## Phylogeny

CSNK1G2 is a member of the casein kinase 1 (CK1) family, which is classified within the CMGC group of kinases alongside cyclin-dependent kinases, mitogen-activated protein kinases, and glycogen synthase kinases (manning2002theproteinkinase pages 7-8, johnson2023anatlasof pages 4-4). The CK1 group also includes the TTBK and VRK kinase families (manning2002theproteinkinase pages 3-3). The CK1 family is highly conserved across eukaryotes, with a broad phylogenetic distribution in mammals, yeast, and plants (anti2009nonspecificserinethreonineprotein pages 19-22, knippschild2014theck1family pages 1-2). Known orthologs include csnk-1 in *C. elegans* and cki3 in fission yeast (*Schizosaccharomyces pombe*) (hu2023caseinkinase1 pages 12-13, hoang2021csnk1g2differentlysensitizes pages 5-7).

## Reaction Catalyzed

As a serine/threonine kinase, CSNK1G2 catalyzes the transfer of the γ-phosphate group from an ATP donor to the hydroxyl group of serine or threonine residues on a protein substrate (agajanian2022proteinproximitynetworks pages 1-2, johnson2023anatlasof pages 3-4, manning2002theproteinkinase pages 7-8). The general chemical reaction is: ATP + protein → ADP + phosphoprotein (anti2009nonspecificserinethreonineprotein pages 19-22, johnson2023anatlasof pages 12-18). The kinase family shows a strong preference for ATP over GTP as the phosphate donor (anti2009nonspecificserinethreonineprotein pages 37-39).

## Cofactor Requirements

The catalytic activity of CSNK1G2 requires a divalent metal ion cofactor (manning2002theproteinkinase pages 3-3). The kinase is Mg²⁺-dependent, as Mg²⁺ ions coordinate with ATP to stabilize its triphosphate moiety and facilitate the phosphoryl transfer reaction (johnson2023anatlasof pages 3-4, johnson2023anatlasof pages 12-18, johnson2023anatlasof pages 7-7). The broader class of non-specific serine/threonine kinases (EC 2.7.11.1) can also exhibit Mn²⁺-dependent activity (anti2009nonspecificserinethreonineprotein pages 19-22).

## Substrate Specificity

The CK1 family, including CSNK1G2, preferentially phosphorylates acidic proteins and often requires a priming phosphorylation on the substrate (knippschild2014theck1family pages 3-5, johnson2023anatlasof pages 1-2). The canonical consensus phosphorylation motif for CK1 kinases is pSer/Thr-X-X-(X)-Ser/Thr, where pSer/Thr is a pre-phosphorylated residue (knippschild2014theck1family pages 3-5). The family also shows a preference for substrates with acidic residues near the phosphorylation site (johnson2023anatlasof pages 2-3). Non-canonical motifs, such as the SLS motif in β-catenin and NFAT or Lys/Arg-X-Lys/Arg-X-X-Ser/Thr, are also recognized (knippschild2014theck1family pages 3-5).

## Structure

Crystal structures of human CK1γ2 (e.g., PDB 2C47) reveal a canonical bi-lobal kinase fold, comprising a smaller N-terminal lobe rich in β-strands and a larger C-terminal lobe that is primarily α-helical (knippschild2014theck1family pages 1-2). These lobes form a catalytic cleft for ATP and substrate binding (knippschild2014theck1family pages 1-2). Key regulatory elements include the C-helix, located in the N-lobe, which is crucial for aligning catalytic residues and ATP coordination, and an activation loop that contributes to substrate specificity (knippschild2014theck1family pages 1-2). The activation loop of CK1 family members is not typically regulated by phosphorylation to modulate activity, which distinguishes it from many other kinase families (knippschild2014theck1family pages 1-2). A conserved structural feature is the hydrophobic spine, which consists of characteristic hydrophobic pockets and stabilizes the active kinase conformation (knippschild2014theck1family pages 1-2). The structure also contains a glycine-rich loop (P-loop) that forms the ceiling of the ATP-binding site (knippschild2014theck1family pages 2-3). Isoform-specific functions are supported by additional domains, such as a kinesin homology domain (KHD) and a putative dimerization domain (DD) (knippschild2014theck1family pages 2-3).

## Regulation

CSNK1G2 activity is regulated by post-translational modifications and protein-protein interactions. The kinase undergoes autophosphorylation on serine/threonine residues; autophosphorylation at Ser211 and Thr215 is required for its interaction with and inhibition of RIPK3 (li2020caseinkinase1g2 pages 11-12). Phosphorylation in the C-terminal domain can be catalyzed by other kinases or via autophosphorylation, affecting substrate affinity and enzyme activation (knippschild2014theck1family pages 3-5). A conserved C-terminal palmitoylation site is also crucial for its function in *C. elegans* (hu2023caseinkinase1 pages 10-12). Dimerization can negatively regulate activity by occluding the ATP-binding site (knippschild2014theck1family pages 3-5). Activity and localization are also modulated by interactions with protein scaffolds such as AKAP450 and the RNA helicase DDX3 (knippschild2014theck1family pages 3-5).

## Function

CSNK1G2 is highly expressed in mouse testis (li2020caseinkinase1g2 pages 1-2). It is an upstream negative regulator of receptor-interacting kinase 3 (RIPK3), which it binds and inhibits to suppress necroptosis (li2020caseinkinase1g2 pages 1-2, li2020caseinkinase1g2 pages 11-12). The kinase participates in Wnt signaling by priming the co-receptor LRP6 for phosphorylation, which facilitates GSK3β activity and pathway activation (agajanian2022proteinproximitynetworks pages 1-2). It is also involved in circadian clock regulation through the phosphorylation of PER proteins, which triggers their proteasomal degradation (schittek2014biologicalfunctionsof pages 2-4). In breast cancer cells, CSNK1G2 modulates the PI3K/AKT/mTOR/S6K signaling pathway in a manner dependent on the estrogen receptor (ER) status (hoang2021csnk1g2differentlysensitizes pages 12-14). Furthermore, CSNK1G2 regulates reactive oxygen species (ROS) homeostasis through physical interaction with the NADPH dual oxidase complex components DUOX and DUOXA (hu2023caseinkinase1 pages 1-2, hu2023caseinkinase1 pages 12-13). Other interacting partners of the CK1γ subfamily include β-catenin, planar cell polarity proteins, GLI family zinc finger proteins, and NFκB subunits (agajanian2022proteinproximitynetworks pages 1-2, schittek2014biologicalfunctionsof pages 2-4).

## Inhibitors

The pan-casein kinase 1 inhibitor D4476 has been shown to suppress ROS production elevated by CSNK1G2 overexpression (hu2023caseinkinase1 pages 12-13, hu2023caseinkinase1 pages 12-13). Two potent, moderately selective chemical inhibitors targeting the CK1γ family have also been characterized; these compounds suppress Wnt-driven phosphorylation and β-catenin stabilization (agajanian2022proteinproximitynetworks pages 1-2).

## Other Comments

Loss of CSNK1G2 function in mice leads to premature testis aging, a phenotype driven by enhanced necroptosis that can be reversed by deletion of *Ripk3* (li2020caseinkinase1g2 pages 1-2, li2020caseinkinase1g2 pages 11-12). In breast cancer, knockdown of CSNK1G2 increases tamoxifen toxicity in ER-positive cells (hoang2021csnk1g2differentlysensitizes pages 5-7). Aberrant Wnt signaling, to which CK1γ kinases contribute, is linked to cancer, neurodegeneration, and bone diseases (agajanian2022proteinproximitynetworks pages 1-2). The broader CK1 family is associated with circadian rhythm disorders (kusuda2000cloningexpressionanalysis pages 1-2). CSNK1G2 is classified as an understudied “dark kinase” by the NIH’s Illuminating the Druggable Genome program (hu2023caseinkinase1 pages 12-13, hu2023caseinkinase1 pages 13-15).

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