1. Phylogeny  
   Cyclin‐dependent kinase‐like 5 (CDKL5) is an X‐linked serine/threonine protein kinase that belongs to the CMGC group of kinases. This group comprises cyclin‐dependent kinases (CDKs), mitogen‐activated protein kinases (MAPKs), glycogen synthase kinases (GSKs), and other CDK‐like kinases. CDKL5 is evolutionarily conserved among vertebrates, with clear orthologs identified in humans and mice, and its unique placement within the CDKL subfamily distinguishes it from classical CDKs by virtue of its extended C‐terminal regulatory region. Its evolutionary history underscores its importance in neuronal development as it is maintained in the common ancestor of mammals and other vertebrates (bergen2022cdkl5deficiencydisorder pages 1-2, kilstrupnielsen2012whatweknow pages 2-3).
2. Reaction Catalyzed  
   CDKL5 catalyzes the transfer of the γ‐phosphate group from adenosine triphosphate (ATP) to the hydroxyl group of serine or threonine residues located within protein substrates. In this reaction, ATP and a protein containing a target serine or threonine residue are converted into ADP, a phosphorylated protein, and a proton (H⁺). This phosphorylation reaction is a key post‐translational modification that modulates the activity and function of its substrates (bergen2022cdkl5deficiencydisorder pages 2-4).
3. Cofactor Requirements  
   The kinase activity of CDKL5 is dependent on the presence of divalent metal ion cofactors; notably, Mg²⁺ is required for the coordination of ATP within the active site and to facilitate the efficient transfer of the phosphate group. This requirement is characteristic of serine/threonine kinases and is essential for maintaining the catalytic efficacy of CDKL5 (bergen2022cdkl5deficiencydisorder pages 2-4).
4. Substrate Specificity  
   CDKL5 exhibits substrate specificity for peptide sequences containing a consensus motif defined as R–P–X–[S/T]–[A/G/P/S]. This precise motif requirement has been delineated through phosphoproteomic analyses and in vitro kinase assays, confirming that substrates must display an arginine followed by a proline and a variable residue, then a serine or threonine that is the site of phosphorylation, and subsequently one of several small amino acids. Among the identified substrates, methyl-CpG-binding protein 2 (MECP2) is a well-characterized target whose phosphorylation state is regulated by CDKL5. In addition to MECP2, other substrates implicated in the regulation of neuronal structure and function have been described, thereby reflecting CDKL5’s role in a broad spectrum of cellular processes including epigenetic modulation and cytoskeletal dynamics (bergen2022cdkl5deficiencydisorder pages 5-6, bahibuisson2012cdkl5relateddisordersfrom pages 13-14, kilstrupnielsen2012whatweknow pages 7-9).
5. Structure  
   CDKL5 is a large protein, comprising approximately 1,030 amino acids as delineated by genetic and biochemical analyses. Its structure is organized into a well-conserved N-terminal catalytic kinase domain and an unusually lengthy C-terminal regulatory region of over 600 amino acids. The catalytic domain, spanning roughly residues 13–297, contains an ATP‐binding pocket that is located between residues 14–47 as well as a catalytic serine/threonine active site between residues 127–144. A key structural hallmark of this catalytic core is the inclusion of a conserved Thr–Xaa–Tyr (TXY) activation motif, which is important for autophosphorylation and full kinase activation. The extended C-terminal region is responsible for modulating subcellular localization; it harbors nuclear localization signals (NLSs) and a nuclear export signal (NES) that facilitate CRM1‐dependent nuclear export. Structural models, including those predicted by AlphaFold, support a bilobal kinase fold with a regulatory tail that is thought to adopt intrinsically disordered conformations under basal conditions. This dual‐domain organization is critical for enabling precise control over kinase activity and for mediating interactions with multiple binding partners (bahibuisson2012cdkl5relateddisordersfrom pages 7-8, kilstrupnielsen2012whatweknow pages 2-3, bergen2022cdkl5deficiencydisorder pages 2-4).
6. Regulation  
   CDKL5 is subject to multiple levels of regulation that ensure its catalytic activity is tightly controlled in neuronal cells. Autophosphorylation within the activation loop is a well-documented event that contributes to full kinase activation. In addition, phosphorylation by upstream kinases, such as DYRK1A, has been demonstrated and is implicated in modulating both the activity and subcellular distribution of CDKL5. The enzyme exhibits a dynamic nucleocytoplasmic shuttling behavior governed by specific sequence elements in its C-terminal domain; these include two nuclear localization signals as well as a nuclear export signal that directs CRM1-dependent export. Mislocalization due to truncating mutations in the C-terminal region has been associated with impaired function, underscoring the importance of proper localization for CDKL5 activity. Collectively, these post-translational modifications and regulated protein–protein interactions form an intricate network that modulates CDKL5 function during critical phases of neuronal development (bahibuisson2012cdkl5relateddisordersfrom pages 8-9, kameshita2008cyclindependentkinaselike5 pages 6-6, kilstrupnielsen2012whatweknow pages 7-9).
7. Function  
   CDKL5 plays an essential role in the development and function of the central nervous system. Its expression is predominantly neuronal, with particularly high levels detected in the cerebral cortex, hippocampus, and striatum. Through phosphorylation of key substrates, most notably MECP2, CDKL5 regulates processes such as neuronal differentiation, dendritic arborization, and synaptic stabilization. These activities are crucial for proper synaptic plasticity and the establishment of neural circuits. In addition to its role in transcriptional regulation via MECP2 phosphorylation, CDKL5 has been implicated in modulating ciliary function—a process that may influence neuronal polarity and connectivity. Loss-of-function mutations in CDKL5 give rise to CDKL5 deficiency disorder (CDD), a severe neurodevelopmental condition characterized by early-onset epileptic encephalopathy, profound intellectual disability, and motor dysfunction. Evidence from knockout mouse models and patient-derived induced pluripotent stem cell (iPSC) systems substantiates its pivotal role in synapse formation and neuronal maturation, thereby confirming its fundamental importance in neurobiology (bergen2022cdkl5deficiencydisorder pages 1-2, bahibuisson2012cdkl5relateddisordersfrom pages 13-14, kilstrupnielsen2012whatweknow pages 7-9, nawaz2016cdkl5andshootin1 pages 17-18, zhu2019molecularandsynaptic pages 3-4).
8. Other Comments  
   Clinically, mutations in CDKL5 have been linked to an early-onset neurodevelopmental disorder known as CDKL5 deficiency disorder (CDD), which presents with severe epileptic encephalopathy, motor deficits, and cognitive impairment. Many of these mutations affect the catalytic domain or result in truncations of the regulatory C-terminal region, leading to a loss of kinase activity and mislocalization of the protein. Protein substitution therapy experiments using TAT-CDKL5 fusion constructs have demonstrated the ability to rescue neurological deficits in mouse models, highlighting a potential therapeutic avenue (trazzi2018cdkl5proteinsubstitution pages 1-1). At present, there are no selective small-molecule modulators that target CDKL5 directly; treatment remains predominantly symptomatic. The interplay between CDKL5 and its substrates—such as MECP2, DNA methyltransferase 1, and proteins involved in cytoskeletal dynamics—continues to be an area of active research, given its implications for both synaptic function and epigenetic regulation. Furthermore, recent phosphoproteomic studies have expanded the list of potential substrates and interaction partners, providing further insight into the kinase’s role in regulating neuronal architecture and function (bahibuisson2012cdkl5relateddisordersfrom pages 9-10, bergen2022cdkl5deficiencydisorder pages 1-2).
9. References
10. Bahi-Buisson, N. and Bienvenu, T., cdkl5-related disorders: from clinical description to molecular genetics. Molecular Syndromology, 2:137–152, Jan 2012. doi:10.1159/000331333. (Used in sections 4, 5, 6, 7, 8)
11. Van Bergen, N. J., Massey, S., Quigley, A., Rollo, B., Harris, A. R., Kapsa, R. M. I., & Christodoulou, J., Cdkl5 deficiency disorder: molecular insights and mechanisms of pathogenicity to fast-track therapeutic development. Biochemical Society Transactions, 50:1207–1224, Aug 2022. doi:10.1042/bst20220791. (Used in sections 1, 2, 4, 7, 8)
12. Hector, R. D., Dando, O., Landsberger, N., Kilstrup-Nielsen, C., Kind, P. C., Bailey, M. E. S., & Cobb, S. R., Characterisation of cdkl5 transcript isoforms in human and mouse. PLOS ONE, 11:e0157758, Jun 2016. doi:10.1371/journal.pone.0157758.
13. Kilstrup-Nielsen, C., Rusconi, L., La Montanara, P., Ciceri, D., Bergo, A., Bedogni, F., & Landsberger, N., What we know and would like to know about cdkl5 and its involvement in epileptic encephalopathy. Neural Plasticity, Jun 2012. doi:10.1155/2012/728267. (Used in sections 1, 4, 5, 6, 7, 8)
14. Massey, S., Ang, C.-S., Davidson, N. M., Quigley, A., Rollo, B., Harris, A. R., Kapsa, R. M. I., Christodoulou, J., & Van Bergen, N. J., Novel cdkl5 targets identified in human ipsc-derived neurons. Cellular and Molecular Life Sciences, Aug 2024. doi:10.1007/s00018-024-05389-8. (Used in sections 1, 4)
15. Nawaz, M. S., Giarda, E., Bedogni, F., La Montanara, P., Ricciardi, S., Ciceri, D., Alberio, T., Landsberger, N., Rusconi, L., & Kilstrup-Nielsen, C., Cdkl5 and shootin1 interact and concur in regulating neuronal polarization. PLOS ONE, 11:e0148634, Feb 2016. doi:10.1371/journal.pone.0148634. (Used in section 7)
16. Silvestre, M., Dempster, K., Mihaylov, S. R., Claxton, S., & Ultanir, S. K., Cell type-specific expression, regulation and compensation of cdkl5 activity in mouse brain. Molecular Psychiatry, 29:1844–1856, Feb 2024. doi:10.1038/s41380-024-02434-7. (Used in section 7)
17. Zhu, Y.-C. and Xiong, Z.-Q., Molecular and synaptic bases of cdkl5 disorder. Developmental Neurobiology, 79:8–19, Oct 2019. doi:10.1002/dneu.22639. (Used in sections 7, 8)
18. Amendola, E., Zhan, Y., Mattucci, C., Castroflorio, E., Calcagno, E., Fuchs, C., Lonetti, G., Silingardi, D., Vyssotski, A. L., Farley, D., Ciani, E., Pizzorusso, T., Giustetto, M., & Gross, C. T., Mapping pathological phenotypes in a mouse model of cdkl5 disorder. PLoS ONE, 9:e91613, May 2014. doi:10.1371/journal.pone.0091613. (Used in section 8)
19. Kameshita, I., Sekiguchi, M., Hamasaki, D., Sugiyama, Y., Hatano, N., Suetake, I., Tajima, S., & Sueyoshi, N., Cyclin-dependent kinase-like 5 binds and phosphorylates dna methyltransferase 1. Biochemical and Biophysical Research Communications, 377(4):1162–1167, Dec 2008. doi:10.1016/j.bbrc.2008.10.113. (Used in sections 4, 6)
20. Kontaxi, C., Davenport, E. C., Kind, P. C., & Cousin, M. A., Epilepsy-related cdkl5 deficiency slows synaptic vesicle endocytosis in central nerve terminals. The Journal of Neuroscience, 43:2002–2020, Feb 2023. doi:10.1523/jneurosci.1537-22.2023. (Used in section 7)
21. Szafranski, P., Golla, S., Jin, W., Fang, P., Hixson, P., Matalon, R., Kinney, D., Bock, H., Craigen, W., Smith, J. L., Bi, W., Patel, A., Cheung, S., Bacino, C., & Stankiewicz, P., Neurodevelopmental and neurobehavioral characteristics in males and females with cdkl5 duplications. European Journal of Human Genetics, 23:915–921, Oct 2015. doi:10.1038/ejhg.2014.217. (Used in section 8)
22. Terzic, B., Davatolhagh, M. F., Ho, Y., Tang, S., Liu, Y.-T., Xia, Z., Cui, Y., Fuccillo, M. V., & Zhou, Z., Temporal manipulation of cdkl5 reveals essential postdevelopmental functions and reversible cdkl5 deficiency disorder–related deficits. Journal of Clinical Investigation, Oct 2021. doi:10.1172/jci143655. (Used in section 8)
23. Trazzi, S., De Franceschi, M., Fuchs, C., Bastianini, S., Viggiano, R., Lupori, L., Mazziotti, R., Medici, G., Lo Martire, V., Ren, E., Rimondini, R., Zoccoli, G., Bartesaghi, R., Pizzorusso, T., & Ciani, E., Cdkl5 protein substitution therapy rescues neurological phenotypes of a mouse model of cdkl5 disorder. Human Molecular Genetics, 27:1572–1592, May 2018. doi:10.1093/hmg/ddy064. (Used in section 8)

References

1. (bergen2022cdkl5deficiencydisorder pages 1-2): Nicole J. Van Bergen, Sean Massey, Anita Quigley, Ben Rollo, Alexander R. Harris, Robert M.I. Kapsa, and John Christodoulou. Cdkl5 deficiency disorder: molecular insights and mechanisms of pathogenicity to fast-track therapeutic development. Biochemical Society Transactions, 50:1207-1224, Aug 2022. URL: https://doi.org/10.1042/bst20220791, doi:10.1042/bst20220791. This article has 43 citations and is from a peer-reviewed journal.
2. (bergen2022cdkl5deficiencydisorder pages 2-4): Nicole J. Van Bergen, Sean Massey, Anita Quigley, Ben Rollo, Alexander R. Harris, Robert M.I. Kapsa, and John Christodoulou. Cdkl5 deficiency disorder: molecular insights and mechanisms of pathogenicity to fast-track therapeutic development. Biochemical Society Transactions, 50:1207-1224, Aug 2022. URL: https://doi.org/10.1042/bst20220791, doi:10.1042/bst20220791. This article has 43 citations and is from a peer-reviewed journal.
3. (bergen2022cdkl5deficiencydisorder pages 5-6): Nicole J. Van Bergen, Sean Massey, Anita Quigley, Ben Rollo, Alexander R. Harris, Robert M.I. Kapsa, and John Christodoulou. Cdkl5 deficiency disorder: molecular insights and mechanisms of pathogenicity to fast-track therapeutic development. Biochemical Society Transactions, 50:1207-1224, Aug 2022. URL: https://doi.org/10.1042/bst20220791, doi:10.1042/bst20220791. This article has 43 citations and is from a peer-reviewed journal.
4. (kilstrupnielsen2012whatweknow pages 2-3): Charlotte Kilstrup-Nielsen, Laura Rusconi, Paolo La Montanara, Dalila Ciceri, Anna Bergo, Francesco Bedogni, and Nicoletta Landsberger. What we know and would like to know about cdkl5 and its involvement in epileptic encephalopathy. Neural Plasticity, Jun 2012. URL: https://doi.org/10.1155/2012/728267, doi:10.1155/2012/728267. This article has 140 citations and is from a peer-reviewed journal.
5. (kilstrupnielsen2012whatweknow pages 7-9): Charlotte Kilstrup-Nielsen, Laura Rusconi, Paolo La Montanara, Dalila Ciceri, Anna Bergo, Francesco Bedogni, and Nicoletta Landsberger. What we know and would like to know about cdkl5 and its involvement in epileptic encephalopathy. Neural Plasticity, Jun 2012. URL: https://doi.org/10.1155/2012/728267, doi:10.1155/2012/728267. This article has 140 citations and is from a peer-reviewed journal.
6. (nawaz2016cdkl5andshootin1 pages 17-18): Mohammad Sarfaraz Nawaz, Elisa Giarda, Francesco Bedogni, Paolo La Montanara, Sara Ricciardi, Dalila Ciceri, Tiziana Alberio, Nicoletta Landsberger, Laura Rusconi, and Charlotte Kilstrup-Nielsen. Cdkl5 and shootin1 interact and concur in regulating neuronal polarization. PLOS ONE, 11:e0148634, Feb 2016. URL: https://doi.org/10.1371/journal.pone.0148634, doi:10.1371/journal.pone.0148634. This article has 64 citations and is from a peer-reviewed journal.
7. (kameshita2008cyclindependentkinaselike5 pages 6-6): Isamu Kameshita, Mari Sekiguchi, Daisuke Hamasaki, Yasunori Sugiyama, Naoya Hatano, Isao Suetake, Shoji Tajima, and Noriyuki Sueyoshi. Cyclin-dependent kinase-like 5 binds and phosphorylates dna methyltransferase 1. Biochemical and biophysical research communications, 377 4:1162-7, Dec 2008. URL: https://doi.org/10.1016/j.bbrc.2008.10.113, doi:10.1016/j.bbrc.2008.10.113. This article has 125 citations and is from a peer-reviewed journal.
8. (trazzi2018cdkl5proteinsubstitution pages 1-1): Stefania Trazzi, Marianna De Franceschi, Claudia Fuchs, Stefano Bastianini, Rocchina Viggiano, Leonardo Lupori, Raffaele Mazziotti, Giorgio Medici, Viviana Lo Martire, Elisa Ren, Roberto Rimondini, Giovanna Zoccoli, Renata Bartesaghi, Tommaso Pizzorusso, and Elisabetta Ciani. Cdkl5 protein substitution therapy rescues neurological phenotypes of a mouse model of cdkl5 disorder. Human Molecular Genetics, 27:1572–1592, May 2018. URL: https://doi.org/10.1093/hmg/ddy064, doi:10.1093/hmg/ddy064. This article has 66 citations and is from a domain leading peer-reviewed journal.
9. (zhu2019molecularandsynaptic pages 3-4): Yong‐Chuan Zhu and Zhi‐Qi Xiong. Molecular and synaptic bases of cdkl5 disorder. Developmental Neurobiology, 79:8-19, Oct 2019. URL: https://doi.org/10.1002/dneu.22639, doi:10.1002/dneu.22639. This article has 97 citations and is from a peer-reviewed journal.