## Phylogeny

CSNK2A2 encodes the catalytic subunit CK2α′ of protein kinase CK2. Within the kinome it belongs to the CMGC group and CK2 family of Ser/Thr kinases (Manning et al., 2002; Cesaro et al., 2023; Johnson et al., 2023). CSNK2A2 and its paralog CSNK2A1 (CK2α) arose from a gene-duplication event (Pirrello et al., 2005). Orthologs are conserved in major model organisms, including mouse, fruit fly and yeast, underscoring its evolutionary conservation (Pirrello et al., 2005; Unni et al., 2022).

## Reaction Catalyzed

Protein-Ser/Thr + ATP + Mg²⁺ ⇌ Protein-Ser/Thr-P + ADP + Mg²⁺ (Johnson et al., 2023).  
(The enzyme can also use GTP, but only the ATP-dependent reaction is shown.)

## Cofactor Requirements

Requires divalent metal ions—primarily Mg²⁺; Mn²⁺ can substitute (Cesaro et al., 2023; Manning et al., 2002; Strum et al., 2022).

## Substrate Specificity

CK2α′ is an acidophilic Ser/Thr kinase that favors acidic or phosphorylated residues near the phospho-acceptor site. The consensus motif is S/T-X-X-D/E/pS (Roffey & Litchfield, 2021; Johnson et al., 2023).

## Structure

CK2α′ adopts the classical bilobal kinase fold: a β-sheet-rich N-lobe (with an αC-helix) and an α-helical C-lobe (Johnson et al., 2023). It functions as a monomer or within a heterotetrameric holoenzyme composed of two catalytic (α/α′) and two regulatory β subunits (Trembley et al., 2023; Roffey & Litchfield, 2021). Unique structural features include:  
• an unusually long activation loop that locks the kinase in a constitutively active conformation, and  
• substitution of the third Gly in the canonical G-x-G-x-x-G motif by Ser, influencing substrate recognition (Roffey & Litchfield, 2021; Unknown authors, 2016).

## Regulation

CK2α′ is constitutively active and does not require activation-loop phosphorylation or second messengers (Rabalski et al., 2016; Roffey & Litchfield, 2021). Regulation occurs through:  
• post-translational modifications (phosphorylation, glycosylation, acetylation),  
• subcellular relocalisation, and  
• assembly with the regulatory CK2β dimer, which modulates substrate specificity but is not essential for catalysis (St-Denis & Litchfield, 2009; Roffey & Litchfield, 2021).

## Function

Expression: Highly expressed in brain (especially hippocampus and prefrontal cortex) and testes; peaks during late spermatogenesis. Nuclear in G1 and cytoplasmic in S phase (Montenarh & Götz, 2023).  
Cellular roles: Phosphorylates hundreds of substrates to regulate cell-cycle progression, apoptosis, transcription and DNA repair (Rabalski et al., 2016).  
Pathways: Participates in Wnt, JAK-STAT, PI3K/AKT and NF-κB signalling (Strum et al., 2022; Unknown authors, 2016).  
Documented substrates / partners include TP53, AKT, PTEN, STAT3, RELA, caspase-3, RAD51 and EIF2β; 155 direct interactors have been catalogued (Strum et al., 2022; Roffey & Litchfield, 2021; Unknown authors, 2020).

## Inhibitors

Experimental inhibitors under clinical/ pre-clinical evaluation:  
• CX-4945 (Silmitasertib) – ATP-competitive small-molecule inhibitor.  
• CIGB-300 – cell-permeable cyclic-peptide inhibitor.  
Both exhibit antitumor activity (Rabalski et al., 2016; Roffey & Litchfield, 2021).

## Other Comments

CK2α′ dysregulation is linked to numerous cancers (breast, lung, prostate, colon) and often correlates with poor prognosis (Rabalski et al., 2016; Strum et al., 2022). Associations have also been reported with neurodegenerative diseases (Roffey & Litchfield, 2021). Loss-of-function CSNK2A2 mutations cause Okur-Chung Neurodevelopmental Syndrome, and complete CK2 knockout is embryonic-lethal (Trembley et al., 2023; Unni et al., 2022).

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