## Phylogeny

• CSNK1A1L belongs to the Casein Kinase 1 (CK1) group within the CMGC kinase superfamily defined by kinome‐wide phylogenetics (manning2002theproteinkinase pages 3-3).  
• The CK1 branch is most closely related to the TTBK and VRK families (cheong2011caseinkinase1 pages 1-2).  
• Experimentally validated orthologs include Mus musculus Csnk1a1, Danio rerio csnk1a1a, Drosophila melanogaster dco, and Caenorhabditis elegans kin-3 (venerando2014caseinkinasethe pages 10-11).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-O-phospho-Ser/Thr (cullati2024substratedisplacementof pages 15-15).

## Cofactor Requirements

Catalysis requires divalent Mg²⁺; all in-vitro assays include 10 mM MgCl₂ for activity (cullati2024substratedisplacementof pages 15-15).

## Substrate Specificity

• Highest efficiency on primed motifs pS/pT-X-X-S/T where the −3 position carries a phospho-Ser/Thr docking into a basic pocket of the kinase (cheong2011caseinkinase1 pages 2-3).  
• An acidic cluster (Asp/Glu) from positions −3 to −1 can substitute for the priming phosphate (cheong2011caseinkinase1 pages 2-3).  
• Large-scale motif profiling in yeast CK1 orthologs shows strong preference for acidic residues from −5 to −3 and minimal constraints at +1, confirming an acidophilic signature (mok2010decipheringproteinkinase pages 4-5).  
• Basic residues Lys229–Lys232 within the catalytic cleft engage the upstream acidic/phospho group and are essential for high-affinity substrate binding (jiang2018caseinkinase1α pages 1-3).

## Structure

Domain organisation  
– N-terminal kinase domain (Ile12–Ala282) executes catalysis (jiang2018caseinkinase1α pages 1-3).  
– C-terminal regulatory tail (~120 aa) contains autophosphorylation sites that modulate activity (cheong2011caseinkinase1 pages 1-2).

Three-dimensional architecture  
– The catalytic core adopts the canonical bilobal kinase fold and possesses the CK1-specific S-I-N triad in subdomain VIII (venerando2014caseinkinasethe pages 8-9).  
– Crystal structures of family members (e.g., CK1 catalytic domain PDB 1CSN and apo CK1δ PDB 1CKJ) reveal key catalytic elements: Lys41 (VAIK motif) for ATP anchoring, Asp131 (HRD motif) as catalytic base, and Ser22 in the glycine-rich loop for nucleotide coordination (mashhoon2000crystalstructureof pages 6-7).  
– The activation segment is constitutively in an active conformation; CK1 activity does not depend on activation-loop phosphorylation (cheong2011caseinkinase1 pages 1-2).  
– Molecular dynamics and recent crystal complexes show two activation-loop states (“loop up” vs “loop down”) that remodel a +1 hydrophobic pocket formed by Tyr225 and Leu173, thereby tuning substrate selection (ricci2025markovianstatemodels pages 15-18).  
– The AlphaFold model AF-Q8N752-F1 predicts a flexible, disordered C-tail tethered to the rigid kinase core, consistent with autoinhibitory behaviour (venerando2014caseinkinasethe pages 8-9).

## Regulation

• Multisite autophosphorylation within the C-terminal tail converts the enzyme to a low-activity state; okadaic-acid-sensitive phosphatases restore activity (cheong2011caseinkinase1 pages 1-2).  
• cis-Autophosphorylation of Thr220 in the catalytic lobe alters substrate preference (cullati2024substratedisplacementof pages 14-15).  
• Substrate binding displaces the phosphorylated tail, providing an allosteric re-activation mechanism (cullati2024substratedisplacementof pages 14-15).  
• Oxidative stress triggers tail dephosphorylation of the long splice variant, promoting hnRNP-C interaction in nuclear speckles (bedri2007regulationofprotein pages 14-17).  
• CRL4ᶜʳᵇⁿ E3 ligase recognises residues 35-41, enabling lenalidomide-dependent ubiquitination and degradation (jiang2018caseinkinase1α pages 15-17).  
• Lys49 acetylation antagonises Ser45 phosphorylation, linking HDAC6 activity to kinase output (jiang2018caseinkinase1α pages 15-17).

## Function

Expression & localisation  
– Ubiquitously expressed; the long splice variant contains an NLS and accumulates in nuclear speckles (bedri2007regulationofprotein pages 14-17).

Signalling roles  
– WNT/β-catenin: phosphorylates β-catenin at Ser45 within the destruction complex, priming GSK3β-mediated degradation (cheong2011caseinkinase1 pages 3-5).  
– Also associates with LRP6-containing signalosomes to modulate receptor phosphorylation (agajanian2022proteinproximitynetworks pages 1-2).  
– Circadian clock: family members phosphorylate PER proteins, influencing period length; CK1α activity contributes to this regulation (cheong2011caseinkinase1 pages 3-5).  
– Genome maintenance: mutation of catalytic-loop Thr220 in yeast orthologs causes hypersensitivity to replication stress, pointing to roles in DNA integrity pathways (cullati2024substratedisplacementof pages 14-15).  
– Interacts with PRMT1 to support stem-cell pluripotency and with the RNA helicase DDX3 to amplify WNT signals (jiang2018caseinkinase1α pages 15-17).

## Inhibitors

• IC261 – ATP-competitive inhibitor stabilising an intermediate conformation of the kinase (mashhoon2000crystalstructureof pages 3-3).  
• D4476 – sub-micromolar ATP-competitive inhibitor (jiang2018caseinkinase1α pages 15-17).  
• CKI-7 – low-potency ATP-competitive inhibitor (jiang2018caseinkinase1α pages 15-17).  
• TG003 and longdaysin – dual CLK/CK1 inhibitors that reduce CK1 activity in cells (jiang2018caseinkinase1α pages 15-17).  
• Pyrvinium pamoate and analogues SSTC-104/SSTC-3 – allosteric activators that enhance CK1α activity in the β-catenin destruction complex (cheong2011caseinkinase1 pages 3-5).

## Other Comments

• Loss of CK1α activity stabilises β-catenin and is implicated in colorectal cancer, ABC-DLBCL, and del(5q) myelodysplastic syndrome (jiang2018caseinkinase1α pages 15-17).  
• Hyperactivity of CK1 family isoforms contributes to tau hyperphosphorylation in neurodegenerative disorders (schittek2014biologicalfunctionsof pages 1-2).  
• The vertebrate-specific 28-aa “L-insert” within the long splice variant mediates oxidative-stress-responsive nuclear localisation (bedri2007regulationofprotein pages 14-17).

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