## Phylogeny

PRKACG encodes the catalytic γ‐subunit of cAMP-dependent protein kinase (PKA), a member of the AGC group of protein kinases (Johnson et al., 2023; Søberg et al., 2013; Francis & Corbin, 1999). Humans possess five PKA catalytic genes (PRKACA, PRKACB, PRKX, PRKY, and PRKACG); PRKACG clusters closely with PRKACA and PRKACB within a compact PKA clade (Søberg et al., 2013). The gene is intron-less, retroposon-derived, and restricted to primates (Søberg et al., 2013; Francis & Corbin, 1999).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + O-phospho-L-seryl/threonyl-[protein] (Ekhator et al., 2025; Johnson et al., 2023; Søberg et al., 2013).

## Cofactor Requirements

Two divalent cations are needed, preferentially Mg²⁺; Ca²⁺ or Mn²⁺ can substitute under some conditions (Ekhator et al., 2025; Søberg et al., 2017; Johnson et al., 2023).

## Substrate Specificity

PKA is a basophilic kinase that favours basic residues (Arg/Lys) at positions −3 and −2, and a hydrophobic residue (often Leu) at +1 relative to the phospho-Ser/Thr. The consensus motif is R-R-x-S/T-L (Johnson et al., 2023). Lack of +1 Pro or acidic residue preference distinguishes PKA from other kinase classes.

## Structure

The catalytic subunit is ~350 aa with an asymmetric bilobed fold (Francis & Corbin, 1999; Søberg & Skålhegg, 2018).  
• N-lobe: five antiparallel β-strands, αB/αC helices, and a glycine-rich loop (res. 50–55) that binds Mg²⁺/ATP.  
• C-lobe: predominantly α-helical, containing substrate-binding and catalytic elements.  
Key motifs include the catalytic loop (Asp-166, Lys-168, Asn-171), the DFG motif, and the activation loop (Asp-184–Phe-186). Crystal structures are available (e.g., PDB 1ATP, 1CMK, 3FJQ).

## Regulation

Inactive holoenzyme: two catalytic subunits bound to a regulatory (R)-subunit dimer. cAMP binding to R-subunits releases active C-subunits (Ekhator et al., 2025; Turnham & Scott, 2016).  
Post-translational control:  
• Phosphorylation—Thr-197 (activation loop) is required for full activity; Ser-338 affects activity/stability (Ekhator et al., 2025; Liu et al., 2022).  
• Redox—Cys-199 is a conserved redox-sensitive residue (Ekhator et al., 2025).  
Localization: interaction with A-kinase anchoring proteins (AKAPs) targets PKA to specific compartments (Liu et al., 2022; Francis & Corbin, 1999).

## Function

PRKACG transcripts are most abundant in testis, suggesting tissue-restricted roles (Ekhator et al., 2025; Turnham & Scott, 2016). As a PKA catalytic subunit, it phosphorylates diverse substrates regulating gene expression, metabolism, proliferation, and apoptosis. Upstream activation occurs through cAMP; downstream partners include PKA regulatory subunits and AKAP scaffolds (Liu et al., 2022).

## Inhibitors

Activity can be blocked by the small heat-stable protein kinase inhibitor (PKI), a high-affinity pseudosubstrate. Small-molecule ATP-competitive inhibitors exist but lack PKA-Cγ selectivity (Turnham & Scott, 2016; Liu et al., 2022).

## Other Comments

PRKACG may be a transcribed pseudogene; corresponding protein has not been detected in vivo (Søberg et al., 2013; Ekhator et al., 2025). While no direct disease link is confirmed, alterations in PKA catalytic subunits, including PRKACG, are associated with infertility in animal models (Liu et al., 2022; Stratakis, 2018).

## 9. References

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