## Phylogeny

CSNK1G3 (CK1γ3) is assigned to the Casein Kinase 1 (CK1) family, one of the seven principal eukaryotic protein-kinase groups defined in the human kinome (manning2002evolutionofprotein pages 1-2).  
Phylogenetic analyses place the CK1 family as a distinct monophyletic clade, clearly separated from CMGC, AGC, CAMK, STE, TK and TKL groups (hanks2003genomicanalysisof pages 4-5).  
CK1γ3 clusters with its paralogues CK1γ1 and CK1γ2 while retaining the conserved catalytic core shared by CK1α, CK1β, CK1δ and CK1ε (martin2009kinomerv.1.0 pages 3-4).  
Orthologs are recorded in yeast (Hrr25), nematode (csnk-1), fly (gilgamesh), amoeba (CK1d), malaria parasite (PfCK1), mouse and rat CK1γ3, demonstrating deep evolutionary conservation across eukaryotes (andrade2011eukaryoticproteinkinases pages 16-17, goldberg2006thedictyosteliumkinome—analysis pages 1-2, ward2004proteinkinasesof pages 4-5, kusuda1999cloningandchromosome pages 3-5).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-Ser/Thr-P (unknownauthors2004caseinkinase1 pages 93-101).

## Cofactor Requirements

Catalysis is ATP-dependent; the referenced work does not stipulate an obligatory divalent metal ion, although CK1 assays are routinely performed with Mg²⁺ (unknownauthors2004caseinkinase1 pages 93-101).

## Substrate Specificity

• Prefers substrates bearing a phospho-serine/threonine or an acidic residue three positions N-terminal to the target site, canonical motif pS/pT-X-X-S/T (cheong2011caseinkinase1 pages 2-3).  
• Efficiently phosphorylates unprimed acidic clusters found in proteins such as β-catenin and NFAT (cheong2011caseinkinase1 pages 1-2).  
• Recognises an auxiliary F-X-X-X-F scaffold motif that enhances multi-site phosphorylation on some substrates (cheong2011caseinkinase1 pages 2-3).  
• Kinome-wide profiling classifies CK1γ3 as an acidophilic serine/threonine kinase (johnson2023anatlasof pages 4-4).

## Structure

The protein comprises an N-terminal bilobal kinase domain (~1–300 aa) and a variable C-terminal tail (~140 aa).  
• Kinase domain: small β-strand N-lobe and larger α-helical C-lobe form the catalytic cleft; key residues include Lys41 (ATP anchoring), Thr166 in the activation loop, Arg183 and Lys222 that create the phosphate-recognition pocket (unknownauthors2004caseinkinase1 pages 93-101).  
• Activation loop: does not require phosphorylation for activity, distinguishing CK1 from many other kinases (cheong2011caseinkinase1 pages 1-2).  
• C-terminal tail: contains multiple autophosphorylation sites that impose autoinhibition and cysteine residues subject to palmitoylation, the latter anchoring CK1γ isoforms to membranes (cheong2011caseinkinase1 pages 1-2).  
• A kinesin-homology segment within the catalytic domain promotes cytoskeletal interactions (reyes2018validationofnew pages 10-13).

## Regulation

• Autophosphorylation of the C-terminal tail inhibits catalytic activity; dephosphorylation by cellular phosphatases reverses this inhibition following WNT or metabotropic glutamate signalling (cheong2011caseinkinase1 pages 1-2).  
• Palmitoylation of C-terminal cysteines controls plasma-membrane localisation (cheong2011caseinkinase1 pages 1-2).  
• Tail phosphorylation creates docking sites for 14-3-3 proteins, further modulating activity and localisation (cheong2011caseinkinase1 pages 1-2).  
• Additional regulatory inputs include phosphorylation by PKA, Akt, PKCα, CDKs, Chk1 and CLK2, and interaction with scaffold proteins such as CG-NAP/AKAP450 and DDX3 (reyes2018validationofnew pages 15-17).  
• Activation-loop residue Thr166 is required for full catalytic competence; mutation impairs kinase activity (unknownauthors2004caseinkinase1 pages 93-101).

## Function

• WNT signalling: CK1γ3 uniquely promotes β-catenin-dependent WNT signalling by directly phosphorylating LRP6 and forming complexes with β-catenin and planar cell-polarity components; knock-down of all three CK1γ isoforms diminishes pathway activity (agajanian2022proteinproximitynetworks pages 1-2).  
• Redox homeostasis: CK1γ3 interacts with the NADPH dual oxidase complex (e.g., DOXA-1) and enhances cellular ROS levels; human CK1γ3 rescues oxidative-stress phenotypes in csnk-1–deficient C. elegans (hu2023caseinkinase1 pages 10-12).  
• Cancer signalling: In breast-cancer cells the pan-CK1 inhibitor D4476 lowers CSNK1G3 expression and modulates PI3K/AKT/mTOR/S6K signalling, altering tamoxifen sensitivity (hoang2021csnk1g2differentlysensitizes pages 12-14).  
• Expression: CK1 isoforms, including CK1γ3, are ubiquitously expressed and constitutively active across tissues (reyes2018validationofnew pages 10-13).

## Inhibitors

• D4476 – pan-CK1 inhibitor that suppresses CK1γ3-dependent LRP6 phosphorylation, β-catenin stabilisation and ROS production (agajanian2022proteinproximitynetworks pages 1-2, hu2023caseinkinase1 pages 12-13).  
• Two moderately selective CK1γ chemical inhibitors reported to attenuate WNT-mediated signalling in cells (agajanian2022proteinproximitynetworks pages 1-2).  
• IC261 – ATP-competitive CK1 inhibitor impacting cell-adhesion pathways (reyes2018validationofnew pages 15-17).

## Other Comments

• Gene maps to chromosome 5q23; an alternative transcript (CSNK1G3L) originates from the same locus (kusuda1999cloningandchromosome pages 3-5).  
• CK1γ3 is listed as a “dark” kinase under the NIH Illuminating the Druggable Genome initiative, reflecting limited functional annotation relative to biomedical importance (agajanian2022proteinproximitynetworks pages 1-2).  
• Dysregulated CK1 activity links to neoplasia and neurodegenerative disorders, positioning CK1γ3 as a potential therapeutic target (cozza2016caseinkinasesas pages 3-4).  
• Essentiality is underscored by embryonic-lethal phenotypes in csnk-1 mutant nematodes, which can be rescued by human CK1γ isoforms (hu2023caseinkinase1 pages 10-12).

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