## Phylogeny

PI4KA is the α-isoform of the type III phosphatidylinositol 4-kinase sub-family within the phosphoinositide-3-kinase–related kinase (PIKK) branch of the human kinome (dornan2016typeiiiphosphatidylinositol pages 1-2).  
Type III PI4Ks share closest evolutionary ancestry with class III PI3Ks, retaining the bilobal helical-kinase fold characteristic of the PI3K/PIKK superfamily (burke2023beyondpi3kstargeting pages 7-8).  
A Saccharomyces cerevisiae ortholog is Stt4, underscoring conservation from yeast to mammals (kumar2024phosphatidylinositol4kinases pages 12-12).  
Caenorhabditis elegans pifk-1 is a nematode ortholog of PI4KA (kumar2024phosphatidylinositol4kinases pages 12-12).  
Drosophila melanogaster expresses PI4KIIIα as the insect ortholog (kumar2024phosphatidylinositol4kinases pages 12-12).  
Danio rerio encodes pi4kaa, a vertebrate ortholog with conserved catalytic motifs (kumar2024phosphatidylinositol4kinases pages 12-12).

## Reaction Catalyzed

ATP + phosphatidylinositol ⇌ ADP + phosphatidylinositol-4-phosphate (boura2015phosphatidylinositol4kinikesfunction pages 2-3).

## Cofactor Requirements

Catalytic turnover requires Mg²⁺, while Mn²⁺ can substitute in vitro (kumar2024phosphatidylinositol4kinases pages 4-6).

## Substrate Specificity

PI4KA selectively phosphorylates membrane-embedded phosphatidylinositol and does not recognize peptide consensus motifs (tai2011ahomogeneousand pages 6-6).

## Structure

The 2 102-residue enzyme comprises an N-terminal proline-rich region (≈1-450), an extensive α-solenoid/ARM scaffold (≈450-1300), a central dimerisation domain (≈1300-1500), a helical sub-domain (≈1500-1600) and a C-terminal bilobal lipid-kinase domain (≈1600-2102) (burke2023beyondpi3kstargeting pages 14-15).  
Cryo-EM structures of PI4KA bound to TTC7 and FAM126 (PDB 6BQ0, 6BQ1) reveal a dimer of heterotrimers in which the α-solenoid cradles both regulators and positions the kinase domains toward the membrane (burke2018structuralbasisfor pages 11-12).  
The active site contains Lys1838 in the VAIK motif and Asp1957 in the DRH catalytic loop, flanked by vertebrate-specific Cys1839 and Cys1843 that influence inhibitor binding (kumar2024phosphatidylinositol4kinases pages 12-12).  
A unique N-lobe helical extension completes the hydrophobic spine and locks the C-helix in a catalytically competent orientation (burke2023beyondpi3kstargeting pages 7-8).  
The solenoid “horn” (residues 31-59) forms part of a calcineurin docking surface, creating an allosteric interface external to the kinase core (shaw2024structureofcalcineurin pages 4-7).

## Regulation

Stable association with TTC7A/B and FAM126A/B is obligatory for enzymatic activity and membrane recruitment via TTC7 interaction with palmitoylated EFR3A/B (burke2018structuralbasisfor pages 11-12).  
TMEM150A modulates the dwell time of the PI4KA complex at the plasma membrane, providing an additional regulatory layer (boura2015phosphatidylinositol4kinasesfunction pages 3-4).  
Calcineurin binds the solenoid horn and FAM126, suggesting phosphatase-coupled conformational control (shaw2024structureofcalcineurin pages 4-7).  
Phosphorylation at Ser1290 by PKC and CK2 down-regulates catalytic output (kumar2024phosphatidylinositol4kinases pages 12-12).  
Substitution of Lys1838, Asp1899 or Asp1957 abolishes activity, defining critical catalytic residues (unknownauthors2022functionalimportanceof pages 14-19).  
Oxidation or covalent modification of Cys1839/Cys1843 near the ATP pocket alters sensitivity to small-molecule inhibitors, indicating redox-responsive regulation (balla2008designofdrugresistant pages 8-9).

## Function

GTEx and Human Protein Atlas datasets show ubiquitous expression with pronounced enrichment in brain and gastrointestinal tissues (burke2023beyondpi3kstargeting pages 14-15).  
PI4KA generates the dominant plasma-membrane PI4P pool that is converted to PI(4,5)P₂ and PI(3,4,5)P₃, thereby governing membrane identity, actin dynamics and vesicular trafficking (burke2018structuralbasisfor pages 2-2).  
The PI4P gradient created by PI4KA drives inter-organelle transfer of cholesterol and phosphatidylserine (burke2018structuralbasisfor pages 2-2).  
Positive-strand RNA viruses, including hepatitis C virus and encephalomyocarditis virus, hijack PI4KA to construct PI4P-rich replication organelles (burke2023beyondpi3kstargeting pages 14-15).  
Genetic or pharmacological inactivation causes embryonic lethality and acute intestinal degeneration in mice, underscoring essential roles in development and tissue homeostasis (burke2018structuralbasisfor pages 11-12).  
Pharmacological blockade of PI4KA synergises with KRAS inhibition to suppress growth of KRAS-mutant pancreatic cancer cells (burke2023beyondpi3kstargeting pages 16-17).

## Inhibitors

GSK-A1, a quinazoline derivative, inhibits PI4KA with a reported IC₅₀ of 0.16 nM and >100-fold selectivity over PI4KB and PI4K2A (burke2018structuralbasisfor pages 4-5).  
Additional quinazoline and 2-aminobenzothiazole series compounds maintain sub-nanomolar potency but exhibit dose-limiting gastrointestinal toxicity in rodents (burke2023beyondpi3kstargeting pages 14-15).  
PIK93 preferentially targets PI4KB yet inhibits PI4KA at higher concentrations, whereas wortmannin acts as a covalent pan-PI3K/PI4K inhibitor (balla2008designofdrugresistant pages 8-9).

## Other Comments

Biallelic loss-of-function mutations in PI4KA cause severe neurodevelopmental delay, cortical malformations and spastic paraplegia (burke2023beyondpi3kstargeting pages 14-15).  
Missense or truncating mutations in TTC7A weaken PI4KA complex formation and result in combined immunodeficiency (burke2018structuralbasisfor pages 11-12).  
Early reports placed PI4KA at the endoplasmic reticulum, whereas recent cryo-EM and interactome data support primary plasma-membrane anchoring via EFR3–TTC7, constituting an unresolved localisation contradiction (unknownauthors2022functionalimportanceof pages 14-19).

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