## Phylogeny

• Classified in the “Other” group of the human kinome table created with the Manning 2002 scheme (sekigawa2010comprehensivescreeningof pages 5-5)  
• Member of new kinase family 4 (NKF4) together with paralogue STK35 (unknownauthors2020anuclearphosphatasekinase pages 108-112)  
• Additional vertebrate paralogue STK35L3 is absent from placental mammals (goyal2009identifyingandcharacterizing pages 1-2)  
• Orthologous genes reported in mouse, rat, zebrafish, frog and chicken based on comparative genomics (goyal2009identifyingandcharacterizing pages 11-13)  
• A putative ancestral gene is present in sea-squirt (Ciona), indicating conservation across chordates (goyal2009identifyingandcharacterizing pages 13-14)

## Reaction Catalyzed

• ATP + protein‐L-Ser/Thr → ADP + phospho-protein-L-Ser/Thr (generic serine/threonine kinase chemistry; experimental confirmation for PDIK1L not yet reported) (unknownauthors2020anuclearphosphatasekinase pages 119-123)

## Cofactor Requirements

• Divalent-metal requirement has not been experimentally examined; no data available (unknownauthors2020anuclearphosphatasekinase pages 119-123)

## Substrate Specificity

• Consensus phosphorylation motif: unknown; no peer-reviewed substrate-profiling study available as of 2024 (unknownauthors2020anuclearphosphatasekinase pages 127-132)  
• Machine-learning prediction (KolossuS) proposes a motif but remains unpublished in a peer-reviewed journal (jha2025deeplearningcoupledproximity pages 11-12)

## Structure

• Single polypeptide of 341 aa comprising an N-terminal low-complexity segment (~1-60) and a canonical bilobal serine/threonine kinase domain (~65-341) (unknownauthors2020anuclearphosphatasekinase pages 119-123)  
• AlphaFold model AF-Q8N165-F1 shows preserved Gly-rich loop, VAIK Lys, HRD catalytic triad and DFG motif; no crystallographic structure is deposited (unknownauthors2020anuclearphosphatasekinase pages 123-127)  
• Activation segment spans Ser194–Thr221; Ser194 is the DFG+2 residue exposed on the protein surface (unknownauthors2020anuclearphosphatasekinase pages 127-132)  
• Predicted inward positioning of the C-helix completes the Lys-Glu ion pair typical of active kinases (unknownauthors2020anuclearphosphatasekinase pages 123-127)  
• Hydrophobic regulatory spine residues are conserved according to the AlphaFold model (unknownauthors2020anuclearphosphatasekinase pages 123-127)

## Regulation

• Phosphorylation at Ser194 within the activation loop is inhibitory; S194D mutant abolishes pro-proliferative function in AML cells (unknownauthors2020anuclearphosphatasekinase pages 127-132)  
• Additional activation-loop sites Ser216, Thr217 and Thr221 are phosphorylated in cells; Ser216 is dephosphorylated by SCP4 in vitro (unknownauthors2020anuclearphosphatasekinase pages 132-134)  
• Nuclear phosphatase SCP4 directly dephosphorylates pSer194 and pSer216 with k\_cat/K\_M values of 12.63 and 45.96 mM⁻¹ min⁻¹, respectively (unknownauthors2020anuclearphosphatasekinase pages 127-132)  
• Forms a stable 1:1 nuclear complex with SCP4 via non-catalytic docking surfaces, positioning the activation loop for dephosphorylation (unknownauthors2020anuclearphosphatasekinase pages 145-149)  
• Loss of SCP4 reduces PDIK1L protein stability and recruits Hsp70 chaperones, suggesting quality-control-linked degradation (unknownauthors2020anuclearphosphatasekinase pages 163-166)

## Function

• Predominantly nuclear and chromatin-associated in MOLM-13 acute myeloid leukemia (AML) cells (unknownauthors2020anuclearphosphatasekinase pages 163-166)  
• GFP-fusion studies show nuclear localisation in COS-7 cells (guo2003molecularcloningand pages 1-3)  
• mRNA detected in liver, kidney, pancreas, spleen, thymus and prostate, with weaker expression in heart and brain (guo2003molecularcloningand pages 3-6)  
• Expressed in human endothelial, HeLa and HEK-293 cells (goyal2009identifyingandcharacterizing pages 1-2)  
• Core interactors: SCP4 phosphatase (unknownauthors2020anuclearphosphatasekinase pages 108-112), paralogue kinase STK35 (unknownauthors2020anuclearphosphatasekinase pages 119-123) and cytoskeletal adaptor PDLIM1 inferred from sequence homology to CLIK1 (guo2003molecularcloningand pages 1-3)  
• Either PDIK1L or STK35 suffices to rescue proliferation after dual-knockout, indicating redundant function in AML cells (unknownauthors2020anuclearphosphatasekinase pages 119-123)  
• CRISPR knockout of PDIK1L and STK35 together causes G1/G0 arrest and apoptosis in AML cell lines (unknownauthors2020anuclearphosphatasekinase pages 163-166)

## Other Comments

• SCP4–PDIK1L phosphatase-kinase complex constitutes an AML-biased genetic dependency and potential therapeutic target (polyanskaya2022scp4stk35pdik1lcomplexis pages 3-5)  
• No disease-linked somatic or germline mutations have been reported to date (unknownauthors2020anuclearphosphatasekinase pages 145-149)

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