## Phylogeny

IPPK (Q9H8X2) belongs to the IPK1 sub-family of inositol phosphate kinases, a lineage that is structurally and evolutionarily separate from the protein-kinase-fold IP3K/IPMK enzymes and from the ATP-grasp-fold ITPK/PPIP5K families (unknownauthors2014structuralstudiesof pages 48-52).  
Conserved single-copy orthologs occur in Saccharomyces cerevisiae (ScIpk1), Arabidopsis thaliana (AtIPK1), Danio rerio (DrIpk1) and Mus musculus (MmIpk1) (laha2021inositolphosphatekinases pages 2-3, laha2021inositolphosphatekinases pages 5-7).  
Plants show lineage-specific IPPK amplifications, whereas several Alveolata parasites have lost the gene, apparently relying on host-derived InsP₆ (laha2021inositolphosphatekinases pages 5-7).

## Reaction Catalyzed

ATP + Ins(1,3,4,5,6)P₅ ⇌ ADP + Ins(1,2,3,4,5,6)P₆ (gonzalez2010inositol13456pentakisphosphate2kinase pages 5-5, cridland2020inositolpyrophosphatepathways pages 3-5).

## Cofactor Requirements

Catalysis requires two Mg²⁺ ions that chelate ATP phosphates and stabilise the transition state (gonzalez2010inositol13456pentakisphosphate2kinase pages 5-5, unknownauthors2014structuralstudiesof pages 57-62).

## Substrate Specificity

IPPK phosphorylates only Ins(1,3,4,5,6)P₅; no peptide consensus motif is involved (gonzalez2010inositol13456pentakisphosphate2kinase pages 5-5).  
• 5- and 6-phosphates mediate high-affinity binding to the basic C-lobe pocket (unknownauthors2014structuralstudiesof pages 75-85).  
• The 1-phosphate engages Arg130, locking the N-lobe; removal of the 1- or 3-phosphate abolishes activity (unknownauthors2014structuralstudiesof pages 90-93).  
• Asp368 interrogates the axial 2-OH, conferring absolute positional specificity (gonzalez2010inositol13456pentakisphosphate2kinase pages 5-5).

## Structure

Single-chain ~55 kDa kinase with an N-lobe, hinge, and C-lobe forming an ATP/InsP cleft (unknownauthors2014structuralstudiesof pages 142-155).  
Key catalytic features (PDB 4O3V):  
• Gly-rich loop (residues 80-85) securing ATP (unknownauthors2014structuralstudiesof pages 57-62).  
• Lys168 neutralising negative charge during transfer (gonzalez2010inositol13456pentakisphosphate2kinase pages 5-5).  
• Asp368 and Ser409 coordinating Mg²⁺ and recognising the axial 2-OH (gonzalez2010inositol13456pentakisphosphate2kinase pages 5-5).  
• Arg130 anchoring the 1-phosphate and completing N-lobe closure (unknownauthors2014structuralstudiesof pages 75-85).  
The inositide pocket is unusually deep and basic; an ~103° ATP-to-substrate angle supports in-line phosphoryl transfer (unknownauthors2014structuralstudiesof pages 57-62).

## Regulation

No experimentally verified post-translational modifications have been reported for human IPPK (chakraborty2018theinositolpyrophosphate pages 39-44).  
Activation follows a two-step substrate-induced conformational change: initial docking via 4/5/6-phosphates, then 1-phosphate-triggered N-lobe locking (unknownauthors2014structuralstudiesof pages 142-155).  
IPPK participates in an ATP-responsive metabolic cassette with ITPK1; reversible phosphate transfer between the two enzymes buffers diphosphoinositol phosphate levels in response to cellular energy charge (whitfield2020anatpresponsivemetabolic pages 11-13).  
Allosteric inhibitors that bind outside the InsP pocket display non-competitive kinetics versus InsP₅, but their chemical identities remain unpublished (unknownauthors2014structuralstudiesof pages 199-202, unknownauthors2014structuralstudiesof pages 155-158).

## Function

Expression is highest in brain, heart, placenta and testes; the protein localises to nucleus (euchromatin, nucleoli) and cytoplasm (unknownauthors2014structuralstudiesof pages 43-48).  
Pathway context:  
• Upstream kinases IPMK and ITPK1 provide Ins(1,3,4,5,6)P₅ substrate (unknownauthors2025characterizationofppip5ks pages 30-33).  
• IPPK-derived InsP₆ is the precursor for IP₇/IP₈ synthesis by IP6Ks and PPIP5Ks (unknownauthors2025characterizationofppip5ks pages 30-33).  
InsP₆ produced by IPPK mediates:  
– Gle1-dependent activation of Dbp5 ATPase, enabling bulk mRNA export through the nuclear pore (seeds2007rolesforinositol pages 6-8, chatree2020roleofinositols pages 3-5).  
– Activation of Ku/DNA-PKcs complex, promoting non-homologous end-joining (seeds2007rolesforinositol pages 6-8).  
– Regulation of endocytosis, ion-channel activity and protection from TNF-α-induced apoptosis (unknownauthors2014structuralstudiesof pages 219-222).

## Other Comments

Ipk1⁻/⁻ mice are embryonic-lethal at E8.5, confirming the essentiality of InsP₆ synthesis in mammalian development (seeds2007rolesforinositol pages 6-8).  
Knock-down of zebrafish ipk1 disrupts left-right axis formation, indicating a conserved role in vertebrate morphogenesis (unknownauthors2014structuralstudiesof pages 43-48).

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