## Phylogeny

CDKL1 is assigned to the CDK-like (CDKL) subfamily within the CMGC kinase group in the Manning et al. 2002 kinome classification (canning2018cdklfamilykinases pages 1-3).  
Orthologs are documented in mammals (Homo sapiens, Mus musculus, Bos taurus, Panthera tigris) (rout2018deepinsightsinto pages 15-18), avians (Gallus gallus) (rout2018deepinsightsinto pages 15-18), and teleost fish including Danio rerio and Tetraodon nigroviridis (hsu2011zebrafishcyclindependentprotein pages 1-4).  
The kinase domain shares 77 % identity between zebrafish and human and exceeds 90 % identity among teleost paralogs (hsu2011zebrafishcyclindependentprotein pages 1-4).  
Single-copy orthologs exist in Caenorhabditis elegans (cdkl-1) and Drosophila melanogaster (CG7236), whereas CDKL2/3/5 were lost in Diptera (martincarrascosa2025aphylogeneticanalysis pages 8-10).  
Saccharomyces cerevisiae and related yeasts lack CDKL1 homologs (martincarrascosa2025aphylogeneticanalysis pages 5-6).  
Phylogenetically, CDKL1 forms a branch separate from classical cell-cycle CDKs yet retains the MAPK-type activation-loop TDY motif (rout2018deepinsightsinto pages 1-6).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-O-phospho-Ser/Thr (hsu2011zebrafishcyclindependentprotein pages 1-4).

## Cofactor Requirements

Divalent-cation dependence has not been explicitly reported; available in vitro assays did not specify Mg²⁺ or Mn²⁺ usage (hsu2011zebrafishcyclindependentprotein pages 1-4).

## Substrate Specificity

• Zebrafish CDKL1 phosphorylates serine within the proline-directed motif X-Ser-Pro-X, exemplified by myelin basic protein and histone H1 (hsu2011zebrafishcyclindependentprotein pages 9-11).  
• Human CDKL1 displays very weak activity toward RPXSA motifs on MAP1S Ser900 and CEP131 Ser35 under standard HEK293 conditions (munoz2018phosphoproteomicscreeningidentifies pages 4-5).  
• No comprehensive kinome-wide substrate profiling data are yet available for CDKL1 (karimbayli2024insightsintothe pages 1-2).

## Structure

CDKL1 comprises an N-terminal serine/threonine kinase domain (~residues 1–308) followed by a short C-terminal tail (endicott2013structuralcharacterizationof pages 3-5).  
Crystal structures of the kinase domain (PDB 4AGU, 4AAA, 4BBM) reveal the canonical bilobed fold and a distinctive C-terminal αJ helix occupying the MAPK common-docking groove (canning2018cdklfamilykinases pages 1-3).  
Catalytic motifs are conserved: VAIK (Lys33), HRD, DFG, and the activation-loop Thr-Asp-Tyr sequence (rout2018deepinsightsinto pages 1-6).  
The C-helix contains the CDKL-signature KKIALRE variant instead of the PSTAIRE motif of canonical CDKs (endicott2013structuralcharacterizationof pages 3-5).  
Molecular-dynamics simulations show an ATP-binding pocket closely superposable with human CDK2, confirming canonical nucleotide coordination (rout2018deepinsightsinto pages 15-18).

## Regulation

No experimentally validated post-translational modifications have been reported for CDKL1; phosphorylation of the TDY motif and other regulatory events remain unconfirmed (rout2018deepinsightsinto pages 1-6).

## Function

CDKL1 transcripts are enriched in brain, lung, kidney, and ovary in mammals (rout2018deepinsightsinto pages 1-6).  
The protein localises to the neuronal ciliary transition zone and contributes to cilium length control (canning2018cdklfamilykinases pages 1-3).  
In zebrafish, cdkl1 is required for floor-plate formation, brain and eye morphogenesis, and anterior–posterior axis patterning within the Sonic Hedgehog pathway (hsu2011zebrafishcyclindependentprotein pages 9-11).  
Comparative studies support a broader role in Hedgehog signalling and ciliogenesis across metazoans (martincarrascosa2025aphylogeneticanalysis pages 1-2).  
Clinical data link elevated CDKL1 expression with poor prognosis in colorectal cancer (chowdhury2023cmgckinasesin pages 12-13).

## Inhibitors

Crystal structures capture ATP-competitive inhibitors bound to the active site, although the ligand identities were not disclosed (canning2018cdklfamilykinases pages 3-4).

## Other Comments

CDKL1 is classified among understudied “dark kinases,” highlighting the limited biochemical and pharmacological characterisation currently available (karimbayli2024insightsintothe pages 1-2).

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