## Phylogeny

• Classified within the AGC kinase group, PKA family; archetype of this lineage (taylor2013pkalessonslearned pages 1-2).  
• Vertebrate gene duplication generated the paralog PRKACB, sharing ≈93 % identity with PRKACA (welsh2023interactionnetworksexplain pages 5-6).  
• Orthologs documented in Mus musculus, Rattus norvegicus, Danio rerio, Drosophila melanogaster, Caenorhabditis elegans, Saccharomyces cerevisiae and Arabidopsis thaliana, reflecting conservation in >90 species (turnham2016proteinkinasea pages 8-9).  
• Comparative analyses confirm deep conservation of catalytic architecture from yeast to man (søberg2018themolecularbasis pages 21-22).  
• Evolutionary placement within the AGC clade is consistent with kinome surveys referencing Manning et al. 2002 (welsh2023interactionnetworksexplain pages 21-22).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-O-phospho-Ser/Thr (welsh2023interactionnetworksexplain pages 6-8).

## Cofactor Requirements

Catalysis absolutely requires two Mg²⁺ ions that coordinate ATP and govern the rate-limiting release of Mg²⁺-ADP (søberg2018themolecularbasis pages 21-22, bastidas2015molecularfeaturesof pages 9-9).

## Substrate Specificity

• Canonical consensus: Arg-Arg/Lys-X-Ser/Thr\* (RR/K-X-S*/T*) (bathon2019alterationsinprotein pages 10-11, turnham2016proteinkinasea pages 3-4).  
• Extended motif: Arg-X-X-Arg-X-X-Ser/Thr-Hydrophobic, with substrate Arg residues engaging active-site Glu127, Glu170 and Glu230 (welsh2023interactionnetworksexplain pages 6-8).  
• +1 position preferentially accepts small hydrophobics (Gly, Ala, Val, Met); the oncogenic L206R variant accentuates this bias (bathon2019alterationsinprotein pages 7-8).  
• Large-scale motif profiling corroborates these preferences across the serine/threonine kinome (welsh2023interactionnetworksexplain pages 21-22).

## Structure

• Full-length 351 aa protein: N-terminal tail (1-39), bilobal kinase core (40-300), C-terminal tail (301-351) (welsh2023interactionnetworksexplain pages 5-6).  
• N-tail harbours Asn2 myristoylation within a stable αA helix that docks onto the core and modulates membrane association (turnham2016proteinkinasea pages 3-4, welsh2023interactionnetworksexplain pages 5-6).  
• N-lobe: five-stranded β-sheet and αC helix; Lys72–Glu91 salt bridge aligns ATP (welsh2023interactionnetworksexplain pages 5-6).  
• C-lobe: predominantly helical; catalytic base Asp166 (HRD) and DFG motif Asp184 coordinate Mg²⁺ ions (welsh2023interactionnetworksexplain pages 6-8).  
• Activation loop (184-208) contains Thr197; phosphorylation locks the regulatory spine and is essential for activity (welsh2023interactionnetworksexplain pages 6-8).  
• Dual hydrophobic spines (R-spine/C-spine) span both lobes, defining the active kinase fold (taylor2013pkalessonslearned pages 1-2).  
• C-tail bears the conserved FDDY motif and autophosphorylation site Ser338 that stabilise the kinase (taylor2012assemblyofallosteric pages 5-7).  
• Myristoyl pocket adjacent to the N-tail influences holoenzyme regulation (bathon2019alterationsinprotein pages 4-5).  
• αC-β4 loop dynamics, revealed by F100A mutation, couple inter-lobe motions to nucleotide positioning (wu2023proteinkinasestructure pages 23-25).  
• Representative crystal structures: holoenzyme complexes PDB 3TNP/3TNQ resolve catalytic–regulatory interfaces and an ordered activation segment (bathon2019alterationsinprotein pages 4-5).

## Regulation

Post-translational modifications  
– Thr197: autophosphorylation or phosphorylation by PDK1; required for full catalytic activity (welsh2023interactionnetworksexplain pages 5-6).  
– Ser338: cis-autophosphorylation in the C-tail; stabilises the active conformation (taylor2012assemblyofallosteric pages 5-7).  
– Ser139: reported regulatory phosphorylation site (turnham2016proteinkinasea pages 3-4).  
– N-terminal myristoylation at Asn2/Lys7 by N-myristoyltransferase governs membrane affinity and holoenzyme stability (turnham2016proteinkinasea pages 3-4).  
– Ubiquitination of regulatory subunits is triggered by PRKACA-mediated phosphorylation of the E3 ligase PJA2, leading to proteolysis of those subunits (turnham2016proteinkinasea pages 3-4).

Allosteric and conformational control  
– Inactive tetrameric holoenzyme (R₂C₂); binding of four cAMP molecules to RI or RII subunits releases active catalytic monomers (taylor2013pkalessonslearned pages 1-2).  
– AKAPs tether discrete holoenzymes to membranes, mitochondria or cytoskeleton, enforcing spatial specificity (taylor2012assemblyofallosteric pages 3-5).  
– Distinct quaternary organisations: elongated RIα₂C₂ acts as an ATP sensor, whereas compact RIIβ₂C₂ localises to the plasma membrane and is activated via RIIβ phosphorylation (welsh2023interactionnetworksexplain pages 15-17).  
– Intracellular Mg²⁺ levels tune nucleotide binding and ADP release, modulating turnover (søberg2018themolecularbasis pages 21-22).  
– High-affinity inhibitory peptide PKI binds the catalytic cleft and mediates nuclear export of free C-subunits (welsh2023interactionnetworksexplain pages 2-5).

## Function

Expression  
– Cα1 isoform is ubiquitous; highest levels in adrenal zona glomerulosa (weigand2017differentialexpressionof pages 9-10).  
– Cα2 isoform is restricted to sperm and is essential for motility and fertilisation (welsh2023interactionnetworksexplain pages 5-6).

Signalling context and substrates  
– Principal effector of GPCR→adenylyl-cyclase→cAMP signalling cascades (welsh2023interactionnetworksexplain pages 1-2).  
– Upstream activation loop phosphorylation can be supplied by PDK1 (welsh2023interactionnetworksexplain pages 5-6).  
– Nuclear substrates: CREB Ser133 (goh2014recurrentactivatingmutation pages 1-3), histone H1.4 Ser36 (bathon2019alterationsinprotein pages 10-11).  
– Cytoplasmic substrates include VASP, integrins and myosin light chain, affecting cytoskeletal dynamics and migration (welsh2023interactionnetworksexplain pages 5-6).  
– PRKACA activity influences metabolism, apoptosis and ion-channel regulation through a broad substrate spectrum (welsh2023interactionnetworksexplain pages 17-18).

## Inhibitors

• H-89 and KT-5720 are widely used ATP-competitive inhibitors of PKA catalytic activity (bathon2019alterationsinprotein pages 10-11, turnham2016proteinkinasea pages 3-4).

## Other Comments

• Somatic Leu206Arg (L206R) disrupts PRKAR1A binding, produces constitutive kinase activity and appears in ≈65 % of cortisol-producing adrenal adenomas (goh2014recurrentactivatingmutation pages 16-16, bathon2019alterationsinprotein pages 4-5).  
• Additional activating indels and substitutions near the autoinhibitory interface (199\_200insW, 200\_201insV, W197R, d2442248+E249Q) re-wire substrate specificity and contribute to Cushing syndrome (bathon2019alterationsinprotein pages 6-7).  
• DNAJB1–PRKACA fusion encodes an oncogenic kinase that drives fibrolamellar hepatocellular carcinoma (welsh2023interactionnetworksexplain pages 21-22, turnham2016proteinkinasea pages 8-9).  
• Reduced regulatory subunit levels arising from PRKAR1A mutations cause Carney complex via unrestrained PRKACA activity (turnham2016proteinkinasea pages 6-8).

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