Phosphatidylinositol 4-phosphate 5-kinase-like protein 1 (PIP5KL1, PIPKH, UniProt Q5T9C9)

## Phylogeny

• PIP5KL1 arose from a type I PIP5K gene duplication and is conserved across vertebrates; validated orthologs exist in mouse (Pipkh), rat and other mammals (xia2011thelocalisationand pages 31-36).  
• Yeast MSS4 and Drosophila sktl cluster within the broader phosphoinositide kinase lineage but are not direct orthologs (xia2011thelocalisationand pages 31-36).  
• Kinome placement: PI lipid kinase group, type I PIP5K family, classified as a pseudokinase branch distinct from catalytically active PIP5K1A/B/C in the Manning schema (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4, xia2011thelocalisationand pages 36-40).

## Reaction Catalyzed

No intrinsic phosphotransferase reaction has been detected; bacterially expressed or immunoprecipitated PIP5KL1 fails to phosphorylate PI4P or PI5P, and low activity in cell lysates is attributable to co-precipitated PIP5Kα/β (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4, yang2018enforcedexpressionof pages 1-3, yang2019enforcedexpressionof pages 2-3).

## Cofactor Requirements

None established; lack of catalytic activity renders canonical Mg²⁺/ATP dependence irrelevant (yang2018enforcedexpressionof pages 1-3).

## Substrate Specificity

Not applicable—substrate motif and amino-acid preferences have not been defined because the protein is catalytically inactive (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4).

## Structure

• Monomeric ~44 kDa protein lacking the complete type I PIP5K catalytic core, including segments required for ATP binding and the 25-residue activation loop (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4).  
• No experimental crystal or cryo-EM structure is available; AlphaFold predicts a truncated PI kinase fold with discontinuities in the catalytic loop, consistent with pseudokinase status (yang2018enforcedexpressionof pages 1-3).  
• Absence of Lys-Asp-Asp triad critical for catalysis in active PIP5Ks; the putative C-helix and hydrophobic spines are incomplete (xia2011thelocalisationand pages 28-31).  
• N- and C-terminal extensions mediate heterodimerization with PIP5Kα/β, functioning as a localization scaffold (yang2018enforcedexpressionof pages 3-5).

## Regulation

• Protein–protein interaction: direct binding to PIP5Kα and PIP5Kβ via heterodimerization domains; interaction persists in the absence of PI(4,5)P₂ (yang2019enforcedexpressionof pages 1-2).  
• Relocates bound PIP5Ks from plasma membrane to endomembranes, thereby altering spatial pools of PI(4,5)P₂ and PI(3,4,5)P₃ (yang2018enforcedexpressionof pages 3-5).  
• No documented post-translational modifications or allosteric regulators.

## Function

• Tissue expression: highest mRNA levels in brain and testis; protein detected in gastric epithelial cells (yang2019enforcedexpressionof pages 2-3).  
• Acts as a scaffold that localizes type I PIP5Ks to specific intracellular compartments for localized PI(4,5)P₂ synthesis (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4, yang2018enforcedexpressionof pages 3-5).  
• Downstream effects: redistribution of PI(4,5)P₂ leads to secondary PI(3,4,5)P₃ accumulation and relocalization of polycationic small G-proteins (e.g., K-Ras, Rac1) (yang2018enforcedexpressionof pages 3-5).  
• Upstream partners: forms complexes with active PIP5Kα/β; no kinase phosphorylates PIP5KL1 for activation.

## Other Comments

• Disease association: loss of PIP5KL1 expression in ~65 % of gastric cancer samples; re-expression suppresses proliferation and migration in gastric cancer cell lines (yang2019enforcedexpressionof pages 2-3).  
• Classified as a lipid-kinase pseudokinase; functional impact arises from spatial regulation of bona fide PIP5Ks rather than catalytic activity (bout2009pip5kdrivenptdins(45)p2synthesis pages 2-4).

References

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