## Phylogeny

PIK3CG encodes p110γ, the single catalytic subunit of class IB phosphoinositide-3-kinases within the PI3K branch of the human kinome (Wymann et al., 2003). The p110γ kinase domain shares ~35 % sequence identity with the class IA isoform p110β, underscoring close evolutionary relatedness across class I PI3Ks (Nürnberg & Beer-Hammer, 2019). Orthologues are present in Mus musculus, Rattus norvegicus, Danio rerio, Drosophila melanogaster and Caenorhabditis elegans, reflecting conservation from vertebrates to invertebrates (Lanahan et al., 2022; Wymann et al., 2003).

## Reaction Catalyzed

ATP + PI(4,5)P₂ ⇌ ADP + PI(3,4,5)P₃ + H⁺ (Nürnberg & Beer-Hammer, 2019; Lanahan et al., 2022).

## Cofactor Requirements

Mg²⁺ is required for catalysis (Nürnberg & Beer-Hammer, 2019).

## Substrate Specificity

• Primary substrate: phosphatidylinositol-4,5-bisphosphate in the inner leaflet of the plasma membrane (Nürnberg & Beer-Hammer, 2019).  
• Intrinsic protein-kinase activity is weak; no reproducible sequence motif has been identified for protein substrates (Nürnberg & Beer-Hammer, 2019).

## Structure

Full-length p110γ (1–1102 aa) comprises five ordered modules (Nürnberg & Beer-Hammer, 2019; Gu et al., 2024):  
1. ABD-like region (1–108) – lacks p85 binding.  
2. Ras-binding domain (220–311) – interacts with Ras-GTP (Gu et al., 2024).  
3. C2 domain (312–480) – contributes to membrane association.  
4. Helical domain (481–685) – platform for adaptor and Gβγ contacts; contains regulatory Ser502/Ser582 (Nürnberg & Beer-Hammer, 2019).  
5. Bilobal kinase domain (686–1102) – houses ATP pocket, αC helix and activation loop (Qiu et al., 2019).

Catalytic pocket residues Lys833, Tyr867 and Val882 line the adenine site, while Glu814, Gly829 and Ala885 create an isoform-specific semi-hydrophobic cleft exploited by selective inhibitors (Qiu et al., 2019). Active-state crystal structures of human p110γ–p101 complexes (PDB 6AUD, 6XRM) show outward rotation of helix kα12 that generates a membrane-interactive surface (Gu et al., 2024; Gangadhara et al., 2019). Adaptor interfaces: p101/p84 bind the RBD–C2 linker and helical domain; a basic 552-RK motif in the C2–helical linker contacts Gβγ (Vadas et al., 2013). Ras-GTP bridges the RBD and kinase C-lobe via eleven RBD residues (Unknown Authors, 2022).

## Regulation

Post-translational modifications  
• Ser502 and Ser582 (helical domain) are phosphorylated by PKCβ; Ser582 phosphorylation doubles lipid-kinase activity and releases p84, whereas Ser502 phosphorylation weakens p87 binding (Nürnberg & Beer-Hammer, 2019; Walser et al., 2013).  
• Thr1024 is phosphorylated by PKA, providing negative feedback in β-adrenergic signalling (Walser et al., 2013).  
• Ser1101 undergoes autophosphorylation with minimal catalytic effect (Nürnberg & Beer-Hammer, 2019).

Allosteric control  
• Gβγ dimers engage the helical domain and regulatory subunits; p101 confers high-affinity, p87 weaker stimulation (Nürnberg & Beer-Hammer, 2019).  
• Ras-GTP binding to the RBD synergises with Gβγ to enhance membrane recruitment and turnover (Unknown Authors, 2022).

## Function

Expression  
Highly expressed in leukocytes (neutrophils, macrophages, dendritic cells, mast cells, T and B lymphocytes) and present in cardiomyocytes, endothelial cells, CNS, kidney, pancreas and prostate (Lanahan et al., 2022; Nürnberg & Beer-Hammer, 2019).

Upstream regulators  
GPCR agonists via Gβγ, small GTPases Ras and Rab8a, and TLR/cytokine receptors through p101 (Lanahan et al., 2022; Nürnberg & Beer-Hammer, 2019).

Downstream effectors  
PIP₃ produced by p110γ recruits AKT, PDPK1 and mTOR components; the kinase also forms complexes with PDE3B/PDE4B, PKA regulatory subunits, GRK2 and β-arrestins (Nürnberg & Beer-Hammer, 2019).

Physiological roles  
• Directs chemotaxis of neutrophils, dendritic cells, NK cells and T-lymphocytes.  
• Controls ROS production in neutrophils and mast-cell degranulation.  
• Reprogrammes tumour-associated macrophages to enhance immunotherapy.  
• Modulates cardiac β-adrenergic signalling and vascular tone.  
• Regulates nociception and synaptic plasticity via cAMP compartmentalisation (Lanahan et al., 2022; Gu et al., 2024; Nürnberg & Beer-Hammer, 2019).

## Inhibitors

Pan-PI3K inhibitors: wortmannin, LY294002 (Nürnberg & Beer-Hammer, 2019).  
PI3Kγ-selective: AS-605240 (IC₅₀ 8 nM), CZC24832 (K\_d 19 nM) (Qiu et al., 2019; Bergamini et al., 2012).  
Clinical-stage: IPI-549 (Eganelisib; IC₅₀ 16 nM, >200-fold selectivity) (Evans et al., 2016).  
Dual PI3Kδ/γ: TG100-115 (Unknown Authors, 2011).  
Active-state binders targeting kα12 displacement: AZ2, AZ3 (Gangadhara et al., 2019).  
Additional isoform-selective series include N-alkyl isoindolinones, thiazolopiperidines and 7-azaindoles (Gu et al., 2024).

## Other Comments

Bi-allelic loss-of-function mutations cause inactivated PI3K-γ syndrome with antibody deficiency, cytopenias, pneumonitis and colitis (Takeda et al., 2019). Over-expression of p101 is oncogenic, whereas phosphorylated p87 may act as a tumour suppressor (Nürnberg & Beer-Hammer, 2019). RBD mutation Val282Ala disrupts Ras binding and is linked to chronic infection phenotypes (Nürnberg & Beer-Hammer, 2019). Aberrant PI3Kγ signalling contributes to hypertension, atherosclerosis, pancreatic and prostate cancers, and heart-failure pathology (Lanahan et al., 2022; Nürnberg & Beer-Hammer, 2019).

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