## Phylogeny

PIK3R4/Vps15 is evolutionarily conserved from yeast to mammals and sits within the protein-kinase superfamily as a lipid-kinase–related pseudokinase in the eukaryotic protein kinase branch (Backer, 2008; Ohashi, 2021; Unknown Authors, 2020; Cook et al., 2025).

## Reaction Catalyzed

Phosphatidylinositol (PtdIns) + ATP ⇌ Phosphatidylinositol-3-phosphate (PtdIns3P) + ADP  
(This reaction is executed by the catalytic VPS34 subunit of the PI3KC3 complex that is regulated by PIK3R4/Vps15) (Backer, 2008; Cook et al., 2025).

## Cofactor Requirements

Mg²⁺ (or other divalent cations) and ATP are required for PI3KC3 catalysis (Backer, 2008; Cook et al., 2025).  
The VPS15 pseudokinase domain uniquely binds GTP, which is essential for complex activity (Cook et al., 2025).

## Substrate Specificity

PIK3R4/Vps15 itself is catalytically impaired; therefore, no protein substrate motif has been identified. The PI3KC3 complex that it regulates is specific for membrane-embedded phosphatidylinositol lipids (Backer, 2008; Bilanges et al., 2019).

## Structure

PIK3R4/Vps15 comprises an N-terminal pseudokinase domain (VPS15PKD), a central HEAT-repeat scaffold, and a C-terminal WD40 propeller linked by a flexible connector (Cook et al., 2025; Baskaran et al., 2014; Unknown Authors, 2020). Cryo-EM structures (~2.3 Å in regions) show the HEAT repeats form an arch, contributing to the V-shaped architecture of the PI3KC3 complex (Cook et al., 2025; Baskaran et al., 2014; Unknown Authors, 2020). Arg103 occupies the gatekeeper site in VPS15PKD, enabling GTP binding and positioning the domain to sequester the VPS34 activation loop (Cook et al., 2025).

## Regulation

• N-terminal Gly2 is N-myristoylated; the myristate inserts into a VPS15PKD pocket, anchoring the complex to membranes and stabilizing the inactive VPS34 conformation (Cook et al., 2025; Bilanges et al., 2019).  
• GTP binding to VPS15PKD is a key allosteric switch (Cook et al., 2025).  
• Conformational transitions are modulated by binding partners such as Rab5A and RAB1A, which interact with the WD40 domain to promote activation (Cook et al., 2025; Unknown Authors, 2020).

## Function

PIK3R4/Vps15 acts as a scaffold and regulatory subunit that stabilizes VPS34/PIK3C3 and targets the PI3KC3 complexes to membranes (Backer, 2008; Reidick et al., 2014).  
• Complex I (PI3KC3-C1: VPS34-PIK3R4-BECN1-ATG14) initiates autophagy (Backer, 2008; Chu et al., 2021). Regulators include NRBF2 and AMBRA1 (Chu et al., 2021).  
• Complex II (PI3KC3-C2: VPS34-PIK3R4-BECN1-UVRAG) controls endocytic trafficking and autophagosome–lysosome fusion; Rubicon is a negative regulator (Backer, 2008; Reidick et al., 2014; Chu et al., 2021).  
Upstream recruitment is mediated by Rab5A binding to the WD40 domain, and a VPS34-independent VPS15–GM130 complex operates at the Golgi (Unknown Authors, 2020).

## Inhibitors

• Bcl-2 binds Beclin-1 within the complex, suppressing activity and autophagy (Backer, 2008).  
• Small-molecule inhibitors of VPS34 include 3-methyladenine and wortmannin, which are non-selective PI3K inhibitors (Bilanges et al., 2019; Backer, 2008).  
• Rubicon protein inhibits PI3KC3-C2 by binding UVRAG (Reidick et al., 2014).

## Other Comments

Mis-regulation of PI3KC3 complexes is linked to cancer progression, chemoresistance, ciliopathy, renal insufficiency, Fanconi-like syndrome, and X-linked centronuclear myopathy (Backer, 2008; Chu et al., 2021; Unknown Authors, 2020; Bilanges et al., 2019). Mutations are more frequently reported in partner proteins (BECN1, UVRAG) than in PIK3R4 itself, although disease-associated VPS15 variants have been described (Chu et al., 2021).

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