## Phylogeny

CSNK1A1 is a member of the Casein Kinase 1 (CK1) group, a discrete branch of the human kinome distinct from AGC, CAMK, CMGC, STE, TK and TKL groups (manning2002theproteinkinase pages 3-3).  
Within this group it clusters with tau-tubulin (TTBK) and vaccinia-related (VRK) kinases, reflecting an ancient serine/threonine lineage (venerando2014caseinkinasethe pages 8-9).  
Orthologs are conserved across fungi—Saccharomyces cerevisiae HRR25 and YCK1-3, Schizosaccharomyces pombe Cki1/2 and Hhp1/2—demonstrating early eukaryotic origin (gross1998caseinkinasei pages 2-4).  
Dictyostelium discoideum retains two CK1 genes, whereas Caenorhabditis elegans shows ~85 paralogs and Drosophila melanogaster ~10, exemplifying lineage-specific expansion (goldberg2006thedictyosteliumkinome—analysis pages 2-3, manning2002evolutionofprotein pages 1-2).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr ⇌ ADP + protein-L-Ser/Thr-phosphate (cullati2024substratedisplacementof pages 15-15).

## Cofactor Requirements

Catalysis is Mg²⁺-dependent; the kinase does not utilize GTP as an alternative phosphate donor (venerando2014caseinkinasethe pages 16-20, unknownauthors2020effectsofck1 pages 10-14).

## Substrate Specificity

CK1α preferentially phosphorylates serine or threonine residues that lie three to four positions C-terminal to a pre-existing phospho-Ser/Thr or an acidic residue, generating the consensus pS/pT-X-X-S/T with a strong Asp/Glu bias at −3 (xu2019structureregulationand pages 9-11).  
High-density peptide arrays confirm maximal activity when an aspartate or phospho-serine occupies the −3 position (cullati2024substratedisplacementof pages 10-11).  
An SLS (Ser-Leu-Ser) motif followed by acidic residues, as found in β-catenin and NFAT, constitutes a recognized variant (xu2019structureregulationand pages 9-11).

## Structure

The protein contains an N-terminal ~300-residue kinase domain followed by a variable autoinhibitory C-terminal tail (venerando2014caseinkinasethe pages 8-9).  
Paralog structures CK1δ (PDB 1CKI) and CK1γ (PDB 2CMW) reveal the canonical bilobal fold used to model CK1α (unknownauthors2023reversibleandcovalent pages 30-33, unknownauthors2020effectsofck1 pages 10-14).  
Key catalytic elements include Lys46 for ATP anchoring, Asp133 in the HRD motif as catalytic base, and Asp149 of the DFG motif coordinating Mg²⁺ (xu2019structureregulationand pages 4-6).  
Subdomain VIII possesses the CK1-signature SIN (Ser-Ile-Asn) triad replacing the conventional APE sequence (venerando2014caseinkinasethe pages 8-9).  
Met82 acts as the gatekeeper residue controlling inhibitor access (xu2019structureregulationand pages 4-6).  
The activation loop (L-9D) opens for catalysis, whereas a multi-phosphorylated C-tail can fold across the substrate pocket, enforcing autoinhibition (knippschild2014theck1family pages 1-2, cullati2024substratedisplacementof pages 10-11).

## Regulation

• Autophosphorylation at Ser318/321/326 creates a pseudo-substrate segment that suppresses activity (jiang2018caseinkinase1α pages 23-24).  
• PKA phosphorylation at Ser370 further decreases catalytic efficiency (knippschild2014theck1family pages 3-5).  
• SCF^FBXW7-mediated ubiquitination promotes proteasomal degradation; SUMOylation alters localization (knippschild2014theck1family pages 3-5).  
• Proteolytic removal or substrate-induced displacement of the C-tail relieves inhibition (venerando2014caseinkinasethe pages 10-11, cullati2024substratedisplacementof pages 10-11).  
• A dimer interface observed in CK1δ structures can occlude the ATP site, suggesting a transient inhibitory assembly for CK1α (xu2019structureregulationand pages 8-9).  
• Binding of phosphatidylinositol-4,5-bisphosphate diminishes activity in specific cell types (venerando2014caseinkinasethe pages 10-11).

## Function

CK1α is ubiquitously expressed, with high levels in intestinal epithelium, melanomas, multiple myeloma, lung and breast cancers, and hematopoietic progenitors (jiang2018caseinkinase1α pages 14-15).  
It initiates canonical Wnt signalling turnover by phosphorylating β-catenin at Ser45 (janovska2020targetingcaseinkinase pages 13-14).  
Phosphorylation of PER1/2 integrates CK1α into the circadian clock (jiang2018caseinkinase1α pages 6-7).  
By phosphorylating DEPTOR at Ser286/287/291, the kinase activates mTORC1/2 under nutrient-rich conditions (jiang2018caseinkinase1α pages 6-7).  
Association with the mitotic spindle supports chromosome segregation during cell division (gross1998caseinkinasei pages 1-2).  
Targeting of keratin intermediate filaments facilitates cytoskeletal remodeling and epithelial migration (unknownauthors2020effectsofck1 pages 17-20).  
CK1α phosphorylation of NLRP3 restrains inflammasome assembly and innate immune activation (knippschild2014theck1family pages 2-3).

## Inhibitors

D4476: ATP-competitive inhibitor, IC₅₀ ≈ 0.2–0.3 µM against CK1 isoforms; >20-fold selectivity over unrelated kinases (perez2011proteinkinasesck1 pages 11-13).  
PF-670462: Imidazol-pyrazol-pyrimidine derivative; IC₅₀ ≈ 0.013 µM for CK1δ with partial cross-activity toward CK1α (cozza2016caseinkinasesas pages 10-12).  
SR-3029: Nanomolar inhibitor selective for CK1δ yet active on CK1α (knippschild2014theck1family pages 18-21).  
IC261: Indolinone compound; IC₅₀ ≈ 1 µM for CK1δ/ε and ~10 µM for CK1α; also binds tubulin (cozza2016caseinkinasesas pages 10-12).  
CK1α shows relative resistance to staurosporine, requiring ≥100 µM for inhibition (venerando2014caseinkinasethe pages 16-20).

## Other Comments

Haploinsufficiency of CSNK1A1 caused by 5q deletion activates β-catenin and expands hematopoietic stem cells in myelodysplastic syndrome (unknownauthors2017pathophysiologyandtreatment pages 30-35).  
Missense mutations E98K, H134L and D140A occur in ~5–7 % of del(5q) MDS cases and impair kinase function (bello2015csnk1a1mutationsand pages 1-2).  
Combined CSNK1A1 haploinsufficiency and mutant TP53 elevate MYC expression and accelerate leukemic transformation (fuchs2024collaborativeeffectof pages 10-11).  
Low CK1α expression associates with poor prognosis in colorectal cancer (jiang2018caseinkinase1α pages 22-23).  
CK1α activity modulates resistance to EGFR inhibitors and chemotherapeutics in solid tumours and multiple myeloma (jiang2018caseinkinase1α pages 22-23).  
Phosphorylation of tau and α-synuclein by CK1 family members links the kinase to Alzheimer-related pathology (qiao2019smallmoleculemodulators pages 2-2).

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