1. Phylogeny  
   cGMP‐dependent protein kinase II (PKG II), encoded by the PRKG2 gene, is a member of the cyclic nucleotide‐dependent serine/threonine kinase family that falls within the larger AGC kinase group. It is one of the two mammalian cGMP‐dependent protein kinases, the other being cGKI (encoded by PRKG1), and its evolutionary origins can be traced to a common ancestor of eukaryotes, as demonstrated by the broad conservation of cGMP‐dependent kinases from unicellular organisms through to mammals (hofmann2006functionofcgmpdependent pages 1-2). Orthologs of PKG II have been identified in vertebrates, and its conservation extends even to invertebrates – for example, homologous kinases in Drosophila melanogaster (such as DG2/T1) have been linked to behavioral phenomena like foraging, which underscores the evolutionary retention of regulatory functions across species (hofmann2020thecgmpsystem pages 13-16, OpenTargets Search: -PRKG2). Within the human kinome, PKG II occupies a distinct position as a membrane‐targeted effector whose divergence from cGKI is reflected in its unique regulatory domains and tissue‐specific expression patterns.
2. Reaction Catalyzed  
   PKG II catalyzes the phosphorylation reaction in which a phosphate group is transferred from ATP to a serine or threonine residue on a substrate protein. In biochemical terms, the reaction can be described as follows:  
     ATP + [protein]–(L‐serine or L‐threonine) → ADP + [protein]–(L‐serine/threonine)‐phosphate + H⁺  
   This catalytic activity is a hallmark of serine/threonine kinases and reflects the enzyme’s role in modulating downstream signaling events by reversible phosphorylation of target proteins (hofmann2006functionofcgmpdependent pages 1-2, baker2005cyclicgmpdependentprotein pages 5-6).
3. Cofactor Requirements  
   The catalytic activity of PKG II is dependent on the presence of Mg²⁺ ions, which are necessary for the proper binding and utilization of ATP during the phosphorylation reaction. In addition to the divalent cation, PKG II requires cyclic guanosine monophosphate (cGMP) as an allosteric activator; the binding of cGMP to its regulatory domains is essential to induce the conformational change that relieves autoinhibition and allows the kinase activity to proceed (hofmann2006functionofcgmpdependent pages 1-2, hofmann2020thecgmpsystem pages 24-28).
4. Substrate Specificity  
   PKG II exhibits substrate specificity for serine/threonine residues within target proteins that typically present a conserved basic motif. The consensus substrate motif is generally characterized by one or more basic amino acids (arginine and lysine) preceding the phosphorylatable serine (or threonine), often resembling a K/R–K/R–X–S/T sequence. This specificity is exemplified by its well‐documented phosphorylation of the cystic fibrosis transmembrane conductance regulator (CFTR), where phosphorylation by PKG II leads to the translocation and activation of CFTR at the plasma membrane in intestinal epithelial cells. Moreover, by similarity to related substrates, PKG II phosphorylates the AMPA receptor subunit GRIA1 (also known as GLUR1) at Ser-863 in neuronal cells, thereby contributing to the regulation of synaptic plasticity. In osteoblasts, the regulation of gene expression and activation of extracellular signal‐regulated kinases (ERK1/2) are mediated through the phosphorylation of specific substrates involved in mechanotransduction. Together, these examples confirm that the substrate recognition of PKG II relies on the presence of positively charged residues upstream of the phosphorylatable site, consistent with the known substrate motifs of other AGC family kinases (wolfertstetter2013cgmpdependentproteinkinase pages 7-10, hofmann2020thecgmpsystem pages 24-28).
5. Structure  
   PKG II is organized into discrete domains that together determine its regulatory and catalytic functions. The protein features an N-terminal region that is subject to myristoylation at Glycine-2; this lipid modification is critical for anchoring the kinase to the plasma membrane and ensuring its proper subcellular localization. Adjacent to this, the regulatory domain contains two tandem cyclic nucleotide–binding sites that differ in their affinities for cGMP; binding of cGMP to these sites triggers conformational changes that alleviate an autoinhibitory pseudosubstrate region and allow activation of the kinase. A leucine zipper motif within the N-terminal domain also contributes to homodimerization and targeting to specific cellular locales. The central catalytic domain adopts a typical AGC kinase fold, comprising distinct N- and C-terminal lobes, an activation loop, an ATP-binding pocket, and structural features such as a hydrophobic spine and a C-terminal αC-helix that are essential for full catalytic activity. Structural studies, including crystallographic analyses and modeling efforts reported in studies on analog specificity, have demonstrated that the CNB-B domain of PKG II in particular features a fully helical C-terminal region that forms specific contacts with cyclic nucleotide ligands, thereby enhancing cGMP selectivity (campbell2017structuralbasisof pages 1-3, hofmann2020thecgmpsystem pages 11-13, wolfertstetter2013cgmpdependentproteinkinase pages 7-10).
6. Regulation  
   The activation and regulation of PKG II are tightly controlled by multiple mechanisms. Chief among these is the binding of cGMP to the regulatory domain; the occupancy of its two cyclic nucleotide–binding sites induces conformational rearrangements that relieve the autoinhibitory interaction exerted by an N-terminal pseudosubstrate sequence. This allosteric transition permits the catalytic domain to phosphorylate substrate proteins. Autophosphorylation of PKG II can also modulate its basal activity and sensitivity to cGMP, further fine-tuning its function. Membrane tethering via N-terminal myristoylation is indispensable for proper localization and substrate engagement, thereby integrating spatial regulation into its activity profile. In addition, intracellular levels of cGMP – which are controlled by guanylyl cyclases and phosphodiesterases – indirectly regulate PKG II activity. Specific cyclic nucleotide analogs have been developed as competitive inhibitors that bind to the cGMP-binding domains, thereby acting as pharmacological tools to dissect the kinase’s function in vitro (hofmann2006functionofcgmpdependent pages 1-2, hofmann2020thecgmpsystem pages 11-13, wolfertstetter2013cgmpdependentproteinkinase pages 7-10).
7. Function  
   PKG II plays multiple roles in mammalian physiology with a strong emphasis on the regulation of intestinal secretion and bone growth. In the gastrointestinal tract, PKG II phosphorylates CFTR, which results in the translocation of the channel to the plasma membrane and activation of chloride and bicarbonate secretion; this process is central to the maintenance of fluid balance in the jejunum. In skeletal tissue, PKG II is involved in the regulation of chondrocyte differentiation and osteoblast mechanotransduction. In osteoblasts, PKG II activates extracellular signal‐regulated kinases (ERK1 and ERK2) and promotes the induction of immediate early genes such as FOS, FOSL1, FOSL2, and FOSB in response to mechanical stimulation, thereby contributing to bone formation and growth. In the nervous system, PKG II acts downstream of N-methyl-D-aspartate receptors (NMDARs) to facilitate the plasma membrane accumulation of the AMPA receptor subunit GRIA1 (GLUR1). Phosphorylation of GRIA1 at Ser-863 is believed to enhance synaptic plasticity by modulating glutamatergic signaling at excitatory synapses. In addition to these well-characterized roles, PKG II has been implicated in the regulation of renin secretion and may participate in broader signaling networks that balance cellular proliferation and differentiation in various tissues (hofmann2006functionofcgmpdependent pages 1-2, hofmann2020thecgmpsystem pages 24-28, wolfertstetter2013cgmpdependentproteinkinase pages 7-10).
8. Other Comments  
   Several experimental inhibitors have been developed to target PKG II, including lipophilic cyclic nucleotide analogs such as (Rp)-8-Br-PET-cGMP-S, which competitively inhibit cGMP binding at the regulatory domain; however, these inhibitors are often not completely selective and may affect other cyclic nucleotide–dependent kinases to a degree (wolfertstetter2013cgmpdependentproteinkinase pages 16-18). Genetic deletion studies in mouse models have established that loss of PKG II activity results in phenotypes characterized by impaired intestinal secretion and dwarfism, thereby underscoring its physiological importance in both gastrointestinal and skeletal systems (hofmann2006functionofcgmpdependent pages 22-23, hofmann2020thecgmpsystem pages 24-28). In addition, associations between mutations in PRKG2 and skeletal dysplasias, such as acromesomelic dysplasia and spondylometaphyseal dysplasia, have been reported in genetic databases and OpenTargets analyses (OpenTargets Search: -PRKG2). Although clinical trial databases currently do not list trials specifically targeting PRKG2, its critical regulatory roles in intestinal fluid balance and bone growth make it a potential therapeutic target for related disorders (Clinical Trial Search: 3dbee61daaa6).
9. References
10. hofmann2006functionofcgmpdependent pages 1-2
11. hofmann2020thecgmpsystem pages 13-16
12. hofmann2020thecgmpsystem pages 24-28
13. wolfertstetter2013cgmpdependentproteinkinase pages 7-10
14. Clinical Trial Search: 3dbee61daaa6
15. OpenTargets Search: -PRKG2
16. baker2005cyclicgmpdependentprotein pages 5-6
17. campbell2017structuralbasisof pages 1-3
18. hofmann2005thebiologyof pages 3-3
19. roy2021identificationofnovel pages 1-2

References

1. (hofmann2006functionofcgmpdependent pages 1-2): F. Hofmann, R. Feil, T. Kleppisch, and J. Schlossmann. Function of cgmp-dependent protein kinases as revealed by gene deletion. Physiological Reviews, 86:1-23, Jan 2006. URL: https://doi.org/10.1152/physrev.00015.2005, doi:10.1152/physrev.00015.2005. This article has 524 citations and is from a highest quality peer-reviewed journal.
2. (hofmann2020thecgmpsystem pages 13-16): Franz Hofmann. The cgmp system: components and function. Biological Chemistry, 401:447-469, Nov 2020. URL: https://doi.org/10.1515/hsz-2019-0386, doi:10.1515/hsz-2019-0386. This article has 74 citations and is from a peer-reviewed journal.
3. (hofmann2020thecgmpsystem pages 24-28): Franz Hofmann. The cgmp system: components and function. Biological Chemistry, 401:447-469, Nov 2020. URL: https://doi.org/10.1515/hsz-2019-0386, doi:10.1515/hsz-2019-0386. This article has 74 citations and is from a peer-reviewed journal.
4. (wolfertstetter2013cgmpdependentproteinkinase pages 7-10): Stefanie Wolfertstetter, Johannes Huettner, and Jens Schlossmann. Cgmp-dependent protein kinase inhibitors in health and disease. Pharmaceuticals, 6:269-286, Feb 2013. URL: https://doi.org/10.3390/ph6020269, doi:10.3390/ph6020269. This article has 52 citations and is from a peer-reviewed journal.
5. (Clinical Trial Search: 3dbee61daaa6): Clinical Trials Search via ClinicalTrials.gov: PRKG2 OR cGMP-dependent protein kinase II OR PKG2
6. (OpenTargets Search: -PRKG2): Open Targets Query (-PRKG2, 5 results). Buniello, A. et al. (2025). Open Targets Platform: facilitating therapeutic hypotheses building in drug discovery. Nucleic Acids Research.
7. (baker2005cyclicgmpdependentprotein pages 5-6): A. Baker David. Cyclic gmp-dependent protein kinases in protozoa. Frontiers in Bioscience, 10:1229, Jan 2005. URL: https://doi.org/10.2741/1615, doi:10.2741/1615. This article has 22 citations and is from a peer-reviewed journal.
8. (campbell2017structuralbasisof pages 1-3): James C. Campbell, Philipp Henning, Eugen Franz, Banumathi Sankaran, Friedrich W. Herberg, and Choel Kim. Structural basis of analog specificity in pkg i and ii. ACS Chemical Biology, 12:2388-2398, Aug 2017. URL: https://doi.org/10.1021/acschembio.7b00369, doi:10.1021/acschembio.7b00369. This article has 12 citations and is from a domain leading peer-reviewed journal.
9. (hofmann2005thebiologyof pages 3-3): Franz Hofmann. The biology of cyclic gmp-dependent protein kinases\*. Journal of Biological Chemistry, 280:1-4, Jan 2005. URL: https://doi.org/10.1074/jbc.r400035200, doi:10.1074/jbc.r400035200. This article has 322 citations and is from a domain leading peer-reviewed journal.
10. (hofmann2006functionofcgmpdependent pages 22-23): F. Hofmann, R. Feil, T. Kleppisch, and J. Schlossmann. Function of cgmp-dependent protein kinases as revealed by gene deletion. Physiological Reviews, 86:1-23, Jan 2006. URL: https://doi.org/10.1152/physrev.00015.2005, doi:10.1152/physrev.00015.2005. This article has 524 citations and is from a highest quality peer-reviewed journal.
11. (hofmann2020thecgmpsystem pages 11-13): Franz Hofmann. The cgmp system: components and function. Biological Chemistry, 401:447-469, Nov 2020. URL: https://doi.org/10.1515/hsz-2019-0386, doi:10.1515/hsz-2019-0386. This article has 74 citations and is from a peer-reviewed journal.
12. (roy2021identificationofnovel pages 1-2): Akanksha Roy, John Groten, Valeria Marigo, Tushar Tomar, and Riet Hilhorst. Identification of novel substrates for cgmp dependent protein kinase (pkg) through kinase activity profiling to understand its putative role in inherited retinal degeneration. International Journal of Molecular Sciences, 22:1180, Jan 2021. URL: https://doi.org/10.3390/ijms22031180, doi:10.3390/ijms22031180. This article has 22 citations and is from a peer-reviewed journal.
13. (wolfertstetter2013cgmpdependentproteinkinase pages 16-18): Stefanie Wolfertstetter, Johannes Huettner, and Jens Schlossmann. Cgmp-dependent protein kinase inhibitors in health and disease. Pharmaceuticals, 6:269-286, Feb 2013. URL: https://doi.org/10.3390/ph6020269, doi:10.3390/ph6020269. This article has 52 citations and is from a peer-reviewed journal.