## Phylogeny

• PAK3 belongs to the STE20 family, Group I/Group A p21-activated kinases together with PAK1 and PAK2 (rane2014p21activatedkinases pages 1-2).  
• Group I members share high sequence identity within the kinase domain and a conserved regulatory architecture (eswaran2008unpakingtheclass pages 1-2).  
• Orthologs are present in Mus musculus (Pak3), demonstrated by targeted knockout studies (wang2022groupipaks pages 41-43).  
• An ortholog functions in Drosophila melanogaster where Pak3 participates in memory regulation (kumar2017structurebiochemistryand pages 11-12).  
• PAK homologs occur in the amoebozoan Dictyostelium discoideum, showing evolutionary conservation from amoeba to humans (gul2019phosphorylationdependentactivitybasedconformational pages 1-2).  
• Within the human kinome dendrogram, PAK3 clusters with PAK1/2 in the Group I PAK clade distinct from Group II PAK4-6 (eswaran2008unpakingtheclass pages 10-10).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-O-phospho-Ser/Thr (gul2019phosphorylationdependentactivitybasedconformational pages 1-2).

## Cofactor Requirements

Published biochemical studies of Group I PAKs, including PAK3, do not specify an obligate divalent metal cofactor (gul2019phosphorylationdependentactivitybasedconformational pages 1-2).

## Substrate Specificity

Consensus phosphorylation motifs for PAK3 have not been defined in the literature surveyed (kumar2017structurebiochemistryand pages 25-29).

## Structure

• Domain organization comprises an N-terminal CRIB/p21-binding domain overlapping an autoinhibitory domain, followed by proline-rich SH3-binding motifs and a C-terminal bilobal kinase domain (combeau2012thep21activatedkinase pages 1-2).  
• The isolated kinase domain structure (PDB 6FD3) adopts the canonical β-sheet N-lobe and α-helical C-lobe architecture (duarte2020pak3mutationsresponsible pages 5-9).  
• Pathogenic residues Ala365, Lys389 and Gly424 map to the C-lobe surface outside the catalytic cleft (duarte2020pak3mutationsresponsible pages 5-9).  
• Core catalytic elements include the Lys-Glu salt bridge, DFG motif and activation-loop Thr421 equivalent to PAK1 Thr423 (gul2019phosphorylationdependentactivitybasedconformational pages 1-2).  
• Phosphorylation of Thr421 stabilises the hydrophobic regulatory spine and aligns the αC-helix for catalysis (wang2022groupipaks pages 3-4).  
• Autoinhibition is achieved by insertion of the AID helix into the catalytic cleft across a trans-dimer interface (rane2014p21activatedkinases pages 1-2).  
• PAK3 forms heterodimers with PAK1 through the same AID interface, enabling trans-regulatory suppression (combeau2012thep21activatedkinase pages 1-2).

## Regulation

• Binding of GTP-loaded CDC42 or RAC1 to the CRIB domain disengages the AID and initiates activation (zhao2012pakfamilykinases pages 1-3).  
• Autophosphorylation on Ser139 and Thr421 within the activation segment accompanies catalytic activation (wang2022groupipaks pages 3-4).  
• Additional autophosphorylation events on multiple serine/threonine residues further enhance activity (sells1997emergingfromthe pages 2-3).  
• Heterodimerisation with PAK1 enforces trans-inhibition that is relieved upon dimer dissociation (combeau2012thep21activatedkinase pages 1-2).  
• Splice variants bearing AID insertions display reduced dimerisation and higher constitutive activity (combeau2012thep21activatedkinase pages 1-2).  
• Filamin A binding disrupts autoinhibition and stimulates kinase activation (unknownauthors2010paks1& pages 49-55).  
• Interaction with αPIX/ARHGEF6 promotes membrane recruitment and augments activation (duarte2020pak3mutationsresponsible pages 5-9).  
• Group I PAK activity can be down-regulated by POPX family phosphatases, although specific sites on PAK3 were not detailed (eswaran2008unpakingtheclass pages 10-10).  
• No non-phosphorylation post-translational modifications were reported for PAK3 in the cited sources (gul2019phosphorylationdependentactivitybasedconformational pages 20-20).

## Function

• PAK3 is highly enriched in neurons, localising to dendritic spines and postsynaptic densities (boda2006centralnervoussystem pages 1-3).  
• Pak3-deficient mice exhibit impaired late-phase hippocampal long-term potentiation and reduced CREB phosphorylation (wang2022groupipaks pages 41-43).  
• Combined Pak1/Pak3 deletion causes diminished brain size and dendritic arbor complexity, highlighting partial redundancy with PAK1 (wang2022groupipaks pages 41-43).  
• PAK3 phosphorylates myosin VI on Ser406, enhancing actin-based translocation (unknownauthors2010paks1& pages 49-55).  
• PAK3 phosphorylates filamin A to modulate membrane ruffling (unknownauthors2010paks1& pages 49-55).  
• Phosphorylation of stathmin/Op18 at Ser16 by PAK3 regulates microtubule dynamics (unknownauthors2010paks1& pages 49-55).  
• PAK3 contributes to MAPK pathway modulation through phosphorylation of MAPK4/6, influencing downstream actin dynamics (unknownauthors2010paks1& pages 49-55).  
• In oligodendroglial lineage cells, PAK3 controls proliferation, differentiation and myelination in white-matter tracts (wang2022groupipaks pages 41-43).  
• Loss-of-function mutants K389N and G424R disrupt adhesion point dynamics and inhibit neuronal cell migration, linking PAK3 to corpus callosum development (duarte2020pak3mutationsresponsible pages 5-9).

## Inhibitors

• FRAX486 is an ATP-competitive inhibitor with nanomolar potency against Group I PAKs, including PAK3 (wang2022groupipaks pages 41-43).  
• PF-3758309 is a pan-PAK aminopyrazole inhibitor that reached phase I clinical evaluation before discontinuation (rudolph2015inhibitorsofp21activated pages 1-2).  
• Pyrido[2,3-d]pyrimidin-7-one derivatives display Group I selectivity, though isoform-specific potency for PAK3 remains to be established (rudolph2015inhibitorsofp21activated pages 1-2).  
• Additional chemical series with patent coverage have been reported but lacked detailed PAK3 profiling (crawford2012p21activatedkinaseinhibitors pages 1-2).

## Other Comments

• Hemizygous PAK3 mutations cause X-linked intellectual disability with variable brain structural anomalies (unknownauthors2010paks1& pages 49-55).  
• Missense variants Ala365Glu, Lys389Asn, Gly424Arg and Trp446Ser abolish kinase activity (duarte2020pak3mutationsresponsible pages 5-9).  
• Arg67Cys within the CRIB domain alters GTPase preference and leads to immature dendritic spine morphology (dobrigna2023themolecularbasis pages 7-8).  
• Severe intellectual-disability variants Lys389Asn and Gly424Arg retain protein stability yet increase αPIX binding and markedly impair cell migration (duarte2020pak3mutationsresponsible pages 5-9).

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