1. Phylogeny  
   Putative serine/threonine‐protein kinase PRKY is encoded on the human Y chromosome and is classified as a member of the cAMP‐dependent protein kinase catalytic subunit family within the larger AGC kinase group. Nearly all kinases are conserved between human and mouse; however, PRKY is one of the few that appears to be uniquely detected in human because the mouse Y chromosome has not been fully sequenced, which has prevented the identification of a clear mouse ortholog (caenepeel2004themousekinome pages 2-3). PRKY’s closest identified paralog is PRKX, with sequence similarity of approximately 92–94%, and it is believed that both genes arose as a result of a sex chromosome–specific gene duplication event, thereby establishing a lineage-specific branch within the PKA family (huang2016prkxanovel pages 1-2, thiriet2013cytoplasmicproteinserinethreonine pages 27-30, søberg2013evolutionarypathsof pages 1-2). Phylogenetic analyses that mapped the complement of eukaryotic protein kinases place PRKY in the cAMP-dependent kinome; in contrast to the canonical PKA catalytic subunits (PRKACA and PRKACB), PRKY is evolutionarily more remote yet retains the core catalytic machinery, a finding that is supported by high-throughput kinome classification methods such as KinOrtho (caenepeel2004themousekinome pages 2-3, huang2021kinorthoamethod pages 7-9).
2. Reaction Catalyzed  
   The chemical reaction catalyzed by PRKY follows the canonical kinase mechanism in which the enzyme binds ATP and a protein substrate and transfers the γ-phosphate group from ATP to an L-serine or L-threonine residue on the substrate. In doing so, the reaction converts ATP into ADP and yields a phosphorylated protein along with the release of a proton, as represented by the equation: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (zimmermann1999prkxisa pages 3-4, skroblin2010mechanismsofprotein pages 4-6).
3. Cofactor Requirements  
   The catalytic activity of PRKY, much like other serine/threonine kinases belonging to the AGC group, is dependent on the presence of divalent metal ions. In particular, Mg²⁺ ions are required as cofactors to facilitate ATP binding and stabilize the transition state during phosphoryl transfer. This metal ion dependency is a characteristic feature of protein kinases and is observed in both the classical PKA catalytic subunits as well as in PRKY by homology (zimmermann1999prkxisa pages 5-6, caenepeel2004themousekinome pages 2-3).
4. Substrate Specificity  
   PRKY, as a member of the cAMP-dependent protein kinase family, is expected to phosphorylate serine and threonine residues that reside in substrate motifs enriched in basic amino acids. In kinases of the PKA subfamily, a consensus sequence of the form R-R-X-(S/T) is frequently observed, where two consecutive arginines precede the phosphorylatable serine or threonine residue. Although direct experimental data on the substrate specificity of PRKY is limited, its high sequence similarity to PRKX and other PKA catalytic subunits supports the inference that it recognizes a similar substrate motif (skroblin2010mechanismsofprotein pages 4-6, pearce2010thenutsand pages 1-2).
5. Structure  
   PRKY displays the typical architecture of AGC kinases, with a centrally located catalytic domain composed of an N-terminal lobe that is predominantly β‐sheet in structure and a C-terminal lobe rich in α‐helices. Within this catalytic core, there are conserved features such as the glycine-rich loop involved in ATP binding, the catalytic loop, and the activation segment that houses the key phosphorylation site. Notably, sequence analysis reveals that PRKY contains an activation segment motif “TLCGT” with a putative phosphorylation site corresponding to threonine (often denoted as T203 in analogous sequences), which is critical for catalytic activation (pearce2010thenutsand pages 1-2). Unlike many other AGC kinases, however, PRKY appears to lack a well-defined turn motif or hydrophobic motif phosphorylation site, indicating that its regulatory features may be divergent; furthermore, the Y-linked PRKY is reported to be truncated by approximately 81 amino acids at its C-terminus relative to its X-linked paralog PRKX, a difference that may influence both its subcellular localization and regulatory interactions (huang2016prkxanovel pages 7-8, caenepeel2004themousekinome pages 2-3).
6. Regulation  
   Regulation of PRKY is anticipated to follow mechanisms similar to those governing other cAMP-dependent protein kinases. In the inactive state, the catalytic subunits are bound by regulatory subunits, typically of the RI type, which inhibit kinase activity until cAMP binding induces a conformational change and dissociation of the holoenzyme complex. Based on its high sequence similarity to PRKX, PRKY is presumed to be inhibited by interaction with regulatory subunits, with activation ensuing via an increase in intracellular cAMP concentration (zimmermann1999prkxisa pages 1-1, huang2016prkxanovel pages 7-8). In addition, phosphorylation within the activation loop of the catalytic domain is a common mode of regulation in the PKA family, although the specific phosphorylation sites on PRKY have not been extensively characterized; moreover, redox regulation – via oxidative modifications of conserved cysteine residues – is an established regulatory mechanism in related PKA catalytic subunits and may similarly impact PRKY’s activity (cuello2021regulationofcardiac pages 17-18, li2002prkxaphylogenetically pages 3-4).
7. Function  
   The biological function of PRKY is not yet fully elucidated; however, as a member of the cAMP-dependent protein kinase family its role is expected to include the phosphorylation of target proteins involved in a variety of cellular signaling pathways. Expression of PRKY from the male-specific region of the Y chromosome signifies its lineage-specific role and suggests involvement in sex-specific developmental processes. PRKY has been implicated in disorders of sex development, such as cases of XY sex reversal, and its unique chromosomal location links it to abnormalities arising from chromosomal rearrangements (caenepeel2004themousekinome pages 2-3, jangravi2013afreshlook pages 1-2). In addition, by virtue of its similarity to PRKX, PRKY may participate in innate immune signaling cascades and other cellular processes that are regulated by cAMP-dependent phosphorylation events, including aspects of cell growth, differentiation, and metabolism (ouyang2014transforminggrowthfactor pages 7-8, thiriet2013cytoplasmicproteinserinethreonine pages 27-30).
8. Other Comments  
   Inhibitors developed for the cAMP-dependent protein kinase family, such as protein kinase inhibitor peptide (PKI) and agents that mimic the inhibitory function of regulatory subunits, are known to modulate the activity of related kinases and are expected to similarly affect PRKY (zimmermann1999prkxisa pages 8-9, skroblin2010mechanismsofprotein pages 4-6). Moreover, PRKY has been highlighted in several musings on its potential involvement in sex chromosome–linked developmental disorders, given its occurrence as an X-degenerate gene in the male-specific region of the Y chromosome (caenepeel2004themousekinome pages 2-3, jangravi2013afreshlook pages 1-2). Kinome profiling studies have also classified PRKY as an orphan kinase, which reflects its limited detection across species outside of humans and underscores the need for further experimental characterization of its biochemical properties and cellular roles (glebovmccloud2024proteinkinasea pages 8-9, huang2021kinorthoamethod pages 7-9).
9. References
10. Caenepeel, S., Charydczak, G., Sudarsanam, S., Hunter, T., & Manning, G. “The mouse kinome: discovery and comparative genomics of all mouse protein kinases.” Proceedings of the National Academy of Sciences of the United States of America, pages 2-3.
11. Huang, S., Li, Q., Alberts, I., & Li, X. “Prkx, a novel camp‐dependent protein kinase member, plays an important role in development.” Journal of Cellular Biochemistry, pages 1-2; pages 2-4; pages 7-7; pages 7-8.
12. Li, X., Li, H.-P., Amsler, K., Hyink, D., Wilson, P. D., & Burrow, C. R. “Prkx, a phylogenetically and functionally distinct camp‐dependent protein kinase.” Proceedings of the National Academy of Sciences, pages 3-4; pages 4-5.
13. Ouyang, C., Nie, L., Gu, M., Wu, A., Han, X., Wang, X., Shao, J., & Xia, Z. “Transforming growth factor (tgf)-β-activated kinase 1 (tak1) activation requires phosphorylation of serine 412 by protein kinase a catalytic subunit α (pkacα) and x-linked protein kinase (prkx).” Journal of Biological Chemistry, pages 7-8; pages 8-11; pages 11-12.
14. Thiriet, M. “Cytoplasmic protein serine/threonine kinases.” In Biomathematical and Biomechanical Modeling of the Circulatory and Ventilatory Systems, pages 27-30.
15. Zimmermann, B., Chiorini, J. A., Ma, Y., Kotin, R. M., & Herberg, F. W. “Prkx is a novel catalytic subunit of the camp-dependent protein kinase regulated by the regulatory subunit type i\*.” The Journal of Biological Chemistry, pages 1-1; pages 3-4; pages 5-6; pages 8-9; pages 9-9.
16. Cuello, F., Herberg, F., Stathopoulou, K., Henning, P., & Diering, S. “Regulation of cardiac pka signaling by camp and oxidants.” Antioxidants, pages 17-18; pages 18-20; pages 20-21; pages 8-9.
17. Glebov-McCloud, A. G. P., Saide, W. S., Gaine, M. E., & Strack, S. “Protein kinase a in neurological disorders.” Journal of Neurodevelopmental Disorders, pages 8-9; pages 10-10.
18. Huang, L.-C., Taujale, R., Gravel, N., Venkat, A., Yeung, W., Byrne, D. P., Eyers, P. A., & Kannan, N. “Kinortho: a method for mapping human kinase orthologs across the tree of life and illuminating understudied kinases.” BMC Bioinformatics, pages 15-17; pages 7-9; pages 1-2.
19. Jangravi, Z., Alikhani, M., Arefnezhad, B., Sharifi Tabar, M., Taleahmad, S., Karamzadeh, R., Jadaliha, M., Mousavi, S. A., Ahmadi Rastegar, D., Parsamatin, P., Vakilian, H., Mirshahvaladi, S., Sabbaghian, M., Mohseni Meybodi, A., Mirzaei, M., Shahhoseini, M., Ebrahimi, M., Piryaei, A., Moosavi-Movahedi, A. A., Nasr-Esfahani, M. H., Baharvand, H., Sedighi Gilani, M. A., Gourabi, H., & Hosseini Salekdeh, G. “A fresh look at the male-specific region of the human y chromosome.” Journal of Proteome Research, pages 1-2.
20. Liu, Y., Chen, J., Fontes, S. K., Bautista, E. N., & Cheng, Z. “Physiological and pathological roles of protein kinase a in the heart.” Cardiovascular Research, pages 9-9.
21. Pearce, L. R., Komander, D., & Alessi, D. R. “The nuts and bolts of agc protein kinases.” Nature Reviews Molecular Cell Biology, pages 1-2.
22. Søberg, K., Jahnsen, T., Rognes, T., Skålhegg, B. S., & Laerdahl, J. K. “Evolutionary paths of the camp-dependent protein kinase (pka) catalytic subunits.” PLoS ONE, pages 1-2; pages 2-2.

References

1. (caenepeel2004themousekinome pages 2-3): Sean Caenepeel, Glen Charydczak, Sucha Sudarsanam, Tony Hunter, and Gerard Manning. The mouse kinome: discovery and comparative genomics of all mouse protein kinases. Proceedings of the National Academy of Sciences of the United States of America, 101 32:11707-12, Aug 2004. URL: https://doi.org/10.1073/pnas.0306880101, doi:10.1073/pnas.0306880101. This article has 379 citations and is from a highest quality peer-reviewed journal.
2. (huang2016prkxanovel pages 1-2): Sizhou Huang, Qian Li, Ian Alberts, and Xiaohong Li. Prkx, a novel camp‐dependent protein kinase member, plays an important role in development. Journal of Cellular Biochemistry, Mar 2016. URL: https://doi.org/10.1002/jcb.25304, doi:10.1002/jcb.25304. This article has 27 citations and is from a peer-reviewed journal.
3. (li2002prkxaphylogenetically pages 3-4): Xiaohong Li, Hsi-Ping Li, Kurt Amsler, Deborah Hyink, Patricia D. Wilson, and Christopher R. Burrow. Prkx, a phylogenetically and functionally distinct camp-dependent protein kinase, activates renal epithelial cell migration and morphogenesis. Proceedings of the National Academy of Sciences, 99:9260-9265, Jun 2002. URL: https://doi.org/10.1073/pnas.132051799, doi:10.1073/pnas.132051799. This article has 73 citations.
4. (ouyang2014transforminggrowthfactor pages 7-8): Chuan Ouyang, Li Nie, Meidi Gu, Ailing Wu, Xu Han, Xiaojian Wang, Jianzhong Shao, and Zongping Xia. Transforming growth factor (tgf)-β-activated kinase 1 (tak1) activation requires phosphorylation of serine 412 by protein kinase a catalytic subunit α (pkacα) and x-linked protein kinase (prkx). Journal of Biological Chemistry, 289:24226-24237, Aug 2014. URL: https://doi.org/10.1074/jbc.m114.559963, doi:10.1074/jbc.m114.559963. This article has 61 citations and is from a domain leading peer-reviewed journal.
5. (thiriet2013cytoplasmicproteinserinethreonine pages 27-30): M Thiriet M Thiriet. Cytoplasmic protein serine/threonine kinases. Biomathematical and Biomechanical Modeling of the Circulatory and Ventilatory Systems, pages 175-310, Jul 2013. URL: https://doi.org/10.1007/978-1-4614-4370-4\_5, doi:10.1007/978-1-4614-4370-4\_5. This article has 11 citations.
6. (zimmermann1999prkxisa pages 1-1): Bastian Zimmermann, John A. Chiorini, Yuliang Ma, Robert M. Kotin, and Friedrich W. Herberg. Prkx is a novel catalytic subunit of the camp-dependent protein kinase regulated by the regulatory subunit type i\*. The Journal of Biological Chemistry, 274:5370-5378, Feb 1999. URL: https://doi.org/10.1074/jbc.274.9.5370, doi:10.1074/jbc.274.9.5370. This article has 136 citations.
7. (zimmermann1999prkxisa pages 3-4): Bastian Zimmermann, John A. Chiorini, Yuliang Ma, Robert M. Kotin, and Friedrich W. Herberg. Prkx is a novel catalytic subunit of the camp-dependent protein kinase regulated by the regulatory subunit type i\*. The Journal of Biological Chemistry, 274:5370-5378, Feb 1999. URL: https://doi.org/10.1074/jbc.274.9.5370, doi:10.1074/jbc.274.9.5370. This article has 136 citations.
8. (zimmermann1999prkxisa pages 5-6): Bastian Zimmermann, John A. Chiorini, Yuliang Ma, Robert M. Kotin, and Friedrich W. Herberg. Prkx is a novel catalytic subunit of the camp-dependent protein kinase regulated by the regulatory subunit type i\*. The Journal of Biological Chemistry, 274:5370-5378, Feb 1999. URL: https://doi.org/10.1074/jbc.274.9.5370, doi:10.1074/jbc.274.9.5370. This article has 136 citations.
9. (zimmermann1999prkxisa pages 8-9): Bastian Zimmermann, John A. Chiorini, Yuliang Ma, Robert M. Kotin, and Friedrich W. Herberg. Prkx is a novel catalytic subunit of the camp-dependent protein kinase regulated by the regulatory subunit type i\*. The Journal of Biological Chemistry, 274:5370-5378, Feb 1999. URL: https://doi.org/10.1074/jbc.274.9.5370, doi:10.1074/jbc.274.9.5370. This article has 136 citations.
10. (cuello2021regulationofcardiac pages 17-18): Friederike Cuello, F. Herberg, K. Stathopoulou, Philipp Henning, and Simon Diering. Regulation of cardiac pka signaling by camp and oxidants. Antioxidants, Apr 2021. URL: https://doi.org/10.3390/antiox10050663, doi:10.3390/antiox10050663. This article has 10 citations and is from a peer-reviewed journal.
11. (glebovmccloud2024proteinkinasea pages 8-9): Alexander G. P. Glebov-McCloud, Walter S. Saide, Marie E. Gaine, and Stefan Strack. Protein kinase a in neurological disorders. Journal of Neurodevelopmental Disorders, Mar 2024. URL: https://doi.org/10.1186/s11689-024-09525-0, doi:10.1186/s11689-024-09525-0. This article has 12 citations and is from a peer-reviewed journal.
12. (huang2016prkxanovel pages 7-8): Sizhou Huang, Qian Li, Ian Alberts, and Xiaohong Li. Prkx, a novel camp‐dependent protein kinase member, plays an important role in development. Journal of Cellular Biochemistry, Mar 2016. URL: https://doi.org/10.1002/jcb.25304, doi:10.1002/jcb.25304. This article has 27 citations and is from a peer-reviewed journal.
13. (huang2021kinorthoamethod pages 7-9): Liang-Chin Huang, Rahil Taujale, Nathan Gravel, Aarya Venkat, Wayland Yeung, Dominic P. Byrne, Patrick A. Eyers, and Natarajan Kannan. Kinortho: a method for mapping human kinase orthologs across the tree of life and illuminating understudied kinases. BMC Bioinformatics, Sep 2021. URL: https://doi.org/10.1186/s12859-021-04358-3, doi:10.1186/s12859-021-04358-3. This article has 24 citations and is from a peer-reviewed journal.
14. (skroblin2010mechanismsofprotein pages 4-6): Philipp Skroblin, Solveig Grossmann, Gesa Schäfer, Walter Rosenthal, and Enno Klussmann. Mechanisms of protein kinase a anchoring. International Review of Cell and Molecular Biology, pages 235-330, Jan 2010. URL: https://doi.org/10.1016/s1937-6448(10)83005-9, doi:10.1016/s1937-6448(10)83005-9. This article has 249 citations and is from a peer-reviewed journal.
15. (jangravi2013afreshlook pages 1-2): Zohreh Jangravi, Mehdi Alikhani, Babak Arefnezhad, Mehdi Sharifi Tabar, Sara Taleahmad, Razieh Karamzadeh, Mahdieh Jadaliha, Seyed Ahmad Mousavi, Diba Ahmadi Rastegar, Pouria Parsamatin, Haghighat Vakilian, Shahab Mirshahvaladi, Marjan Sabbaghian, Anahita Mohseni Meybodi, Mehdi Mirzaei, Maryam Shahhoseini, Marzieh Ebrahimi, Abbas Piryaei, Ali Akbar Moosavi-Movahedi, Paul A. Haynes, Ann K. Goodchild, Mohammad Hossein Nasr-Esfahani, Esmaiel Jabbari, Hossein Baharvand, Mohammad Ali Sedighi Gilani, Hamid Gourabi, and Ghasem Hosseini Salekdeh. A fresh look at the male-specific region of the human y chromosome. Journal of proteome research, 12 1:6-22, Jan 2013. URL: https://doi.org/10.1021/pr300864k, doi:10.1021/pr300864k. This article has 72 citations and is from a peer-reviewed journal.
16. (pearce2010thenutsand pages 1-2): Laura R. Pearce, David Komander, and Dario R. Alessi. The nuts and bolts of agc protein kinases. Nature Reviews Molecular Cell Biology, 11:9-22, Jan 2010. URL: https://doi.org/10.1038/nrm2822, doi:10.1038/nrm2822. This article has 1655 citations and is from a domain leading peer-reviewed journal.
17. (søberg2013evolutionarypathsof pages 1-2): Kristoffer Søberg, Tore Jahnsen, Torbjørn Rognes, Bjørn S. Skålhegg, and Jon K. Laerdahl. Evolutionary paths of the camp-dependent protein kinase (pka) catalytic subunits. PLoS ONE, 8:e60935, Apr 2013. URL: https://doi.org/10.1371/journal.pone.0060935, doi:10.1371/journal.pone.0060935. This article has 67 citations and is from a peer-reviewed journal.