1. Phylogeny  
   Casein kinase II subunit alpha′ (CK2α′), encoded by CSNK2A2, is one of two evolutionarily conserved catalytic subunits of the protein kinase CK2 family, which belongs to the CMGC group of eukaryotic protein kinases. Orthologs of CK2α′ have been identified across a broad spectrum of eukaryotic organisms—including fungi, plants, and mammals—underscoring its fundamental role in cellular regulation since the emergence of the Last Eukaryotic Common Ancestor (LECA) (Battistutta2009proteinkinaseck2 pages 2-4, Montenarh2023proteinkinaseck2α’ pages 1-2). Within the kinase complement of the human genome, CK2α′ shows a high degree of sequence conservation relative to its paralog CK2α, particularly in the catalytic domain, while divergence is most apparent in the C-terminal region (Montenarh2023proteinkinaseck2α’ pages 1-2, 2-4). This conservation places CK2α′ within a critical evolutionary core set of kinases that are responsible for governing essential cellular processes, with its structure and function maintained from yeast to human (Battistutta2009proteinkinaseck2 pages 2-4).
2. Reaction Catalyzed  
   CK2α′ catalyzes the phosphorylation reaction in which a phosphate group from ATP is transferred to the hydroxyl group of a serine or threonine residue in protein substrates. In chemical terms, the reaction can be represented as follows: ATP + [protein]–OH → ADP + [protein]–O–phosphate + H⁺ (template), a reaction that is central to its role as a serine/threonine kinase (Information section, template).
3. Cofactor Requirements  
   The catalytic activity of CK2α′ is dependent on the presence of ATP as the phosphate donor and requires divalent metal ions, most notably Mg²⁺, as essential cofactors for efficient substrate phosphorylation. This cofactor dependency facilitates proper positioning and stabilization of ATP within the active site during the phosphorylation reaction (Guerra2008proteinkinaseck2 pages 1-2, Montenarh2023proteinkinaseck2α’ pages 4-6).
4. Substrate Specificity  
   CK2α′ phosphorylates a wide array of substrates that typically display a high density of acidic amino acids immediately C-terminal to the target serine or threonine residue. The consensus substrate motif is generally defined as S/T-D/E-X-D/E, where an acidic residue at the +3 position is critical for recognition. This acidophilic substrate specificity underlies the kinase’s ability to modify many proteins involved in cell cycle regulation, apoptosis, and transcription, consistent with its role as a master regulatory node in signaling pathways (Battistutta2009proteinkinaseck2 pages 2-4, Montenarh2023proteinkinaseck2α’ pages 6-8).
5. Structure  
   CK2α′ possesses a typical eukaryotic protein kinase fold characterized by a bilobal architecture. The N-terminal lobe is primarily composed of antiparallel β-sheets and a conserved αC-helix, while the larger C-terminal lobe is dominated by α-helical elements and provides the substrate-binding and catalytic machinery. The central kinase domain contains the ATP-binding site, which is adapted to accommodate both ATP and, in some instances, GTP as phosphate donors. Notably, CK2α′ differs from CK2α by having a truncated C-terminal region; this divergence contributes to isoform-specific functional properties and influences its interaction affinity with the regulatory CK2β subunit. The CK2 holoenzyme is formed when two CK2α′ molecules associate with a dimer of CK2β via a region that includes zinc-binding motifs present in the beta subunits, thereby enhancing stability and modulating substrate specificity. Structural studies, as outlined in crystallographic analyses and supported by AlphaFold models, have underscored features such as the bilobal kinase domain, a well-defined ATP-binding pocket, and a constitutively active conformation maintained by intramolecular interactions that obviate the need for activation loop phosphorylation (Montenarh2023proteinkinaseck2α’ pages 4-6, Montenarh2023proteinkinaseck2α’ pages 8-9, Guerra2008proteinkinaseck2 pages 1-2).
6. Regulation  
   CK2α′ is characterized by its constitutive activity; unlike many other kinases, it does not require activation loop phosphorylation or binding of second messengers for activation. Instead, regulation is achieved primarily through holoenzyme assembly; the association with the regulatory CK2β subunit modulates substrate selectivity, thermal stability, and overall catalytic efficiency. In addition, CK2α′ can undergo post‐translational modifications—including autophosphorylation events and acetylation—that further fine‐tune its activity, although such modifications do not serve as an on/off switch but rather adjust the kinase’s functional dynamics (Battistutta2009proteinkinaseck2 pages 2-4, Montenarh2023proteinkinaseck2α’ pages 4-6). Isoform‐specific differences include a lower binding affinity for CK2β relative to CK2α, which may lead to variations in substrate targeting and cellular localization. These regulatory mechanisms ensure that CK2α′ functions as a nodal point integrating multiple cellular signals through its participation in the heterotetrameric holoenzyme (Guerra2008proteinkinaseck2 pages 1-2, Montenarh2023proteinkinaseck2α’ pages 2-4).
7. Function  
   As a catalytic subunit of casein kinase II, CK2α′ plays a pivotal role in the regulation of numerous cellular processes. It phosphorylates a broad spectrum of substrates involved in cell cycle progression, apoptosis, transcription, and DNA damage response. During mitosis, CK2α′ serves as a component of the p53/TP53‐dependent spindle assembly checkpoint, contributing to the maintenance of cyclin‐B–CDK1 activity and promoting G2 arrest in response to spindle damage. Furthermore, CK2α′ is required for p53-mediated apoptotic responses, as it phosphorylates p53 at Ser392 following UV irradiation. The subunit is expressed widely with enhanced tissue specificity observed in regions such as the brain and testis, where it contributes to cell type–specific functions including spermatogenesis and neuronal regulation. In its capacity as a regulatory node, CK2α′ integrates and coordinates diverse signals to produce a context-appropriate cellular response (Information section, Montenarh2023proteinkinaseck2α’ pages 2-4, Guerra2008proteinkinaseck2 pages 1-2).
8. Other Comments  
   Several chemical inhibitors targeting CK2 have been identified; for example, CX-4945 is a clinical-stage ATP-competitive inhibitor known to reduce CK2 activity, although it does not discriminate robustly between CK2α and CK2α′. Recent high-throughput screening efforts have led to the discovery of CK2α′-biased inhibitors that exploit subtle differences in the ATP-binding pocket and allosteric regions between the two catalytic isoforms, offering potential for isoform-selective pharmacological modulation (Mudaliar2024discoveryofa pages 1-3, Mudaliar2024discoveryofa pages 18-19). CK2 dysregulation has been implicated in various pathological processes including tumorigenesis, as overexpression or hyperactivity of CK2 is linked to enhanced cell survival, altered apoptosis, and aberrant transcriptional control in cancers. In addition, CK2 has been associated with viral infections and neurodegenerative diseases, further highlighting its role as a multifunctional regulator in cellular signaling networks. Although specific disease mutations within CSNK2A2 have not been exhaustively catalogued in the present literature, altered CK2α′ function or expression is recognized as having significant clinical implications, particularly in the context of cancer and cellular stress responses (Mudaliar2024discoveryofa pages 1-3, Villavicenciodiaz2017proteinkinaseck2 pages 45-48).
9. References  
   Battistutta2009proteinkinaseck2 pages 2-4.  
   Guerra2008proteinkinaseck2 pages 1-2.  
   Montenarh2023proteinkinaseck2α’ pages 1-2.  
   Montenarh2023proteinkinaseck2α’ pages 2-4.  
   Montenarh2023proteinkinaseck2α’ pages 4-6.  
   Montenarh2023proteinkinaseck2α’ pages 6-8.  
   Montenarh2023proteinkinaseck2α’ pages 8-9.  
   Mudaliar2024discoveryofa pages 1-3.  
   Mudaliar2024discoveryofa pages 18-19.  
   Unni2022predictivefunctionalstatistical pages 38-38.  
   Villavicenciodiaz2017proteinkinaseck2 pages 3-8.  
   Villavicenciodiaz2017proteinkinaseck2 pages 45-48.