## Phylogeny

PIP5K1B is a Type I phosphatidylinositol-4-phosphate 5-kinase (PIP5K) within the phosphatidylinositol phosphate kinase (PIPK) superfamily of the human lipid kinome (unknownauthors, 2018, pp. 11-13; Sasaki et al., 2009, p. 2; unknownauthors, 2022, pp. 41-47). Sequence identity across the catalytic domain is ~77 % to PIP5K1A and ~82 % to PIP5K1C (unknownauthors, Unknown year, pp. 76-80). Orthologues are present throughout eukaryotes—including mammals, birds, fish, fungi, plants and Apicomplexa—indicating ancient evolutionary conservation (unknownauthors, 2022, pp. 41-47; Narkis et al., 2007; Zeng et al., 2018; Sasaki et al., 2009, p. 32).

## Reaction Catalyzed

PI(4)P + ATP ⇌ PI(4,5)P₂ + ADP (Burke et al., 2023, pp. 27-28; unknownauthors, 2018, pp. 11-13).

## Cofactor Requirements

Catalysis requires Mg²⁺; Mn²⁺ can substitute (Burke et al., 2023, pp. 27-28; Xia, 2011, pp. 28-31). Phosphatidic acid acts as an activity-enhancing lipid cofactor (unknownauthors, 2018, pp. 11-13).

## Substrate Specificity

The preferred substrate is phosphatidylinositol 4-phosphate (PI(4)P) (unknownauthors, 2018, pp. 11-13; Burke, 2018, p. 2). PIP5K family members can also phosphorylate PI3P and PI5P with lower efficiency (Xia, 2011, pp. 28-31; Jin & Xue, 2023, pp. 1-2). A determinant residue in the activation loop modulates lipid selectivity (unknownauthors, 2018, pp. 6-9). PIP5K1B additionally autophosphorylates on serine residues (unknownauthors, 2018, pp. 11-13).

## Structure

AlphaFold modelling (UniProt O14986) and homology with related isoforms reveal an N-lobe/C-lobe protein-kinase fold incorporating: (i) a central catalytic domain, (ii) a PIP-binding motif within the C-lobe, and (iii) an N-terminal dimerisation interface (unknownauthors, 2022, pp. 41-47; Zeng et al., 2018, pp. 8-9). The N- and C-termini are largely disordered and poorly conserved, consistent with isoform-specific localisation (unknownauthors, Unknown year, pp. 76-80). Key catalytic elements include a conserved lysine for ATP anchoring and an invariant aspartate essential for phosphoryl transfer; a C-terminal activation loop becomes ordered upon phospholipid engagement (Zeng et al., 2018, pp. 9-11; unknownauthors, Unknown year, pp. 76-80). The kinase displays a flat membrane-binding surface that, together with the dimer interface, contributes to regulation (Xia, 2011, pp. 28-31).

## Regulation

• Autophosphorylation on serine residues inhibits lipid-kinase activity (unknownauthors, 2018, pp. 11-13).  
• PKA/PKC phosphorylation at Ser214 and PKC-mediated phosphorylation at Ser413 reduce activity (~40 %) (unknownauthors, 2018, pp. 11-13; unknownauthors, Unknown year, pp. 84-87).  
• Dephosphorylation by PP1 re-activates the enzyme (unknownauthors, 2018, pp. 11-13).  
• Small GTPases Arf1, Arf5, Arf6 and members of the Rho family stimulate activity, especially in the presence of phosphatidic acid (unknownauthors, 2018, pp. 11-13; Sasaki et al., 2009, p. 32).  
• PIP4Ks can bind and inhibit PIP5K1B independently of their own catalytic function (Wang et al., 2019, pp. 10-14).

## Function

Highly expressed in heart tissue and localises to the plasma membrane and perinuclear vesicles (unknownauthors, 2018, pp. 6-9). Upon Arf6 activation, PIP5K1B is recruited to membrane ruffles and endosomes (unknownauthors, 2018, pp. 11-13). By producing PI(4,5)P₂, it governs plasma-membrane remodelling, clathrin-mediated endocytosis, exocytosis, actin-cytoskeleton dynamics, and neuronal growth-cone behaviour (unknownauthors, 2018, pp. 6-13). The generated PI(4,5)P₂ also serves as precursor for PI(3,4,5)P₃, coupling PIP5K1B activity to PI3K-dependent insulin signalling (Jin & Xue, 2023, pp. 1-2; Wang et al., 2019, pp. 10-14; unknownauthors, 2022, pp. 41-47).

## Other Comments

Biallelic mutations in PIP5K1B cause Lethal Congenital Contracture Syndrome 7 (LCCS7), a severe recessive neuromuscular disorder featuring fetal akinesia and multiple joint contractures (unknownauthors, 2022, pp. 41-47; Narkis et al., 2007; unknownauthors, 2023, pp. 19-22). Pathogenic missense or splice-site variants abolish kinase activity and PI(4,5)P₂ synthesis; a conserved catalytic aspartate is especially critical, with certain substitutions reducing activity ~100-fold (Zeng et al., 2018, pp. 8-11; Chen et al., 2022, pp. 11-12). Historical nomenclature confusion between murine and human isoforms has been resolved in current databases (unknownauthors, 2022, pp. 41-47).

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