## Phylogeny

• Classified within the Casein Kinase 1 (CK1) group of the eukaryotic protein-kinase superfamily in kinome surveys (fulcher2020functionsandregulation pages 1-2).  
• Forms a distinct branch that clusters near tau-tubulin and vaccinia-related kinases in kinome trees (cheong2011caseinkinase1 pages 1-2).  
• Shares >96 % sequence identity in the kinase domain with its closest human paralog CK1ε (francisco2022caseinkinase1 pages 1-2).  
• Experimentally verified orthologs include Saccharomyces cerevisiae Hrr25, Drosophila melanogaster Doubletime, Mus musculus Csnk1d transcription variants TV1–TV3, Danio rerio ck1δ and protozoan CK1 homologues, illustrating deep evolutionary conservation (xu2019structureregulationand pages 1-3).  
• Yeast Hrr25 and fly Doubletime retain conserved regulatory motifs and localization patterns found in human CK1δ (fulcher2020functionsandregulation pages 1-2).

## Reaction Catalyzed

ATP + [protein] Ser/Thr → ADP + [protein] phospho-Ser/Thr (xu2019structureregulationand pages 4-6).

## Cofactor Requirements

Catalytic turnover requires a divalent Mg²⁺ ion coordinated by the DFG149-151 motif of the activation loop (xu2019structureregulationand pages 4-6).

## Substrate Specificity

• Prefers primed motifs pSer/pThr-X-X-Ser/Thr with a phospho- or acidic determinant three residues N-terminal to the acceptor site (cheong2011caseinkinase1 pages 1-2).  
• Executes highly processive phosphorylation on the circadian motif pSxx(S/T)xx(S/T) within PER2 (francisco2022caseinkinase1 pages 2-3).  
• Catalyzes slower initiation on unprimed acidic sequences exemplified by the Ser-Leu-Ser motif of β-catenin and NFAT (xu2019structureregulationand pages 9-11).  
• Basic residues Arg178 and Lys224 in the catalytic cleft create ionic complementarity to acidic or phospho-primed substrates, governing selectivity (xu2019structureregulationand pages 3-4).

## Structure

• Domain organisation: N-terminal kinase domain (aa 9-277) harboring Lys38 (VAIK), Asp128 (HRD) and the DFG149-151 catalytic triad; C-terminal intrinsically disordered tail (~124 aa) that mediates autoinhibition (xu2019structureregulationand pages 4-6, francisco2022caseinkinase1 pages 1-2).  
• High-resolution crystal structures of truncations ending at residue 318 define the ATP pocket and hydrophobic spine (fulcher2020functionsandregulation pages 1-2).  
• Gatekeeper Met82 controls access to the selectivity pocket; mutation alters inhibitor affinity without abolishing catalysis (xu2019structureregulationand pages 4-6).  
• Activation loop adopts “Loop-Down” and “Loop-Up” conformers that bias the enzyme toward primed or unprimed substrates (francisco2022caseinkinase1 pages 2-3).  
• Tail phosphoserines dock into anion pockets within the kinase domain, creating pseudosubstrate motifs pSer/pThr-X-X-Tyr and suppressing activity (xu2019structureregulationand pages 4-6).  
• Dimerisation: an α-helix from one protomer inserts Arg13 into the partner’s adenine pocket, blocking nucleotide binding and reducing activity (xu2019structureregulationand pages 8-9).

## Regulation

• Autophosphorylation at Ser318, Thr323, Ser328, Thr329, Ser331 and Thr337 produces intramolecular pseudosubstrate sequences that inhibit the kinase (xu2019structureregulationand pages 8-9).  
• PKA/Akt and CLK2 phosphorylate Ser370, modulating Wnt/β-catenin signaling (eng2017sitespecificphosphorylationof pages 16-17).  
• PKCα targets Ser53 and Ser328; Chk1 modifies Ser181 and Thr347; CDK2/E and CDK5/p35 phosphorylate additional C-tail sites, collectively tuning catalytic efficiency (eng2017sitespecificphosphorylationof pages 16-17, xu2019structureregulationand pages 9-11).  
• Protein phosphatase 1 removes inhibitory tail phosphates, accelerating the PER phosphorylation cycle (francisco2022caseinkinase1 pages 1-2).  
• SCF-β-TRCP–mediated ubiquitination controls CK1δ stability and couples phosphorylation of PER proteins and YAP1 to proteasomal degradation (cheong2011caseinkinase1 pages 3-5).  
• Heparin binding, C-terminal truncation or disruption of the dimer interface relieve autoinhibition and elevate catalytic rate (xu2019structureregulationand pages 6-8).  
• Scaffold interactions with PER1/2, Axin, FAM83 proteins, DDX3X and AKAP450 localise CK1δ to defined cellular compartments (cheong2011caseinkinase1 pages 3-5, xu2019structureregulationand pages 6-8).

## Function

• Ubiquitously expressed; shuttles between cytoplasm and nucleus and concentrates at peri-Golgi membranes, centrosomes and nuclear speckles via discrete NLS and CLS motifs (cheong2011caseinkinase1 pages 1-2, xu2019structureregulationand pages 11-12).  
• Circadian clock: hierarchical phosphorylation of PER1/2 dictates period length, nuclear entry and β-TRCP-dependent turnover (eng2017sitespecificphosphorylationof pages 16-17, cheong2011caseinkinase1 pages 3-5).  
• Wnt signaling: primes β-catenin at Ser45 and phosphorylates LRP5/6 and Dishevelled, promoting β-catenin degradation (cheong2011caseinkinase1 pages 3-5).  
• DNA damage response: phosphorylates p53 and MDM2, modulating stability and apoptotic output (cheong2011caseinkinase1 pages 3-5).  
• Hippo pathway: phosphorylation of YAP1 forms a β-TRCP degron that triggers proteolysis (cheong2011caseinkinase1 pages 3-5).  
• Additional substrates—Connexin-43, MAP1A, SNAPIN, TAU, TOP2A, DNMT1, ESR1, AIB1, HIF-1α, NFAT1, DARPP-32 and PGC-1α—connect CK1δ to cell-cell communication, cytoskeletal dynamics, transcription and metabolism (cheong2011caseinkinase1 pages 3-5, xu2019structureregulationand pages 22-24).  
• Regulates centrosome integrity, ciliogenesis, spindle checkpoint, neurite outgrowth and dopaminergic signaling (xu2019structureregulationand pages 37-39).

## Inhibitors

• PF-670462: ATP-competitive CK1δ/ε inhibitor with low-nanomolar cellular IC50; lengthens circadian period and resets behavioral rhythms (fulcher2020functionsandregulation pages 1-2).  
• D4476: competitive inhibitor with micromolar IC50 widely used to probe CK1δ/ε biology (fulcher2020functionsandregulation pages 1-2).  
• IC261: dual CK1δ/ε inhibitor displaying nanomolar potency in colon cancer cell lines and inducing G2/M arrest (roth2021assessingtheinhibitory pages 18-18).  
• Difluoro-dioxolo-benzoimidazol-benzamides: nanomolar CK1δ/ε inhibitors that suppress cancer cell proliferation (richter2014difluorodioxolobenzoimidazolbenzamidesaspotent pages 14-14).  
• Newly developed CK1-specific inhibitors exhibit enhanced potency against CK1δ mutants and colorectal cancer cells (liu2019newlydevelopedck1specific pages 25-26).  
• PF-5006739 is a brain-penetrant CK1δ/ε inhibitor active in addiction and metabolic models (xu2019structureregulationand pages 22-24).

## Other Comments

• Heterozygous T44A mutation reduces kinase activity and underlies familial advanced sleep-phase syndrome and familial migraine (francisco2022caseinkinase1 pages 2-3).  
• Hyperactive T67S variant enhances Wnt signaling and exhibits oncogenic potential in colorectal cancer models (xu2019structureregulationand pages 4-6).  
• N172D and T176I substitutions impair substrate binding and catalysis (xu2019structureregulationand pages 4-6).  
• Over-expression or activating mutations contribute to tumor progression in breast, colorectal, pancreatic and lymphoid malignancies; pharmacological inhibition induces apoptosis independent of Wnt status (xu2019structureregulationand pages 19-21).  
• CK1δ levels are elevated in Alzheimer’s disease; the kinase phosphorylates TAU, α-synuclein and TDP-43, linking it to neurodegenerative pathology (xu2019structureregulationand pages 37-39).

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