## Phylogeny

• Member of the New Kinase Family 3 (NKF3) pseudokinases together with PEAK2/Pragmin and PEAK3 (ha2018thecrystalstructure pages 1-2, hou2021peak3pseudokinaserepresents pages 1-3).  
• Shares >45 % sequence identity in the kinase fold with PEAK2/Pragmin (ha2018thecrystalstructure pages 1-2).  
• Phylogenetic analyses place PEAK1 and PEAK2 as a duplication that occurred after divergence from the PEAK3 lineage early in vertebrate evolution (ounoughene2021sheddependentoncogenicsignaling pages 2-4).  
• Orthologs are present in Mus musculus (Peak1) and Danio rerio peak1a/peak1b, indicating conservation across vertebrates (wang2010pseudopodiumenrichedatypicalkinase pages 2-3, yang2024feedforwardstimulationof pages 4-7).  
• Initially omitted from the human kinome survey because of extensive low-complexity regions; later classified in the “Other/atypical” kinase group (lopez2019peak3c19orf35pseudokinasea pages 1-2).

## Reaction Catalyzed

ATP + protein → ADP + phosphoprotein; no nucleotide binding or catalytic turnover has been detected in structural or biochemical assays (ha2018thecrystalstructure pages 7-8).

## Cofactor Requirements

No divalent metal requirement has been reported because catalytic activity is undetectable (ha2018thecrystalstructure pages 7-8).

## Substrate Specificity

• The tyrosine-kinome substrate atlas reports no intrinsic kinase activity and therefore no defined consensus motif (hou2021peak3pseudokinaserepresents pages 1-3).  
• Early in-vitro assays showed weak autophosphorylation and phosphorylation of myelin basic protein without motif definition (wang2010pseudopodiumenrichedatypicalkinase pages 2-3).

## Structure

• Domain organisation: N-terminal low-complexity region (~1–1200) containing SH2/SH3 docking motifs; central split helical dimerization (SHED) module; C-terminal pseudokinase domain (residues 1330–1664) (ha2018thecrystalstructure pages 1-2, wang2010pseudopodiumenrichedatypicalkinase pages 2-3).  
• Crystal structure (PDB 6FJ3) shows a canonical bilobal kinase fold with occluded nucleotide pocket; glycine-rich loop is degenerate, HRD→HCD and DFG→NFL substitutions abolish catalytic geometry (ha2018thecrystalstructure pages 7-8).  
• αC helix is displaced and hydrophobic spines are disrupted (ha2018thecrystalstructure pages 7-8).  
• SHED forms an ‘XL’ four-helix bundle burying ~1900 Å² that mediates obligate dimerization (ha2018thecrystalstructure pages 1-2).  
• Structural alignment reveals highest similarity to RET and Aurora A kinase cores despite loss of catalytic residues (ha2018thecrystalstructure pages 7-8).

## Regulation

• Tyrosine phosphorylation  
– Y665 by Src; required for focal adhesion turnover and migration (wang2010pseudopodiumenrichedatypicalkinase pages 2-3, kelber2010peak1anovel pages 1-3, agajanian2015peak1actsas pages 18-18).  
– Y635 by Src, generating a Grb2 SH2 docking site (hou2021peak3pseudokinaserepresents pages 1-3).  
– Y1188 by Src, enabling Shc1 PTB binding (hou2021peak3pseudokinaserepresents pages 1-3).  
– Y797 by Abl (wang2010pseudopodiumenrichedatypicalkinase pages 2-3).  
• Ser/Thr phosphorylation  
– S779 and T783 by ERK (wang2010pseudopodiumenrichedatypicalkinase pages 2-3).  
– Multiple sites phosphorylated by CAMK2 after binding via the R297-L301-R303 interaction motif (yang2024feedforwardstimulationof pages 11-14, yang2024feedforwardstimulationof pages 14-18).  
• Phosphatase regulation: PTPN12 reduces PEAK phosphorylation levels (hou2021peak3pseudokinaserepresents pages 16-18).  
• Oligomerization: homo- and heterodimerization through the SHED domain is mandatory for signalling (ha2018thecrystalstructure pages 1-2, hou2021peak3pseudokinaserepresents pages 3-5).

## Function

• Expression is ubiquitous with highest levels in brain, kidney and spleen (wang2010pseudopodiumenrichedatypicalkinase pages 2-3, ounoughene2021sheddependentoncogenicsignaling pages 2-4).  
• Acts as a scaffolding pseudokinase regulating cytoskeletal organisation, focal adhesion dynamics, cell spreading and migration (ha2018thecrystalstructure pages 1-2, kelber2010peak1anovel pages 3-4).  
• Upstream activators: EGFR and specific integrins drive Src-dependent phosphorylation of PEAK1 (hou2021peak3pseudokinaserepresents pages 1-3).  
• Interacting partners: Src family kinases, Grb2, Shc1, Csk, Crk/CrkL, Paxillin, p130Cas, FAK, ASAP1, PYK2, CAMK2 isoforms and 14-3-3 proteins (hou2021peak3pseudokinaserepresents pages 3-5, yang2024feedforwardstimulationof pages 4-7, kelber2010peak1anovel pages 3-4, yang2024feedforwardstimulationof pages 11-14).  
• Downstream pathways:  
– Src–p130Cas–Crk–Paxillin axis (kelber2010peak1anovel pages 3-4).  
– Ras/MAPK via Grb2 (hou2021peak3pseudokinaserepresents pages 1-3).  
– EGFR/Src/ErbB2 amplification loop (patel2020thepeakfamily pages 13-14).  
– JAK1/STAT3 signalling in pancreatic epithelial cells (tactacan2015thepseudokinasesgk223 pages 11-11).  
– Feed-forward Ca²⁺/CAMK2 signalling promoting migration and invasion (yang2024feedforwardstimulationof pages 14-18).

## Other Comments

• Overexpressed in breast, colon (>80 % of lesions), lung and pancreatic cancers (kelber2010peak1anovel pages 3-4, hou2021peak3pseudokinaserepresents pages 1-3, patel2020thepeakfamily pages 1-2).  
• High co-expression of PEAK1 with CAMK2D correlates with poor prognosis in triple-negative breast cancer (yang2024feedforwardstimulationof pages 14-18).  
• Overexpression induces epithelial–mesenchymal transition, whereas knockdown drives mesenchymal–epithelial transition (hou2021peak3pseudokinaserepresents pages 1-3).

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