## Phylogeny

PRKG2 encodes the type II cGMP-dependent protein kinase (cGK II), one of only two such kinases in mammals; the other gene, PRKG1, encodes cGK I. cGK II belongs to the AGC / cyclic-nucleotide-dependent branch of the kinome and is most closely related to cGK I, with greater evolutionary distance from the Drosophila DG1/DG2 kinases (Vaandrager et al., 2005; Bijvelds et al., 2018). Orthologues with intact catalytic domains are conserved in mouse, rat, cattle, dog and human, and loss-of-function alleles in each species cause proportionate dwarfism, highlighting strong functional conservation (Koltes et al., 2009; Bijvelds et al., 2018; Garcés et al., 2021).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-O-phospho-Ser/Thr (Vaandrager et al., 2005).

## Cofactor Requirements

Requires Mg²⁺ for efficient ATP binding and phosphotransfer (Bijvelds et al., 2018).

## Substrate Specificity

• Preferred consensus motif: RRXS/T with two basic residues N-terminal to the phospho-acceptor (Vaandrager et al., 2005).  
• Validated substrates:  
– CFTR regulatory domain; phosphorylation at Ser700 and additional sites activates chloride conductance (Vaandrager et al., 2005).  
– Raf-1; phosphorylation at Ser43 suppresses FGF-induced ERK1/2 signalling in chondrocytes (Díaz-González et al., 2022).

## Structure

cGK II forms a parallel homodimer of 762-aa subunits. Dimerisation is mediated by an N-terminal leucine-zipper that is myristoylated for membrane anchoring (Vaandrager et al., 2005; Bijvelds et al., 2018). Domain layout: N-terminal myristoylation signal + leucine-zipper, autoinhibitory pseudosubstrate, two cyclic-nucleotide-binding domains (CNB-A low-affinity, CNB-B high-affinity; order reversed relative to cGK I), and a C-terminal Ser/Thr kinase domain containing canonical HRD and DFG motifs (Bijvelds et al., 2018; Kim et al., 2011). Crystal and modelling studies show that cGMP binding induces conformational changes that displace the pseudosubstrate and align catalytic elements for activity (Kim et al., 2011).

## Regulation

• Allosterically activated by cGMP binding to CNB-A and CNB-B (Akgun-Dogan et al., 2024; Kim et al., 2011).  
• Autophosphorylation at Ser110, Ser114, Ser126 and Ser445 modulates activation kinetics and can confer partial cGMP independence (Vaandrager et al., 2005).  
• N-terminal myristoylation is essential for membrane association and efficient phosphorylation of membrane substrates such as CFTR (Vaandrager et al., 2005).  
• Association with PDZ-domain scaffolds NHERF2/E3KARP positions the kinase at the apical membrane near CFTR and NHE3 (Vaandrager et al., 2005).  
• High intracellular ATP concentrations elevate the cGMP EC₅₀ and alter autophosphorylation patterns, indicating competition between ATP and cGMP at catalytic and regulatory sites (Vaandrager et al., 2005).

## Function

Expression is high in intestinal epithelium, growth-plate cartilage, brain, kidney, lung and pancreas (Koltes et al., 2009; Vaandrager et al., 2005).  
• Intestinal secretion: phosphorylates CFTR and inhibits NHE3 downstream of guanylin/uroguanylin–GC-C signalling; Prkg2-null mice show impaired jejunal chloride and water secretion (Vaandrager et al., 2005; Bijvelds et al., 2018).  
• Skeletal development: acts downstream of CNP/NPR-B; Raf-1 Ser43 phosphorylation dampens FGF2-ERK1/2 signalling, enabling chondrocyte hypertrophy; PRKG2 loss causes dwarfism in several species (Díaz-González et al., 2022; Koltes et al., 2009).  
• Transcriptional control: phosphorylates SOX9, limiting its nuclear entry and modulating COL2A1/COL10A1 expression during endochondral ossification (Garcés et al., 2021).  
• Neuronal signalling: regulates synaptic plasticity via phosphorylation-dependent trafficking of the AMPA-receptor subunit GRIA1 (Bonnet et al., 2010).  
• Renal and adrenal epithelia: phosphorylates TRPV5 and StAR, contributing to calcium reabsorption and aldosterone synthesis (Vaandrager et al., 2005).

## Inhibitors

Imidazole-aminopyrimidines AP-C5 and AP-C6 are ATP-competitive inhibitors that selectively block cGK II over cGK I and PKA in cells (Bijvelds et al., 2018). KT5823 and the peptide DT-2 inhibit PKG activity in vitro but show limited potency or isoform selectivity in intact cells (Bijvelds et al., 2018).

## Other Comments

Pathogenic PRKG2 variants—p.Asn164Lysfs*2, p.Arg569*, p.Asp761Glufs*34, p.Val470Gly in humans; p.Arg678* in cattle; splice-site c.1634+1G>T in Dogo Argentino dogs—abolish kinase activity and cause autosomal-recessive acromesomelic dysplasia or disproportionate dwarfism (Díaz-González et al., 2022; Akgun-Dogan et al., 2024; Pagnamenta et al., 2022; Koltes et al., 2009; Garcés et al., 2021). Loss-of-function prevents Raf-1 Ser43 phosphorylation leading to unchecked ERK1/2 activity in growth-plate cartilage (Díaz-González et al., 2022; Akgun-Dogan et al., 2024).

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