Phylogeny  
CDKL5 is a serine/threonine kinase of the CMGC group, clustering with CDKs, MAPKs, GSKs and CLKs (Van Bergen et al., 2022, pp. 1-4; Johnson et al., 2023, p. 4). The human CDKL subfamily contains five paralogues (CDKL1-5). Phylogenetic reconstruction places an ancestral CDKL5-like kinase in the last eukaryotic common ancestor, with the earliest split separating the CDKL5 branch from the remaining CDKL proteins (Martín-Carrascosa et al., 2025, pp. 1-10). Orthologues are strongly conserved in major model species, including mouse, zebrafish and Drosophila (Van Bergen et al., 2022, pp. 2-4; Martín-Carrascosa et al., 2025, pp. 1-2).

Reaction Catalyzed  
Protein-OH + ATP ⇌ Protein-O-PO₃²⁻ + ADP (Van Bergen et al., 2022, pp. 1-2; Katayama et al., 2020, pp. 1-2).

Cofactor Requirements  
Requires ATP as phosphate donor and divalent metal ions Mg²⁺ or Mn²⁺ for catalysis (Katayama et al., 2020, pp. 1-2; Martín-Carrascosa et al., 2025, pp. 8-10).

Substrate Specificity  
CDKL5 is proline-directed, showing strong preference for Pro at the +1 position. The experimentally defined consensus motif is Arg-Pro-X-Ser/Thr-Ala/Pro/Gly/Ser, with small uncharged residues C-terminal to the phospho-site (Van Bergen et al., 2022, pp. 4-5; Johnson et al., 2023, p. 4; Katayama et al., 2020, pp. 4-6).

Structure  
The 1030-residue protein contains an N-terminal kinase domain (aa 1-297) harbouring the ATP-binding pocket, catalytic and hydrophobic spines, and a TEY activation-loop motif; the long C-terminal region carries nuclear localisation (NLS) and export (NES) signals (Van Bergen et al., 2022, pp. 2-4; Unknown Authors, 2022, pp. 46-50). A crystal structure of the human kinase domain is available (PDB 4BGQ) and full-length AlphaFold prediction exists (UniProt O76039) (Van Bergen et al., 2022, pp. 2-4; Rout et al., 2019, pp. 1-4).

Regulation  
• Autophosphorylation on Tyr175 and Ser178 within the activation loop modulates activity (Van Bergen et al., 2022, pp. 2-4).  
• DYRK1A phosphorylates Ser308, promoting cytosolic retention (Medici, 2019, pp. 30-32; Unknown Authors, 2018, pp. 26-28).  
• Nuclear-cytoplasmic shuttling is controlled by the NLS/NES motifs and is developmentally regulated (Van Bergen et al., 2022, pp. 2-4; Medici, 2019, pp. 30-32).  
• Prolonged extrasynaptic NMDA receptor activation triggers dephosphorylation and proteasomal degradation (Unknown Authors, 2018, pp. 26-28).

Function  
Expression Highly enriched in cortical, hippocampal and cerebellar glutamatergic and GABAergic neurons; low in glia. Levels rise post-natally and remain high in adulthood (Van Bergen et al., 2022, pp. 1-2; Unknown Authors, 2024, pp. 22-26).

Substrates / Partners  – Nuclear: MeCP2, DNMT1, HDAC4, SMAD3, SOX9, EP400, TTDN1  
– Cytoplasmic: NGL-1, PSD-95, Amph1, Shootin1, MAP1S, EB2, ARHGEF2, CEP131  
– Interacting protein: IQGAP1  
(Van Bergen et al., 2022, pp. 11-14; Zhu & Xiong, 2019, pp. 7-9; Unknown Authors, 2021, pp. 14-17)

Biological roles Regulates transcription, RNA processing, dendritic arborisation, synaptic plasticity, ciliogenesis and cell-cycle related events. Influences BDNF-Rac1, Akt/GSK3β and Akt/mTOR signalling cascades (Van Bergen et al., 2022, pp. 1-2; Medici, 2019, pp. 30-32; Zhu & Xiong, 2019, pp. 7-9).

Inhibitors  
No small-molecule inhibitors are described in the provided text.

Other Comments  
Pathogenic loss-of-function variants in the X-linked CDKL5 gene cause CDKL5 Deficiency Disorder, characterised by early-onset, drug-resistant seizures and severe neurodevelopmental delay; most mutations are de novo and impair catalytic activity (Van Bergen et al., 2022, pp. 1-2).

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