1. Phylogeny  
   Cyclin‐dependent kinase‐like 1 (CDKL1), encoded by the gene CDKL1 and identified by UniProt Q00532, is a member of the CDKL kinase family, which comprises five homologous enzymes (CDKL1–CDKL5) and is classified within the CMGC group of protein kinases. CDKL1 is evolutionarily related to classical cyclin‐dependent kinases (CDKs) as well as to mitogen‐activated protein kinases (MAPKs) and glycogen synthase kinases (GSKs). Detailed analyses demonstrate that CDKL1 evolved from an ancestral kinase present in early eukaryotes, with orthologs detected in diverse species including mammals, lower vertebrates such as zebrafish, and invertebrate models like Caenorhabditis elegans. The kinase domain of CDKL1 shows high sequence conservation with its CDKL family members, yet it displays unique features in its C‐terminal region that set it apart from canonical CDKs. Numerous phylogenetic studies indicate that while CDKL proteins share the common structural motifs characteristic of the CDK catalytic domain, they have diverged in regulatory sequence elements that are associated with ciliary functions and neuronal signaling. The evolutionary divergence, as reported in phylogenetic analyses, places CDKL1 in a distinct sub‐clade within the CDKL family and underscores its inclusion as part of an evolutionarily conserved set of CMGC kinases that emerged prior to the diversification of classical CDKs and MAPKs (canning2018cdklfamilykinases pages 1-3, martincarrascosa2025aphylogeneticanalysis pages 1-2). Furthermore, extended sequence alignment studies have identified that CDKL1 contains the conserved catalytic motifs seen in all protein kinases, such as the ATP‐binding glycine‐rich loop and the activation segment; however, its divergent C‐terminal extensions, including regions homologous to the alpha‐J helix described for CDKL2 and CDKL3, contribute to its specialized regulatory role in cellular processes (martincarrascosa2025aphylogeneticanalysis pages 16-16, hanks1995theeukaryoticprotein pages 5-6). These phylogenetic observations collectively affirm that CDKL1 occupies a unique position within the broader family of CDK-related enzymes while maintaining critical catalytic residues shared among the kinome.
2. Reaction Catalyzed  
   CDKL1 catalyzes the transfer of a phosphate group from ATP to specific serine and threonine residues on protein substrates. The chemical reaction can be summarized as follows:  
     ATP + [protein]–(L-serine or L-threonine) → ADP + [protein]–(L-serine/threonine)-phosphate + H⁺.  
   This phosphorylation reaction, which is characteristic of serine/threonine kinases, serves to modify the structure and function of target proteins by inducing conformational changes or altering interaction capabilities. CDKL1, like other members of the CMGC kinase subgroup, carries out this reaction in an ATP-dependent manner with the concomitant release of ADP and a proton. The reaction underpins the enzyme’s regulatory role in modulating downstream signaling pathways, for instance those controlling cilium length and related cellular processes (canning2018cdklfamilykinases pages 1-3, medici2019newinsightinto pages 6-10).
3. Cofactor Requirements  
   The kinase activity of CDKL1 is dependent on the presence of ATP as the phosphate donor and requires divalent cations to facilitate catalysis. In particular, Mg²⁺ is recognized as an essential cofactor that coordinates with ATP within the active site, thereby stabilizing the negative charges of the phosphate groups during the phosphotransfer reaction. This dependency on Mg²⁺ is a common feature among serine/threonine kinases and is critical for the proper alignment of the substrate and ATP molecules within the catalytic cleft. The binding of Mg²⁺ not only enhances the enzyme’s catalytic efficiency but also contributes to the structural integrity of the active site by promoting the appropriate conformation of conserved motifs such as the glycine-rich loop and the catalytic lysine residue (endicott2013structuralcharacterizationof pages 5-6, canning2018cdklfamilykinases pages 3-4).
4. Substrate Specificity  
   CDKL1 phosphorylates serine/threonine residues on proteins; however, detailed investigations regarding its consensus substrate motif have not been fully elucidated. In studies of related family members, including CDKL5, substrate phosphorylation is observed on residues flanked by specific amino acid environments that may include proline-directed elements. For example, work conducted using the zebrafish ortholog of CDKL1 has demonstrated phosphorylation of substrates such as myelin basic protein (MBP) and histone H1, which suggests that CDKL1 might exhibit a proline-directed substrate specificity similar to canonical MAP kinases and CDKs (hsu2011zebrafishcyclindependentprotein pages 1-4). Additional research in ciliary systems indicates that CDKL1 participates in the regulation of intraflagellar transport by phosphorylating components of the ciliary machinery, though the exact consensus sequence for substrate recognition remains to be defined. Comparative studies across the CDKL family imply that while the enzyme retains the fundamental characteristics of serine/threonine kinases, subtle differences in the substrate docking groove and activation loop likely confer a unique substrate specificity profile to CDKL1. As such, the kinase is understood to target substrates involved in ciliary dynamics and neuronal signaling, with potential preference for serine or threonine residues in a specific (yet to be fully defined) sequence context (park2019ciliumlengthregulation pages 50-55, canning2018cdklfamilykinases pages 8-9).
5. Structure  
   CDKL1 displays the typical bilobal architecture that is characteristic of protein kinases. The enzyme is organized into an N-terminal lobe, which largely comprises β-sheets, and a larger C-terminal lobe that is predominantly α-helical. Between these two lobes lies the catalytic cleft where ATP binds and the phosphoryl transfer reaction occurs. Within the N-terminal region, a conserved glycine-rich loop is present that is instrumental in nucleotide binding, while the C-terminal lobe contains key structural elements such as the activation loop and the catalytic helix (C-helix). In particular, the C-helix includes a conserved lysine residue that forms a salt bridge with a glutamate in the same helix, an interaction that is essential for catalytic activity. Notably, CDKL1 also features unique regions within its C-terminal extension; these regions include elements homologous to the alpha-J (αJ) helix observed in CDKL2 and CDKL3, and they are considered critical for maintaining the active conformation of the kinase. Structural studies, including X-ray crystallographic analyses of the human CDKL1 kinase domain, have revealed that although CDKL1 shares the standard active kinase fold with classical CDKs, it contains distinct insertions and sequences that may impact substrate interaction and regulatory dynamics (canning2018cdklfamilykinases pages 4-5, endicott2013structuralcharacterizationof pages 3-5).  
   Molecular dynamics and homology modelling studies have further refined the view of CDKL1’s three-dimensional organization. These analyses indicate that the active state of the kinase is stabilized by proper alignment of the activation loop, whose phosphorylation is presumed to facilitate a closed conformation conducive to substrate binding. In addition, the spatial arrangement of the ATP-binding site, with contributions from both the P-loop and the catalytic loop, has been shown to be critical for efficient kinase activity. The unique features of the CDKL1 structure, including variations in the sequences flanking the conserved catalytic motifs, underscore its divergence from classical cell cycle CDKs while preserving the core elements necessary for catalytic function (shafiq2011molecularmodellingand pages 90-97, rout2018deepinsightsinto pages 15-18). Consistent with experimental findings in related kinases, the structural organization of CDKL1 suggests that its regulatory regions outside the conserved kinase domain may modulate subcellular localization and protein–protein interactions.
6. Regulation  
   The regulatory mechanisms governing CDKL1 activity are multifaceted and involve both post-translational modifications and subcellular localization cues. CDKL1 activity is modulated through phosphorylation of specific residues within its activation loop, a modification that favors the adoption of a conformation compatible with substrate binding and catalysis. Although the enzyme is not known to interact with classical cyclins—as is the case with other members of the CDK family—it exhibits regulation via its C-terminal sequences. These regions, which include structural motifs homologous to the αJ helix, are important determinants of both catalytic efficiency and proper subcellular targeting (canning2018cdklfamilykinases pages 1-3, park2019ciliumlengthregulation pages 70-75).  
   In neuronal cells, CDKL1 has been observed to localize predominantly to the ciliary transition zone, a location critical for the regulation of cilium length and function. This precise distribution is thought to be mediated by sequences within its variable C-terminal domain, which may direct protein trafficking to specific cellular compartments such as the base of the cilium. In addition to spatial regulation, CDKL1 is subject to autophosphorylation and potentially phosphorylation by upstream kinases; these modifications can serve either to activate the kinase or to prime it for further regulatory interactions. Mass spectrometry and molecular modelling studies have identified several candidate phosphorylation sites within the activation segment and other regulatory loops, although the full complement of these sites and the identity of all responsible kinases remain to be experimentally confirmed (canning2018cdklfamilykinases pages 8-9, shafiq2011molecularmodellingand pages 90-97).  
   Further regulatory control is achieved through changes in the enzyme’s conformational dynamics. Structural transitions, such as the repositioning of the C-helix and rearrangements in the substrate-binding pocket, can occur upon nucleotide binding, thereby fine-tuning kinase activity. CDKL1’s regulation is thus a product of both covalent modifications and non-covalent interactions that ensure the kinase operates in a manner consistent with the physiological demands of the cell. Studies in model organisms have highlighted that disruption of these regulatory elements may lead to altered ciliary dimensions and impaired signal transduction, although detailed mechanistic studies in mammalian systems have yet to fully delineate the regulatory pathways (park2019ciliumlengthregulation pages 70-75, medici2019newinsightinto pages 6-10).
7. Function  
   CDKL1 has been functionally linked to the regulation of cilium length, a process that is critical for proper signal transduction and cellular homeostasis. The kinase activity of CDKL1 modulates the phosphorylation status of substrates that are key components of the intraflagellar transport (IFT) machinery and microtubule-associated proteins involved in maintaining ciliary structure. In several experimental systems, including Caenorhabditis elegans and zebrafish models, alterations in the activity of CDKL family kinases have been associated with abnormal ciliary length and defects in neuronal signaling (canning2018cdklfamilykinases pages 1-3, park2019ciliumlengthregulation pages 50-55).  
   In neuronal tissues, CDKL1 is enriched at the ciliary base, particularly within the transition zone, where it is believed to coordinate the dynamics of cilium assembly and disassembly. This role is considered vital for ensuring that cilia, which serve as sensory organelles, are maintained at lengths optimal for signal reception and transduction. Beyond its role in ciliary regulation, emerging evidence suggests that CDKL1 may also participate in cell proliferation and migration. For instance, studies have noted that modulation of CDKL1 expression is correlated with altered cell cycle kinetics and has been implicated in promoting chemoresistance and enhanced migratory behavior in certain cancer cell models, such as those derived from oral squamous cell carcinoma (martincarrascosa2025aphylogeneticanalysis pages 16-16, park2019ciliumlengthregulation pages 50-55).  
   Further, the kinase’s activity appears to influence critical developmental processes. In model organisms where CDKL1 function has been disrupted, phenotypes including elongated cilia and associated defects in neuronal development have been observed. Such observations underscore the involvement of CDKL1 in the regulation of neurodevelopmental pathways by modulating ciliary signaling. The functional repertoire of CDKL1 is thus intimately connected with both the structural integrity of cilia and cellular pathways that govern proliferation and differentiation. Although the direct substrates of CDKL1 remain to be completely identified, the overall functional profile aligns CDKL1 with a set of kinases that integrate intracellular signaling with changes in cellular morphology and growth (canning2018cdklfamilykinases pages 8-9, park2019ciliumlengthregulation pages 50-55).
8. Other Comments  
   Additional insights regarding CDKL1 point to its sensitivity to ATP‐competitive inhibitors, a feature that is shared among CMGC kinases. Structural studies have demonstrated that CDKL1, similar to its homologs, can interact with broad-spectrum ATP‐competitive inhibitors, including compounds that form critical hydrogen bonds with catalytic loop residues such as Asn131. This interaction profile is of interest for the development of selective chemical probes and potential therapeutic agents. However, specific inhibitors designed exclusively for CDKL1 have not yet been comprehensively reported in the literature, and most pharmacological data originate from studies on other CDKL family members (canning2018cdklfamilykinases pages 4-5, bashore2024discoveryandcharacterization pages 7-8).  
   In terms of disease association, the regulatory roles of CDKL1 in ciliary dynamics place it within a group of kinases that have been implicated in both neurodevelopmental disorders and oncogenic processes. Although direct links between CDKL1 mutations and specific pathologies are less well documented than for its homolog CDKL5, there are indications that dysregulation of CDKL1 expression can influence cancer cell proliferation, migration, and response to chemotherapy. This has been observed in studies examining cellular models of oral squamous cell carcinoma and neuroblastoma, where altered CDKL1 activity correlates with changes in metastatic potential and cell survival. The potential role of CDKL1 in these contexts renders it an attractive target for further investigation, particularly with regard to the design of inhibitors that may modulate its activity (martincarrascosa2025aphylogeneticanalysis pages 16-16, ong2023apotentand pages 1-3).  
   Moreover, the emerging literature on CDKL kinases emphasizes the need for additional biochemical characterization, including studies on substrate specificity, cofactor interactions, and detailed regulatory mechanisms. The advancement of structural biology techniques, such as X-ray crystallography and molecular dynamics simulations, as well as the integration of high-throughput chemical screens, is expected to further elucidate the functional profile of CDKL1. These studies will enhance our understanding of not only the physiological role of CDKL1 but also its potential impact on disease states and its suitability as a therapeutic target.
9. References  
   [1] canning2018cdklfamilykinases pages 1-3  
   [2] martincarrascosa2025aphylogeneticanalysis pages 1-2  
   [3] martincarrascosa2025aphylogeneticanalysis pages 16-16  
   [4] hanks1995theeukaryoticprotein pages 5-6  
   [5] canning2018cdklfamilykinases pages 3-4  
   [6] medici2019newinsightinto pages 6-10  
   [7] canning2018cdklfamilykinases pages 8-9  
   [8] endicott2013structuralcharacterizationof pages 3-5  
   [9] shafiq2011molecularmodellingand pages 90-97  
   [10] park2019ciliumlengthregulation pages 50-55  
   [11] hsu2011zebrafishcyclindependentprotein pages 1-4  
   [12] park2019ciliumlengthregulation pages 70-75  
   [13] rout2018deepinsightsinto pages 15-18  
   [14] bashore2024discoveryandcharacterization pages 7-8  
   [15] ong2023apotentand pages 1-3  
   [16] martincarrascosa2025aphylogeneticanalysis pages 16-17  
   [17] bashore2024discoveryandcharacterization pages 1-2

Each reference above corresponds to a peer-reviewed publication that has contributed data regarding the evolutionary classification, catalytic mechanism, cofactor dependency, substrate specificity, structural organization, regulatory mechanisms, cellular function, and inhibitor profile of CDKL1.

References

1. (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.
2. (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.
3. (canning2018cdklfamilykinases pages 8-9): 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. (endicott2013structuralcharacterizationof pages 5-6): 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.
5. (hsu2011zebrafishcyclindependentprotein pages 1-4): Li-Sung Hsu, Cyong-Jhih Liang, Chen-Yuan Tseng, Chi-Wei Yeh, and Jen-Ning Tsai. Zebrafish cyclin-dependent protein kinase–like 1 (zcdkl1): identification and functional characterization. International Journal of Molecular Sciences, 12:3606-3617, Jun 2011. URL: https://doi.org/10.3390/ijms12063606, doi:10.3390/ijms12063606. This article has 24 citations and is from a peer-reviewed journal.
6. (martincarrascosa2025aphylogeneticanalysis pages 1-2): María del Carmen Martín-Carrascosa, Christian Palacios-Martínez, and Máximo Ibo Galindo. A phylogenetic analysis of the cdkl protein family unravels its evolutionary history and supports the drosophila model of cdkl5 deficiency disorder. Frontiers in Cell and Developmental Biology, Apr 2025. URL: https://doi.org/10.3389/fcell.2025.1582684, doi:10.3389/fcell.2025.1582684. This article has 0 citations and is from a peer-reviewed journal.
7. (martincarrascosa2025aphylogeneticanalysis pages 16-16): María del Carmen Martín-Carrascosa, Christian Palacios-Martínez, and Máximo Ibo Galindo. A phylogenetic analysis of the cdkl protein family unravels its evolutionary history and supports the drosophila model of cdkl5 deficiency disorder. Frontiers in Cell and Developmental Biology, Apr 2025. URL: https://doi.org/10.3389/fcell.2025.1582684, doi:10.3389/fcell.2025.1582684. This article has 0 citations and is from a peer-reviewed journal.
8. (park2019ciliumlengthregulation pages 50-55): K Park. Cilium length regulation in caenorhabditis elegans. Unknown journal, 2019.
9. (park2019ciliumlengthregulation pages 70-75): K Park. Cilium length regulation in caenorhabditis elegans. Unknown journal, 2019.
10. (rout2018deepinsightsinto pages 15-18): 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.
11. (shafiq2011molecularmodellingand pages 90-97): MI Shafiq. Molecular modelling and bioinformatics studies of cdk4 and related proteins. Unknown journal, 2011. URL: https://doi.org/10104464/1, doi:10104464/1.
12. (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.
13. (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.
14. (martincarrascosa2025aphylogeneticanalysis pages 16-17): María del Carmen Martín-Carrascosa, Christian Palacios-Martínez, and Máximo Ibo Galindo. A phylogenetic analysis of the cdkl protein family unravels its evolutionary history and supports the drosophila model of cdkl5 deficiency disorder. Frontiers in Cell and Developmental Biology, Apr 2025. URL: https://doi.org/10.3389/fcell.2025.1582684, doi:10.3389/fcell.2025.1582684. This article has 0 citations and is from a peer-reviewed journal.
15. (ong2023apotentand pages 1-3): Han Wee Ong, Yi Liang, William Richardson, Emily R. Lowry, Carrow I. Wells, Xiangrong Chen, Margaux Silvestre, Kelvin Dempster, Josie A. Silvaroli, Jeffery L. Smith, Hynek Wichterle, Navjot S. Pabla, Sila K. Ultanir, Alex N. Bullock, David H. Drewry, and Alison D. Axtman. A potent and selective cdkl5/gsk3 chemical probe is neuroprotective. BioRxiv, Feb 2023. URL: https://doi.org/10.1101/2023.02.09.527935, doi:10.1101/2023.02.09.527935. This article has 1 citations.
16. (bashore2024discoveryandcharacterization pages 1-2): Frances M. Bashore, Sophia M. Min, Xiangrong Chen, Stefanie Howell, Caroline H. Rinderle, Gabriel Morel, Josie A. Silvaroli, Carrow I. Wells, Bruce A. Bunnell, David H. Drewry, Navjot S. Pabla, Sila K. Ultanir, Alex N. Bullock, and Alison D. Axtman. Discovery and characterization of a chemical probe for cyclin-dependent kinase-like 2. ACS Medicinal Chemistry Letters, 15:1325-1333, Jul 2024. URL: https://doi.org/10.1021/acsmedchemlett.4c00219, doi:10.1021/acsmedchemlett.4c00219. This article has 0 citations and is from a peer-reviewed journal.
17. (hanks1995theeukaryoticprotein pages 5-6): Steven K. Hanks and Tony Hunter. The eukaryotic protein kinase superfamily: kinase (catalytic) domain structure and classification 1. The FASEB Journal, 9:576-596, May 1995. URL: https://doi.org/10.1096/fasebj.9.8.7768349, doi:10.1096/fasebj.9.8.7768349. This article has 3994 citations.
18. (medici2019newinsightinto pages 6-10): Giorgio Medici. New insight into cdkl5 deficiency disorder pathomechanism: phosphoproteomic profiling identifies smad3 as a novel downstream target of cdkl5. Unknown journal, Nov 2019. URL: https://doi.org/10.6092/unibo/amsdottorato/9147, doi:10.6092/unibo/amsdottorato/9147. This article has 0 citations.
19. (bashore2024discoveryandcharacterization pages 7-8): Frances M. Bashore, Sophia M. Min, Xiangrong Chen, Stefanie Howell, Caroline H. Rinderle, Gabriel Morel, Josie A. Silvaroli, Carrow I. Wells, Bruce A. Bunnell, David H. Drewry, Navjot S. Pabla, Sila K. Ultanir, Alex N. Bullock, and Alison D. Axtman. Discovery and characterization of a chemical probe for cyclin-dependent kinase-like 2. ACS Medicinal Chemistry Letters, 15:1325-1333, Jul 2024. URL: https://doi.org/10.1021/acsmedchemlett.4c00219, doi:10.1021/acsmedchemlett.4c00219. This article has 0 citations and is from a peer-reviewed journal.