Phylogeny CSNK2A3 is part of the human serine/threonine protein kinase family and is classified within the casein kinase 2 (CK2) group (johnson2023anatlasof pages 4-4). The protein kinase CK2 family belongs to the CMGC group of kinases (unknownauthors2024decipheringtherole pages 32-36, unknownauthors2016proteinkinaseck2 pages 30-35, unknownauthors2024decipheringtherole pages 199-202). CSNK2A3 is also classified within the Protein Kinase Like (PKL) group and possesses a eukaryotic protein kinase (ePK) fold (moret2020aresourcefor pages 7-10). It is considered an ‘IDG dark kinase’ because it is absent from the canonical Manning kinome but is present in the UniProt database (moret2020aresourcefor pages 7-10, moret2020aresourcefor pages 4-7). A significant debate exists regarding its status; some sources identify CSNK2A3 as an active kinase gene, while many others classify it as a pseudogene (johnson2023anatlasof pages 4-4, trembley2023proteinkinaseck2 pages 1-2, unknownauthors2016proteinkinaseck2 pages 30-35). The gene is intronless, located on chromosome 11p15, and has high sequence homology to *CSNK2A1* (trembley2023proteinkinaseck2 pages 1-2). It is described as a processed pseudogene, characterized by the lack of introns and the presence of a poly(A) tail, suggesting a retrotransposed origin (unknownauthors2024decipheringtherole pages 208-211, unknownauthors2024decipheringtherole pages 32-36).

Reaction Catalyzed The enzyme catalyzes the phosphorylation of serine or threonine residues on substrate proteins by transferring the gamma-phosphate group from a phosphate donor (johnson2023anatlasof pages 4-4, unknownauthors2016proteinkinaseck2 pages 30-35). Both ATP and GTP can be utilized as phosphate donors (trembley2023proteinkinaseck2 pages 1-2, unknownauthors2016proteinkinaseck2 pages 35-38, unknownauthors2024decipheringtherole pages 32-36).

ATP + [a protein] → ADP + [a phosphoprotein] (unknownauthors2016proteinkinaseck2 pages 35-38, unknownauthors2024decipheringtherole pages 208-211).

Cofactor Requirements Catalytic activity is dependent on divalent cations, such as Mg²⁺ or Mn²⁺, which act as cofactors (johnson2023anatlasof pages 4-4, trembley2023proteinkinaseck2 pages 1-2, unknownauthors2016proteinkinaseck2 pages 30-35). The kinase shows a preference for Mg²⁺ with ATP as the phosphate donor and Mn²⁺ with GTP (unknownauthors2024decipheringtherole pages 32-36).

Substrate Specificity CK2 family kinases, including CSNK2A3, preferentially phosphorylate acidophilic consensus motifs enriched in acidic residues surrounding the phosphorylation site (johnson2023anatlasof pages 4-4). The consensus motif is characterized as S/T–X–X–D/E, where acidic residues are positioned C-terminally to the phosphoacceptor site and X can be any amino acid except proline (unknownauthors2024decipheringtherole pages 199-202, unknownauthors2024decipheringtherole pages 208-211, unknownauthors2024decipheringtherole pages 32-36). The work by Johnson et al. (2023) provided a comprehensive atlas of substrate specificities for the human serine/threonine kinome, including the CK2 family (johnson2023anatlasof pages 4-4, johnson2023anatlasof pages 1-2). Substrate recognition is also influenced by unique structural features, such as a serine replacing the third glycine in the glycine-rich loop, which affects binding at the n-2 position, and basic residues near the α-helix C that bind substrates at the n+1 and n+3 positions (unknownauthors2016proteinkinaseck2 pages 35-38).

Structure CK2 kinases have a conserved catalytic domain with accessory domains for interacting with regulatory subunits and substrates; this includes an ATP-binding site and substrate recognition grooves (johnson2023anatlasof pages 4-4). The catalytic domain consists of a small N-terminal lobe rich in β-strands and a larger C-terminal lobe that is primarily α-helical, connected by a hinge region (unknownauthors2016proteinkinaseck2 pages 30-35). The CK2 holoenzyme is typically a heterotetramer composed of two catalytic subunits (α and/or α’) and two regulatory β subunits (trembley2023proteinkinaseck2 pages 1-2, unknownauthors2016proteinkinaseck2 pages 30-35). Unique structural features of the catalytic subunit include a constitutively active T-loop stabilized by the N-terminal 1-30 residues without phosphorylation and a serine substituting the third glycine in the glycine-rich loop (unknownauthors2016proteinkinaseck2 pages 30-35, unknownauthors2016proteinkinaseck2 pages 35-38). The nucleotide-binding cleft is shaped by bulky residues, including Val66 and Met163 (unknownauthors2016proteinkinaseck2 pages 35-38).

Regulation CK2 kinases exhibit constitutive catalytic activity and do not require activation loop phosphorylation or the displacement of inhibitory proteins (johnson2023anatlasof pages 4-4, trembley2023proteinkinaseck2 pages 1-2, unknownauthors2016proteinkinaseck2 pages 30-35). Regulation is primarily achieved through association with the CK2β regulatory subunits, which modulate activity, stabilize the catalytic subunits, serve as docking platforms, and influence substrate specificity (johnson2023anatlasof pages 4-4, unknownauthors2016proteinkinaseck2 pages 30-35, unknownauthors2024decipheringtherole pages 208-211). Autophosphorylation of the β subunit on Ser2 and Ser3 stabilizes the enzyme’s structure but does not alter its activity (unknownauthors2016proteinkinaseck2 pages 35-38).

Function CK2 kinases phosphorylate a vast number of substrates involved in diverse signaling pathways, including those that regulate cell cycle progression, transcription, apoptosis, cell survival, and proliferation (johnson2023anatlasof pages 4-4, unknownauthors2016proteinkinaseck2 pages 30-35). CK2 impacts pro-survival signaling through the NF-κB, Wnt/β-catenin, and PI3K/Akt pathways (unknownauthors2016proteinkinaseck2 pages 35-38). Key substrates include IκBα, β-catenin, Dishevelled, PTEN, Akt (at Ser129), c-Fos, c-Jun, c-Myb, and c-Myc (unknownauthors2016proteinkinaseck2 pages 35-38, unknownauthors2024decipheringtherole pages 199-202). Despite its debated functional role, *CSNK2A3* mRNA overexpression has been reported in certain human cancers, including Jurkat T cell leukemia and lung tumors (unknownauthors2024decipheringtherole pages 32-36). Knockout of the canonical CK2α or CK2β subunits results in embryonic lethality (trembley2023proteinkinaseck2 pages 1-2).

Inhibitors CX-4945 (silmitasertib) is a selective, ATP-competitive small molecule inhibitor that targets the catalytic activity of CK2, including CSNK2A3 (johnson2023anatlasof pages 4-4, unknownauthors2016proteinkinaseck2 pages 30-35, unknownauthors2024decipheringtherole pages 199-202). It binds to the kinase’s nucleotide-binding site and is used in research and clinical investigations (johnson2023anatlasof pages 4-4, unknownauthors2016proteinkinaseck2 pages 35-38). Another experimental inhibitor is 4,5,6,7-tetrabromotriazole (unknownauthors2024decipheringtherole pages 77-80).

Other Comments The functional status of *CSNK2A3* is a subject of controversy, with some studies suggesting it is an active kinase and others classifying it as a pseudogene that does not produce a functional protein (johnson2023anatlasof pages 4-4, trembley2023proteinkinaseck2 pages 1-2, unknownauthors2016proteinkinaseck2 pages 30-35). Despite its pseudogene annotation, *CSNK2A3* has shown transcriptional activity in various human cancers; its overexpression has been correlated with a worse prognosis in cervical cancer but with higher survival rates in renal clear cell carcinoma and lung adenocarcinoma (unknownauthors2024decipheringtherole pages 32-36). Dysregulation of CK2 is associated with cancer and neurodegenerative disorders (johnson2023anatlasof pages 4-4). Mutations in the related CK2 genes *CSNK2A1* and *CSNK2B* have been linked to Okur-Chung Neurodevelopmental Syndrome (OCNDS) (unknownauthors2024decipheringtherole pages 208-211, unknownauthors2024decipheringtherole pages 59-61).

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