1. Phylogeny  
   Casein kinase I isoform gamma‑1 (CK1γ1), encoded by the CSNK1G1 gene and referenced by UniProt accession Q9HCP0, is a member of the casein kinase I (CK1) family, a well‐conserved group of serine/threonine protein kinases present from yeast to mammals (knippschild2014theck1family pages 1-2). Within the CK1 family, isoforms are classified into several subgroups, including CK1α, CK1δ, CK1ε, and the gamma isoforms (γ1, γ2, and γ3); the gamma subgroup—of which CK1γ1 is a representative member—is distinguished primarily by its divergent non‑catalytic regulatory regions that are not conserved with the catalytic domains shared by all CK1 family members (fulcher2020functionsandregulation pages 1-2, schittek2014biologicalfunctionsof pages 1-2). The conserved kinase domain of CK1γ1, which is responsible for substrate phosphorylation, is evolutionarily related to the kinase domains of other CK1 isoforms, reflecting an origin that can be traced back to the common ancestor of eukaryotes (knippschild2014theck1family pages 1-2, fulcher2020functionsandregulation pages 1-2). Orthologs of CK1γ1 are present throughout mammalian species, and the gamma isoforms as a whole are recognized as an evolutionarily distinct subgroup within the larger CK1 kinome that participates in phylogenetically conserved cellular processes such as circadian regulation, stress response, receptor signaling, and cell cycle progression (schittek2014biologicalfunctionsof pages 1-2, venerando2022editorialcaseinkinases pages 1-3).
2. Reaction Catalyzed  
   CK1γ1 catalyzes the transfer of the γ‑phosphate from adenosine triphosphate (ATP) to specific serine or threonine residues in target proteins, resulting in the formation of ADP and a phosphorylated protein product plus the release of a proton (fulcher2020functionsandregulation pages 1-2, knippschild2014theck1family pages 1-2). In biochemical terms, the reaction can be summarized by the following equation:  
     ATP + [protein]-(L‑serine or L‑threonine) → ADP + [protein]-(L‑serine/threonine‑phosphate) + H⁺  
   This phosphorylation is critical for modulating the activity, stability, subcellular localization, and protein–protein interactions of the substrates, thereby integrating CK1γ1 activity into a wide range of cellular signaling networks (knippschild2014theck1family pages 1-2).
3. Cofactor Requirements  
   The catalytic function of CK1γ1 is dependent on the presence of divalent metal ions, a common requirement among protein kinases. Specifically, Mg²⁺ is necessary to coordinate the binding of ATP in the active site and to stabilize the transition state during the phosphoryl transfer reaction (fulcher2020functionsandregulation pages 1-2, knippschild2014theck1family pages 1-2). This cofactor requirement is essential for optimal enzymatic activity and ensures proper alignment of the ATP molecule within the catalytic cleft of the kinase domain (fulcher2020functionsandregulation pages 1-2).
4. Substrate Specificity  
   CK1γ1 displays a substrate specificity that is characteristic of the CK1 family, favoring serine and threonine residues that are flanked by acidic amino acids or contain a prior phosphorylation event at a nearby residue. A prevalent consensus motif for CK1-mediated phosphorylation is one where an acidic or phosphorylated residue occupies the −3 position relative to the target serine/threonine residue (knippschild2014theck1family pages 1-2, schittek2014biologicalfunctionsof pages 2-4). This acidotropic substrate preference allows CK1γ1 to phosphorylate a wide variety of substrates including casein, which historically provided the basis for its original naming, as well as regulatory proteins involved in signal transduction pathways such as those mediating Wnt signaling and stress response (fulcher2020functionsandregulation pages 4-5, schittek2014biologicalfunctionsof pages 2-4). In addition, CK1γ1’s ability to recognize both canonical acidic motifs and non‑canonical sequences contributes to its broad substrate spectrum, enabling phosphorylation of substrates such as CLSPN, a key effector in the DNA damage response (knippschild2014theck1family pages 1-2).
5. Structure  
   CK1γ1 is organized around a central kinase domain that is conserved across the CK1 family and exhibits the classical bilobal architecture of eukaryotic protein kinases. The N‑terminal lobe is predominantly composed of β‑strands and contains the glycine‑rich (P‑loop) region responsible for coordinating ATP binding, while the larger C‑terminal lobe is mainly formed of α‑helices and houses the catalytic loop and activation segment (kusuda2000cloningexpressionanalysis pages 1-2, fulcher2020functionsandregulation pages 4-5). These two lobes are connected by a hinge region that forms the catalytic cleft where ATP and substrate come into close proximity for the phosphotransfer reaction to occur (knippschild2014theck1family pages 1-2, schittek2014biologicalfunctionsof pages 1-2).  
   In CK1γ1, the catalytic core is flanked by variable non‑catalytic extensions, which include distinctive regulatory sequences in the C‑terminal region. These regions contribute to isoform‑specific substrate interactions and may contain post‑translational modification sites that modulate kinase activity. Structural studies, aided by crystallographic analysis, have provided evidence for the precise arrangement of these domains—for instance, crystallization efforts yielding structures such as PDB entry 2CMW have contributed to detailed insights into the molecular architecture and potential inhibitor binding sites of CK1γ1 (knippschild2014theck1family pages 2-3, kusuda2000cloningexpressionanalysis pages 1-2). Moreover, the extended regulatory domains in CK1γ1 are thought to play roles in subcellular targeting, possibly through membrane association signals like prenylation or palmitoylation motifs, which distinguish CK1γ isoforms from other family members (kusuda2000cloningexpressionanalysis pages 3-4, schittek2014biologicalfunctionsof pages 1-2).
6. Regulation  
   Although CK1γ1 is characterized by a constitutively active kinase domain, its activity is subject to multiple levels of regulation. Autophosphorylation within the flexible C‑terminal tail can serve as an autoinhibitory mechanism, reducing the kinase’s activity under basal conditions (fulcher2020functionsandregulation pages 14-15, knippschild2014theck1family pages 3-5). In addition to self‑phosphorylation, CK1γ1 activity is modulated by phosphorylation events mediated by other kinases, which can alter its conformation and adjust substrate recognition. Protein–protein interactions also contribute significantly to its regulation; binding to scaffold proteins, such as members of the FAM83 family, facilitates the proper subcellular localization of CK1γ1 and enhances its ability to encounter and phosphorylate substrates in specific cellular compartments (venerando2022editorialcaseinkinases pages 1-3, fulcher2020functionsandregulation pages 14-15). Furthermore, the presence of membrane‑targeting signals in the extended C‑terminal region may direct CK1γ1 to particular membrane subdomains where it participates in signaling events, including the regulation of the Wnt pathway (schittek2014biologicalfunctionsof pages 2-4, kusuda2000cloningexpressionanalysis pages 4-5). These diverse regulatory mechanisms ensure that CK1γ1 activity is tightly coordinated in response to changing cellular conditions and that its phosphotransfer function is appropriately integrated with cell signaling networks (fulcher2020functionsandregulation pages 14-15).
7. Function  
   CK1γ1 serves as a multifunctional serine/threonine‐protein kinase with a broad substrate repertoire that underlies its involvement in numerous cellular processes. A critical function of CK1γ1 is its participation in the Wnt signaling pathway; it phosphorylates components of the receptor complex such as the Wnt co‑receptor, thereby modulating downstream β‑catenin‑dependent signal transduction events (agajanian2022proteinproximitynetworks pages 1-2, knippschild2014theck1family pages 1-2). In addition, CK1γ1 phosphorylates CLSPN, a mediator of the DNA damage response, linking its activity to the regulation of cell cycle checkpoints and cellular responses to genotoxic stress (knippschild2014theck1family pages 1-2). Beyond these pathways, CK1γ1 is also implicated in the modulation of fast synaptic transmission mediated by glutamate, with its kinase activity potentially regulating synaptic components in a manner similar to other CK1 family members that influence receptor signaling and cytoskeletal dynamics (schittek2014biologicalfunctionsof pages 2-4, chergui2005physiologicalrolefor pages 8-9). The wide-ranging substrate specificity of CK1γ1 empowers it to act in diverse signal transduction cascades, affecting cellular processes such as proliferation, differentiation, apoptosis, and receptor trafficking (fulcher2020functionsandregulation pages 7-10, knippschild2014theck1family pages 1-2). In several contexts, the phosphorylation events mediated by CK1γ1 ensure proper timing and amplitude of signaling responses, which are essential for maintaining cellular homeostasis and an appropriate stress response (schittek2014biologicalfunctionsof pages 2-4).
8. Other Comments  
   Selective inhibition of CK1γ isoforms has been an area of active investigation due to the kinases’ central roles in oncogenesis, neurodegeneration, and regulation of cell signaling pathways. For example, small‑molecule inhibitors based on 2‑phenylamino‑6‑cyano‑1H‑benzimidazole derivatives have been developed to achieve isoform selectivity and potent inhibition of CK1γ activity, with such compounds showing promising specificity in preclinical studies (knippschild2014theck1family pages 21-22, cozza2016caseinkinasesas pages 21-21). The involvement of CK1γ1 in the phosphorylation of proteins implicated in Wnt signaling and in the cellular stress response positions it as a potential therapeutic target in diseases where these processes are aberrant. Moreover, mutations or dysregulation of CK1 isoforms, including CK1γ1, have been correlated with pathological conditions such as various carcinomas and neurodegenerative disorders linked to tau phosphorylation (schittek2014biologicalfunctionsof pages 1-2, fulcher2020functionsandregulation pages 18-19). In addition, studies highlighting the role of CK1γ isoforms in modulating fast synaptic transmission and receptor signaling further underscore the clinical interest in these kinases as targets for neurological disorders (chergui2005physiologicalrolefor pages 8-9). These characteristics—combined with the kinase’s defined substrate specificity and regulatory mechanisms—support continued exploration of CK1γ1 inhibitors as potential therapeutic agents (cozza2016caseinkinasesas pages 21-21, venerando2022editorialcaseinkinases pages 1-3).
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