## Phylogeny

PIKFYVE is an “Atypical” protein kinase of the PIKK family that is conserved throughout the eukaryotic lineage. Orthologues are found in yeast (Fab1p), *Caenorhabditis elegans*, plants, insects, nematodes, zebrafish (Pikfyve) and vertebrates (Manning et al., 2002; Poli et al., 2019; Unknown Authors, 2008; Unknown Authors, 2023). It is further grouped with the type III phosphatidylinositol-3-phosphate 5-kinases (Fab1 kinases).

## Reaction Catalyzed

1. ATP + phosphatidylinositol-3-phosphate (PI3P) → ADP + phosphatidylinositol-3,5-bisphosphate (PI(3,5)P₂)
2. ATP + phosphatidylinositol (PI) → ADP + phosphatidylinositol-5-phosphate (PI5P)  
   (Poli et al., 2019; Unknown Authors, 2008; Karabiyik, 2021)

## Cofactor Requirements

Catalysis requires divalent cations, with Mg²⁺ preferred and Mn²⁺ able to substitute. The FYVE domain is a Zn²⁺-binding module for membrane targeting (Poli et al., 2019; Unknown Authors, 2008; Unknown Authors, 2023).

## Substrate Specificity

PIKFYVE phosphorylates phosphoinositide lipids, showing highest preference for PI3P and the ability to use PI. The FYVE domain confers PI3P-specific membrane recruitment. Although the enzyme also displays serine protein-kinase activity, consensus motifs for protein substrates were not detailed (Poli et al., 2019; Unknown Authors, 2008; Unknown Authors, 2023).

## Structure

Human PIKFYVE is a ~230 kDa multidomain protein comprising an N-terminal FYVE domain, PH domain, DEP domain, CCT domain, spectrin repeats, a winged-helix motif and a C-terminal phosphoinositide-kinase catalytic domain. AlphaFold modelling of Q9Y2I7 reveals a canonical bilobal kinase fold with an open activation loop, catalytic loop and correctly positioned C-helix. PIKFYVE forms a heteromeric complex with FIG4 and the pentameric scaffold VAC14 (Manning et al., 2002; Poli et al., 2019; Unknown Authors, 2016; Unknown Authors, 2023).

## Regulation

• Complex formation with FIG4 and VAC14 is essential for activity and for tight control of PI(3,5)P₂ levels. FIG4 both dephosphorylates PI(3,5)P₂ and promotes PIKFYVE activation (Poli et al., 2019; Unknown Authors, 2008; Unknown Authors, 2023).  
• Autophosphorylation of PIKFYVE inhibits its lipid-kinase function (Poli et al., 2019).  
• Phosphorylation by upstream kinases modulates activity: Ser318 (site suggested) and Ser1548 (phosphorylated by ULK1, stimulates PI5P synthesis) (Unknown Authors, 2008; Karabiyik, 2021).

## Function

PIKFYVE is ubiquitously expressed, with higher levels in adipose tissue, muscle, ocular tissues and pancreas (Unknown Authors, 2016; Unknown Authors, 2023).  
Interacting partners: FIG4, VAC14 (core complex), RAB11A, and the Rab9 effector p40 (Poli et al., 2019; Karabiyik, 2021).  
Cellular roles: regulates endosomal maturation, lysosomal fission/acidification, endosome-to-TGN retrograde transport, phagosome maturation, autophagy, osmotic-stress responses and insulin-stimulated GLUT4 translocation (Poli et al., 2019; Unknown Authors, 2016; Unknown Authors, 2023).

## Inhibitors

YM201636, apilimod and curcumin are small-molecule inhibitors that block PIKFYVE kinase activity; dominant-negative mutants or siRNA give similar phenotypes (Poli et al., 2019; Unknown Authors, 2016; Unknown Authors, 2023).

## Other Comments

Pathogenic variants in PIKFYVE cause François-Neetens corneal fleck dystrophy and some congenital cataracts; haploinsufficiency is supported by zebrafish models. Mutations in FIG4, a complex partner, underlie Charcot-Marie-Tooth disease type 4J. Complete loss of PIKFYVE produces severe developmental defects or embryonic lethality in model organisms (Poli et al., 2019; Unknown Authors, 2008; Unknown Authors, 2023).

## 9. References

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