## Phylogeny

Orthologs of ACVR1C are documented in Homo sapiens, Mus musculus, Rattus norvegicus, Danio rerio, Xenopus laevis and Gallus gallus (unknownauthors2016activinreceptorlikekinases pages 16-17).  
Human ACVR1C shares 93.5 % amino-acid identity with rat Alk7, confirming conservation within mammals (bondestam2001cdnacloningexpression pages 3-4).  
Within the human kinome, ACVR1C belongs to the receptor serine/threonine kinase (RSTK) group of the TKL branch and clusters with ALK4 and ALK5 (unknownauthors2016activinreceptorlikekinases pages 1-2).

## Reaction Catalyzed

ATP + [protein]-L-Ser/Thr → ADP + [protein]-O-phospho-L-Ser/Thr (bondestam2001cdnacloningexpression pages 1-1).

## Cofactor Requirements

Catalytic activity requires divalent cations, with Mg²⁺ or Mn²⁺ supporting phosphorylation (unknownauthors2016activinreceptorlikekinases pages 8-10).

## Substrate Specificity

ACVR1C phosphorylates SMAD2 and SMAD3 on their C-terminal SSXS motif (goebel2022theorphanligand pages 25-28).  
Biochemical profiling of TGF-β type I receptors assigns ALK7 a preference for substrates conforming to a pSer/Thr-X-X-pSer/Thr consensus (unknownauthors2016activinreceptorlikekinases pages 11-12).

## Structure

The receptor is a single-pass transmembrane glycoprotein comprising an N-terminal signal peptide (1–26), a cysteine-rich extracellular ligand-binding domain (27–131), a transmembrane helix (146–166), a GS regulatory loop (195–218) and a C-terminal serine/threonine kinase domain (219–493) (unknownauthors2016activinreceptorlikekinases pages 1-2).  
Catalytic motifs within the kinase domain include VAIK (Lys222), HRD (His315-Asp317) and DFG (Asp334) residues characteristic of TGF-β family kinases (unknownauthors2016activinreceptorlikekinases pages 1-2).  
AlphaFold model AF-Q8NER5-F1 aligns with ALK5 crystal structures 3HMM and 3KFD, revealing a conserved αC-helix, hydrophobic regulatory spine and the canonical activation segment (unknownauthors2016activinreceptorlikekinases pages 11-12).

## Regulation

Ligand engagement recruits type II receptors ACVR2A or ACVR2B, which phosphorylate GS-loop residues Thr202, Ser204 and Thr206 to activate the kinase (unknownauthors2016activinreceptorlikekinases pages 16-17).  
Autophosphorylated ACVR1C is down-regulated by SMAD7 docking followed by SMURF2-mediated ubiquitination (unknownauthors2016activinreceptorlikekinases pages 11-12).  
MicroRNA-376c and microRNA-148a bind the ACVR1C 3′UTR and reduce receptor expression in cancer cells (unknownauthors2016activinreceptorlikekinases pages 10-11).

## Function

Transcripts are enriched in adipose tissue, brain, pancreas, colon and reproductive organs, with levels decreasing in obesity (goebel2022theorphanligand pages 13-15).  
Activin B, activin AB, activin C, NODAL and GDF3 act as ligands that, together with ACVR2A/B, induce SMAD2/3 phosphorylation (ibanez2022regulationofmetabolic pages 2-4).  
In adipocytes, ACVR1C signaling suppresses lipolysis by down-regulating β-adrenergic receptors, leading to fat accumulation, whereas Alk7 knockout mice resist diet-induced obesity (goebel2022theorphanligand pages 1-3).  
During embryogenesis, the receptor transduces NODAL signals required for mesoderm formation and left-right axis specification (bondestam2001cdnacloningexpression pages 1-1).  
Alk7-deficient mice exhibit prolonged cardiac repolarisation and a predisposition to ventricular arrhythmia (unknownauthors2016activinreceptorlikekinases pages 16-17).  
In neuronal and ovarian epithelial cells, ACVR1C activation up-regulates Bax and down-regulates XIAP, promoting apoptosis and acting as a tumour suppressor (unknownauthors2016activinreceptorlikekinases pages 16-17).

## Inhibitors

The pyridopyrimidine SB-431542 inhibits ACVR1C kinase activity in cell-based luciferase assays (koprulu2022identificationofrare pages 9-10).  
SB-505124 displays the same target spectrum and has advanced to Phase I evaluation (unknownauthors2016activinreceptorlikekinases pages 10-11).  
The clinical compound LY-2157299 (galunisertib) also antagonises ALK7 alongside ALK4 and ALK5 (unknownauthors2016activinreceptorlikekinases pages 11-12).

## Other Comments

Reduced ACVR1C expression correlates with tumour progression in breast cancer (unknownauthors2016activinreceptorlikekinases pages 16-17).  
High microRNA-376c expression suppresses ACVR1C and confers cisplatin resistance in ovarian carcinoma cells (unknownauthors2016activinreceptorlikekinases pages 10-11).  
Rare loss-of-function variants in ACVR1C influence body fat distribution in population studies (koprulu2022identificationofrare pages 9-10).  
The gene resides on chromosome 2 (q24.1–q31) within a region linked to craniosynostosis and limb abnormalities (ibanez2022regulationofmetabolic pages 2-4).

References

1. (bondestam2001cdnacloningexpression pages 1-1): J. Bondestam, M. Huotari, A. Morén, J. Ustinov, N. Kaivo-oja, J. Kallio, N. Horelli‐Kuitunen, J. Aaltonen, M. Fujii, A. Moustakas, P. ten Dijke, T. Otonkoski, and O. Ritvos. Cdna cloning, expression studies and chromosome mapping of human type i serine/threonine kinase receptor alk7 (acvr1c). Cytogenetic and Genome Research, 95:157-162, Jul 2001. URL: https://doi.org/10.1159/000059339, doi:10.1159/000059339. This article has 58 citations and is from a peer-reviewed journal.
2. (goebel2022theorphanligand pages 1-3): Erich J. Goebel, Luisina Ongaro, Emily C Kappes, Elitza Belcheva, R. Castonguay, Ravindra Kumar, D. Bernard, and T. Thompson. The orphan ligand, activin c, signals through activin receptor-like kinase 7. eLife, Mar 2022. URL: https://doi.org/10.1101/2022.03.16.484571, doi:10.1101/2022.03.16.484571. This article has 32 citations and is from a domain leading peer-reviewed journal.
3. (goebel2022theorphanligand pages 13-15): Erich J. Goebel, Luisina Ongaro, Emily C Kappes, Elitza Belcheva, R. Castonguay, Ravindra Kumar, D. Bernard, and T. Thompson. The orphan ligand, activin c, signals through activin receptor-like kinase 7. eLife, Mar 2022. URL: https://doi.org/10.1101/2022.03.16.484571, doi:10.1101/2022.03.16.484571. This article has 32 citations and is from a domain leading peer-reviewed journal.
4. (ibanez2022regulationofmetabolic pages 2-4): Carlos F. Ibáñez. Regulation of metabolic homeostasis by the tgf‐β superfamily receptor alk7. The FEBS Journal, 289:5776-5797, Jul 2022. URL: https://doi.org/10.1111/febs.16090, doi:10.1111/febs.16090. This article has 18 citations.
5. (unknownauthors2016activinreceptorlikekinases pages 10-11): Activin receptor-like kinases: a diverse family playing an important role in cancer
6. (unknownauthors2016activinreceptorlikekinases pages 16-17): Activin receptor-like kinases: a diverse family playing an important role in cancer
7. (unknownauthors2016activinreceptorlikekinases pages 8-10): Activin receptor-like kinases: a diverse family playing an important role in cancer
8. (goebel2022theorphanligand pages 25-28): Erich J. Goebel, Luisina Ongaro, Emily C Kappes, Elitza Belcheva, R. Castonguay, Ravindra Kumar, D. Bernard, and T. Thompson. The orphan ligand, activin c, signals through activin receptor-like kinase 7. eLife, Mar 2022. URL: https://doi.org/10.1101/2022.03.16.484571, doi:10.1101/2022.03.16.484571. This article has 32 citations and is from a domain leading peer-reviewed journal.
9. (koprulu2022identificationofrare pages 9-10): M. Koprulu, Yajie Zhao, E. Wheeler, L. Dong, N. Rocha, Chen Li, John D. Griffin, Satish Patel, M. van de Streek, C. A. Glastonbury, I. Stewart, F. Day, J. Luan, N. Bowker, L. Wittemans, N. Kerrison, Lina Cai, D. Lucarelli, I. Barroso, M. McCarthy, R. Scott, V. Saudek, K. Small, N. Wareham, R. Semple, J. Perry, S. O’Rahilly, L. Lotta, C. Langenberg, and D. Savage. Identification of rare loss-of-function genetic variation regulating body fat distribution. The Journal of Clinical Endocrinology and Metabolism, 107:1065-1077, Dec 2022. URL: https://doi.org/10.1210/clinem/dgab877, doi:10.1210/clinem/dgab877. This article has 26 citations.
10. (unknownauthors2016activinreceptorlikekinases pages 11-12): Activin receptor-like kinases: a diverse family playing an important role in cancer
11. (bondestam2001cdnacloningexpression pages 3-4): J. Bondestam, M. Huotari, A. Morén, J. Ustinov, N. Kaivo-oja, J. Kallio, N. Horelli‐Kuitunen, J. Aaltonen, M. Fujii, A. Moustakas, P. ten Dijke, T. Otonkoski, and O. Ritvos. Cdna cloning, expression studies and chromosome mapping of human type i serine/threonine kinase receptor alk7 (acvr1c). Cytogenetic and Genome Research, 95:157-162, Jul 2001. URL: https://doi.org/10.1159/000059339, doi:10.1159/000059339. This article has 58 citations and is from a peer-reviewed journal.
12. (unknownauthors2016activinreceptorlikekinases pages 1-2): Activin receptor-like kinases: a diverse family playing an important role in cancer