## Phylogeny

PRKD2 orthologs have been experimentally verified in mouse, rat, zebrafish, Drosophila and C. elegans, underscoring broad metazoan conservation (Ellwanger & Hausser, 2013). Within the human kinome, PRKD2 belongs to the Ca²⁺/calmodulin-dependent protein kinase (CAMK) group, PKD subfamily, together with PRKD1 and PRKD3 (Zhang et al., 2021). Phylogenetic analyses indicate that PRKD1 and PRKD2 are the closest paralogs; PRKD2 appears to have arisen later in mammalian evolution, whereas a PKD1-like isoform exists in earlier vertebrates (Azoitei et al., 2018).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-O-phospho-Ser/Thr (Anti, 2009; Cobbaut et al., 2017).

## Cofactor Requirements

Catalytic activity requires divalent Mg²⁺ or Mn²⁺; in vitro assays typically employ ~10 mM MgCl₂ (Cobbaut et al., 2017; Unknown Author(s), 2023).

## Substrate Specificity

A quantitative motif analysis defined a preferred consensus (L/I/V)-x-R-x-x-S/T with a hydrophobic residue at ‑5 and an Arg at ‑3 (Unknown Author(s), 2023). Phosphoproteomics in vasopressin-stimulated collecting-duct cells confirmed enrichment of L-X-R-(R/H)-X-pS/T motifs (Datta et al., 2021). Peptide-array screens show tolerance for diverse flanking residues but a strict requirement for a central Ser/Thr (Cobbaut et al., 2017).

## Structure

Domain organisation: Ubiquitin-like dimerisation domain (ULD) → tandem C1a/C1b domains → PH domain → Ser/Thr kinase domain → C-terminal PDZ-binding tail (Reinhardt et al., 2020; Zhang et al., 2021).  
3-D information: crystal/NMR structures exist for the C. elegans ULD-C1a cassette (PDB 6RAO) and the human PH domain (PDB 2COA). AlphaFold modelling supports a canonical bilobal kinase fold and a face-to-face homodimer interface (Unknown Author(s), 2023).  
Key features: the activation loop contains Ser706/Ser710 and a P+1-loop Tyr717 between the conserved DFG and APE motifs; an LNQ sequence C-terminal to APE modulates Abl docking (Cobbaut et al., 2017). ULD-mediated dimerisation juxtaposes the two activation loops for trans-autophosphorylation; subsequent phosphorylation disrupts the dimer to allow substrate access (Reinhardt et al., 2020). The αG-helix acidic patch and hydrophobic spine aid dimer stabilisation and inhibitor binding (Unknown Author(s), 2014).

## Regulation

• Ser706 (activation loop) is phosphorylated by novel PKC isoforms, relieving PH-domain autoinhibition (Cobbaut et al., 2017).  
• Ser710 undergoes autophosphorylation and cooperates with Ser706 for full activity (Cobbaut et al., 2017).  
• Tyr717 is phosphorylated by Abl during oxidative stress, increasing catalytic turnover; this requires prior Ser706/Ser710 phosphorylation (Cobbaut et al., 2017).  
• Additional sites: Tyr87 (oxidant-induced), Tyr438 (BCR-Abl-dependent), Ser876 (C-terminal autophosphorylation marker) (Bernhart et al., 2014; Cobbaut et al., 2017).  
• Allosteric controls include DAG binding to C1 domains, ULD-driven dimerisation, and PH-domain autoinhibition (Reinhardt et al., 2020).

## Function

Expression: high in lung, brain, kidney, heart, smooth muscle, pancreas and prostate (Zhang et al., 2021).  
Immune system: abundant in thymocytes and peripheral T cells; required for TCR-driven cytokine production and extensive phospho-signalling networks in cytotoxic T lymphocytes (Ellwanger & Hausser, 2013; Navarro et al., 2014).  
Upstream activators: DAG-activated PKCδ targets Ser706; oxidative stress activates Abl for Tyr717 phosphorylation (Steinberg, 2012; Cobbaut et al., 2017).  
Downstream signalling: maintains ERK1/2 activation, phosphorylates PI4KIIIβ and other Golgi substrates to regulate vesicle fission, mediates oxidative-stress-induced NF-κB activation, and enhances MMP-9 secretion to support invasion (Cobbaut et al., 2017; Navarro et al., 2014; Zhang et al., 2021).

## Inhibitors

• CRT0066101 – ATP-competitive pan-PKD inhibitor; IC₅₀ ≈ 1 nM (PKD1) / 2.5 nM (PKD2); orally bioavailable and anti-tumour in vivo (Unknown Author(s), 2011).  
• CID755673 – non-ATP-competitive; biochemical IC₅₀ ≈ 200 nM for all PKD isoforms; limited PKC cross-reactivity (Unknown Author(s), 2011).  
• kb-NB142-70 – improved CID755673 analog; IC₅₀ ≈ 28 nM for PKD1 with higher potency toward PKD2/3; cellular IC₅₀ ≈ 2 µM (Unknown Author(s), 2011).  
• Imatinib – indirectly suppresses Tyr717 phosphorylation by inhibiting Abl (Cobbaut et al., 2017).

## Other Comments

PRKD2 promotes survival and invasion of prostate-cancer cells and is linked to poor prognosis in several solid tumours (Azoitei et al., 2018; Zhang et al., 2021). In chronic myeloid leukaemia, BCR-Abl-mediated Tyr438 phosphorylation couples PRKD2 to NF-κB activation (Mihailovic et al., 2004; Cobbaut et al., 2017). PKD family inhibition mitigates pressure-overload-induced cardiac hypertrophy, although isoform redundancy complicates interpretation (Unknown Author(s), 2014). Ser876 autophosphorylation influences glioma cell proliferation and senescence (Bernhart et al., 2014).

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