## Phylogeny

ALPK1 belongs to the eukaryote-restricted atypical α-kinase family, one of six human members in the ‘Atypical’ group of the kinome (Manning et al., 2002; Ko et al., 2022). Although its catalytic domain is structurally related to myosin heavy-chain kinases from Dictyostelium, it shares little primary-sequence identity with conventional kinases (García-Weber et al., 2023a). The family appears to have arisen relatively late in evolution (Middelbeek et al., 2010). Orthologues are widespread; the ADPH-contact residue Thr237, for example, is conserved in primate, rodent, canine, bovine, equine and murine ALPK1 proteins (Williams et al., 2019).

## Reaction Catalyzed

ATP + protein → ADP + phosphoprotein (García-Weber et al., 2023a; Snelling et al., 2024).

## Cofactor Requirements

Requires Mg²⁺ for catalytic activity (García-Weber et al., 2023b).

## Substrate Specificity

• Ser/Thr kinase that predominantly phosphorylates threonine residues (García-Weber et al., 2023a).  
• Main physiological substrate is the adaptor TIFA, principally at Thr9 and secondarily at Thr2, Thr12 and Thr19 (García-Weber et al., 2023a; García-Weber et al., 2023b).  
• Does not phosphorylate generic substrate MBP, demonstrating narrow selectivity (García-Weber et al., 2023a).  
• No global consensus motif was identified in the kinome-wide peptide atlas (Johnson et al., 2023).  
• Like other α-kinases, favours phosphorylation sites situated in α-helical regions (Ko et al., 2022; Middelbeek et al., 2010).

## Structure

ALPK1 is a 139 kDa protein comprising:  
1. N-terminal α-helical domain (NTD; residues 1–473) – contains 18 α-helices organised into seven antiparallel pairs forming a solenoid that binds ADP-L-β-D-manno-heptose (ADPH) (PDB 5Z2C) (García-Weber et al., 2023a; Snelling et al., 2024). Key ligand-contact residues include Arg150 (phosphate interactions) and Thr237 (sugar hydrogen bond) (Snelling et al., 2024).  
2. Flexible linker.  
3. C-terminal α-kinase catalytic domain – houses Lys1067 essential for ATP binding (Snelling et al., 2024). By homology with ChaK1/TRPM7 the domain features an elongated C-helix, a very short “kinked” activation loop and a modified hydrophobic spine that still positions catalytic residues correctly (Drennan & Ryazanov, 2004; Middelbeek et al., 2010).

## Regulation

• Allosterically activated by pathogen- or host-derived nucleotide sugars that bind the NTD, most potently ADPH; UDP-α-D-mannose and related metabolites also activate (García-Weber et al., 2023a; Snelling et al., 2023).  
• Ligand binding triggers conformational changes that open the catalytic cleft (García-Weber et al., 2023a).  
• Undergoes Mg²⁺-dependent autophosphorylation after ADPH sensing; this modification, independent of TIFA, is required for full activation (García-Weber et al., 2023a; García-Weber et al., 2023b).

## Function

Tissue / cellular distribution  
– Detected in macular retina, RPE/choroid, optic nerve, spleen, fibroblasts, ARPE-19 cells, monocytes and kidney cells (Williams et al., 2019; Ko et al., 2022).  
– Localises to centrosomes, spindle poles and primary cilia including photoreceptor basal bodies (Williams et al., 2019).  
– Expression is lower in lung and colorectal tumours than in matched normal tissues (Liao et al., 2016).

Signalling role  
Acts as an intracellular pattern-recognition receptor for Gram-negative bacterial ADPH. Upon ligand binding ALPK1 phosphorylates TIFA, promoting TIFAsome assembly, TRAF6 recruitment and activation of NF-κB and AP-1 pathways to drive pro-inflammatory gene expression (García-Weber et al., 2023a; Snelling et al., 2024). ALPK1 also phosphorylates non-muscle myosin IIA to regulate TNF-α trafficking during monosodium-urate–induced gouty inflammation (Lee et al., 2016).

## Other Comments

Germ-line or somatic ALPK1 mutations are linked to diverse disorders, often through gain-of-function effects:  
• Thr237Met (ROSAH syndrome) – constitutive kinase/TIFAsome activity (García-Weber et al., 2023a; Snelling et al., 2023).  
• Val1092Ala (spiradenoma/spiradenocarcinoma) – heightened ADPH-stimulated activity (García-Weber et al., 2023a).  
• Ser277Phe (ROSAH syndrome) – ligand-independent NF-κB/AP-1 activation (Snelling et al., 2024).  
Rare variants have been associated with gout, PFAPA periodic fever and chronic kidney disease (Sangiorgi et al., 2019; García-Weber et al., 2023a).

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