## Phylogeny

CSNK1G1 is a member of the Casein Kinase 1 (CK1) family of serine/threonine kinases (unknownauthors2021kinaseregulationof pages 28-33, hu2023caseinkinase1 pages 1-2). Based on the phylogenetic classification by Manning et al., 2002, it belongs to the CK1 group (unknownauthors2021kinaseregulationof pages 28-33, schittek2014biologicalfunctionsof pages 12-13). The vertebrate CK1 family includes seven isoforms: α, β, γ1, γ2, γ3, δ, and ε (kusuda2000cloningexpressionanalysis pages 1-2, schittek2014biologicalfunctionsof pages 1-2). CSNK1G1 is part of the CK1γ subgroup, along with CSNK1G2 and CSNK1G3 (agajanian2022proteinproximitynetworks pages 1-2). The Drosophila homolog is ‘gish’, and mammalian CK1 isoforms show evolutionary relationships to yeast isoforms like YCK1 and YCK2 (gold2020heterozygousdenovo pages 6-12, unknownauthors2003characterizationofthe pages 16-20).

## Reaction Catalyzed

CSNK1G1 catalyzes the transfer of the γ-phosphate group from ATP to the hydroxyl group of serine or threonine residues on a protein substrate (agajanian2022proteinproximitynetworks pages 8-9, schittek2014biologicalfunctionsof pages 2-4).

## Cofactor Requirements

The catalytic activity of CSNK1G1 requires a divalent cation, typically Mg²⁺ or Mn²⁺, as a cofactor (unknownauthors2021kinaseregulationof pages 28-33, hu2023caseinkinase1 pages 1-2, agajanian2022proteinproximitynetworks pages 15-16).

## Substrate Specificity

CSNK1G1 is an acidophilic kinase that belongs to motif cluster 3, which is characterized by a preference for negatively charged residues surrounding the phosphorylation site (johnson2023anatlasof pages 2-3). The experimentally determined consensus substrate motif involves a phosphorylated serine/threonine (pS/pT) or an acidic residue (Asp/Glu) at the -3 position relative to the phospho-acceptor site (johnson2023anatlasof pages 12-18). The kinase also shows a preference for acidic residues (D/E) at the +1 and/or +2 positions (johnson2023anatlasof pages 12-18, johnson2023anatlasof pages 3-4). This requirement for a priming phosphorylation or nearby acidic side chains is a key feature of its substrate recognition (unknownauthors2021kinaseregulationof pages 28-33, johnson2023anatlasof pages 2-3). The general consensus motif has been characterized as pS/pT-X-X-S/T (unknownauthors2021kinaseregulationof pages 28-33).

## Structure

CSNK1G1 has a domain organization typical of the CK1 family, with a highly conserved N-terminal kinase domain and a more variable C-terminal regulatory domain (gold2020heterozygousdenovo pages 6-12, kusuda2000cloningexpressionanalysis pages 1-2). The AlphaFold model for CSNK1G1 (Q9HCP0) reveals a canonical bilobal kinase fold (johnson2023anatlasof pages 2-3, unknownauthors2004caseinkinase1 pages 88-93). The C-terminal region contains palmitoylation sites for membrane anchoring (unknownauthors2021kinaseregulationof pages 28-33). Key structural features include a C-helix involved in ATP binding, an activation loop that regulates substrate access, and a hydrophobic spine that stabilizes the active conformation (johnson2023anatlasof pages 2-3, unknownauthors2004caseinkinase1 pages 93-101). The activation loop of CK1 is analogous to the T-loop of other kinases and contains a critical threonine residue (T166 in yeast Cki1) that is a site for regulatory phosphorylation (unknownauthors2004caseinkinase1 pages 88-93, unknownauthors2004caseinkinase1 pages 93-101). Conserved residues R183 and K222 are located in the substrate-binding cleft and are important for activity (unknownauthors2004caseinkinase1 pages 93-101). Two splice variants exist, a long (hCK1γ1L) and a short (hCK1γ1S) form, which differ in the C-terminal tail sequence (kusuda2000cloningexpressionanalysis pages 1-2).

## Regulation

The activity of CSNK1G1 is regulated by post-translational modifications (gold2020heterozygousdenovo pages 6-12). Palmitoylation at its C-terminus is necessary for its function and localization to the plasma membrane (agajanian2022proteinproximitynetworks pages 8-9, hu2023caseinkinase1 pages 12-13). ZDHHC8, a palmitoyltransferase, is an identified proximal interactor (agajanian2022proteinproximitynetworks pages 8-9). Autophosphorylation, which occurs predominantly in the C-terminal domain, can act as an auto-inhibitory mechanism, as demonstrated for other CK1 isoforms (schittek2014biologicalfunctionsof pages 1-2, unknownauthors2021kinaseregulationof pages 28-33).

## Function

CSNK1G1 is ubiquitously expressed, with notable expression in the brain (gold2020heterozygousdenovo pages 1-6). The long isoform (hCK1γ1L) is broadly expressed, while the short isoform (hCK1γ1S) is predominant in the testis (kusuda2000cloningexpressionanalysis pages 1-2).

CSNK1G1 is a key component of the Wnt signaling pathway, where it localizes to the plasma membrane as part of the Wnt signalosome (unknownauthors2021kinaseregulationof pages 28-33). A primary function is the phosphorylation of the Wnt co-receptor LRP6 at threonine 1479, which primes it for further phosphorylation by GSK3β and facilitates the recruitment of AXIN, leading to pathway activation (unknownauthors2021kinaseregulationof pages 28-33, unknownauthors2021kinaseregulationof pages 92-99). However, there is functional redundancy among the CK1γ isoforms; silencing of CK1γ1 alone does not significantly affect Wnt signaling, whereas co-silencing of all three CK1γ isoforms suppresses it (agajanian2022proteinproximitynetworks pages 1-2). CSNK1G1 does not activate Wnt reporter assays as robustly as CK1γ3 (unknownauthors2021kinaseregulationof pages 104-109). Its interacting partners include Wnt pathway components such as DVL, LRP6, AXIN1, β-catenin, and CELSR2 (unknownauthors2021kinaseregulationof pages 99-104, agajanian2022proteinproximitynetworks pages 1-2).

Beyond Wnt signaling, CSNK1G1 regulates oxidative stress by interacting with the NADPH dual oxidase component DUOXA2 (hu2023caseinkinase1 pages 12-13). It also inhibits RIG-I-mediated signaling via phosphorylation of the NF-κB subunit p65, promotes TNFα-induced necroptosis, and regulates NOTCH signaling (schittek2014biologicalfunctionsof pages 12-13, unknownauthors2021kinaseregulationof pages 99-104, unknownauthors2021kinaseregulationof pages 92-99). In the brain, it influences fast synaptic transmission by phosphorylating NMDA receptors (gold2020heterozygousdenovo pages 1-6).

## Inhibitors

The small molecule AKI00000062a inhibits CSNK1G1 with an IC50 of 5.2 nM (agajanian2022proteinproximitynetworks pages 8-9). Another potent inhibitor has been reported with an IC50 of approximately 5.29 nM (unknownauthors2021kinaseregulationof pages 99-104). The non-specific CK1 inhibitor D4476 also suppresses CSNK1G activity (hu2023caseinkinase1 pages 12-13). Generally, available CK1 modulators show limited selectivity across isoforms (unknownauthors2021kinaseregulationof pages 28-33).

## Other Comments

Heterozygous de novo variants in the CSNK1G1 gene are pathogenic, causing syndromic developmental delay and autism spectrum disorder (gold2020heterozygousdenovo pages 1-6, gold2020heterozygousdenovo pages 6-12). Associated clinical features can include dysmorphic features, epilepsy, and motor delays (gold2020heterozygousdenovo pages 6-12). These pathogenic variants include missense mutations within the kinase domain, as well as nonsense and splice-site mutations (gold2020heterozygousdenovo pages 1-6). The gene is considered intolerant to loss-of-function mutations (gold2020heterozygousdenovo pages 1-6). Given its critical role in Wnt signaling, dysregulation of CSNK1G1 is implicated in tumorigenesis (unknownauthors2021kinaseregulationof pages 28-33). The gene maps to chromosome 15q22.1–q22.31 (kusuda2000cloningexpressionanalysis pages 1-2).

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