## Phylogeny

CLK2 is classified within the CMGC kinase group, CDC-like kinase (CLK) sub-family in the human kinome, as established by comparative kinome analyses that cite the original Manning 2002 framework (song2023cdc2likekinasesstructure pages 20-21).  
Paralog relationships: CLK2 shares 67–87 % sequence identity with human CLK1, CLK3 and CLK4 (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 2-4).  
Orthologs retaining the canonical CLK fold have been documented with kinase-domain identity of 98 % in Mus musculus, 90 % in Xenopus tropicalis, 84 % in Danio rerio, 72 % in Drosophila melanogaster (Doa), 63 % in Caenorhabditis elegans (MADD-3), 48 % in Arabidopsis thaliana (AFC2) and 44 % in Schizosaccharomyces pombe (Lkh1) (ogle2024comparisonofthe pages 7-9).  
Structure-based phylogeny positions CLK2 closest to casein kinase 2 within CMGC enzymes, despite low primary-sequence identity, reflecting marked structural similarity (lee2019structuralbasisfor pages 1-2).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr/Tyr → ADP + [protein]-O-phospho-Ser/Thr/Tyr (moyano2020cdclikekinases(clks) pages 1-3, lee2019structuralbasisfor pages 1-2).

## Cofactor Requirements

Catalytic turnover requires ATP and divalent Mg²⁺ ions, consistent with biochemical assays on CLK family members (song2023cdc2likekinasesstructure pages 21-22).

## Substrate Specificity

• Preferred linear consensus: R-x-x-S/T within arginine/serine-rich (RS) regions, concordant with the CLK substrate classes catalogued in the Johnson 2023 serine/threonine atlas referenced by Song et al. (song2023cdc2likekinasesstructure pages 21-22).  
• Documented cellular substrates include SRSF1-12, PTPN1, SRSF3, PPP2R5B, PPARGC1A, PAGE4 and the tissue-factor pre-mRNA product F3 (song2023cdc2likekinasesstructure pages 3-3, song2023cdc2likekinasesstructure pages 21-22).  
• Dual-specificity toward tyrosine is supported by autophosphorylation on an activation-loop Tyr, aligning with intrinsic specificity data from the Yaron-Barir 2024 atlas cited in Lindberg et al. (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 4-7).

## Structure

Domain organisation: intrinsically disordered RS-rich region (residues 1-≈120); bilobal kinase domain R130–D496 containing the invariant EHLAMMERILG/LAMMER motif (kallen2018x‐raystructuresand pages 8-9).  
Experimental structures: apo CLK2 (PDB 3NR9) and inhibitor complexes 6FYL and 6KHE resolved at 1.8–2.2 Å (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 4-7).  
Key catalytic and regulatory elements:  
– Lys–Glu salt bridge stabilising the N-lobe/C-helix interface and a continuous hydrophobic spine spanning β4-αC-DFG (song2023cdc2likekinasesstructure pages 3-3).  
– Activation loop bearing an autophosphorylated Tyr critical for activity and responsible for temperature-sensitive structural rearrangements (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 10-12).  
– β-hairpin and MAPK-like insertions flank the ATP pocket, modulating substrate access (song2023cdc2likekinasesstructure pages 3-3).  
– Active-site cavity is the largest and most hydrophobic among CLKs; Val326 forms a decisive hydrophobic contact with benzonaphthyridine inhibitors, underpinning high affinity of CX-4945 (lee2019structuralbasisfor pages 7-9).

## Regulation

Post-translational modifications  
– Autophosphorylation on the activation-loop Tyr activates the kinase (lee2019structuralbasisfor pages 1-2).  
– AKT1 phosphorylates Ser34, Thr127 and Thr344, providing cross-talk with insulin signalling (prak2016benzobisthiazolesrepresenta pages 1-5).  
– Temperature-dependent conformational shifts within the activation segment modulate catalytic output (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 10-12).  
Transcriptional / post-transcriptional control  
– Insulin pathway effectors and microRNAs miR-573 and miR-144 down-regulate CLK2 expression (song2023cdc2likekinasesstructure pages 7-8).  
– Autoregulatory intron retention analogous to CLK1 is proposed for CLK2 (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 10-12).

## Function

Expression and localisation  
– Broad tissue distribution with higher expression in nervous tissue and colon; predominant nuclear localisation (song2023cdc2likekinasesstructure pages 21-22).  
Splicing regulation  
– Phosphorylation of SR proteins redistributes them from speckles to nucleoplasm, altering splice-site selection including Tau exon-10 (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 10-12).  
Metabolic control  
– Phosphorylation of PPARGC1A suppresses hepatic gluconeogenic gene expression and glucose output (moyano2020cdclikekinases(clks) pages 8-10).  
Signal transduction  
– Phosphorylates PPP2R5B, promoting PP2A assembly with AKT1 and facilitating AKT1 dephosphorylation (song2023cdc2likekinasesstructure pages 21-22).  
– Multisite phosphorylation of PAGE4 attenuates JUN-mediated transcription (song2023cdc2likekinasesstructure pages 21-22).  
Additional roles  
– Supports HIV-1 gene expression; concurrent inhibition of CLK2, CLK3 and CLK4 blocks viral production (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 10-12).  
– Enhances migration and invasion of breast, prostate and gastrointestinal cancer cells (song2023cdc2likekinasesstructure pages 16-17).

## Inhibitors

CX-4945 (silmitasertib), ATP-competitive; IC₅₀ = 3.8 nM on CLK2 (lee2019structuralbasisfor pages 1-2).  
CC-671, dual CLK2/TTK inhibitor; IC₅₀ = 6 nM on CLK2 (song2023cdc2likekinasesstructure pages 20-21).  
MU1210, selective probe; IC₅₀ = 20 nM on CLK2 with broad kinome selectivity (moyano2020cdclikekinases(clks) pages 19-23).  
SM08502 (lorecivivint), pan-CLK inhibitor with low-nanomolar potency on CLK2 (moyano2020cdclikekinases(clks) pages 19-23).  
Indazole series (e.g., Indazole1); IC₅₀ < 50 nM, ΔTₘ > 4 °C in thermal-shift assay (kallen2018x‐raystructuresand pages 8-9).  
KuWal151, 6,7-dihydropyrrolo[3,4-g]indol-8-one scaffold; potent against CLK1/2/4 with minimal DYRK crossover (walter2018molecularstructuresof pages 1-2).  
Benzobisthiazole 3A5; IC₅₀ = 68 nM on CLK2 (prak2016benzobisthiazolesrepresenta pages 14-18).  
Additional tool compounds TG003, T-025 and DB18 inhibit CLK2-mediated SR-protein phosphorylation at nanomolar concentrations (song2023cdc2likekinasesstructure pages 16-17).

## Other Comments

Disease associations include sporadic Alzheimer’s disease via Tau mis-splicing, Phelan–McDermid syndrome, intellectual disability, knee osteoarthritis, tendinopathy, obesity, MYC-driven and triple-negative breast cancer, glioblastoma and HIV infection (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 10-12, kallen2018x‐raystructuresand pages 8-9, moyano2020cdclikekinases(clks) pages 8-10).  
No recurrent pathogenic point mutations in CLK2 have been reported as of the latest surveys, although oncogenic mutations are documented for related family members (song2023cdc2likekinasesstructure pages 21-22).

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