## Phylogeny

PIP5K1B is classified within the lipid kinase group of the human kinome (unknownauthorsUnknownyeartranscriptomealterationsfollowing pages 46-52). It belongs to the phosphatidylinositol-4-phosphate 5-kinase (PIP5K) family, which is part of the larger phosphatidylinositol phosphate kinase (PIPK) superfamily (unknownauthors2018theroleofa pages 11-13, unknownauthors2022characterisationofalternative pages 41-47). Based on the Manning et al. classification, the phosphoinositide kinases are categorized into three families (PI3Ks, PI4Ks, and PIPKs), with PIP5K1B assigned to the PIPKs (unknownauthors2022characterisationofalternative pages 41-47). Specifically, it is a Type I PIPK (sasaki2009mammalianphosphoinositidekinases pages 2-2, unknownauthors2022characterisationofalternative pages 41-47). The human kinase domain of PIP5K1B shares approximately 77% sequence identity with PIP5K1α and 82% with PIP5K1γ (unknownauthorsUnknownyeartranscriptomealterationsfollowing pages 76-80). Orthologs are conserved across eukaryotes, including mammals (human, mouse), birds, fish (zebrafish), fungi, plants, and Apicomplexa, indicating an early evolutionary emergence of this signaling system (unknownauthors2022characterisationofalternative pages 41-47, narkis2007lethalcontracturalsyndrome pages 1-2, zeng2018structuralinsightsinto pages 8-9, sasaki2009mammalianphosphoinositidekinases pages 32-32).

## Reaction Catalyzed

The enzyme catalyzes the phosphorylation of phosphatidylinositol 4-phosphate (PI(4)P) at the D5 position of the inositol ring to generate phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) (unknownauthors2018theroleofa pages 11-13, unknownauthors2018theroleofa pages 6-9).

PI(4)P + ATP → PI(4,5)P2 + ADP (burke2023beyondpi3kstargeting pages 27-28, unknownauthors2018theroleofa pages 11-13).

## Cofactor Requirements

Catalytic activity requires ATP and Mg2+ as cofactors (burke2023beyondpi3kstargeting pages 27-28, sasaki2009mammalianphosphoinositidekinases pages 2-2). The lipid kinase activity is also enhanced by the cofactor phosphatidic acid (PA) (unknownauthors2018theroleofa pages 11-13). The PIP5K family can also utilize Mn2+ (xia2011thelocalisationand pages 28-31).

## Substrate Specificity

The primary substrate is phosphatidylinositol 4-phosphate (PI(4)P) (unknownauthors2018theroleofa pages 11-13, burke2018structuralbasisfor pages 2-2). To a lesser extent, PIP5K family members can also phosphorylate other phosphoinositides, such as PI3P and PI5P (xia2011thelocalisationand pages 28-31, jin2023lipidkinasespip5ks pages 1-2). Substrate specificity is influenced by a key amino acid residue within the activation loop (unknownauthors2018theroleofa pages 6-9). In addition to its role as a lipid kinase, PIP5Kβ possesses an intrinsic protein kinase activity that allows it to autophosphorylate, mainly on serine residues (unknownauthors2018theroleofa pages 11-13).

## Structure

AlphaFold models (O14986) and homology modeling based on related isoforms reveal that PIP5K1B contains a central, conserved kinase domain, a dimerization domain, and a PIP-binding domain in the C-lobe (unknownauthors2022characterisationofalternative pages 41-47, unknownauthors2023elucidatingtherole pages 19-22, zeng2018structuralinsightsinto pages 8-9). The kinase domain is composed of an N-lobe and a C-lobe, with a tertiary structure of α-helices, β-sheets, and disordered loops (unknownauthors2022characterisationofalternative pages 41-47, unknownauthorsUnknownyeartranscriptomealterationsfollowing pages 76-80). The N- and C-termini are largely disordered and show poor sequence conservation among isoforms, which may contribute to isozyme-specific localization (unknownauthorsUnknownyeartranscriptomealterationsfollowing pages 76-80).

Key catalytic features predicted by structural models include a signature PIP-binding (PIPB) motif and conserved residues essential for ATP binding and phosphoryl transfer, such as an invariant aspartate and a conserved lysine (zeng2018structuralinsightsinto pages 8-9, zeng2018structuralinsightsinto pages 9-11). A conserved C-terminal activation loop mediates substrate processing and plasma membrane recruitment, and can switch from an unstructured to a structured state upon binding phospholipids (unknownauthorsUnknownyeartranscriptomealterationsfollowing pages 76-80). The enzyme also possesses a flat membrane-binding surface and a dimerization interface implicated in its regulation and function (xia2011thelocalisationand pages 28-31, zeng2018structuralinsightsinto pages 11-13).

## Regulation

The lipid kinase activity of PIP5K1B is regulated by post-translational modifications, protein-protein interactions, and allosteric factors (unknownauthors2018theroleofa pages 11-13).

PIP5K1B undergoes autophosphorylation on serine residues, which decreases its lipid kinase activity (unknownauthors2018theroleofa pages 11-13). Phosphorylation generally acts as an inhibitory mechanism; specific sites include Ser214, regulated by PKA and PKC, and Ser413, phosphorylated by PKC in response to cellular stress, which reduces kinase activity by approximately 40% (unknownauthors2018theroleofa pages 11-13, unknownauthorsUnknownyeartranscriptomealterationsfollowing pages 84-87). Conversely, dephosphorylation by protein phosphatase 1 (PP1) activates the enzyme (unknownauthors2018theroleofa pages 11-13).

Allosteric activation is mediated by the small GTPases Arf1, Arf5, and Arf6, particularly in the presence of phosphatidic acid (PA) (unknownauthors2018theroleofa pages 11-13). The Rho family GTPases also regulate its activity (sasaki2009mammalianphosphoinositidekinases pages 32-32). In contrast, PIP4K family members can directly inhibit PIP5K activity through physical interactions on membranes, a mechanism that is independent of PIP4K’s own catalytic function (wang2019pip4kssuppressinsulin pages 10-14).

## Function

PIP5K1B is strongly expressed in heart tissue and localizes predominantly to the plasma membrane and perinuclear vesicles (unknownauthors2018theroleofa pages 6-9). It functions as a downstream effector of the small GTPase Arf6, which recruits PIP5Kβ to membrane ruffles and endosomal compartments upon activation (unknownauthors2018theroleofa pages 11-13).

The primary function of PIP5K1B is the synthesis of PI(4,5)P2, a critical signaling lipid that regulates plasma membrane remodeling, clathrin-mediated endocytosis, exocytosis, actin cytoskeleton dynamics, and neuronal growth cone dynamics (unknownauthors2018theroleofa pages 11-13, unknownauthors2018theroleofa pages 6-9). The PI(4,5)P2 produced by PIP5K1B serves as a precursor for other second messengers, including PI(3,4,5)P3, thereby linking its activity to downstream pathways such as PI3K-mediated insulin signaling (jin2023lipidkinasespip5ks pages 1-2, wang2019pip4kssuppressinsulin pages 10-14, unknownauthors2022characterisationofalternative pages 41-47).

## Other Comments

Mutations in the *PIP5K1B* gene cause Lethal Congenital Contracture Syndrome 7 (LCCS7), a severe autosomal recessive neuromuscular disorder characterized by fetal akinesia and multiple joint contractures (unknownauthors2022characterisationofalternative pages 41-47, unknownauthors2023elucidatingtherole pages 19-22, narkis2007lethalcontracturalsyndrome pages 1-2, sasaki2009mammalianphosphoinositidekinases pages 32-32).

Disease-causing missense and splice site mutations disrupt or abolish kinase activity, leading to deficient PI(4,5)P2 synthesis (unknownauthors2022characterisationofalternative pages 41-47, chen2022theroleof pages 11-12). Missense mutations affecting a conserved aspartate residue within the catalytic PIPB motif have been shown to diminish kinase activity by approximately 100-fold by disrupting critical hydrogen bonds necessary for ATP binding and orientation (zeng2018structuralinsightsinto pages 8-9, zeng2018structuralinsightsinto pages 9-11). This loss of function impairs downstream signaling and cellular processes critical for cytoskeletal dynamics and neuromuscular development, resulting in the LCCS7 disease phenotype (unknownauthors2023elucidatingtherole pages 19-22, sasaki2009mammalianphosphoinositidekinases pages 32-32). Historical confusion in nomenclature between murine and human isoforms has been resolved in modern databases such as UniProt (unknownauthors2022characterisationofalternative pages 41-47).

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