## Phylogeny

PRKG1 is classified within the AGC kinase group, PKG family, in the canonical human kinome taxonomy (arencibia2013agcproteinkinases pages 2-3, manning2002evolutionofprotein pages 1-2).  
Representative orthologs with experimental or bioinformatic support include: Homo sapiens PRKG1, Mus musculus Prkg1, Rattus norvegicus Prkg1 (arencibia2013agcproteinkinases pages 1-2); Drosophila melanogaster DG1/PKG-like and Caenorhabditis elegans egl-4 (arencibia2013agcproteinkinases pages 1-2); Plasmodium falciparum and P. vivax PKG (bakkouri2019structuresofthe pages 1-2). Saccharomyces cerevisiae lacks a direct PKG counterpart but retains other AGC kinases (arencibia2013agcproteinkinases pages 1-2). Phylogenetically, PRKG1 clusters closest to PRKG2 and shares the PIF-pocket sub-family feature with PKA and PKC isoforms (arencibia2013agcproteinkinases pages 2-3).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr → ADP + protein-L-Ser/Thr-phosphate (arencibia2013agcproteinkinases pages 2-3).

## Cofactor Requirements

Catalytic turnover requires divalent Mg²⁺ ions; MgCl₂ is routinely included in kinase assays and Mg²⁺ is coordinated in nucleotide-bound crystal structures (guo2013recurrentgainoffunctionmutation pages 4-5, chan2020asubstitutionin pages 6-8, bakkouri2019structuresofthe pages 1-2).

## Substrate Specificity

PRKG1 recognises basic residues at −3/−2 and a hydrophobic residue at +1 relative to the phosphoacceptor, yielding a consensus R/K-R/K-X-X-S/T-Φ motif (thomas1990substrateandkinasedirected pages 6-7, arencibia2013agcproteinkinases pages 18-18). Established cellular targets that conform to this pattern include VASP Ser239, MYPT1 Ser695/Thr696, and cG-BPDE serine sites (hofmann2006functionofcgmpdependent pages 23-23, thomas1990substrateandkinasedirected pages 1-1, vaandrager1996signallingbycgmpdependent pages 6-7).

## Structure

Domain organisation  
• N-terminal leucine-zipper dimerisation/targeting region containing an autoinhibitory segment (hofmann2005thebiologyof pages 1-1).  
• Tandem cyclic nucleotide-binding domains: CNB-A (high-affinity) and CNB-B (low-affinity) (campbell2016structuralbasisof pages 1-2).  
• C-terminal serine/threonine kinase domain with canonical AGC fold and PIF-pocket (arencibia2013agcproteinkinases pages 2-3).

3D information  
Human structures: CNB-B (PDB 4KU8), CNB-A (5C53), isolated kinase domain (4O4X) resolve nucleotide-recognition and catalytic motifs (chan2020asubstitutionin pages 1-1). Full-length Plasmodium PKG structures show a pentagonal arrangement in which the autoinhibitory segment occupies the substrate groove; sequential cGMP binding releases this segment, a mechanism conserved in PRKG1 (bakkouri2019structuresofthe pages 1-2). The catalytic core exhibits an ordered activation loop and hydrophobic C- and R-spines typical of active AGC kinases (bakkouri2019structuresofthe pages 4-5). Arg177 in CNB-A anchors the cyclic-phosphate of cGMP; the pathogenic Arg177Gln substitution disrupts this contact and favours an active conformation (guo2013recurrentgainoffunctionmutation pages 2-4).

## Regulation

• Allosteric: sub-micromolar cGMP binding to CNB-A/B displaces the autoinhibitory segment and activates the kinase (hofmann2005thebiologyof pages 1-1).  
• Autophosphorylation: Ser65 in PKG1α and Ser80 in PKG1β enhance and stabilise activation (chan2020asubstitutionin pages 1-1). Additional N-terminal autophosphorylations modulate substrate selectivity (hofmann2005thebiologyof pages 1-1).  
• Allosteric PIF-pocket provides an additional regulatory site targeted by small molecules (arencibia2013agcproteinkinases pages 2-3).

## Function

Expression: highly abundant in vascular and visceral smooth muscle, platelets, cerebellum, hippocampus and dorsal root ganglia; lower in cardiac muscle and other neurons (hofmann2006functionofcgmpdependent pages 2-3).

Upstream signalling: NO-stimulated soluble guanylate cyclase and natriuretic peptide receptor guanylate cyclases elevate cGMP, engaging PRKG1 (hofmann2005thebiologyof pages 1-1).

Downstream actions  
• Smooth-muscle relaxation via MYPT1 phosphorylation and subsequent myosin light-chain dephosphorylation (hofmann2006functionofcgmpdependent pages 23-23).  
• Platelet inhibition through VASP phosphorylation and cytoskeletal remodelling (arencibia2013agcproteinkinases pages 2-3).  
• Reduction of cardiac L-type Ca²⁺ current by stimulating phosphodiesterase II (vaandrager1996signallingbycgmpdependent pages 6-7).  
• Neuronal roles in axon guidance, synaptic plasticity and nociception (hofmann2006functionofcgmpdependent pages 16-17).

## Inhibitors

• Rp-8-pCPT-cGMPS and Rp-8-pCPT-PET-cGMPS competitively block cyclic nucleotide binding and partially inhibit wild-type and R177Q mutant PRKG1 (chan2020asubstitutionin pages 4-5, chan2020asubstitutionin pages 8-9).  
• DT-2 peptide inhibits mutant and wild-type kinase activity (chan2020asubstitutionin pages 6-8).  
• H-8, a pan-AGC small molecule, diminishes PRKG1 signalling in cellular systems (jafari2015pharmacologicalinhibitionof pages 5-6).

## Other Comments

Gain-of-function variant p.Arg177Gln causes autosomal-dominant thoracic aortic aneurysm and dissection with full penetrance; the mutant kinase is constitutively active independent of cGMP (guo2013recurrentgainoffunctionmutation pages 1-2). A de novo p.Gly370Ser substitution in the glycine-rich ATP-binding loop is likely pathogenic, associating with aortic dissection and tortuosity (zhang2018exomesequencingreveals pages 3-4). PRKG1 is recognised as a category A hereditary TAAD gene in clinical genetics guidelines (takeda2019geneticbasisof pages 1-2).

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