## Phylogeny

CSNK2A1 (CK2α) is classified within the CMGC group of the human kinome, which also includes Cyclin-dependent kinases (CDK), Mitogen-activated protein kinases (MAPK), Glycogen synthase kinases (GSK), and CDK-like kinases (CLKs) (borgo2021proteinkinaseck2 pages 14-14, unni2022predictivefunctionalstatistical pages 2-3). Within the CMGC group, it belongs to the Casein kinase 2 (CK2) family (borgo2021proteinkinaseck2 pages 1-2, rabalski2016molecularpathwaysemergence pages 5-6). The protein is highly conserved, with known orthologs in key model organisms including yeast (*Saccharomyces cerevisiae*), fruit fly (*Drosophila melanogaster*), and mouse (*Mus musculus*) (ayoubi2024aguideto pages 1-3, nakashima2019identificationofde pages 1-2, manning2002theproteinkinase pages 2-3). The gene is located on human chromosome 20p13 and is highly homologous to its paralog CK2α′ (CSNK2A2) (trembley2023proteinkinaseck2 pages 1-2). A pseudogene, CSNK2A3 (or CSNK2A1P), which is highly homologous to CSNK2A1, is located on chromosome 11p15 (trembley2023proteinkinaseck2 pages 1-2, unknownauthors2024decipheringtherole pages 32-36).

## Reaction Catalyzed

CK2α is a serine/threonine protein kinase that catalyzes the transfer of the γ-phosphate from a phosphate donor to the hydroxyl group of serine or threonine residues on substrate proteins (borgo2021proteinkinaseck2 pages 14-14, borgo2021proteinkinaseck2 pages 16-17). It is unique in its ability to utilize both ATP and GTP as cosubstrates (trembley2023proteinkinaseck2 pages 1-2, unknownauthors2024decipheringtherole pages 32-36, unni2022predictivefunctionalstatistical pages 2-3). It has also been reported to catalyze tyrosine phosphorylation in certain contexts (villavicenciodiaz2017proteinkinaseck2 pages 15-16).

Reaction: ATP + protein -> ADP + phosphoprotein (borgo2021proteinkinaseck2 pages 14-14). Reaction: GTP + protein -> GDP + phosphoprotein (trembley2023proteinkinaseck2 pages 1-2, unni2022predictivefunctionalstatistical pages 2-3).

## Cofactor Requirements

The catalytic activity of CK2α requires divalent metal ions as cofactors (borgo2021proteinkinaseck2 pages 14-14). Mg²⁺ is commonly required for optimal activity, and Mn²⁺ can also serve as a cofactor, affecting substrate preference (borgo2021proteinkinaseck2 pages 16-17, unknownauthors2024decipheringtherole pages 32-36).

## Substrate Specificity

CK2α is an acidophilic kinase, demonstrating a strong preference for phosphorylating serine or threonine residues located within acidic sequence contexts (borgo2021proteinkinaseck2 pages 1-2, borgo2021proteinkinaseck2 pages 16-17). The kinase favors serine over threonine as the phosphoacceptor (borgo2021proteinkinaseck2 pages 14-14). The consensus phosphorylation motif is characterized by the presence of acidic residues (Aspartic acid, D; or Glutamic acid, E) near the phosphorylation site, particularly downstream (johnson2023anatlasof pages 4-5, rabalski2016molecularpathwaysemergence pages 5-6).

Multiple consensus motifs have been described: - A preference for acidic residues primarily at positions +1 to +3 relative to the phosphoacceptor (borgo2021proteinkinaseck2 pages 14-14, unni2022predictivefunctionalstatistical pages 38-38). - A minimal consensus motif of S/T-D/E-X-D/E, where S/T is the phosphorylated residue and X is any amino acid (johnson2023anatlasof pages 4-5, unni2022predictivefunctionalstatistical pages 2-3). - A similar motif described as S/T–X–X–D/E, where X is any amino acid except proline (unknownauthors2024decipheringtherole pages 32-36, unknownauthors2024decipheringtherole pages 45-49). - Other described motifs include Ser-X-X-acidic and [ST]xx[DEpS], the latter indicating that a pre-existing phosphoserine can serve as the acidic determinant (strum2022csnk2incancer pages 1-2, villavicenciodiaz2017proteinkinaseck2 pages 1-3, villavicenciodiaz2017proteinkinaseck2 pages 3-8).

Substrate recognition is facilitated by two anion binding sites (P+1 and P+3) located at the activation segment (unni2022predictivefunctionalstatistical pages 2-3).

## Structure

CK2α exists as a monomer or as a catalytic subunit within a heterotetrameric holoenzyme, typically composed of two catalytic subunits (α and/or α′) and two regulatory β subunits (unni2022predictivefunctionalstatistical pages 1-2, borgo2021proteinkinaseck2 pages 1-2). The holoenzyme can form as α2β2, αα′β2, or α′2β2 complexes (trembley2023proteinkinaseck2 pages 1-2). CK2α has a kinase-typical bilobal architecture, with an N-terminal domain containing a central five-stranded β-sheet and an α-helical C-terminal domain (unni2022predictivefunctionalstatistical pages 2-3). The N-terminal segment is essential for its constitutive activity (villavicenciodiaz2017proteinkinaseck2 pages 15-16).

Unique structural features distinguish it from other kinases. The catalytic site is smaller compared to most kinases (borgo2021proteinkinaseck2 pages 1-2). It is structurally fixed in its active conformation and lacks the large conformational changes common to other kinases upon activation (unni2022predictivefunctionalstatistical pages 2-3). A key feature is a distinctive DWG motif at the start of the activation loop, which replaces the more common DFG motif and serves to stabilize the active conformation (unni2022predictivefunctionalstatistical pages 2-3). The regulatory CK2β subunit interacts with CK2α via its C-terminal hairpin loop and regions around helix αF (unni2022predictivefunctionalstatistical pages 2-3).

## Regulation

CK2α is a constitutively active kinase that does not require classical activation mechanisms such as phosphorylation of an activation loop or direct response to second messengers (borgo2021proteinkinaseck2 pages 1-2, borgo2021proteinkinaseck2 pages 14-14, rabalski2016molecularpathwaysemergence pages 8-9). Its regulation is atypical and occurs primarily through several mechanisms: - **Subunit Assembly**: Interaction with the regulatory CK2β subunit within the tetrameric holoenzyme modulates CK2α stability, substrate specificity, and localization (borgo2021proteinkinaseck2 pages 1-2, johnson2023anatlasof pages 4-5, unni2022predictivefunctionalstatistical pages 2-3). - **Protein-Protein Interactions**: Activity is modulated by interactions with substrates and other regulatory proteins (unni2022predictivefunctionalstatistical pages 38-38, villavicenciodiaz2017proteinkinaseck2 pages 15-16). - **Subcellular Localization**: Shifts in subcellular localization affect access to substrates (borgo2021proteinkinaseck2 pages 16-17). - **Post-Translational Modifications**: The activity and substrate specificity of CK2α can be influenced by modifications such as phosphorylation, O-linked glycosylation, and acetylation (trembley2023proteinkinaseck2 pages 1-2). - **Transcriptional Regulation**: CK2α can influence the expression of its regulatory β subunit and can autoactivate its own promoter, potentially through the phosphorylation of transcription factors like ETS1 and SP1 (unknownauthors2024decipheringtherole pages 32-36).

## Function

CK2α is a pleiotropic kinase that phosphorylates hundreds of substrates, contributing to approximately 10% of the human phosphoproteome (borgo2021proteinkinaseck2 pages 1-2, strum2022csnk2incancer pages 1-2). It is essential for embryonic development, with knockout models being embryonically lethal (trembley2023proteinkinaseck2 pages 1-2, unni2022predictivefunctionalstatistical pages 1-2). It is ubiquitously expressed, with particularly high levels in the brain (unknownauthors2024decipheringtherole pages 45-49).

CK2α regulates numerous cellular processes, including cell cycle control, proliferation, apoptosis suppression, DNA damage response and repair, transcription, translation, and cell invasion/metastasis (borgo2021proteinkinaseck2 pages 1-2, strum2022csnk2incancer pages 1-2, trembley2023proteinkinaseck2 pages 1-2). It modulates several major signaling pathways, including PI3K/Akt, IKK/NFκB, JAK/STAT, Wnt/β-catenin, and androgen receptor (AR) signaling (borgo2021proteinkinaseck2 pages 1-2).

Key substrates and interacting partners include: - **Signaling Proteins**: Akt1 (promotes activity), PTEN (inhibits activity), IκBα (induces degradation), JAK2, STAT3, and RELA (NFκB) (borgo2021proteinkinaseck2 pages 1-2, strum2022csnk2incancer pages 1-2, strum2022csnk2incancer pages 7-8). - **Cell Cycle and Apoptosis Regulators**: β-catenin (stabilizes), TP53 (borgo2021proteinkinaseck2 pages 1-2, strum2022csnk2incancer pages 1-2). - **DNA Repair Proteins**: XRCC1, XRCC4, Rad51 (borgo2021proteinkinaseck2 pages 1-2, rabalski2016molecularpathwaysemergence pages 6-7). - **Neural Substrates**: Alpha-synuclein, tau, Groucho/TLE1, PACSIN1, and NMDA receptor subunits (borgo2021proteinkinaseck2 pages 16-17, unknownauthors2024decipheringtherole pages 45-49).

## Inhibitors

Several highly specific and effective inhibitors targeting CK2α have been developed, including both ATP-competitive and allosteric molecules (borgo2021proteinkinaseck2 pages 1-2). These include: - **CX-4945 (Silmitasertib)**: An ATP-competitive small-molecule inhibitor that has been evaluated in clinical trials for its anti-cancer activities (borgo2021proteinkinaseck2 pages 14-14, rabalski2016molecularpathwaysemergence pages 5-6). - **CIGB-300**: A peptide inhibitor that blocks the phosphorylation of specific substrates (borgo2021proteinkinaseck2 pages 14-14, rabalski2016molecularpathwaysemergence pages 1-2). - **CX-5011**: A small-molecule inhibitor with cytotoxic activity against drug-resistant cancer cells (rabalski2016molecularpathwaysemergence pages 8-9). - **Quinalizarin**: An inhibitor used to probe CK2α function (villavicenciodiaz2017proteinkinaseck2 pages 8-10).

## Other Comments

Dysregulation of CSNK2A1 is implicated in diverse human diseases. - **Cancer**: Elevated expression and activity of CK2α are common in many solid and hematological malignancies, where it regulates malignant hallmarks such as tumorigenesis, apoptosis evasion, invasion, and drug resistance. It is considered a therapeutic target in oncology (borgo2021proteinkinaseck2 pages 1-2, borgo2021proteinkinaseck2 pages 16-17, strum2022csnk2incancer pages 1-2). - **Neurological Disorders**: CSNK2A1 is linked to neurodegenerative diseases such as Parkinson’s and Alzheimer’s disease through its phosphorylation of substrates like alpha-synuclein (Ser129) and tau (borgo2021proteinkinaseck2 pages 16-17). Heterozygous *de novo* missense mutations in CSNK2A1 cause Okur-Chung Neurodevelopmental Syndrome (OCNDS), which is characterized by intellectual disability and developmental delay (unni2022predictivefunctionalstatistical pages 1-2, unknownauthors2024decipheringtherole pages 32-36). - **Other Diseases**: CSNK2A1 has also been associated with viral infections (including SARS-CoV-2), autoimmune disorders, cardiovascular diseases, diabetes, obesity, cystic fibrosis, and psychiatric syndromes (borgo2021proteinkinaseck2 pages 1-2).

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