## Phylogeny

Member of the AGC kinase group, PKA family, and considered the archetypal catalytic subunit (Taylor et al., 2013). A vertebrate-specific duplication generated the closely related paralogue PRKACB (~93 % identity) (Welsh et al., 2023). Orthologues are present from yeast and plants to mammals—>90 species—underscoring deep evolutionary conservation of catalytic architecture (Turnham & Scott, 2016; Søberg & Skålhegg, 2018). Placement within the AGC clade is consistent with kinome-wide surveys (Welsh et al., 2023).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-O-phospho-Ser/Thr (Welsh et al., 2023).

## Cofactor Requirements

Catalysis requires two Mg²⁺ ions that coordinate ATP and govern Mg²⁺-ADP release (Søberg & Skålhegg, 2018; Bastidas et al., 2015).

## Substrate Specificity

• Canonical consensus: Arg-Arg/Lys-X-Ser/Thr\* (RR/K-X-S*/T*) (Bathon et al., 2019; Turnham & Scott, 2016).  
• Extended motif: Arg-X-X-Arg-X-X-Ser/Thr-hydrophobic; substrate Arg residues interact with Glu127, Glu170 and Glu230 in the active site (Welsh et al., 2023).  
• +1 position favours small hydrophobics (Gly, Ala, Val, Met); the oncogenic L206R variant accentuates this bias (Bathon et al., 2019).  
• Large-scale motif profiling corroborates these preferences across the serine/threonine kinome (Welsh et al., 2023).

## Structure

Full-length 351-aa protein comprises an N-terminal tail (1–39), bilobal kinase core (40–300) and C-terminal tail (301–351) (Welsh et al., 2023).  
– N-tail: Asn2 myristoylation within αA helix; docks on the core and modulates membrane association (Turnham & Scott, 2016; Welsh et al., 2023).  
– N-lobe: five-stranded β-sheet, αC helix; Lys72-Glu91 salt bridge aligns ATP (Welsh et al., 2023).  
– C-lobe: helical, with catalytic Asp166 (HRD) and DFG Asp184 binding Mg²⁺ ions (Welsh et al., 2023).  
– Activation loop (184–208) carries Thr197; phosphorylation locks the regulatory spine (Welsh et al., 2023).  
– Dual hydrophobic spines define the active fold (Taylor et al., 2013).  
– C-tail harbours FDDY motif and autophosphorylation site Ser338 (Taylor et al., 2012).  
– Myristoyl pocket adjacent to the N-tail influences holoenzyme regulation (Bathon et al., 2019).  
– αC-β4 loop dynamics couple inter-lobe motions to nucleotide positioning (Wu et al., 2023).  
Representative crystal structures of RIα₂C₂ holoenzyme (PDB 3TNP/3TNQ) show ordered activation segment and regulatory interfaces (Bathon et al., 2019).

## Regulation

Post-translational modifications  
– Thr197: auto- or PDK1-mediated phosphorylation, essential for activity (Welsh et al., 2023).  
– Ser338: cis-autophosphorylation stabilises the active conformation (Taylor et al., 2012).  
– Ser139: additional regulatory phosphorylation (Turnham & Scott, 2016).  
– N-terminal myristoylation (Asn2/Lys7) controls membrane affinity and holoenzyme stability (Turnham & Scott, 2016).  
– PRKACA phosphorylation of E3 ligase PJA2 triggers ubiquitination of regulatory subunits (Turnham & Scott, 2016).

Allosteric/conformational control  
– Inactive R₂C₂ holoenzyme; binding of four cAMP molecules to RI or RII releases active C-subunits (Taylor et al., 2013).  
– AKAPs anchor holoenzymes to specific compartments (Taylor et al., 2012).  
– Distinct quaternary assemblies: elongated RIα₂C₂ (ATP sensor) vs. compact RIIβ₂C₂ (membrane-localised) (Welsh et al., 2023).  
– Intracellular Mg²⁺ levels tune nucleotide binding/ADP release (Søberg & Skålhegg, 2018).  
– High-affinity inhibitor peptide PKI occludes the catalytic cleft and mediates nuclear export (Welsh et al., 2023).

## Function

Expression  
– Cα1 isoform: ubiquitous, highest in adrenal zona glomerulosa (Weigand et al., 2017).  
– Cα2 isoform: sperm-specific, required for motility and fertilisation (Welsh et al., 2023).

Signalling context and substrates  
– Principal effector of GPCR → adenylyl cyclase → cAMP signalling (Welsh et al., 2023).  
– Upstream activation loop phosphorylation can be supplied by PDK1 (Welsh et al., 2023).  
– Nuclear substrates: CREB Ser133 (Goh et al., 2014); histone H1.4 Ser36 (Bathon et al., 2019).  
– Cytoplasmic targets include VASP, integrins and myosin light chain, impacting cytoskeletal dynamics (Welsh et al., 2023).  
– Activity influences metabolism, apoptosis and ion-channel regulation via a broad substrate spectrum (Welsh et al., 2023).

## Inhibitors

H-89 and KT-5720 are widely used ATP-competitive inhibitors of catalytic activity (Bathon et al., 2019; Turnham & Scott, 2016).

## Other Comments

Somatic Leu206Arg disrupts PRKAR1A binding, yielding constitutive activity in ~65 % of cortisol-producing adrenal adenomas (Goh et al., 2014; Bathon et al., 2019). Additional activating indels/substitutions near the autoinhibitory interface contribute to Cushing syndrome (Bathon et al., 2019). The DNAJB1–PRKACA fusion drives fibrolamellar hepatocellular carcinoma (Welsh et al., 2023; Turnham & Scott, 2016). Loss-of-function PRKAR1A mutations cause Carney complex through unrestrained catalytic activity (Turnham & Scott, 2016).

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