (His286-Arg287-Asp288), DFG motif (Asp354-Phe355-Gly356), and intact hydrophobic spine aligning upon GS-loop phosphorylation (agnew2021structuralbasisfor pages 1-2)  
• Pathogenic mutations R206H (GS), G328V/W/E and R258S (kinase core) cluster at the GS–kinase interface or activation segment, weakening autoinhibition (anwar2023navigatingthecomplex pages 2-3, pacifici2016commonmutationsin pages 1-3)

## Regulation

• Type II receptors BMPR2, ACVR2A, ACVR2B phosphorylate GS-loop residues Thr189/Ser190/Ser192/Ser194 to initiate activation (anwar2023navigatingthecomplex pages 2-3, allen2023reducedgsdomain pages 4-8)  
• FKBP1A binds the unphosphorylated GS loop, maintaining basal inactivity; R206H disrupts this interaction, enabling ligand-independent signaling (katagiri2021accumulatedknowledgeof pages 13-13)  
• Autophosphorylation within the activation loop stabilizes the active conformation and enhances SMAD docking (agnew2021structuralbasisfor pages 1-2)  
• Inhibitory SMAD6/7 recruit SMURF1/2 E3 ligases for ubiquitin-mediated down-regulation; specific lysine sites on ACVR1 remain unmapped (sanchezduffhues2020bonemorphogeneticprotein pages 3-4)

## Function

• Broad expression with pronounced levels in bone, cartilage, heart, neural, and reproductive tissues (valer2019acvr1functionin pages 1-4)  
• Upstream ligands BMP2, BMP4, BMP7, BMP9 and Activin A bind heterotetrameric complexes with type II receptors to trigger SMAD1/5/8 phosphorylation (anwar2023navigatingthecomplex pages 2-3, valer2019acvr1functionin pages 1-4)  
• Competes with activin for type II receptors, thereby attenuating TGF-β/activin signaling (rooney2021recentadvancesin pages 1-2)  
• Activates non-canonical pathways including p38 MAPK and PI3K/AKT/mTOR, influencing chondrogenesis and osteogenesis (valer2019acvr1functionin pages 6-8)  
• Complete knockout in mice leads to embryonic lethality due to failed primitive streak formation, underscoring essential developmental roles (pacifici2016commonmutationsin pages 1-3)

## Inhibitors

• Dorsomorphin: pyrazolo[1,5-a]pyrimidine, biochemical IC₅₀ ≈ 109 nM against ALK2, first-generation probe (rooney2021recentadvancesin pages 1-2)  
• LDN-193189: improved analog, enzymatic IC₅₀ ≈ 10 nM, suppresses heterotopic ossification in vivo (katagiri2021accumulatedknowledgeof pages 10-11)  
• LDN-212854: ALK2-biased analog, sub-100 nM potency and >100-fold selectivity over ALK5 (unknownauthorsUnknownyeardevelopmentofa pages 1-6)  
• Saracatinib: ATP-competitive inhibitor, IC₅₀ 6 nM, blocks aberrant SMAD1/5 signaling and prevents heterotopic ossification in FOP mouse models (williams2021saracatinibisan pages 31-37)  
• Momelotinib: hinge-binding inhibitor, biochemical IC₅₀ ≈ 72 nM, displays CNS penetration for DIPG applications (rooney2021recentadvancesin pages 5-6, rooney2021recentadvancesin pages 6-6)

## Other Comments

• Germ-line R206H (>95 % of cases) confers neofunctional responsiveness to Activin A, causing fibrodysplasia ossificans progressiva (anwar2023navigatingthecomplex pages 2-3, katagiri2021accumulatedknowledgeof pages 13-13)  
• Somatic kinase-domain mutations G328V/W/E and R258S drive diffuse intrinsic pontine glioma (rooney2021recentadvancesin pages 1-2)  
• K400E associates with diffuse idiopathic skeletal hyperostosis, while H286N and L343P loss-of-function alleles underlie congenital heart defects (katagiri2021accumulatedknowledgeof pages 6-8)

References

1. (anwar2023navigatingthecomplex pages 2-3): Saeed Anwar and Toshifumi Yokota. Navigating the complex landscape of fibrodysplasia ossificans progressiva: from current paradigms to therapeutic frontiers. Genes, Nov 2023. URL: https://doi.org/10.3390/genes14122162, doi:10.3390/genes14122162. This article has 9 citations and is from a peer-reviewed journal.
2. (katagiri2021accumulatedknowledgeof pages 13-13): Takenobu Katagiri, Sho Tsukamoto, and Mai Kuratani. Accumulated knowledge of activin receptor-like kinase 2 (alk2)/activin a receptor, type 1 (acvr1) as a target for human disorders. Biomedicines, 9:736, Jun 2021. URL: https://doi.org/10.3390/biomedicines9070736, doi:10.3390/biomedicines9070736. This article has 18 citations and is from a peer-reviewed journal.
3. (rooney2021recentadvancesin pages 1-2): Lisa Rooney and Chris Jones. Recent advances in alk2 inhibitors. ACS Omega, 6:20729-20734, Aug 2021. URL: https://doi.org/10.1021/acsomega.1c02983, doi:10.1021/acsomega.1c02983. This article has 24 citations and is from a peer-reviewed journal.
4. (rooney2021recentadvancesin pages 5-6): Lisa Rooney and Chris Jones. Recent advances in alk2 inhibitors. ACS Omega, 6:20729-20734, Aug 2021. URL: https://doi.org/10.1021/acsomega.1c02983, doi:10.1021/acsomega.1c02983. This article has 24 citations and is from a peer-reviewed journal.
5. (valer2019acvr1functionin pages 1-4): José Antonio Valer, Cristina Sánchez-de-Diego, Carolina Pimenta-Lopes, Jose Luis Rosa, and Francesc Ventura. Acvr1 function in health and disease. Cells, 8:1366, Oct 2019. URL: https://doi.org/10.3390/cells8111366, doi:10.3390/cells8111366. This article has 87 citations and is from a peer-reviewed journal.
6. (agnew2021structuralbasisfor pages 1-2): Christopher Agnew, Pelin Ayaz, Risa Kashima, Hanna S. Loving, Prajakta Ghatpande, Jennifer E. Kung, Eric S. Underbakke, Yibing Shan, David E. Shaw, Akiko Hata, and Natalia Jura. Structural basis for alk2/bmpr2 receptor complex signaling through kinase domain oligomerization. Nature Communications, Aug 2021. URL: https://doi.org/10.1038/s41467-021-25248-5, doi:10.1038/s41467-021-25248-5. This article has 31 citations and is from a highest quality peer-reviewed journal.
7. (katagiri2021accumulatedknowledgeof pages 10-11): Takenobu Katagiri, Sho Tsukamoto, and Mai Kuratani. Accumulated knowledge of activin receptor-like kinase 2 (alk2)/activin a receptor, type 1 (acvr1) as a target for human disorders. Biomedicines, 9:736, Jun 2021. URL: https://doi.org/10.3390/biomedicines9070736, doi:10.3390/biomedicines9070736. This article has 18 citations and is from a peer-reviewed journal.
8. (katagiri2021accumulatedknowledgeof pages 2-4): Takenobu Katagiri, Sho Tsukamoto, and Mai Kuratani. Accumulated knowledge of activin receptor-like kinase 2 (alk2)/activin a receptor, type 1 (acvr1) as a target for human disorders. Biomedicines, 9:736, Jun 2021. URL: https://doi.org/10.3390/biomedicines9070736, doi:10.3390/biomedicines9070736. This article has 18 citations and is from a peer-reviewed journal.
9. (katagiri2021accumulatedknowledgeof pages 6-8): Takenobu Katagiri, Sho Tsukamoto, and Mai Kuratani. Accumulated knowledge of activin receptor-like kinase 2 (alk2)/activin a receptor, type 1 (acvr1) as a target for human disorders. Biomedicines, 9:736, Jun 2021. URL: https://doi.org/10.3390/biomedicines9070736, doi:10.3390/biomedicines9070736. This article has 18 citations and is from a peer-reviewed journal.
10. (pacifici2016commonmutationsin pages 1-3): M. Pacifici and E. Shore. Common mutations in alk2/acvr1, a multi-faceted receptor, have roles in distinct pediatric musculoskeletal and neural orphan disorders. Cytokine & growth factor reviews, 27:93-104, Feb 2016. URL: https://doi.org/10.1016/j.cytogfr.2015.12.007, doi:10.1016/j.cytogfr.2015.12.007. This article has 70 citations.
11. (sanchezduffhues2020bonemorphogeneticprotein pages 4-5): Gonzalo Sanchez-Duffhues, Eleanor Williams, Marie-Jose Goumans, Carl-Henrik Heldin, and Peter ten Dijke. Bone morphogenetic protein receptors: structure, function and targeting by selective small molecule kinase inhibitors. Bone, 138:115472, Sep 2020. URL: https://doi.org/10.1016/j.bone.2020.115472, doi:10.1016/j.bone.2020.115472. This article has 115 citations and is from a domain leading peer-reviewed journal.
12. (unknownauthors2014investigationofkinase pages 188-191): Investigation of kinase activation in fibrodysplasia ossificans progressiva
13. (williams2021saracatinibisan pages 31-37): E. Williams, Jana Bagarova, G. Kerr, Dongdong Xia, E. Place, Devaveena Dey, Yue Shen, G. Bocobo, Agustin H. Mohedas, Xiuli Huang, P. Sanderson, Arthur Lee, Wei Zheng, A. Economides, James C. Smith, P. Yu, and A. Bullock. Saracatinib is an efficacious clinical candidate for fibrodysplasia ossificans progressiva. JCI Insight, Oct 2021. URL: https://doi.org/10.1101/2020.10.29.360370, doi:10.1101/2020.10.29.360370. This article has 64 citations and is from a domain leading peer-reviewed journal.
14. (allen2023reducedgsdomain pages 4-8): Robyn S. Allen, William D. Jones, Maya Hale, Bailey N. Warder, Eileen M. Shore, and Mary C. Mullins. Reduced gs domain serine/threonine requirements of fibrodysplasia ossificans progressiva mutant type i bmp receptor acvr1 in the zebrafish. BioRxiv, Dec 2023. URL: https://doi.org/10.1101/2022.12.01.518722, doi:10.1101/2022.12.01.518722. This article has 2 citations.
15. (rooney2021recentadvancesin pages 6-6): Lisa Rooney and Chris Jones. Recent advances in alk2 inhibitors. ACS Omega, 6:20729-20734, Aug 2021. URL: https://doi.org/10.1021/acsomega.1c02983, doi:10.1021/acsomega.1c02983. This article has 24 citations and is from a peer-reviewed journal.
16. (sanchezduffhues2020bonemorphogeneticprotein pages 3-4): Gonzalo Sanchez-Duffhues, Eleanor Williams, Marie-Jose Goumans, Carl-Henrik Heldin, and Peter ten Dijke. Bone morphogenetic protein receptors: structure, function and targeting by selective small molecule kinase inhibitors. Bone, 138:115472, Sep 2020. URL: https://doi.org/10.1016/j.bone.2020.115472, doi:10.1016/j.bone.2020.115472. This article has 115 citations and is from a domain leading peer-reviewed journal.
17. (unknownauthorsUnknownyeardevelopmentofa pages 1-6): Development of a selective inhibitor of the BMP type I receptor kinases
18. (valer2019acvr1functionin pages 6-8): José Antonio Valer, Cristina Sánchez-de-Diego, Carolina Pimenta-Lopes, Jose Luis Rosa, and Francesc Ventura. Acvr1 function in health and disease. Cells, 8:1366, Oct 2019. URL: https://doi.org/10.3390/cells8111366, doi:10.3390/cells8111366. This article has 87 citations and is from a peer-reviewed journal.