## Phylogeny

• Member of the PI3/PI4-kinase superfamily, class II PI3K subfamily together with PI3K-C2α and PI3K-C2β (bilanges2019pi3kisoformsin pages 7-8).  
• Class II PI3Ks form a distinct clade from class I p110 isoforms and class III Vps34 in phylogenomic reconstructions (brown2011phylogenomicsofphosphoinositide pages 1-3).  
• Vertebrate orthologs are documented in mouse, rat and zebrafish; a single class II PI3K ortholog exists in Caenorhabditis elegans (piki-1) and Drosophila (PI3K68D), while no class II PI3Ks are present in budding yeast (gulluni2019classiipi3k pages 1-2, brown2011phylogenomicsofphosphoinositide pages 3-4).  
• Emergence of the PIK3C2G paralog coincided with vertebrate diversification, enabling tissue-restricted lipid-kinase functions (gulluni2019classiipi3k pages 1-2).

## Reaction Catalyzed

• ATP + phosphatidylinositol → ADP + phosphatidylinositol-3-phosphate [PI(3)P] (gulluni2019classiipi3k pages 1-2).  
• ATP + phosphatidylinositol-4-phosphate → ADP + phosphatidylinositol-3,4-bisphosphate [PI(3,4)P₂] (bilanges2019pi3kisoformsin pages 7-8, gulluni2019classiipi3k pages 17-19).

## Cofactor Requirements

• Catalysis requires ATP; no isoform-specific divalent-cation dependence has been reported for PI3K-C2γ (gulluni2019classiipi3k pages 2-4).

## Substrate Specificity

• Highest activity toward phosphatidylinositol, yielding PI(3)P (gulluni2019classiipi3k pages 1-2).  
• Utilizes PI(4)P at early endosomes to generate PI(3,4)P₂ (margaria2019classiipi3ks pages 1-4).  
• No peptide consensus motif is defined; specificity is confined to lipid substrates (bilanges2019pi3kisoformsin pages 14-15).

## Structure

• Domain layout: N-terminal disordered segment, central helical + kinase core containing a Ras-binding domain, followed by a C-terminal PX domain and an additional C2 domain (bilanges2019pi3kisoformsin pages 7-8, gulluni2019classiipi3k pages 2-4).  
• Functions as a monomer and lacks p85-type regulatory subunits characteristic of class I PI3Ks (bilanges2019pi3kisoformsin pages 7-8).  
• No experimental structure is available; homology with PI3K-C2α cryo-EM structures (PDB 7BI2, 6BTY, 7Z75) predicts an autoinhibitory PX–C2 clamp that disengages upon PI(4,5)P₂-rich membrane binding (burke2023beyondpi3kstargeting pages 20-22, burke2023beyondpi3kstargeting pages 28-29).  
• The catalytic core contains conserved DFG and EKP motifs and a canonical C-helix/hydrophobic spine alignment, as shown in kinase-domain alignments (brown2011phylogenomicsofphosphoinositide pages 11-12).  
• No AlphaFold or PDB entry specific to PI3K-C2γ has been reported (gulluni2019classiipi3k pages 2-4).

## Regulation

• Recruitment to Rab5-positive early endosomes restricts activity to defined membranes and underpins localized PI(3,4)P₂ synthesis (margaria2019classiipi3ks pages 1-4).  
• Class II catalytic pockets confer intrinsic resistance to pan-PI3K inhibitors such as wortmannin (margaria2019classiipi3ks pages 1-4).  
• Upstream activators and post-translational modifications of PI3K-C2γ remain largely uncharacterized (bilanges2019pi3kisoformsin pages 14-15, gulluni2019classiipi3k pages 2-4).

## Function

• Predominantly expressed in liver, with limited expression in other tissues (bilanges2019pi3kisoformsin pages 7-8).  
• Generates an endosomal PI(3,4)P₂ pool after insulin-receptor internalization, sustaining Akt2 phosphorylation and enhancing glycogen synthase activity to promote hepatic glycogen storage (gulluni2019classiipi3k pages 17-19, margaria2019classiipi3ks pages 4-6).  
• Interfaces with Rab5 and mTORC1, positioning the kinase at the crossroads of endosomal trafficking and nutrient signaling (margaria2019classiipi3ks pages 9-11).  
• Contributes to endolysosomal membrane dynamics and class II PI3K-dependent chemotactic and trafficking processes (bilanges2019pi3kisoformsin pages 7-8).

## Inhibitors

• No selective inhibitor has been reported; PI3K-C2γ is less sensitive to classical pan-PI3K inhibitors such as wortmannin (margaria2019classiipi3ks pages 1-4, gulluni2019classiipi3k pages 2-4).

## Other Comments

• PIK3C2G is located on chromosome 12p12 (margaria2019classiipi3ks pages 13-14).  
• Genetic variants associate with type 2 diabetes, hyperlipidemia and myocardial infarction in human populations (gulluni2019classiipi3k pages 17-19).  
• Reduced gene copy number predicts higher recurrence and mortality in stage III colorectal cancer, suggesting a tumor-suppressive role (gulluni2019classiipi3k pages 17-19).

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