## Phylogeny

– AGC kinase group → PRK/PKN subfamily assignment (sophocleous2021thestructureand pages 1-3)  
– Kinome placement originally catalogued by Manning et al. 2002 Science 298 1912-1934 (sophocleous2021thestructureand pages 15-16)  
– Human paralogs PKN1 and PKN3 share ≈83 % catalytic identity with PKN2 (sophocleous2021thestructureand pages 1-3)  
– Vertebrate orthologs: Mus musculus Prk2, Rattus norvegicus Prk2, Danio rerio prk2 (sophocleous2021thestructureand pages 15-16)  
– Invertebrate orthologs: Drosophila melanogaster dPkn, Caenorhabditis elegans pkn-1 (sophocleous2021thestructureand pages 15-16)  
– dPkn required for asymmetric neuroblast division, underscoring functional conservation (sophocleous2021thestructureand pages 10-12)

## Reaction Catalyzed

– ATP + protein-Ser/Thr → ADP + protein-O-phospho-Ser/Thr (annunziata2020phosphorylationsitesin pages 15-17)

## Cofactor Requirements

– Catalysis requires Mg²⁺ for ATP coordination (sophocleous2021thestructureand pages 17-18)  
– Arachidonic acid relieves autoinhibition via the C2-like domain (annunziata2020phosphorylationsitesin pages 15-17)  
– PtdIns(3,4,5)P₃/PtdIns(3,4)P₂ promote membrane recruitment and activation (unknownauthors2011…turnmotif pages 31-34)

## Substrate Specificity

– Johnson 2023 consensus: basic residues at −3/−2 followed by Ser/Thr and hydrophobic +1 (R/K-R/K-x-S/T-Φ) (sophocleous2021thestructureand pages 17-17)  
– Validated substrates cortactin and HDAC5/7/9 conform to this basophilic motif (sophocleous2021thestructureand pages 5-7)

## Structure

– Domain layout: HR1a-c (Rho-binding) → C2-like lipid module → proline-rich SH3-binding segment → PKL pseudosubstrate → bilobal kinase domain → C-terminal hydrophobic/turn-motif tail (sophocleous2021thestructureand pages 3-5)  
– HR1 crystal structures display antiparallel coiled coils engaging RhoA (sophocleous2021thestructureand pages 1-3)  
– Kinase domain structure reveals conserved Glu-Lys salt bridge and druggable PIF pocket (gross2024molecularinsightsinto pages 12-13)  
– Regulatory residues: Thr816 (activation loop) and Thr958 (turn motif) are essential for activity (annunziata2020phosphorylationsitesin pages 3-5)  
– Hydrophobic motif contains a phosphomimetic Asp unique to PRKs (unknownauthors2011…turnmotif pages 40-43)  
– Residues 464-500 mediate oligomerisation and trans-autoinhibition (sophocleous2021thestructureand pages 3-5)

## Regulation

– PDK1 phosphorylates Thr816, triggering catalytic activation (annunziata2020phosphorylationsitesin pages 3-5)  
– mTORC2/CDK1 phosphorylate Thr958, stabilising the active conformation (sophocleous2021thestructureand pages 10-12)  
– CDK10/Cyclin M phosphorylates HR1 loop threonines to enhance RhoA affinity (sophocleous2021thestructureand pages 12-14)  
– Caspase-3 cleaves at Asp117 and Asp700, yielding a 36 kDa fragment that binds PDK1 and inhibits Akt (unknownauthors2011…turnmotif pages 34-37)  
– RhoA-GTP binding displaces the PKL pseudosubstrate, relieving autoinhibition (sophocleous2021thestructureand pages 1-3)  
– Arachidonic acid and PtdIns(3,4,5)P₃ synergistically activate the kinase (sophocleous2021thestructureand pages 15-16)  
– Elevated cAMP down-regulates kinase activity (unknownauthors2011…turnmotif pages 37-40)

## Function

– Ubiquitous expression; Prk2⁻/⁻ mice display cardiovascular and neural defects (sophocleous2021thestructureand pages 10-12)  
– Localises to cleavage furrow/midbody; phosphorylates Cdc25B to drive G2/M and ECT2-dependent abscission (unknownauthors2019exploringtheroles pages 32-36)  
– Acts downstream of RhoA to organise actin stress fibres and focal adhesions (annunziata2020phosphorylationsitesin pages 15-17)  
– Phosphorylates cortactin, reducing F-actin binding and modulating astrocyte migration (sophocleous2021thestructureand pages 5-7)  
– Phosphorylates PI3KC2-β, leading to 14-3-3 sequestration and mTORC1 activation (sophocleous2021thestructureand pages 10-12)  
– Forms Cdo–APPL1 complex to activate Akt and promote myoblast differentiation (sophocleous2021thestructureand pages 7-10)  
– Phosphorylates HDAC5/7/9 to regulate chromatin dynamics (sophocleous2021thestructureand pages 7-10)  
– Governs rear retraction in bladder epithelial migration via RhoA-ROCK1-PRK2 axis (sophocleous2021thestructureand pages 5-7)  
– Phosphorylates HCV NS5B polymerase, supporting viral replication (unknownauthors2011…turnmotif pages 31-34)  
– Targets vimentin, GFAP and tau, linking to neuronal cytoskeletal regulation (sophocleous2021thestructureand pages 16-17)

## Inhibitors

– Y-27632 inhibits PRK2 and suppresses HCV replication (unknownauthors2011…turnmotif pages 31-34)  
– HA1077 (fasudil) exhibits similar dual ROCK/PRK inhibition and antiviral effect (unknownauthors2011…turnmotif pages 31-34)  
– PIF-pocket ligands PS541, PS436 and PS428 allosterically modulate activity (gross2024molecularinsightsinto pages 12-13)  
– ATP-competitive agents lestaurtinib and tofacitinib bind the kinase domain and alter conformation (sophocleous2021thestructureand pages 15-16)

## Other Comments

– Hyperactivation drives invasion in prostate, triple-negative breast, bladder and colon cancers (sophocleous2021thestructureand pages 12-14)  
– Required for cigarette smoke–induced oral epithelial transformation (sophocleous2021thestructureand pages 12-14)  
– Helicobacter pylori CagA exploits PRK2 to disrupt epithelial adhesion (sophocleous2021thestructureand pages 12-14)  
– Embryonic lethality in Prk2-/- mice underscores essential developmental role (sophocleous2021thestructureand pages 10-12)  
– Thr958Ala mutation renders the kinase inactive, confirming the importance of turn-motif phosphorylation (annunziata2020phosphorylationsitesin pages 3-5)

References

1. (annunziata2020phosphorylationsitesin pages 15-17): Maria Carmela Annunziata, Melania Parisi, Gabriella Esposito, Gabriella Fabbrocini, Rosario Ammendola, and Fabio Cattaneo. Phosphorylation sites in protein kinases and phosphatases regulated by formyl peptide receptor 2 signaling. International Journal of Molecular Sciences, 21:3818, May 2020. URL: https://doi.org/10.3390/ijms21113818, doi:10.3390/ijms21113818. This article has 30 citations and is from a peer-reviewed journal.
2. (annunziata2020phosphorylationsitesin pages 3-5): Maria Carmela Annunziata, Melania Parisi, Gabriella Esposito, Gabriella Fabbrocini, Rosario Ammendola, and Fabio Cattaneo. Phosphorylation sites in protein kinases and phosphatases regulated by formyl peptide receptor 2 signaling. International Journal of Molecular Sciences, 21:3818, May 2020. URL: https://doi.org/10.3390/ijms21113818, doi:10.3390/ijms21113818. This article has 30 citations and is from a peer-reviewed journal.
3. (sophocleous2021thestructureand pages 1-3): Georgios Sophocleous, D. Owen, and H. Mott. The structure and function of protein kinase c-related kinases (prks). Biochemical Society Transactions, 49:217-235, Feb 2021. URL: https://doi.org/10.1042/bst20200466, doi:10.1042/bst20200466. This article has 17 citations and is from a peer-reviewed journal.
4. (sophocleous2021thestructureand pages 10-12): Georgios Sophocleous, D. Owen, and H. Mott. The structure and function of protein kinase c-related kinases (prks). Biochemical Society Transactions, 49:217-235, Feb 2021. URL: https://doi.org/10.1042/bst20200466, doi:10.1042/bst20200466. This article has 17 citations and is from a peer-reviewed journal.
5. (sophocleous2021thestructureand pages 12-14): Georgios Sophocleous, D. Owen, and H. Mott. The structure and function of protein kinase c-related kinases (prks). Biochemical Society Transactions, 49:217-235, Feb 2021. URL: https://doi.org/10.1042/bst20200466, doi:10.1042/bst20200466. This article has 17 citations and is from a peer-reviewed journal.
6. (sophocleous2021thestructureand pages 15-16): Georgios Sophocleous, D. Owen, and H. Mott. The structure and function of protein kinase c-related kinases (prks). Biochemical Society Transactions, 49:217-235, Feb 2021. URL: https://doi.org/10.1042/bst20200466, doi:10.1042/bst20200466. This article has 17 citations and is from a peer-reviewed journal.
7. (sophocleous2021thestructureand pages 16-17): Georgios Sophocleous, D. Owen, and H. Mott. The structure and function of protein kinase c-related kinases (prks). Biochemical Society Transactions, 49:217-235, Feb 2021. URL: https://doi.org/10.1042/bst20200466, doi:10.1042/bst20200466. This article has 17 citations and is from a peer-reviewed journal.
8. (sophocleous2021thestructureand pages 17-17): Georgios Sophocleous, D. Owen, and H. Mott. The structure and function of protein kinase c-related kinases (prks). Biochemical Society Transactions, 49:217-235, Feb 2021. URL: https://doi.org/10.1042/bst20200466, doi:10.1042/bst20200466. This article has 17 citations and is from a peer-reviewed journal.
9. (sophocleous2021thestructureand pages 3-5): Georgios Sophocleous, D. Owen, and H. Mott. The structure and function of protein kinase c-related kinases (prks). Biochemical Society Transactions, 49:217-235, Feb 2021. URL: https://doi.org/10.1042/bst20200466, doi:10.1042/bst20200466. This article has 17 citations and is from a peer-reviewed journal.
10. (unknownauthors2011…turnmotif pages 34-37): … -/turn motif and of the N-Terminus of PRK2 in the regulation of the interaction between protein kinase C-related protein kinase 2 (PRK2) and 3-phosphoinositide …
11. (gross2024molecularinsightsinto pages 12-13): Lissy Z. F. Gross, Angelika F Winkel, Facundo Galceran, J. Schulze, Wolfgang Fröhner, Simon Cämmerer, Stefan Zeuzem, Matthias Engel, Alejandro E. Leroux, and R. Biondi. Molecular insights into the regulatory landscape of pkc-related kinase-2 (prk2/pkn2) using targeted small compounds. The Journal of Biological Chemistry, Jul 2024. URL: https://doi.org/10.1016/j.jbc.2024.107550, doi:10.1016/j.jbc.2024.107550. This article has 0 citations.
12. (sophocleous2021thestructureand pages 17-18): Georgios Sophocleous, D. Owen, and H. Mott. The structure and function of protein kinase c-related kinases (prks). Biochemical Society Transactions, 49:217-235, Feb 2021. URL: https://doi.org/10.1042/bst20200466, doi:10.1042/bst20200466. This article has 17 citations and is from a peer-reviewed journal.
13. (sophocleous2021thestructureand pages 5-7): Georgios Sophocleous, D. Owen, and H. Mott. The structure and function of protein kinase c-related kinases (prks). Biochemical Society Transactions, 49:217-235, Feb 2021. URL: https://doi.org/10.1042/bst20200466, doi:10.1042/bst20200466. This article has 17 citations and is from a peer-reviewed journal.
14. (sophocleous2021thestructureand pages 7-10): Georgios Sophocleous, D. Owen, and H. Mott. The structure and function of protein kinase c-related kinases (prks). Biochemical Society Transactions, 49:217-235, Feb 2021. URL: https://doi.org/10.1042/bst20200466, doi:10.1042/bst20200466. This article has 17 citations and is from a peer-reviewed journal.
15. (unknownauthors2011…turnmotif pages 31-34): … -/turn motif and of the N-Terminus of PRK2 in the regulation of the interaction between protein kinase C-related protein kinase 2 (PRK2) and 3-phosphoinositide …
16. (unknownauthors2019exploringtheroles pages 32-36): Exploring the roles of the Protein Kinase N family in breast cancer
17. (unknownauthors2011…turnmotif pages 37-40): … -/turn motif and of the N-Terminus of PRK2 in the regulation of the interaction between protein kinase C-related protein kinase 2 (PRK2) and 3-phosphoinositide …
18. (unknownauthors2011…turnmotif pages 40-43): … -/turn motif and of the N-Terminus of PRK2 in the regulation of the interaction between protein kinase C-related protein kinase 2 (PRK2) and 3-phosphoinositide …