## Phylogeny

* CDKL3 is classified within the CMGC super-group, CDKL family, in the canonical human kinome (manning2002theproteinkinase pages 3-3)
* One-to-one orthology between human and chimpanzee CDKL3 (>95 % identity) demonstrates strong conservation among great apes (anamika2008comparativekinomicsof pages 15-16)
* Invertebrate orthologs include Drosophila melanogaster RKIALRE and Caenorhabditis elegans KKIALRE, clustering with CDKL3 in cdc2-related kinase phylogenies (haq2001nkiatreisa pages 7-9)
* Vertebrate genomes typically retain a single CDKL3 copy, indicating limited lineage-specific duplication relative to other kinase families (manning2002theproteinkinase pages 3-3)

## Reaction Catalyzed

* ATP + protein-Ser/Thr-OH ⇌ ADP + protein-Ser/Thr-O-phosphate (unknownauthors1999identificationofnkiamre pages 59-65)

## Cofactor Requirements

* Catalytic activity depends on divalent metal ions (Mg²⁺ or Mn²⁺) that coordinate ATP within the active site (unknownauthorsUnknownyearpřípravanovýchsloučenin pages 24-28)

## Substrate Specificity

* High-throughput profiling places CDKL3 in the proline-directed class with a consensus [S/T]-Pro motif and exclusion of acidic residues at –2/–3 positions (johnson2023anatlasof pages 4-4)
* Position-specific scoring matrices align CDKL3 with classical CDKs, showing preference for hydrophobic or neutral residues at the +2 position (johnson2023anatlasof pages 9-10)

## Structure

* AlphaFold model AF-Q8IVW4-F1 shows a canonical bilobal kinase fold with N-terminal β-sheet/C-helix and α-helical C-lobe linked by an ATP-binding hinge (unknownauthorsUnknownyearpřípravanovýchsloučenin pages 24-28)
* The N-lobe contains an NKIAMRE cyclin-binding–like helix replacing the CDK PSTAIRE motif (unknownauthors1999identificationofnkiamre pages 59-65)
* The activation segment harbors a Thr-Asp-Tyr (TDY) motif characteristic of CDKL kinases and required for full activity (haq2001nkiatreisa pages 7-9)
* Catalytic core retains HRD catalytic loop, DFG Mg²⁺-binding motif and an intact hydrophobic spine consistent with an active conformation (unknownauthorsUnknownyearpřípravanovýchsloučenin pages 24-28)

## Regulation

* TDY activation-loop phosphorylation is not essential for basal activity, distinguishing CDKL3 from classical MAPKs (unknownauthors1999identificationofnkiamre pages 41-46)
* Conserved inhibitory sites Ser14 and Tyr15 correspond to CDK regulatory positions; upstream modifying enzymes are not yet identified (haq2001nkiatreisa pages 7-9)
* Alternative splice isoforms alter nuclear localization sequences, modulating subcellular distribution (haq2001nkiatreisa pages 7-9)

## Function

* Predominant expression in differentiated brain and kidney tissues identified by Northern blot (unknownauthors1999identificationofnkiamre pages 41-46)
* Up-regulated in glioma, where CDKL3 binds RRM2, activates JNK signalling and drives proliferation, migration and in vivo tumor growth (cui2021identificationofcdkl3 pages 1-2)
* JNK pathway activation rescues growth inhibition caused by CDKL3 knock-down, confirming downstream linkage (cui2021identificationofcdkl3 pages 11-13)
* Overexpression promotes Akt/PKB-dependent cell-cycle progression in oesophageal squamous-cell carcinoma and osteosarcoma (zhang2024cdkl3isa pages 17-18)
* Integrated proteomic mapping places CDKL3 within the CMGC kinase interaction network, expanding potential substrate and partner breadth (varjosalo2013theproteininteraction pages 3-4)

## Other Comments

* Balanced t(X;5)(q?;q31.1) translocation disrupting CDKL3 is associated with mild mental retardation (cui2021identificationofcdkl3 pages 13-13)
* CDKL3 loss reported in leukemic blasts from 5q-syndrome patients (unknownauthors1999identificationofnkiamre pages 41-46)
* Elevated CDKL3 levels correlate with poor prognosis across multiple solid tumors, underscoring potential therapeutic relevance (cui2021identificationofcdkl3 pages 1-2)

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