## Phylogeny

Human PINK1 belongs to the TKL (tyrosine-kinase-like) supergroup and is assigned to the PINK kinase family (Manning et al., 2002). A separate sequence-alignment study places it in the “OTHER” category because it does not cluster closely with the nine canonical kinase groups (Modi & Dunbrack, 2019). It shows pronounced similarity to Ca²⁺/calmodulin-dependent kinases and is also listed in the NSKs (nervous-system kinase) family (Unknown Authors, 2012a). PINK1 is highly conserved across metazoans: orthologues are present in Homo sapiens, Macaca mulatta, Mus musculus, Gallus gallus, Danio rerio, Tribolium castaneum, Drosophila melanogaster and Caenorhabditis elegans, but are absent from yeast (Unknown Authors, 2012a; Gonçalves et al., 2024a; Unknown Authors, 2016). Pair-wise identity with the human sequence is ~97 % (macaque), 81 % (mouse), 64 % (chicken), 54 % (zebrafish), 40–45 % (insects) and 32 % (C. elegans) (Unknown Authors, 2012a).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇄ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein]  
(Unknown Authors, 2012b)

## Cofactor Requirements

Catalysis requires a divalent metal ion (Mg²⁺ or Mn²⁺). The DFG motif in the activation loop coordinates Mg²⁺ for ATP binding and phosphoryl transfer (Gonçalves et al., 2024b; Unknown Authors, 2012a).

## Substrate Specificity

Kinome-wide clustering places PINK1 with LKB1, CAMKK and PBK (cluster 14) (Johnson et al., 2023). The preferred phosphorylation motif contains a Ser/Thr preceded by acidic or hydrophobic residues; an acidic residue at –3 and a Pro (or other hydrophobe) at +1 are favoured. No strict polarity requirement exists at +2 (Unknown Authors, 2024; Quinn et al., 2020).

## Structure

The 581-residue protein comprises:  
• Mitochondrial targeting sequence (1–34)  
• N-terminal α-helical extension (NTE)  
• Single transmembrane helix (89–111)  
• Catalytic kinase domain (156–510)  
• C-terminal extension (511–581)  
(Kakade et al., 2022; Unknown Authors, 2019)

An intramolecular NTE–CTE interface stabilises the kinase and is necessary for autophosphorylation/activation (Kakade et al., 2022). Canonical kinase motifs are present (AIK, HRD, DFG, APE) together with a PINK1-specific Ins3 insertion (Biswas et al., 2023).

## Regulation

Under normal mitochondrial membrane potential, PINK1 is imported via TOM/TIM23, sequentially cleaved by MPP and PARL (Ala103), retro-translocated and degraded through the N-end-rule pathway (Quinn et al., 2020; Unknown Authors, 2019). Depolarisation halts import, causing accumulation on the outer mitochondrial membrane (OMM); PINK1 then dimerises and autophosphorylates at Ser228 and Ser402 to become active (Gonçalves et al., 2024a; Kakade et al., 2022). Ubiquitination at Lys137 targets the protein for proteasomal turnover (Unknown Authors, 2024).

## Function

PINK1 mRNA is widely expressed, notably in cortical and striatal neurons, Purkinje cells and the brainstem (Unknown Authors, 2012c). It acts as a sensor of mitochondrial damage and initiates mitophagy. On depolarised mitochondria, active PINK1 phosphorylates ubiquitin Ser65 and Parkin Ser65, relieving Parkin autoinhibition and driving a feed-forward ubiquitination loop (Biswas et al., 2023; Harper et al., 2018; Choubey et al., 2021). Parkin-dependent ubiquitination of OMM proteins earmarks the organelle for autophagic removal. Additional PINK1 substrates (MFN2, Miro, HtrA2, TRAP1) modulate mitochondrial dynamics, Ca²⁺ handling and oxidative stress; interaction with Beclin1 curbs apoptosis, and PINK1 activity can attenuate STING-mediated inflammation (Unknown Authors, 2024; Brunelli et al., 2022).

## Other Comments

More than 130 loss-of-function mutations in PINK1 cause autosomal-recessive early-onset Parkinson’s disease (Biswas et al., 2023; Gonçalves et al., 2024a). Missense changes such as G309D and L347P abolish kinase activity, whereas P296L (Ins3) and Q126P (NTE-CTE interface) disrupt substrate recognition or stabilisation (Biswas et al., 2023; Kakade et al., 2022). The G411S variant enhances kinase stability and activity but its contribution to PD risk is debated (Gonçalves et al., 2024a).

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