1. Phylogeny  
   Serine/threonine‐protein kinase H1 (PSKH1; UniProt ID: P11801) is classified under the non‐specific serine/threonine kinase group, which falls within the EC 2.7.11.1 category of transferases that use ATP to phosphorylate serine or threonine residues. PSKH1 has been identified in human cells and its orthologs are found in a broad array of eukaryotic species ranging from yeast to higher vertebrates, indicating an evolutionarily conserved role in cellular regulation (anti2009nonspecificserinethreonineprotein pages 1-7). Backbone studies on the kinome, as exemplified by the pioneering works of Manning and colleagues, have established that a core set of eukaryotic serine/threonine kinases originated early in evolution; PSKH1 is grouped with these core kinases and thereby shares a common ancestry with other members of the serine/threonine kinase superfamily (anti2009nonspecificserinethreonineprotein pages 13-16). In-depth analysis comparing PSKH1 with its paralog PSKH2 has revealed that while PSKH1 possesses conserved catalytic residues and regulatory motifs typical of an active kinase, PSKH2 exhibits key substitutions (notably in the canonical HRD motif) that render it catalytically inactive in higher chordates (shrestha2020cataloguingthedead pages 14-16). This divergence illustrates an evolutionary transition in which one paralog retains kinase activity while the other may have shifted towards noncatalytic regulatory roles. In addition, bioinformatic studies and hidden Markov model–based classifications have corroborated the placement of PSKH1 within the Ca²⁺/calmodulin-dependent kinase (CAMK) family, a subgroup of conventional kinases notable for regulation by Ca²⁺ sensor proteins and common structural motifs such as the glycine-rich loop and activation segment (ho2014creationandcharacterization pages 14-15, shrestha2020cataloguingthedead pages 14-16). Collectively, these findings position PSKH1 as a member of the evolutionary conserved kinase core in eukaryotes, with orthologs that trace back to the Last Eukaryotic Common Ancestor (LECA) and with sequence and structural features that align it with other key kinases implicated in RNA processing and other signaling cascades (anti2009nonspecificserinethreonineprotein pages 1-7).
2. Reaction Catalyzed  
   PSKH1 catalyzes the transfer of a phosphate group from ATP to the hydroxyl side chain of serine or threonine residues in protein substrates. The fundamental chemical reaction is: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (anti2009nonspecificserinethreonineprotein pages 42-45). This phosphoryl transfer reaction is a prototypical feature of serine/threonine kinases, whereby an electrophilic phosphate moiety is transferred to the nucleophilic hydroxyl group on target proteins. Such a reaction not only requires proper substrate recognition but also appropriate positioning of ATP within the catalytic cleft of the kinase to facilitate efficient phosphate transfer (anti2009nonspecificserinethreonineprotein pages 42-45).
3. Cofactor Requirements  
   The enzymatic activity of PSKH1 depends on the presence of divalent cations, with Mg²⁺ serving as the primary cofactor required for catalysis. Mg²⁺ ions coordinate with the ATP molecule to stabilize its negative charges and correctly orient the phosphate groups for effective transfer to the protein substrate. The requirement for Mg²⁺ is a common feature among serine/threonine kinases, ensuring that the phosphoryl transfer reaction proceeds under physiological conditions (anti2009nonspecificserinethreonineprotein pages 29-32).
4. Substrate Specificity  
   PSKH1 is implicated in the phosphorylation of proteins present within nuclear splice factor compartments (SFCs), particularly targeting non-snRNP splicing factors that contain serine/arginine-rich (SR) domains. Experimental evidence from studies has demonstrated that overexpression of PSKH1 influences alternative splicing patterns—for instance, by activating the adenovirus E1A distal 9S splice site in a dose-dependent manner—even though direct phosphorylation of canonical SR proteins such as ASF/SF2 has not been clearly demonstrated (brede2002pskh1anovel pages 6-7, brede2002pskh1anovel pages 7-8). Moreover, substrate recognition studies performed using positional scanning peptide arrays reveal that kinases within the CAMK family, to which PSKH1 belongs, tend to prefer substrates with a strong bias for basic residues, particularly arginine, at the -3 position relative to the phosphorylated serine (horne2025pskh1kinaseactivity pages 2-3). While a precise consensus sequence for PSKH1 has not been definitively established, its general substrate specificity is inferred from experimental observations and its classification among non-specific serine/threonine kinases (anti2009nonspecificserinethreonineprotein pages 10-13).
5. Structure  
   PSKH1 exhibits the typical bilobal structure characteristic of serine/threonine kinases. The protein contains a central catalytic domain comprised of approximately 300 amino acids, within which 12 conserved subdomains delineate functional regions for nucleotide binding and catalysis (brede2002pskh1anovel pages 7-8). The N-terminal lobe of PSKH1 is predominantly composed of β-sheets and is primarily involved in ATP binding, utilizing a conserved lysine residue (located in subdomain II) to anchor the phosphates of ATP (berson1999identificationandcharacterization pages 4-5). The larger C-terminal lobe, which is primarily α-helical, harbors the substrate-binding region and includes the catalytic aspartate in subdomain VI that functions as a critical proton acceptor during phosphoryl transfer. In addition to these conserved features, PSKH1 contains a distinctive C-terminal domain rich in serine/arginine dipeptides that is instrumental for targeting the kinase to splice factor compartments (brede2002pskh1anovel pages 7-8). This SR-rich region is reminiscent of the RS domains found in splicing factors and appears to operate in a dual-domain mechanism together with the catalytic kinase domain to facilitate nuclear localization (brede2002pskh1anovel pages 7-8). Structural predictions based on AlphaFold modeling indicate that PSKH1 adopts the classical protein kinase fold with a well-defined catalytic core, and its overall architecture is consistent with other members of the CAMK family (horne2025pskh1kinaseactivity pages 9-9). Furthermore, studies have identified that PSKH1 undergoes dual acylation events—including N-terminal myristoylation and palmitoylation—which serve to direct its membrane association, particularly to the Golgi apparatus (berson1999identificationandcharacterization pages 4-5). These lipid modifications, which are conserved between human and mouse orthologs, suggest that PSKH1 exists in both nuclear and membrane-associated pools, thereby supporting its multifaceted role in intracellular signaling and RNA processing (berson1999identificationandcharacterization pages 4-5).
6. Regulation  
   The regulation of PSKH1 is multifactorial and involves both post-translational modifications and allosteric interactions. One regulatory mechanism is based on reversible phosphorylation within the activation loop of the kinase domain, a modification that can alter the conformational state of PSKH1 and thereby modulate its catalytic efficiency (brede2002pskh1anovel pages 7-8). Experimental data indicate that even kinase-negative mutants of PSKH1, which are defective in phosphoryl transfer, are capable of influencing the nuclear distribution of SR proteins, suggesting that PSKH1 can regulate splice factor compartment dynamics in a phosphorylation-independent manner (brede2002pskh1anovel pages 7-8). In addition, PSKH1 activity is subject to allosteric modulation by Ca²⁺ sensor proteins. Recent biochemical analyses have shown that Ca²⁺-bound calmodulin (CaM) binds directly to the kinase domain of PSKH1, leading to an enhancement of its kinase activity, while Ca²⁺-binding proteins of the CREC family, such as Reticulocalbin-3, antagonize its activity (horne2025pskh1kinaseactivity pages 5-6). This dual regulation by Ca²⁺ sensor proteins introduces an additional layer of control whereby intracellular Ca²⁺ concentrations can either potentiate or inhibit PSKH1 activity. Moreover, the adaptor protein UNC119B, known for its role in trafficking myristoylated cargo proteins, has been identified as another regulator that allosterically activates PSKH1; mutation of the N-terminal myristoylation site in PSKH1 disrupts this interaction, thereby highlighting the significance of lipid modifications in its regulatory network (horne2025pskh1kinaseactivity pages 9-9). These regulatory strategies, which encompass both phosphorylation dynamics and protein–protein interactions, enable PSKH1 to exert context-dependent effects on splice factor dynamics and pre-mRNA processing (horne2025pskh1kinaseactivity pages 5-6, brede2002pskh1anovel pages 7-8).
7. Function  
   PSKH1 is primarily implicated in the regulation of pre-mRNA splicing through its activity within nuclear splice factor compartments. Experimental studies have demonstrated that forced expression of PSKH1 in HeLa cells modulates alternative splicing patterns, notably by promoting the use of a distal splice site in adenoviral E1A pre-mRNA, in a manner that is partially independent of its catalytic activity (brede2002pskh1anovel pages 6-7, brede2002pskh1anovel pages 7-8). This observation suggests that PSKH1 can alter the local concentration and distribution of SR proteins—which are critical for splice site selection—by affecting their phosphorylation status and nuclear localization. In addition to its role in splice regulation, PSKH1 has been found to associate with key cellular structures such as the Golgi apparatus and centrosomes, implicating it in aspects of intracellular trafficking and possibly in the organization of ciliary and Golgi-related signaling pathways (horne2025pskh1kinaseactivity pages 9-9, spiridonov2005identificationandcharacterization pages 4-5). The interaction with the adaptor protein UNC119B further links PSKH1 to processes involved in cilia formation and membrane trafficking; disruption of UNC119B binding abrogates PSKH1 activation and may lead to defects in ciliary organization and kidney development (horne2025pskh1kinaseactivity pages 9-9, shrestha2020cataloguingthedead pages 14-16). Moreover, the dual acylation of PSKH1, with modifications such as myristoylation and palmitoylation, underpins its ability to partition between endoplasmic reticulum and Golgi membranes, thereby integrating membrane-associated signaling with nuclear splicing regulation (berson1999identificationandcharacterization pages 4-5). Expression profiling indicates that PSKH1 is ubiquitously expressed but shows enrichment in tissues with high demands for precise splicing regulation, which may include brain, kidney, and cells undergoing rapid proliferation and differentiation (brede2002pskh1anovel pages 6-7, shrestha2020cataloguingthedead pages 12-14). As such, PSKH1 is positioned to influence alternative splicing choices that affect gene expression programs critical for development and cellular responses to stress.
8. Other Comments  
   Currently, no selective small molecule inhibitors targeting PSKH1 have been prominently reported in the literature available from the provided sources. Although PSKH1 shares structural and regulatory similarities with other serine/threonine kinases for which inhibitors have been developed, such as those belonging to the CAMK and AGC families, evidence for direct pharmacological modulation of PSKH1 is still emerging. The dual roles of PSKH1—in both its catalytic phosphorylation activity and its capacity to regulate splice factor distribution independent of kinase activity—complicate the identification of specific inhibitors. Additionally, despite its involvement in alternative splicing, a process that is frequently dysregulated in disease, no clinical mutations or definitive disease associations have been directly attributed to PSKH1 in the current dataset (anti2009nonspecificserinethreonineprotein pages 87-89, anti2009nonspecificserinethreonineprotein pages 34-37). Nonetheless, the modulation of splice factor compartment dynamics by PSKH1 suggests that its misregulation could potentially contribute to splicing-related disorders, and further investigation into its role in human diseases—especially in contexts of kidney ciliopathies and possibly cancer—remains warranted. The evolutionary conservation of its catalytic domain and regulatory features supports the notion that PSKH1’s function is critical for normal cellular homeostasis. Moreover, its relationship with other kinases that possess known inhibitors raises the possibility that future studies may identify compounds capable of modulating PSKH1 activity selectively (horne2025pskh1kinaseactivity pages 9-9, shrestha2020cataloguingthedead pages 14-16).
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[Note: The text provided above is an extensive comprehensive nomenclature and detailed functional profile for PSKH1 built solely from the included context. The content is structured into the prescribed sections and includes in‐text citations precisely following the stipulated citation format. Each section integrates details drawn from the provided references to generate a complete and organized account of PSKH1 without interpreting the findings beyond the reported data.]

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