1. Phylogeny:  
   PSKH1 (Protein serine kinase H1; Uniprot: P11801) is a member of the serine/threonine kinase superfamily that displays significant evolutionary conservation among metazoans. Early sequence analyses of the human PSKH1 gene revealed an overall conservation of the catalytic core with ~50% sequence identity to rat CaMKI, which is a member of the Ca²⁺/calmodulin-dependent kinase (CAMK) group (brede2000characterizationofpskh1 pages 3-6). Comparative studies indicate that PSKH1 is found ubiquitously in various species, with orthologs documented in mammals and in distantly related organisms such as the pearl oyster Pinctada fucata, whose homolog shares conserved kinase subdomains with the human protein (dai2005cloningandcharacterization pages 2-5). Phylogenetic analysis based on conserved catalytic sequences locates PSKH1 within an evolutionary branch that is common to CAMK kinases. In addition, detailed studies have established that, in vertebrates, the PSKH family comprises both PSKH1 and its paralog PSKH2, with PSKH1 retaining catalytic activity and PSKH2 functioning as a pseudokinase in certain species due to key amino acid substitutions (reiterer2014dayofthe pages 6-7). According to the classification framework established by Manning et al. (2002) – “The protein kinase complement of the human genome” and “Evolution of protein kinase signaling from yeast to man” – PSKH1 is assigned to the serine/threonine kinases within the CAMK group. This group represents one of the evolutionarily conserved kinase families, whose origins can be traced back to an ancestral eukaryotic kinase complement. The protein’s evolutionary lineage underscores its inclusion in a core set of kinases that are present in the Last Eukaryotic Common Ancestor (LECA), maintained through extensive speciation events (Manning2002, Manning2002).
2. Reaction Catalyzed:  
   PSKH1 catalyzes the transfer of the γ-phosphate group from ATP to the hydroxyl group of serine or threonine residues on substrate proteins. The generalized reaction is: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺ (brede2000characterizationofpskh1 pages 10-11). This phosphorylation reaction is fundamental for modulating the function, localization, or stability of proteins involved in the regulation of pre-mRNA processing and splice factor compartment dynamics (brede2000characterizationofpskh1 pages 10-11).
3. Cofactor Requirements:  
   The catalytic activity of PSKH1 depends on divalent cations, with Mg²⁺ required as a cofactor to facilitate ATP binding and phosphate transfer (brede2000characterizationofpskh1 pages 10-11). In several biochemical assays, the kinase activity of PSKH1 is measured under conditions that include Mg²⁺ to support efficient catalysis (brede2000characterizationofpskh1 pages 8-10).
4. Substrate Specificity:  
   Studies investigating the substrate specificity of serine/threonine kinases indicate that PSKH1 displays a preference for phosphorylating serine residues, with its substrate recognition motif characterized by the presence of a basic residue – typically arginine – at the –3 position relative to the phosphoacceptor site (horne2025pskh1kinaseactivity pages 2-3). Comprehensive mapping using approaches as outlined in Johnson et al. (2023) has established consensus substrate motifs for the human serine/threonine kinome. Within this atlas, kinases in the CAMK group—including PSKH1—tend to select substrates that conform to a motif that includes a basic residue positioned three residues upstream from the phosphorylatable serine (johnson2023anatlasof pages 4-5). In vitro kinase assays have revealed that PSKH1 does not phosphorylate broad-spectrum substrates such as histone H1 or myelin basic protein, indicating its substrate specificity is relatively narrow and most consistent with proteins involved in nuclear splice factor compartment regulation (brede2000characterizationofpskh1 pages 10-11, brede2002pskh1anovel pages 8-9).
5. Structure:  
   PSKH1 is organized around a conserved kinase catalytic domain that comprises 11 subdomains typical for serine/threonine kinases (brede2000characterizationofpskh1 pages 3-6). The catalytic domain contains the conserved motifs required for ATP binding and phosphotransfer, including the VAIK motif with a critical lysine residue (located at approximately position 220), the HRD catalytic loop, and the DFG motif that coordinates magnesium ions (brede2000characterizationofpskh1 pages 3-6, reiterer2014dayofthe pages 6-7). In addition to the catalytic core, PSKH1 contains a proline-rich N-terminal region and an SR-rich C-terminal region; the latter is characteristic of proteins that interact with splice factor compartments (brede2002pskh1anovel pages 7-8). Structural studies have demonstrated that the kinase domain of PSKH1 is sufficient for homodimerization, with dimer formation being mediated primarily by interaction regions within the catalytic core (brede2000characterizationofpskh1 pages 8-10). While a high-resolution crystal structure of human PSKH1 may not be available, predicted models such as those generated by AlphaFold provide insight into the overall bilobal kinase architecture with an N-terminal lobe predominantly responsible for ATP binding (containing the glycine-rich loop) and a larger C-terminal lobe that contributes to substrate binding and regulatory interactions (horne2025pskh1kinaseactivity pages 7-8). In addition, localization determinants, such as a nuclear localization signal embedded within a basic region in the C-terminus, and motifs likely involved in interactions with other proteins (e.g., splice factors), further contribute to the structural and functional organization of PSKH1 (brede2002pskh1anovel pages 1-2).
6. Regulation:  
   PSKH1 is subject to multiple regulatory mechanisms that include autophosphorylation and protein–protein interactions. Autophosphorylation occurs predominantly on serine residues within a region spanning amino acids approximately 372 to 381, and this modification appears to be an intermolecular event (brede2000characterizationofpskh1 pages 10-11, brede2002pskh1anovel pages 8-9). The kinase’s activity can be modulated by calcium sensor proteins: for example, binding of the Ca²⁺/calmodulin complex to the kinase domain leads to inhibition of its autophosphorylation and catalytic activity (horne2025pskh1kinaseactivity pages 1-2, horne2025pskh1kinaseactivity pages 7-8). In contrast, other regulatory interactors such as UNC119B are capable of activating PSKH1 via direct engagement with the kinase domain, and mutations in the lipidation sites (myristoylation at Gly2 and palmitoylation at Cys3) have been shown to alter its basal activity and responsiveness to such regulatory proteins (horne2025pskh1kinaseactivity pages 7-8, dai2005cloningandcharacterization pages 5-7). Additional post-translational modifications, including potential phosphorylation events by other kinases, may further influence the subcellular localization and function of PSKH1; immunofluorescence studies have documented its presence in nuclear splice factor compartments, centrosomes, and the Golgi apparatus – localizations that are also sensitive to treatments such as Brefeldin A (brede2000characterizationofpskh1 pages 1-2, brede2002pskh1anovel pages 5-6).
7. Function:  
   The primary biological role attributed to PSKH1 is its involvement in the regulation of pre-mRNA splicing. PSKH1 has been shown to phosphorylate components related to the splice factor compartments (SFCs) within the nucleus, which contain non-snRNP splicing factors enriched in serine/arginine (SR) domains (brede2002pskh1anovel pages 1-2, brede2002pskh1anovel pages 6-7). In expression studies using cultured mammalian cells, PSKH1 has been detected in multiple intracellular locations, including the nuclear speckles, which are enriched in splicing regulators such as SC35 and ASF/SF2 (brede2000characterizationofpskh1 pages 1-2, brede2002pskh1anovel pages 7-8). Overexpression of PSKH1 in cell models results in altered nuclear organization of the SR proteins and shifts in the alternative splicing patterns, as evidenced by changes in adenovirus E1A minigene splice site usage (brede2002pskh1anovel pages 5-6, brede2002pskh1anovel pages 8-9). Beyond its nuclear functions, PSKH1 localization at the centrosomes and the Golgi apparatus suggests that it may also participate in the regulation of organelle dynamics, particularly in processes such as membrane trafficking and cell cycle control (brede2000characterizationofpskh1 pages 1-2, horne2025pskh1kinaseactivity pages 9-9). Tissue expression analyses have demonstrated ubiquitous expression with notable enrichment in the testis, specifically in pachytene spermatocytes and round spermatids, pointing to additional roles in germ cell development (brede2000characterizationofpskh1 pages 3-6).
8. Other Comments:  
   At present, specific inhibitors for PSKH1 have not been well established, and the protein remains one of the less intensively studied kinases within the human kinome. Some investigations have linked aberrant expression or mutation of PSKH1 with developmental contexts such as kidney ciliopathies and certain cancers, although detailed clinical correlations and inhibitor profiles require further research (horne2025pskh1kinaseactivity pages 9-9, reiterer2014dayofthe pages 6-7). The role of PSKH1 in regulating splice factor dynamics and alternative splicing presents a potential avenue for therapeutic intervention in diseases where splicing is misregulated. Ongoing studies employing proximity proteomics and site‐directed mutagenesis continue to refine the functional and regulatory map of PSKH1, but no selective small molecule inhibitors have yet been advanced to clinical use. Resources such as kinase inhibitor databases may eventually provide more targeted chemical probes to dissect PSKH1 function in cellular models (buchser2010kinasephosphataseoverexpressionreveals pages 8-10).
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