## Phylogeny

CDKL2 is classified within the CMGC kinase group and, more specifically, belongs to the cyclin-dependent-kinase-like (CDKL) sub-family that contains CDKL1-5 (canning2018cdklfamilykinases pages 1-3).  
The kinase domain shares 35–40 % sequence identity with classical CDK2, indicating divergence from the cell-cycle CDKs while retaining core catalytic elements (endicott2013structuralcharacterizationof pages 3-5).  
CDKL2 and the other CDKL enzymes possess a MAPK-type Thr-X-Tyr (TXY) activation loop, underscoring evolutionary linkage to MAPKs despite the absence of confirmed cyclin binding (canning2018cdklfamilykinases pages 3-4).  
Experimentally documented orthologs include Caenorhabditis elegans CDKL-1, Drosophila melanogaster CDKL representatives, amphibian homologues and the mammalian paralogue Mus musculus Cdkl2, demonstrating conservation from invertebrates to vertebrates (canning2018cdklfamilykinases pages 1-3, martincarrascosa2025aphylogeneticanalysis pages 16-16).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-Ser/Thr-phosphate (endicott2013structuralcharacterizationof pages 3-5).

## Cofactor Requirements

Catalysis requires divalent metal ions, with Mg²⁺ or Mn²⁺ serving as obligatory cofactors for phosphoryl transfer (canning2018cdklfamilykinases pages 1-3, martincarrascosa2025aphylogeneticanalysis pages 16-16).

## Substrate Specificity

A validated cellular substrate is the microtubule-binding protein EB2, which is phosphorylated by CDKL2 in rat primary neurons (bashore2024discoveryandcharacterization pages 1-2).  
A consensus phosphorylation motif has not been defined; large-scale motif profiling did not report a sequence logo for CDKL2 (bashore2024discoveryandcharacterization pages 7-8).

## Structure

The enzyme comprises an N-terminal bilobal kinase domain (residues ~1–300) followed by an extended C-terminal regulatory tail that incorporates a unique αJ helix indispensable for activity (canning2018cdklfamilykinases pages 1-3).  
Crystal structures of the isolated kinase domain have been solved with the ATP-competitive inhibitors TCS 2312 (PDB 4AAA) and an acylaminoindazole probe (PDB 8S6I), each capturing an inactive conformation in which the αJ helix occludes the MAPK common docking groove (canning2018cdklfamilykinases pages 1-3, bashore2024discoveryandcharacterization pages 7-8).  
Catalytic architecture includes the canonical VAIK lysine, HRD catalytic triad, DFG motif, a TXY activation segment and an intact hydrophobic spine; in the solved structures the C-helix is displaced, consistent with an inactive state (endicott2013structuralcharacterizationof pages 3-5).  
The inhibitor-bound complexes reveal a druggable back pocket accommodating heteroaromatic scaffolds, explaining observed selectivity profiles (bashore2024discoveryandcharacterization pages 1-2, canning2018cdklfamilykinases pages 3-4).

## Regulation

Activation involves phosphorylation of the dual Thr-X-Tyr motif in the activation loop, analogous to MAPK regulation mechanisms (bashore2024discoveryandcharacterization pages 1-2).  
Epigenetic modulation is documented: promoter hyper-methylation reduces CDKL2 expression in hepatocellular carcinoma and glioma, whereas elevated expression is observed in breast, stomach, kidney and prostate tumours, correlating with prognosis (bashore2024discoveryandcharacterization pages 7-8).  
Additional post-translational modifications, upstream kinases, phosphatases or allosteric regulators have not yet been experimentally assigned (canning2018cdklfamilykinases pages 3-4).

## Function

Sub-cellular distribution spans cytoplasm, nucleoplasm and centrosome (bashore2024discoveryandcharacterization pages 1-2).  
Transcript and proteomic studies show enriched expression in retina, testis, brain, lung and kidney, with multiple alternatively spliced isoforms (bashore2024discoveryandcharacterization pages 1-2).  
Reported biological roles include control of neuronal development, behaviour, emotion, cognition, regulation of epithelial–mesenchymal transition and participation in antiviral responses (bashore2024discoveryandcharacterization pages 1-2).  
Phosphorylation of EB2 links CDKL2 activity to microtubule dynamics in neurons, implicating the kinase in cytoskeletal regulation (bashore2024discoveryandcharacterization pages 1-2).  
No upstream activators or downstream effector kinases have yet been identified (canning2018cdklfamilykinases pages 3-4).

## Inhibitors

ATP-competitive agents TCS 2312 and CDK1/2 Inhibitor III bind CDKL2 as shown crystallographically (canning2018cdklfamilykinases pages 3-4, bashore2024discoveryandcharacterization pages 1-2).  
A selective acylaminoindazole chemical probe (compound 9) inhibits CDKL2 enzymatic activity and engages the kinase in cells; IC₅₀ and NanoBRET potency values are reported in the primary study (bashore2024discoveryandcharacterization pages 1-2).

## Other Comments

Aberrant CDKL2 expression associates with disease: decreased levels via promoter methylation predict poor outcome in hepatocellular carcinoma and glioma, whereas over-expression correlates with progression in breast, stomach, kidney and prostate cancers (bashore2024discoveryandcharacterization pages 7-8).  
Cdkl2-deficient mice exhibit impairments in contextual and spatial learning, linking the kinase to cognitive processes (martincarrascosa2025aphylogeneticanalysis pages 1-2).

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