1. Phylogeny  
   Cyclin-dependent kinase-like 3 (CDKL3), also known by its alternative name NKIAMRE, is a member of the cyclin-dependent kinase-like (CDKL) family, a subfamily within the CMGC group of serine/threonine protein kinases. This family comprises CDKL1, CDKL2, CDKL4, and CDKL5, which share a high degree of sequence similarity with classic cyclin-dependent kinases (CDKs) but have diverged both structurally and functionally. CDKL3 is phylogenetically grouped with CDKL1–CDKL4, while CDKL5 is more distantly related. The evolutionary analyses based on sequence conservation and domain organization indicate that CDKL3 and its closely related kinases emerged early during eukaryotic evolution, probably sharing ancestry with the primordial CDKs identified in the Last Eukaryotic Common Ancestor (LECA) (canning2018cdklfamilykinases pages 1-3). Orthologs of CDKL3 have been identified in a variety of mammalian species, and its conserved kinase domain implies that the enzymatic function has been maintained across evolution. In addition, although classic CDKs typically require binding to regulatory cyclins for activation, the CDKLs—including CDKL3—have diverged in that no demonstrable cyclin interaction has been observed. This evolutionary separation is supported by phylogenetic studies that position the CDKL subfamily in a distinct branch within the kinome, reflective of conservation in the catalytic motifs along with the emergence of unique structural features such as the C-terminal alphaJ helix (canning2018cdklfamilykinases pages 3-4, endicott2013structuralcharacterizationof pages 2-3). The phylogenetic context of CDKL3 not only highlights its relationship with other CDKL proteins but also underlines its conservation across eukaryotes, suggesting that its cellular role—although not fully defined—is fundamental to processes common to multicellular organisms.
2. Reaction Catalyzed  
   CDKL3 functions as a serine/threonine kinase and, like other CDK family members, catalyzes the phosphorylation of protein substrates by transferring the gamma-phosphate from ATP to the hydroxyl group of serine or threonine residues. The chemical reaction can be summarized as follows:  
     ATP + [protein]–(L-serine or L-threonine) → ADP + [protein]–(L-serine/threonine)-phosphate + H⁺  
   This reaction underscores its role in modifying target proteins, thereby altering their activity, interactions, or subcellular localization (alexander2015theconciseguide pages 1-2, thiriet2013preambletocytoplasmic pages 1-4).
3. Cofactor Requirements  
   The catalytic activity of CDKL3 is dependent on the presence of ATP as a phosphate donor and on divalent metal cofactors. Specifically, Mg²⁺ ions are required to facilitate the proper positioning and stabilization of ATP’s phosphate groups during the phosphoryl transfer reaction. This cofactor dependency is a common characteristic among serine/threonine kinases, aiding in the transition state stabilization during catalysis (alexander2015theconciseguide pages 1-2, thiriet2013preambletocytoplasmic pages 1-4).
4. Substrate Specificity  
   As a serine/threonine kinase, CDKL3 phosphorylates target proteins on serine or threonine residues. Although the detailed substrate consensus motif for CDKL3 has not been completely defined, its catalytic domain contains the MAPK TXY motif commonly present in CDKL kinases that is essential for activity. Current research indicates that CDKL3 likely targets proteins implicated in the regulation of ciliary function and cell cycle progression. In particular, its structural characteristics—including the unique configuration of substrate docking regions—suggest that CDKL3 may recognize peptide motifs that differ from the canonical linear motifs observed in classical CDKs. However, at present, the precise consensus substrate sequence or amino acid preferences for CDKL3 remain to be fully elucidated (canning2018cdklfamilykinases pages 3-4, zhang2024cdkl3isa pages 17-18).
5. Structure  
   CDKL3 exhibits a canonical kinase domain that adopts the typical bilobal architecture found in serine/threonine kinases. The N-terminal lobe is relatively small, comprising mostly beta sheets and a conserved C-helix, while the larger C-terminal lobe is predominantly alpha-helical. Central to its structure is the catalytic domain—which houses the ATP-binding site, the glycine-rich loop, and the activation segment (canning2018cdklfamilykinases pages 4-5). One of the distinguishing structural features of CDKL3 is the presence of a C-terminal alphaJ helix. This helix occupies a region in a manner similar to the MAPK common docking groove, and its orientation is thought to modulate both substrate access and kinase activity. Crystal structures of CDKL family members, including CDKL3, have revealed that this alphaJ helix is critical for full enzymatic activity in some family members while being less essential in others. Furthermore, the kinase domain contains a conserved TXY motif within the activation loop that is essential for phosphorylation and subsequent activation of the enzyme. Structural studies with ATP-competitive inhibitors have shown that CDKL3 can adopt distinct conformations—both active and inactive—highlighting the flexibility of its activation loop and the potential for allosteric regulation. In addition, the domain organization suggests that regions flanking the catalytic core might be intrinsically disordered, potentially serving regulatory roles or mediating protein–protein interactions (canning2018cdklfamilykinases pages 3-4, endicott2013structuralcharacterizationof pages 3-5, alexander2015theconciseguide pages 2-3).
6. Regulation  
   The regulatory mechanisms of CDKL3 involve post-translational modifications and conformational rearrangements that are common among serine/threonine kinases. Phosphorylation within the activation loop, particularly at the conserved TXY motif, is essential for the activation of CDKL3. This phosphorylation event promotes a conformational change that aligns key catalytic residues for efficient phosphoryl transfer. Unlike classical CDKs, however, CDKL3 does not require binding to activating cyclins despite possessing putative cyclin-binding domains; no direct interaction with cyclins has been substantiated to date. Instead, regulation appears to be mediated primarily through activation loop phosphorylation and structural reorganization, notably involving the alphaJ helix, which can adopt different conformations and may serve to modulate substrate access and overall activity. In addition, ATP-competitive inhibitors have been shown to bind both active and inactive forms of CDKL3, underscoring the existence of distinct conformational states that are subject to regulatory control. These regulatory features, including phosphorylation events and conformational plasticity, collectively govern the activity of CDKL3 and distinguish it from classical cyclin-dependent kinases (canning2018cdklfamilykinases pages 1-3, canning2018cdklfamilykinases pages 4-5).
7. Function  
   CDKL3 functions as a serine/threonine kinase with a role in modulating cellular processes associated with ciliary dynamics and neuronal development. It is expressed in the developing brain and other tissues where ciliary function is critical, and its kinase activity is linked to the regulation of ciliary length, assembly, and maintenance. CDKL3 has been implicated in phosphorylation events that influence intraflagellar transport and microtubule stabilization, processes that are essential for proper ciliary signaling. Although the complete spectrum of substrates remains to be identified, the structural and regulatory features of CDKL3 suggest that it participates in signaling pathways that control cell proliferation and neuronal morphogenesis. Furthermore, while detailed mechanistic insights are more fully established for other CDKL family members such as CDKL5, the similarities in the catalytic domain imply that CDKL3 could function in overlapping pathways that govern aspects of neurodevelopment and possibly cell cycle control. Its involvement in these processes is particularly relevant given the documented associations of related kinases with neurological disorders. Overall, CDKL3’s functional profile is defined by its kinase activity, its expression in neuronal and ciliary contexts, and its putative role in regulating key phosphorylation events that maintain cellular architecture and signaling outputs (canning2018cdklfamilykinases pages 1-3, zhang2024cdkl3isa pages 17-18, alexander2015theconciseguide pages 2-3).
8. Other Comments  
   The nomenclature “CDKL3” reflects its alternative designation as NKIAMRE, which is derived from a conserved amino acid sequence within its catalytic domain. Although selective inhibitors specifically targeting CDKL3 have not yet been developed for clinical use, ATP-competitive inhibitors have been identified that bind to CDKL3 in both active and inactive conformations, providing a basis for future pharmacological exploration. CDKL3 has been tentatively linked to neurological impairments, including mild mental retardation, and cell culture studies have suggested potential roles in oncogenic processes, although its disease associations remain less extensively characterized compared with other family members such as CDKL5. The unique structural features of CDKL3, including its alphaJ helix and distinct substrate docking regions, present opportunities for the development of isoform-selective inhibitors and for further elucidation of its specific cellular substrates. These aspects make CDKL3 a protein of interest both for understanding fundamental cellular signaling mechanisms and for its potential implications in neurodevelopmental disorders and cancer (shafiq2011molecularmodellingand pages 97-103, rout2018deepinsightsinto pages 1-6, zhang2024cdkl3isa pages 17-18, endicott2013structuralcharacterizationof pages 2-3).
9. References
10. Canning P, Park K, Gonçalves J, Li C, Howard CJ, Sharpe TD, Holt LJ, Pelletier L, Bullock AN, Leroux MR. Cdkl family kinases have evolved distinct structural features and ciliary function. Cell Reports, 22:885-894, Jan 2018. (canning2018cdklfamilykinases pages 1-3, canning2018cdklfamilykinases pages 3-4, canning2018cdklfamilykinases pages 4-5)
11. Endicott JA, Noble MEM. Structural characterization of the cyclin-dependent protein kinase family. Biochemical Society Transactions, 41(4):1008-1016, Aug 2013. (endicott2013structuralcharacterizationof pages 2-3, endicott2013structuralcharacterizationof pages 3-5)
12. Alexander SPH, Fabbro D, Kelly E, Marrion NA, Peters JA, Benson HE, Faccenda E, Pawson AJ, Sharman JL, Southan C, Davies JA. The concise guide to pharmacology 2015/16: enzymes. British Journal of Pharmacology, 172:6024-6109, Dec 2015. (alexander2015theconciseguide pages 1-2, alexander2015theconciseguide pages 2-3)
13. Zhang H, Lin J, Zheng S, Ma L, Pang Z, Yin H, Meng C, Wang Y, Han Q, Zhang X, Li Z, Cao L, Liu L, Fei T, Gao D, Yang L, Peng X, Ding C, Wang S, Sheng R. Cdkl3 is a targetable regulator of cell cycle progression in cancers. Journal of Clinical Investigation, Jul 2024. (zhang2024cdkl3isa pages 17-18)
14. Lindberg MF, Meijer L. Dual-specificity, tyrosine phosphorylation-regulated kinases (DYRKs) and cdc2-like kinases (CLKs) in human disease, an overview. International Journal of Molecular Sciences, 22:6047, Jun 2021. (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 1-2)
15. Rout AK, Dehury B, Maharana J, Nayak C, Singh B, Behera BK, Das BK. Deep insights into the mode of ATP-binding mechanism in zebrafish cyclin-dependent protein kinase-like 1 (zCDKL1): a molecular dynamics approach. Journal of Molecular Graphics and Modelling, 81:175-183, May 2018. (rout2018deepinsightsinto pages 1-6)

References

1. (canning2018cdklfamilykinases pages 3-4): Peter Canning, Kwangjin Park, João Gonçalves, Chunmei Li, Conor J. Howard, Timothy D. Sharpe, Liam J. Holt, Laurence Pelletier, Alex N. Bullock, and Michel R. Leroux. Cdkl family kinases have evolved distinct structural features and ciliary function. Cell Reports, 22:885-894, Jan 2018. URL: https://doi.org/10.1016/j.celrep.2017.12.083, doi:10.1016/j.celrep.2017.12.083. This article has 80 citations and is from a highest quality peer-reviewed journal.
2. (canning2018cdklfamilykinases pages 1-3): Peter Canning, Kwangjin Park, João Gonçalves, Chunmei Li, Conor J. Howard, Timothy D. Sharpe, Liam J. Holt, Laurence Pelletier, Alex N. Bullock, and Michel R. Leroux. Cdkl family kinases have evolved distinct structural features and ciliary function. Cell Reports, 22:885-894, Jan 2018. URL: https://doi.org/10.1016/j.celrep.2017.12.083, doi:10.1016/j.celrep.2017.12.083. This article has 80 citations and is from a highest quality peer-reviewed journal.
3. (canning2018cdklfamilykinases pages 4-5): Peter Canning, Kwangjin Park, João Gonçalves, Chunmei Li, Conor J. Howard, Timothy D. Sharpe, Liam J. Holt, Laurence Pelletier, Alex N. Bullock, and Michel R. Leroux. Cdkl family kinases have evolved distinct structural features and ciliary function. Cell Reports, 22:885-894, Jan 2018. URL: https://doi.org/10.1016/j.celrep.2017.12.083, doi:10.1016/j.celrep.2017.12.083. This article has 80 citations and is from a highest quality peer-reviewed journal.
4. (thiriet2013preambletocytoplasmic pages 1-4): M Thiriet M Thiriet. Preamble to cytoplasmic protein kinases. Biomathematical and Biomechanical Modeling of the Circulatory and Ventilatory Systems, pages 109-135, Jul 2013. URL: https://doi.org/10.1007/978-1-4614-4370-4\_3, doi:10.1007/978-1-4614-4370-4\_3. This article has 2 citations.
5. (zhang2024cdkl3isa pages 17-18): Haijiao Zhang, Jiahui Lin, Shaoqin Zheng, Lanjing Ma, Zhongqiu Pang, Hongyi Yin, Chengcheng Meng, Yinuo Wang, Qing Han, Xi Zhang, Zexu Li, Liu Cao, Lijun Liu, Teng Fei, Daming Gao, Liang Yang, Xueqiang Peng, Chen Ding, Shixue Wang, and Ren Sheng. Cdkl3 is a targetable regulator of cell cycle progression in cancers. Journal of Clinical Investigation, Jul 2024. URL: https://doi.org/10.1172/jci178428, doi:10.1172/jci178428. This article has 5 citations and is from a highest quality peer-reviewed journal.
6. (alexander2015theconciseguide pages 1-2): Stephen PH Alexander, Doriano Fabbro, Eamonn Kelly, Neil Marrion, John A Peters, Helen E Benson, Elena Faccenda, Adam J Pawson, Joanna L Sharman, Christopher Southan, and Jamie A Davies. The concise guide to pharmacology 2015/16: enzymes. British Journal of Pharmacology, 172:6024-6109, Dec 2015. URL: https://doi.org/10.1111/bph.13354, doi:10.1111/bph.13354. This article has 577 citations and is from a highest quality peer-reviewed journal.
7. (alexander2015theconciseguide pages 2-3): Stephen PH Alexander, Doriano Fabbro, Eamonn Kelly, Neil Marrion, John A Peters, Helen E Benson, Elena Faccenda, Adam J Pawson, Joanna L Sharman, Christopher Southan, and Jamie A Davies. The concise guide to pharmacology 2015/16: enzymes. British Journal of Pharmacology, 172:6024-6109, Dec 2015. URL: https://doi.org/10.1111/bph.13354, doi:10.1111/bph.13354. This article has 577 citations and is from a highest quality peer-reviewed journal.
8. (endicott2013structuralcharacterizationof pages 3-5): Jane A. Endicott and Martin E.M. Noble. Structural characterization of the cyclin-dependent protein kinase family. Biochemical Society transactions, 41 4:1008-16, Aug 2013. URL: https://doi.org/10.1042/bst20130097, doi:10.1042/bst20130097. This article has 48 citations and is from a peer-reviewed journal.
9. (rout2018deepinsightsinto pages 1-6): Ajaya Kumar Rout, Budheswar Dehury, Jitendra Maharana, Chirasmita Nayak, Vishwamitra Singh Baisvar, Bijay Kumar Behera, and Basanta Kumar Das. Deep insights into the mode of atp-binding mechanism in zebrafish cyclin-dependent protein kinase-like 1 (zcdkl1): a molecular dynamics approach. Journal of Molecular Graphics and Modelling, 81:175-183, May 2018. URL: https://doi.org/10.1016/j.jmgm.2018.02.002, doi:10.1016/j.jmgm.2018.02.002. This article has 20 citations and is from a peer-reviewed journal.
10. (shafiq2011molecularmodellingand pages 97-103): MI Shafiq. Molecular modelling and bioinformatics studies of cdk4 and related proteins. Unknown journal, 2011. URL: https://doi.org/10104464/1, doi:10104464/1.
11. (endicott2013structuralcharacterizationof pages 2-3): Jane A. Endicott and Martin E.M. Noble. Structural characterization of the cyclin-dependent protein kinase family. Biochemical Society transactions, 41 4:1008-16, Aug 2013. URL: https://doi.org/10.1042/bst20130097, doi:10.1042/bst20130097. This article has 48 citations and is from a peer-reviewed journal.
12. (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 1-2): Mattias F. Lindberg and Laurent Meijer. Dual-specificity, tyrosine phosphorylation-regulated kinases (dyrks) and cdc2-like kinases (clks) in human disease, an overview. International Journal of Molecular Sciences, 22:6047, Jun 2021. URL: https://doi.org/10.3390/ijms22116047, doi:10.3390/ijms22116047. This article has 92 citations and is from a peer-reviewed journal.