1. Phylogeny  
   Casein kinase I isoform gamma-3 (CK1γ3), encoded by CSNK1G3, is a member of the casein kinase 1 (CK1) family, a group of serine/threonine protein kinases that is evolutionarily conserved across eukaryotes and can be traced from yeast to mammals (kusuda2000cloningexpressionanalysis pages 1-2, knippschild2014theck1family pages 2-3). CK1γ3 belongs to the CK1γ subfamily along with CK1γ1 and CK1γ2, and these isoforms share a conserved catalytic kinase domain yet display divergence in their noncatalytic regions that likely underlies isoform‐specific functions (agajanian2022proteinproximitynetworks pages 1-2, knippschild2014theck1family pages 2-3). Phylogenetically, the CK1 family is positioned within the broader eukaryotic kinome and forms part of a core set of kinases that evolved early, playing crucial roles in fundamental signaling pathways throughout eukaryotic evolution (kusuda2000cloningexpressionanalysis pages 1-2, venerando2022editorialcaseinkinases pages 1-3).
2. Reaction Catalyzed  
   CK1γ3 catalyzes the phosphorylation of serine/threonine residues on substrate proteins by transferring the γ-phosphate from ATP, a reaction that can be summarized as: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(phospho-L-serine/threonine) + H⁺ (agajanian2022proteinproximitynetworks pages 1-2).
3. Cofactor Requirements  
   The enzymatic activity of CK1γ3 depends on ATP as the phosphate donor and typically requires the presence of divalent metal ions, such as Mg²⁺, to stabilize the ATP and facilitate efficient transfer of the phosphate to the substrate (agajanian2022proteinproximitynetworks pages 1-2, cozza2016caseinkinasesas pages 21-21).
4. Substrate Specificity  
   CK1γ3 displays substrate specificity characterized by a preference for acidic substrates, including casein, which is operationally used to define the casein kinase family (agajanian2022proteinproximitynetworks pages 1-2). In addition, like other CK1 isoforms, CK1γ3 preferentially phosphorylates substrates containing pre-phosphorylated or acidic residues adjacent to the target serine/threonine residue, generally consistent with a consensus motif of the form (P)S/T–X–X–S/T, where “P” may represent a priming phosphate or an acidic residue that mimics phosphorylation (cozza2016caseinkinasesas pages 21-21, knippschild2014theck1family pages 3-5). Furthermore, CK1γ3 has been implicated in the regulation of the Wnt signaling pathway through the phosphorylation of key components such as the Wnt co-receptor LRP6, highlighting its role in a substrate network that modulates β-catenin–dependent transcription (agajanian2022proteinproximitynetworks pages 8-9).
5. Structure  
   CK1γ3 comprises a centrally located catalytic kinase domain that adopts the typical bilobal structure common to serine/threonine kinases; the smaller N-terminal lobe is predominantly composed of β-sheets, whereas the larger C-terminal lobe is mainly α-helical (bohm2019thekinasedomain pages 12-13, kusuda2000cloningexpressionanalysis pages 4-5). The two lobes are connected by a hinge region that forms the catalytic cleft, which houses the ATP-binding pocket and contains essential motifs such as the glycine-rich P-loop that coordinates the phosphate groups from ATP (bohm2019thekinasedomain pages 12-13, cozza2016caseinkinasesas pages 21-22). Distinct from other CK1 isoforms, CK1γ3 possesses a divergent C-terminal regulatory region that is thought to influence subcellular localization and protein–protein interactions through mechanisms such as post-translational modifications (for example, S-palmitoylation has been reported for CK1γ isoforms) (kusuda2000cloningexpressionanalysis pages 4-5, yin2006dysbindinstructuralhomologue pages 10-10). These structural features, combined with the conserved catalytic core, enable CK1γ3 to phosphorylate a broad spectrum of substrates while also allowing isoform-specific regulatory interactions within complex signaling networks (agajanian2022proteinproximitynetworks pages 3-3, cozza2016caseinkinasesas pages 21-22).
6. Regulation  
   CK1γ3 is constitutively active and its regulation is primarily achieved through post-translational modifications and protein–protein interactions. Its activity can be modulated via autophosphorylation events within regulatory domains, which may serve as an inhibitory mechanism to fine-tune kinase function (knippschild2014theck1family pages 1-2, venerando2022editorialcaseinkinases pages 1-3). In addition, phosphorylation by other kinases, including checkpoint kinase 1 (Chk1) and protein kinase A (PKA), has been demonstrated for other CK1 family members and is believed to similarly influence CK1γ3 activity by altering substrate affinity or subcellular distribution (bohm2019thekinasedomain pages 13-14, cozza2016caseinkinasesas pages 21-22, knippschild2005theroleof pages 1-2). Moreover, regulatory mechanisms involving the noncatalytic C-terminal region—such as alternative splicing and potential lipid modification motifs that direct membrane localization—are likely contributors to the spatial and temporal control of CK1γ3 function in signal transduction pathways (kusuda2000cloningexpressionanalysis pages 4-5, agajanian2022proteinproximitynetworks pages 8-9).
7. Function  
   CK1γ3 functions as a serine/threonine-protein kinase that phosphorylates a diverse set of substrates, thereby modulating several cellular processes. A prominent role of CK1γ3 is its involvement in the Wnt/β-catenin signaling pathway; it phosphorylates components such as the Wnt co-receptor LRP6, which is essential for the activation of β-catenin–mediated transcription in response to Wnt ligands (agajanian2022proteinproximitynetworks pages 1-2, agajanian2022proteinproximitynetworks pages 8-9). In addition, by its broad substrate repertoire, CK1γ3 contributes to the regulation of various processes including cell growth, differentiation, and fast synaptic transmission as inferred from similarities to other CK1 family members (agajanian2022proteinproximitynetworks pages 1-2, knippschild2014theck1family pages 1-2). CK1γ3 is known to participate in protein complexes that organize key signaling cascades, with its unique interaction network and proximity partners distinguishing its role from related isoforms within the CK1γ subfamily (agajanian2022proteinproximitynetworks pages 3-3, knippschild2014theck1family pages 3-5).
8. Other Comments  
   Several small-molecule inhibitors have been developed that target CK1 family members, and these inhibitors have been shown to reduce phosphorylation events downstream of CK1 activity, such as LRP6 phosphorylation, thereby modulating β-catenin stabilization (agajanian2022proteinproximitynetworks pages 8-9, knippschild2014theck1family pages 2-3). CK1γ3 is classified as one of the understudied or “dark” kinases according to NIH initiatives, highlighting the need for further investigation into its specific substrates, regulatory mechanisms, and potential roles in human diseases including cancer and neurodegenerative disorders (agajanian2022proteinproximitynetworks pages 1-2, knippschild2014theck1family pages 1-2). As ongoing research continues to delineate isoform-specific interaction networks and post-translational modifications, CK1γ3 remains a promising target for therapeutic intervention in signaling pathways governing cell proliferation, synaptic function, and developmental processes (agajanian2022proteinproximitynetworks pages 8-9, knippschild2014theck1family pages 3-5).
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