## Phylogeny

PRKG1 belongs to the AGC protein-kinase group, PKG family, within the canonical human kinome (Arencibia et al., 2013; Manning et al., 2002). Orthologs with experimental or bioinformatic support occur in vertebrates (Homo sapiens PRKG1, Mus musculus Prkg1, Rattus norvegicus Prkg1), insects (Drosophila melanogaster DG1/PKG-like), nematodes (Caenorhabditis elegans egl-4) and apicomplexan parasites (Plasmodium falciparum / P. vivax PKG) (Arencibia et al., 2013; Bakkouri et al., 2019). Saccharomyces cerevisiae lacks a direct PKG but retains other AGC kinases (Arencibia et al., 2013). Phylogenetically PRKG1 clusters most closely with PRKG2 and shares the PIF-pocket sub-family feature with PKA and PKC isoforms (Arencibia et al., 2013).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr ⇌ ADP + protein-L-Ser/Thr-phosphate (Arencibia et al., 2013).

## Cofactor Requirements

Catalytic turnover requires divalent Mg²⁺ ions; MgCl₂ is routinely included in assays and Mg²⁺ is coordinated in nucleotide-bound crystal structures (Guo et al., 2013; Chan et al., 2020; Bakkouri et al., 2019).

## Substrate Specificity

PRKG1 prefers basic residues at −3/−2 and a hydrophobic residue at +1 relative to the phosphoacceptor, giving a consensus R/K-R/K-X-X-S/T-Φ motif (Thomas et al., 1990; Arencibia et al., 2013). Verified cellular targets that match this pattern include VASP Ser239, MYPT1 Ser695/Thr696 and sites in the cGMP-binding phosphodiesterase (Hofmann et al., 2006; Thomas et al., 1990; Vaandrager & de Jonge, 1996).

## Structure

Domain organisation  
• N-terminal leucine-zipper dimerisation/targeting region containing an autoinhibitory segment (Hofmann, 2005).  
• Tandem cyclic-nucleotide-binding domains: high-affinity CNB-A and lower-affinity CNB-B (Campbell et al., 2016).  
• C-terminal Ser/Thr kinase domain with a canonical AGC fold and PIF-pocket (Arencibia et al., 2013).

3D information  
Human fragments have been solved: CNB-B (PDB 4KU8), CNB-A (5C53) and the isolated kinase domain (4O4X), revealing nucleotide-recognition and catalytic motifs (Chan et al., 2020). Full-length Plasmodium PKG structures show a pentagonal assembly in which the autoinhibitory segment blocks the substrate groove; sequential cGMP binding releases this segment—a mechanism conserved in PRKG1 (Bakkouri et al., 2019). The catalytic core displays an ordered activation loop and intact hydrophobic C- and R-spines typical of active AGC kinases (Bakkouri et al., 2019). Arg177 in CNB-A anchors cGMP; the pathogenic Arg177Gln substitution disrupts this contact and favours an active conformation (Guo et al., 2013).

## Regulation

• Allosteric activation: sub-micromolar cGMP binding to CNB-A/B displaces the autoinhibitory segment (Hofmann, 2005).  
• Autophosphorylation: Ser65 (PKG1α) and Ser80 (PKG1β) enhance and stabilise activity; additional N-terminal phosphorylation events tune substrate selectivity (Chan et al., 2020; Hofmann, 2005).  
• The PIF-pocket forms an auxiliary allosteric site that can be targeted by small molecules (Arencibia et al., 2013).

## Function

Expression: highly abundant in vascular and visceral smooth muscle, platelets, cerebellum, hippocampus and dorsal root ganglia; present at lower levels in cardiac muscle and other neurons (Hofmann et al., 2006).

Upstream signalling: nitric-oxide-stimulated soluble guanylate cyclase and natriuretic-peptide receptor guanylate cyclases raise cGMP, thereby engaging PRKG1 (Hofmann, 2005).

Downstream actions  
• Smooth-muscle relaxation via MYPT1 phosphorylation leading to myosin light-chain dephosphorylation (Hofmann et al., 2006).  
• Platelet inhibition through VASP phosphorylation and cytoskeletal remodelling (Arencibia et al., 2013).  
• Reduction of cardiac L-type Ca²⁺ current by stimulation of phosphodiesterase II (Vaandrager & de Jonge, 1996).  
• Neuronal roles in axon guidance, synaptic plasticity and nociception (Hofmann et al., 2006).

## Inhibitors

• Rp-8-pCPT-cGMPS and Rp-8-pCPT-PET-cGMPS competitively block cyclic-nucleotide binding and partially inhibit both wild-type and R177Q PRKG1 (Chan et al., 2020).  
• DT-2 peptide potently inhibits mutant and wild-type kinase activity (Chan et al., 2020).  
• H-8, a pan-AGC small molecule, attenuates PRKG1 signalling in cells (Jafari et al., 2015).

## Other Comments

A recurrent gain-of-function variant, p.Arg177Gln, causes autosomal-dominant thoracic aortic aneurysm and dissection by rendering the kinase constitutively active, independent of cGMP (Guo et al., 2013). A de novo p.Gly370Ser substitution in the glycine-rich loop is also associated with aortic disease (Zhang et al., 2018). PRKG1 is listed as a category A hereditary TAAD gene in clinical guidelines (Takeda & Komuro, 2019).

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