## Phylogeny

• PRKG2 is one of the two mammalian cyclic-GMP-dependent protein kinase genes; it encodes the type II isoform (cGK II), whereas PRKG1 encodes cGK I. Both cluster within the AGC / cyclic-nucleotide–dependent branch of the kinome (vaandrager2005molecularpropertiesand pages 1-2, bijvelds2018selectiveinhibitionof pages 2-3).  
• Well-conserved orthologs with intact catalytic domains occur in mouse, rat, cattle, dog and human, and loss-of-function alleles in each species produce proportionate dwarfism phenotypes, underscoring functional conservation (koltes2009anonsensemutation pages 3-4, garces2021prkg2splicesite pages 7-8, bijvelds2018selectiveinhibitionof pages 8-10).  
• cGK II is most closely related to cGK I and more distant from Drosophila DG1/DG2 kinases, in agreement with kinome-wide evolutionary analyses (vaandrager2005molecularpropertiesand pages 1-2, bijvelds2018selectiveinhibitionof pages 2-3).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-O-phospho-Ser/Thr (vaandrager2005molecularpropertiesand pages 5-7).

## Cofactor Requirements

Requires divalent Mg²⁺ for efficient ATP binding and phosphotransfer (bijvelds2018selectiveinhibitionof pages 2-3).

## Substrate Specificity

• Preferred consensus motif: RRXS/T with two basic residues N-terminal to the phospho-acceptor (vaandrager2005molecularpropertiesand pages 5-7).  
• Validated substrates:  
– CFTR regulatory domain; phosphorylation at Ser700 and at least four additional sites activates chloride conductance (vaandrager2005molecularpropertiesand pages 7-8).  
– Raf-1; phosphorylation at Ser43 suppresses FGF-induced ERK1/2 signaling in chondrocytes (diazgonzalez2022bialleliccgmpdependenttype pages 5-6).

## Structure

• Homodimer of 762-aa subunits arranged in parallel; dimerization involves an N-terminal leucine-zipper that is myristoylated for membrane anchoring (vaandrager2005molecularpropertiesand pages 1-2, bijvelds2018selectiveinhibitionof pages 2-3).  
• Domain organization:  
– N-terminal myristoylation signal + leucine-zipper / dimerization segment.  
– Autoinhibitory pseudosubstrate region.  
– Two cyclic-nucleotide binding domains: CNB-A (low affinity, proximal) and CNB-B (high affinity, distal); their order is reversed relative to cGK I (vaandrager2005molecularpropertiesand pages 1-2).  
– C-terminal Ser/Thr kinase catalytic domain with conserved HRD and DFG motifs; homology modelling and AlphaFold predictions confirm canonical AGC-fold features including the C-helix and activation loop (bijvelds2018selectiveinhibitionof pages 2-3, kim2011cocrystalstructuresof pages 1-3).  
• PKG-family crystal structures show that cyclic-nucleotide binding elicits conformational changes that disengage the pseudosubstrate and align catalytic spines for catalysis (kim2011cocrystalstructuresof pages 1-3).

## Regulation

• Allosteric activation by cGMP binding to CNB-A and CNB-B releases the autoinhibitory sequence and activates the catalytic domain (akgundogan2024twonewpatients pages 5-6, kim2011cocrystalstructuresof pages 1-3).  
• Autophosphorylation of regulatory-domain serines (Ser110, Ser114, Ser126, Ser445) fine-tunes activation kinetics and can render the enzyme partially cGMP-independent (vaandrager2005molecularpropertiesand pages 5-7).  
• N-terminal myristoylation is obligatory for stable membrane association and efficient phosphorylation of membrane substrates such as CFTR (vaandrager2005molecularpropertiesand pages 1-2).  
• Interaction with PDZ-domain scaffolds NHERF2/E3KARP targets cGK II to the apical membrane juxtaposed to CFTR and NHE3 (vaandrager2005molecularpropertiesand pages 7-8).  
• High intracellular ATP shifts the cGMP EC₅₀ upward and modifies autophosphorylation patterns, indicating competitive interplay between ATP and cGMP at catalytic and regulatory sites (vaandrager2005molecularpropertiesand pages 5-7).

## Function

• Expression: high in intestinal epithelium, growth-plate cartilage, brain, kidney, lung and pancreas (koltes2009anonsensemutation pages 3-4, vaandrager2005molecularpropertiesand pages 1-2).  
• Intestinal secretion: phosphorylates CFTR and inhibits NHE3 downstream of guanylin/uroguanylin–GC-C–cGMP signaling; Prkg2-null mice exhibit deficient jejunal chloride and water secretion (vaandrager2005molecularpropertiesand pages 7-8, bijvelds2018selectiveinhibitionof pages 2-3).  
• Skeletal development: acts downstream of CNP/NPR-B; Raf-1 Ser43 phosphorylation dampens FGF2-ERK1/2 signaling, enabling the transition from proliferative to hypertrophic chondrocytes; loss of PRKG2 causes dwarfism in multiple species (diazgonzalez2022bialleliccgmpdependenttype pages 5-6, koltes2009anonsensemutation pages 3-4).  
• Transcriptional control: phosphorylates SOX9, restricting its nuclear entry and modulating COL2A1 and COL10A1 expression during endochondral ossification (garces2021prkg2splicesite pages 7-8).  
• Neuronal signaling: regulates synaptic plasticity via phosphorylation-dependent trafficking of the AMPA-receptor subunit GRIA1/GLUR1 (bonnet2010microdeletionatchromosome pages 8-8).  
• Renal and adrenal epithelia: phosphorylates TRPV5 and StAR, contributing to calcium reabsorption and aldosterone synthesis, respectively (vaandrager2005molecularpropertiesand pages 10-11).

## Inhibitors

• Imidazole-aminopyrimidines AP-C5 and AP-C6 occupy the ATP pocket and selectively inhibit cGK II over cGK I and PKA in cellular assays (bijvelds2018selectiveinhibitionof pages 2-3).  
• KT5823 and the peptide DT-2 inhibit PKG activity in vitro but lack potency or isoform selectivity in intact cells (bijvelds2018selectiveinhibitionof pages 8-10).

## Other Comments

• Pathogenic variants:  
– Human: p.Asn164Lysfs*2, p.Arg569*, p.Asp761Glufs*34, p.Val470Gly; all abolish kinase activity and cause autosomal-recessive acromesomelic dysplasia with severe limb shortening (diazgonzalez2022bialleliccgmpdependenttype pages 6-6, akgundogan2024twonewpatients pages 6-6, pagnamenta2022variableskeletalphenotypes pages 1-1).*  
*– Cattle: p.Arg678* (R678X) leads to dwarfism in American Angus cattle (koltes2009anonsensemutation pages 3-4).  
– Dog: splice-site c.1634+1G>T causes disproportionate dwarfism in Dogo Argentino (garces2021prkg2splicesite pages 7-8).  
• Disease mechanism: loss-of-function mutations prevent Raf-1 Ser43 phosphorylation and fail to repress ERK1/2 signaling in growth-plate cartilage (diazgonzalez2022bialleliccgmpdependenttype pages 6-6, akgundogan2024twonewpatients pages 5-6).

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