## Phylogeny

Serine/threonine-protein kinase H1 (PSKH1; UniProt P11801) is an active member of the eukaryotic protein kinase superfamily and clusters within the Ca²⁺/calmodulin-dependent kinase (CAMK) branch (Brede et al., 2000; Manning & Hunter, 2010). The catalytic domain shares ~50 % identity with rat CaMKI, defining a distinct sub-family of serine/threonine kinases (Brede et al., 2000). PSKH1 is conserved in many vertebrates but is absent from the mouse kinome, indicating a rodent-specific gene loss (Caenepeel et al., 2004). It is clearly distinct from its paralog, the pseudokinase PSKH2 (Shrestha et al., 2020).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Anti, 2009).

## Cofactor Requirements

Mg²⁺ is required for catalysis (Anti, 2009).

## Substrate Specificity

PSKH1 preferentially phosphorylates non-snRNP splicing factors that contain serine/arginine-rich (SR) domains; a strict consensus motif has not been defined (Berson et al., 1999; Shrestha et al., 2020).

## Structure

The protein is ~305 amino acids. An N-terminal segment (residues 1–19) contains a myristoylation site at Gly2 and palmitoylation sites at Cys6 and Cys8, flanked by basic residues resembling SH4 membrane-targeting domains (Berson et al., 1999). The catalytic domain (≈ residues 20–294) exhibits the 12 conserved kinase subdomains; key residues include Lys49 (ATP binding), His146, and the APE motif starting at Ala200, forming a canonical bilobed kinase fold with minimal predicted disorder (Berson et al., 1999).

## Regulation

Activity is modulated by dual fatty acylation: myristoylation at Gly2 is required for subsequent palmitoylation at Cys6/Cys8, directing the kinase to membrane compartments (Berson et al., 1999). PSKH1 autophosphorylates on threonine residues and phosphorylates exogenous substrates such as PHAS-I (Berson et al., 1999). Although it lacks a classical calmodulin-binding domain, an N-terminal stretch resembles a CaMKI motif (Brede et al., 2000; Shrestha et al., 2020). Overall regulation integrates lipid-mediated localization with phosphorylation-dependent control.

## Function

PSKH1 is implicated in pre-mRNA processing by phosphorylating SR proteins within nuclear splice factor compartments; this reversible modification alters their intranuclear distribution and influences alternative splicing (Berson et al., 1999). Cellular studies localize PSKH1 to the Golgi apparatus, centrosomes, and nucleus, consistent with its lipidation-dependent membrane targeting (Brede et al., 2000; Shrestha et al., 2020).

## Inhibitors

No selective inhibitors have been described; inhibitors developed against related serine/threonine kinases may serve as starting points for functional studies (Berson et al., 1999; Shrestha et al., 2020).

## Other Comments

PSKH1 is classified under EC 2.7.11.1 and has been referred to as “protein serine kinase H1.” Its absence from the mouse genome highlights a notable lineage-specific gene loss (Caenepeel et al., 2004). Although not yet linked to specific diseases, its role in alternative splicing suggests potential relevance where splicing is dysregulated (Berson et al., 1999; Shrestha et al., 2020).

## References

Anti, B. (2009). Non-specific serine/threonine protein kinase. In *Class 2 Transferases* (pp. 1–123). https://doi.org/10.1007/978-3-540-85699-3\_1

Berson, A. E., Chi, Y., Morrison, S. L., Fujii, G. H., Sheung, J., Wu, B., Bolen, J. B., & Burkhardt, A. L. (1999). Identification and characterization of a myristylated and palmitylated serine/threonine protein kinase. *Biochemical and Biophysical Research Communications, 259*, 533–538. https://doi.org/10.1006/bbrc.1999.0811

Brede, G., Solheim, J., Tröen, G., & Prydz, H. (2000). Characterization of PSKH1, a novel human protein serine kinase with centrosomal, golgi, and nuclear localization. *Genomics, 70*, 82–92. https://doi.org/10.1006/geno.2000.6365

Caenepeel, S., Charydczak, G., Sudarsanam, S., Hunter, T., & Manning, G. (2004). The mouse kinome: discovery and comparative genomics of all mouse protein kinases. *Proceedings of the National Academy of Sciences of the United States of America, 101*, 11707–11712. https://doi.org/10.1073/pnas.0306880101

Ho, E. Y. F. (2014). *Creation and characterization of a sensitized, inhibitable stress-activated protein kinase*. Unknown journal.

Manning, G., & Hunter, T. (2010). Eukaryotic kinomes: genomics and evolution of protein kinases (pp. 393–397). https://doi.org/10.1016/B978-0-12-374145-5.00056-5

Shrestha, S., Byrne, D. P., Harris, J. A., Kannan, N., & Eyers, P. A. (2020). Cataloguing the dead: breathing new life into pseudokinase research. *The FEBS Journal, 287*, 4150–4169. https://doi.org/10.1111/febs.15246