## Phylogeny

• PIK3CG encodes p110γ, the sole catalytic subunit of class IB phosphoinositide-3-kinases within the PI3K clade of the human kinome described by Manning et al. and reviewed in later work (wymann2003phosphoinositide3kinasesignalling pages 1-2).  
• The kinase domain shares ~35 % identity with the class IA isoform p110β, indicating close evolutionary relatedness inside class I PI3Ks (nurnberg2019functionregulationand pages 3-5).  
• Orthologous genes are documented in Mus musculus, Rattus norvegicus, Danio rerio, Drosophila melanogaster and Caenorhabditis elegans, illustrating conservation from vertebrates to invertebrates (lanahan2022theroleof pages 8-9, wymann2003phosphoinositide3kinasesignalling pages 1-2).

## Reaction Catalyzed

ATP + PI(4,5)P₂ ⇌ ADP + PI(3,4,5)P₃ + H⁺ (nurnberg2019functionregulationand pages 1-3, lanahan2022theroleof pages 1-4).

## Cofactor Requirements

Catalysis requires Mg²⁺ ions (nurnberg2019functionregulationand pages 23-25).

## Substrate Specificity

• Primary lipid substrate: phosphatidylinositol-4,5-bisphosphate located on the inner plasma-membrane leaflet (nurnberg2019functionregulationand pages 17-18).  
• No reproducible consensus motif has been reported for protein substrates; the intrinsic protein-kinase activity is weak and not sequence-defined (nurnberg2019functionregulationand pages 8-9).

## Structure

• Full length: 1-102 aa arranged in five ordered modules (nurnberg2019functionregulationand pages 1-3, gu2024developmentofpi3kγ pages 1-2):  
– ABD-like region, residues 1–108, lacks p85 binding.  
– Ras-binding domain (RBD), residues 220–311, engages GTP-loaded Ras (gu2024developmentofpi3kγ pages 1-2).  
– C2 domain, residues 312–480, mediates membrane association.  
– Helical domain, residues 481–685, hub for adaptor and Gβγ contacts; houses regulatory Ser502/Ser582 (nurnberg2019functionregulationand pages 3-5).  
– Bilobal kinase domain, residues 686–1102, contains the ATP pocket, αC helix and activation loop (qiu2019recentdiscoveryof pages 1-3).  
• Catalytic pocket: Lys833, Tyr867 and Val882 line the adenine site; Glu814, Gly829 and Ala885 form an isoform-specific semi-hydrophobic cleft exploited by selective inhibitors (qiu2019recentdiscoveryof pages 1-3, qiu2019recentdiscoveryof pages 14-16).  
• Active-state crystal structures of human p110γ/p101 complexes (PDB 6AUD, 6XRM) reveal outward rotation of helix kα12, generating a membrane-interactive surface (gu2024developmentofpi3kγ pages 1-2, gangadhara2019aclassof pages 29-29).  
• Adaptor interfaces: p101/p84 bind the RBD-C2 linker and helical domain, while a basic 552-RK motif in the C2-helical linker contacts Gβγ (vadas2013moleculardeterminantsof pages 2-2).  
• Ras-GTP bridges the RBD and a surface on the kinase C-lobe, with eleven RBD residues (F221, K223, T228, etc.) contacting switch I/II of Ras (unknownauthors2022characterizationofras pages 25-29).

## Regulation

Post-translational modifications  
• Ser502 in the helical domain is phosphorylated by PKCβ, weakening p87 binding and promoting complex dissociation (nurnberg2019functionregulationand pages 3-5).  
• Ser582 (helical domain) is phosphorylated by PKCβ, doubles lipid-kinase activity and expels p84, releasing the enzyme from GPCR control (walser2013pkcβphosphorylatespi3kγ pages 10-11).  
• Thr1024 in the kinase domain is phosphorylated by PKA, producing negative feedback in β-adrenergic signalling (walser2013pkcβphosphorylatespi3kγ pages 10-11).  
• Ser1101 undergoes autophosphorylation with minimal catalytic impact (nurnberg2019functionregulationand pages 8-9).

Allosteric control  
• Gβγ dimers bind the helical domain and regulatory subunits, providing potent allosteric activation; p101 confers high-affinity sensitivity, whereas p87 yields weaker stimulation (nurnberg2019functionregulationand pages 3-5).  
• Ras-GTP synergises with Gβγ by engaging the RBD, enhancing membrane recruitment and catalytic turnover (unknownauthors2022characterizationofras pages 25-29).

## Function

Expression  
• High in leukocytes (neutrophils, macrophages, dendritic cells, mast cells, T and B lymphocytes) and detectable in cardiomyocytes, endothelial cells, CNS, kidney, pancreas and prostate (lanahan2022theroleof pages 1-4, nurnberg2019functionregulationand pages 3-5).

Upstream regulators  
• GPCR agonists → Gβγ dimers (nurnberg2019functionregulationand pages 3-5).  
• Small GTPases Ras and Rab8a (nurnberg2019functionregulationand pages 8-9).  
• TLRs and cytokine receptors via p101-mediated recruitment (lanahan2022theroleof pages 4-8).

Downstream effectors and interactors  
• Generates PIP3 that recruits AKT, PDPK1 and mTOR components (nurnberg2019functionregulationand pages 11-13).  
• Forms complexes with PDE3B/PDE4B and PKA regulatory subunits to organise cAMP nanodomains (nurnberg2019functionregulationand pages 9-11).  
• Associates with GRK2 and β-arrestins in β-adrenergic receptor regulation (nurnberg2019functionregulationand pages 13-15).

Physiological roles  
• Directs chemotaxis of neutrophils, dendritic cells, NK cells and T-lymphocytes (nurnberg2019functionregulationand pages 11-13, lanahan2022theroleof pages 4-8).  
• Controls ROS production in neutrophils and degranulation in mast cells (nurnberg2019functionregulationand pages 11-13).  
• Reprogrammes tumour-associated macrophages, aiding immunotherapy efficacy (gu2024developmentofpi3kγ pages 8-9).  
• Modulates β-adrenergic signalling in heart and vascular tone through kinase-dependent and scaffold mechanisms (nurnberg2019functionregulationand pages 13-15).  
• Regulates nociception and synaptic plasticity via cAMP compartmentalisation (nurnberg2019functionregulationand pages 15-17).

## Inhibitors

• Pan-PI3K: Wortmannin and LY294002 (nurnberg2019functionregulationand pages 17-18).  
• PI3Kγ-selective: AS-605240, IC₅₀ 8 nM (qiu2019recentdiscoveryof pages 14-16); CZC24832, Kd 19 nM (bergamini2012aselectiveinhibitor pages 3-4).  
• Clinical-stage: IPI-549 (Eganelisib), IC₅₀ 16 nM, >200-fold isoform selectivity (evans2016discoveryofa pages 7-8).  
• Dual PI3Kδ/γ: TG100-115 under cardiovascular evaluation (unknownauthors2011discoveryanddevelopment pages 66-72).  
• Active-state binders exploiting kα12 displacement: AZ2 and AZ3 (gangadhara2019aclassof pages 29-29).  
• Additional isoform-selective series include N-alkyl isoindolinones, thiazolopiperidines and 7-azaindoles guided by the semi-hydrophobic cleft (gu2024developmentofpi3kγ pages 10-10).

## Other Comments

• Bi-allelic loss-of-function mutations cause inactivated PI3K-γ syndrome with antibody deficiency, cytopenias, pneumonitis and colitis (takeda2019humanpi3kγdeficiency pages 1-2).  
• Over-expression of p101 is oncogenic, whereas phosphorylated p87 may act as a tumour suppressor, indicating regulatory-subunit imbalance in cancer (nurnberg2019functionregulationand pages 15-17).  
• RBD mutation Val282Ala disrupts Ras binding and associates with chronic infection phenotypes (nurnberg2019functionregulationand pages 8-9).  
• PI3Kγ signalling contributes to hypertension, atherosclerosis, pancreatic and prostate cancers, and heart-failure pathology (nurnberg2019functionregulationand pages 13-15, lanahan2022theroleof pages 8-9).

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