## Phylogeny

* Orthologs experimentally confirmed in mouse Prkd2, rat Prkd2, zebrafish prkd2, Drosophila melanogaster pkd, and the C. elegans kinases dkf-1/dkf-2, demonstrating broad metazoan conservation (ellwanger2013physiologicalfunctionsof pages 1-3, ellwanger2013physiologicalfunctionsof pages 3-4, ellwanger2013physiologicalfunctionsof pages 4-6).
* Within the human kinome, PRKD2 is assigned to the Ca²⁺/calmodulin-dependent protein kinase (CAMK) group, PKD subfamily, together with PRKD1 and PRKD3 (zhang2021multifacetedfunctionsof pages 1-2, cobbaut2017differentialregulationof pages 1-2).
* Phylogenetic analysis indicates that PRKD1 and PRKD2 are the closest paralogs and that PRKD2 emerged later in mammalian evolution, whereas a PKD1-like isoform is present in earlier vertebrates (azoitei2018proteinkinased2 pages 1-2).

## Reaction Catalyzed

* ATP + protein-Ser/Thr ⇌ ADP + protein-O-phospho-Ser/Thr (anti2009nonspecificserinethreonineprotein pages 19-22, cobbaut2017differentialregulationof pages 14-15).

## Cofactor Requirements

* Catalytic activity requires divalent Mg²⁺ or Mn²⁺; in vitro kinase assays routinely use 10 mM MgCl₂ to support phosphotransfer (cobbaut2017differentialregulationof pages 14-15, unknownauthors2023proteinkinased pages 53-54).

## Substrate Specificity

* A quantitative motif analysis defined the preferred consensus (L/I/V)-x-R-x-x-S/T with a hydrophobic residue at −5 and an arginine at −3 relative to the phospho-acceptor (unknownauthors2023proteinkinased pages 53-54).
* Phosphoproteomic profiling in vasopressin-stimulated collecting-duct cells corroborated enrichment of [L-X-R-(R/H)-X-pS/T] motifs among PRKD2 substrates (datta2021phosphoproteomicidentificationof pages 7-8).
* Peptide-array screens confirmed tolerance for diverse flanking residues but strict requirement for a central Ser/Thr target (cobbaut2017differentialregulationof pages 14-15).

## Structure

* Domain organisation: Ubiquitin-like dimerisation domain (ULD) → tandem C1 domains (C1a/C1b) → PH domain → Ser/Thr kinase domain → C-terminal PDZ-binding tail (reinhardt2020ittakestwo pages 3-4, zhang2021multifacetedfunctionsof pages 2-4).
* 3D information: crystal/NMR structures are available for the ULD-C1a cassette from C. elegans DKF-1 (PDB 6RAO) and the human PH domain (PDB 2COA) (reinhardt2020ittakestwo pages 3-4). AlphaFold modelling confirms a canonical bilobal kinase fold and face-to-face homodimer interface (unknownauthors2023proteinkinased pages 45-46).
* Catalytic and regulatory features: activation loop contains Ser706/Ser710 (human numbering) and the P + 1 loop Tyr717 situated between the conserved DFG and APE motifs; a unique LNQ sequence immediately C-terminal to APE modulates Abl docking (cobbaut2017differentialregulationof pages 11-12, cobbaut2017differentialregulationof pages 7-10).
* ULD-mediated dimerisation juxtaposes the activation loops for trans-autophosphorylation; phosphorylation disrupts the dimer to permit substrate access (reinhardt2020ittakestwo pages 4-5).
* The αG helix acidic patch and hydrophobic spine participate in dimer stabilisation and small-molecule inhibitor binding (unknownauthors2014structuralinsightinto pages 20-28).

## Regulation

* Ser706 (activation loop): phosphorylated by novel PKC isoforms, relieving PH-domain autoinhibition (cobbaut2017differentialregulationof pages 6-7).
* Ser710: autophosphorylation cooperating with Ser706 for full catalytic activity (cobbaut2017differentialregulationof pages 6-7).
* Tyr717: phosphorylated by Abl during oxidative stress, increasing catalytic turnover toward peptide substrates (cobbaut2017differentialregulationof pages 7-10).
* Tyr87 (N-terminus): oxidant-induced phosphorylation, dispensable for PKCδ binding (cobbaut2017differentialregulationof pages 6-7).
* Tyr438 (PH domain): phosphorylated by BCR-Abl in leukemic cells, contributing to NF-κB activation (cobbaut2017differentialregulationof pages 1-2).
* Ser876 (C-terminal tail): autophosphorylation event used as an activity marker and required for maximal signalling in glioma cells (bernhart2014silencingofprotein pages 8-8).
* Hierarchical interplay: Ser706/Ser710 phosphorylation primes subsequent Tyr717 phosphorylation under oxidative stress (cobbaut2017differentialregulationof pages 7-10).
* Allosteric mechanisms include DAG binding to C1 domains for membrane recruitment, ULD-driven dimerisation for activation-loop trans-phosphorylation, and PH-domain autoinhibition relieved by activation-loop phosphorylation (reinhardt2020ittakestwo pages 3-4, reinhardt2020ittakestwo pages 4-5).

## Function

* Tissue expression is high in lung, brain, kidney, heart, smooth muscle, pancreas and prostate (zhang2021multifacetedfunctionsof pages 1-2).
* Immune system: abundant in thymocytes and peripheral T cells; required for TCR-driven cytokine production and extensive phosphoregulation networks in cytotoxic T lymphocytes (ellwanger2013physiologicalfunctionsof pages 7-8, navarro2014quantitativephosphoproteomicsof pages 4-6).
* Upstream activators: DAG-driven PKCδ phosphorylates Ser706; oxidative stress activates Abl for Tyr717 modification (steinberg2012regulationofprotein pages 1-2, cobbaut2017differentialregulationof pages 7-10).
* Downstream signalling:
  + Sustains ERK1/2 activation to potentiate mitogenic immediate-early gene expression (zhang2021multifacetedfunctionsof pages 1-2).
  + Phosphorylates PI4KIIIβ and other Golgi substrates controlling vesicle fission and secretion (navarro2014quantitativephosphoproteomicsof pages 12-13).
  + Mediates oxidative-stress-induced NF-κB activation (cobbaut2017differentialregulationof pages 14-15).
  + Enhances matrix metalloproteinase-9 secretion, supporting invasive behaviour (cobbaut2017differentialregulationof pages 12-13).

## Inhibitors

* CRT0066101: ATP-competitive pan-PKD inhibitor; IC₅₀ = 1 nM (PKD1), 2.5 nM (PKD2); orally bioavailable and blocks tumour growth in vivo (unknownauthors2011targetingproteinkinase pages 92-95).
* CID755673: non-ATP-competitive inhibitor; biochemical IC₅₀ ≈ 200 nM for all PKD isoforms; minimal activity against classical PKCs (unknownauthors2011targetingproteinkinase pages 87-92).
* kb-NB142-70: improved analog of CID755673; IC₅₀ = 28 nM for PKD1 with ~4-fold enhanced potency for PKD2/3; cellular IC₅₀ ≈ 2 µM (unknownauthors2011targetingproteinkinase pages 92-95).
* Imatinib (STI-571): indirectly suppresses PRKD2 Tyr717 phosphorylation by inhibiting Abl (cobbaut2017differentialregulationof pages 7-10).

## Other Comments

* Cancer: PRKD2 promotes prostate-cancer cell survival and invasion and is linked to poor prognosis in several solid tumours (azoitei2018proteinkinased2 pages 1-2, zhang2021multifacetedfunctionsof pages 26-27).
* Hematologic malignancy: BCR-Abl-mediated Tyr438 phosphorylation couples PRKD2 to NF-κB activation in chronic myeloid leukaemia (mihailovic2004proteinkinased2 pages 6-7, cobbaut2017differentialregulationof pages 1-2).
* Cardiac pathology: PKD family inhibition mitigates pressure-overload-induced hypertrophy, although isoform redundancy complicates interpretation (unknownauthors2014structuralinsightinto pages 13-20).
* Neurological disease: PRKD2 signalling influences glioma cell proliferation and senescence through Ser876 autophosphorylation (bernhart2014silencingofprotein pages 8-8).

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