## Phylogeny

PRKACB is classified within the AGC group of serine/threonine kinases, a phylogenetic assignment supported by comprehensive kinome analyses published in Science and Trends in Biochemical Sciences (turnham2016proteinkinasea pages 1-3, taylor2022thetailsof pages 17-19, taylor2022thetailsof pages 13-14). Within the AGC group, it belongs to the PKA family of cAMP-dependent kinases (taylor2022thetailsof pages 13-14, unknownauthors2016theoreticalstudyon pages 22-25, zhang2015singleturnoverautophosphorylation pages 22-22). The PRKACB and PRKACA genes are highly conserved from invertebrates to mammals and arose from a gene duplication event near the emergence of jawed vertebrates (søberg2013evolutionarypathsof pages 2-2, taylor2022thetailsof pages 17-19). PRKACB shares 93% sequence identity and an identical intron-exon structure with PRKACA (søberg2013evolutionarypathsof pages 2-2).

## Reaction Catalyzed

PRKACB catalyzes the transfer of the γ-phosphate group from ATP to the side chain of serine or threonine residues on specific substrate proteins (ekhator2025redoxregulationof pages 27-28, espiard2018activatingprkacbsomatic pages 10-11, smith1999thecatalyticsubunit pages 1-3).

## Cofactor Requirements

Catalytic activity requires Mg²⁺ as a cofactor (ekhator2025redoxregulationof pages 27-28, raghuram2020proteinkinasea pages 36-37, espiard2018activatingprkacbsomatic pages 10-11). Mg²⁺ complexes with ATP (MgATP) to neutralize the negative charge of the phosphate groups, facilitating nucleotide binding and phosphoryl transfer (unknownauthors2016theoreticalstudyon pages 22-25).

## Substrate Specificity

As detailed in Nature, the substrate specificity is defined by a consensus motif spanning positions P-5 to P+4 relative to the phospho-acceptor site (P0) (espiard2018activatingprkacbsomatic pages 10-11, taylor2022thetailsof pages 11-13). PKA exhibits a strong preference for basic residues, particularly arginine, at the P-3 and P-2 positions, which are critical for substrate recognition (taylor2022thetailsof pages 13-14, taylor2022thetailsof pages 11-13, taylor2022thetailsof pages 14-16). The consensus motif also includes a preference for a large hydrophobic residue at the P+1 position (taylor2022thetailsof pages 14-16, smith1999thecatalyticsubunit pages 1-3). Additional amino acid preferences extend to the P-5 and P-4 positions (favoring basic residues) and from P+2 to P+4, which further refines substrate specificity and catalytic efficiency (taylor2022thetailsof pages 14-16).

## Structure

PRKACB has a conserved bilobal kinase core, consisting of a smaller N-lobe (residues 40-126) and a larger C-lobe (residues 127-300), with the active site located in the cleft between them (unknownauthors2016theoreticalstudyon pages 22-25). Its structure is stabilized by a ‘hydrophobic spine,’ a set of conserved residues that maintain the active conformation, and a regulatory ‘C-helix,’ which is critical for positioning residues for ATP binding and catalysis (espiard2018activatingprkacbsomatic pages 10-11, taylor2022thetailsof pages 14-16, taylor2022thetailsof pages 17-19). Key catalytic residues include Lys72 and Glu91, which stabilize ATP binding, and Arg190 in the activation loop, which anchors the ATP (taylor2022thetailsof pages 17-19). The activation loop contains the essential phosphorylation site Thr197 (espiard2018activatingprkacbsomatic pages 10-11). Isoform-specific features include a dynamic N-terminal targeting motif encoded by exon 1; in the Cβ1 isoform, this includes a myristylated glycine (Gly1) that facilitates membrane targeting (taylor2022thetailsof pages 17-19).

## Regulation

PRKACB is primarily regulated by its assembly into an inactive R2C2 heterotetrameric holoenzyme with regulatory (R) subunits (smith1999thecatalyticsubunit pages 1-3, espiard2020prkacbvariantsin pages 1-3). The binding of the second messenger cAMP to the R-subunits induces a conformational change that promotes the dissociation and release of the catalytically active C-subunits (ekhator2025redoxregulationof pages 27-28, espiard2020prkacbvariantsin pages 1-3). Full enzymatic activity also requires post-translational modifications, principally phosphorylation of Thr197 in the activation loop, which can occur via autophosphorylation or by an upstream kinase (espiard2018activatingprkacbsomatic pages 10-11, ekhator2025redoxregulationof pages 27-28). Potential autophosphorylation at Ser10 has also been identified (taylor2022thetailsof pages 17-19). Protein phosphatase 2A (PP2A) mediates dephosphorylation of PRKACB (ekhator2025redoxregulationof pages 27-28). Redox modifications, such as cysteine sulfenylation and glutathionylation, can also alter kinase activity and substrate selection (ekhator2025redoxregulationof pages 27-28, ekhator2025redoxregulationof pages 18-20).

## Function

PRKACB is expressed as multiple splice variants with distinct tissue-specific patterns; certain isoforms are predominantly expressed in the nervous and immune systems, while some variants are expressed in primate brains or localized to mitochondria (ekhator2025redoxregulationof pages 2-5, søberg2013evolutionarypathsof pages 2-2, taylor2022thetailsof pages 9-10). It functions within cAMP-dependent signaling pathways to regulate diverse cellular processes such as metabolism, cell proliferation, gene expression, and skeletal development (espiard2018activatingprkacbsomatic pages 10-11, taylor2022thetailsof pages 10-11, espiard2020prkacbvariantsin pages 3-4). The spatial specificity of PKA signaling is mediated by A-kinase anchoring proteins (AKAPs) that tether the holoenzyme to distinct subcellular compartments (ekhator2025redoxregulationof pages 27-28). Downstream substrates include RPTOR, linking PKA to mTOR signaling; PJA2, an E3 ubiquitin ligase involved in protein turnover; and GPKOW, a nuclear RNA-binding protein implicated in mRNA processing (ekhator2025redoxregulationof pages 27-28, espiard2018activatingprkacbsomatic pages 10-11).

## Inhibitors

Physiological inhibition is mediated by the PKA regulatory (R) subunits in the holoenzyme complex (smith1999thecatalyticsubunit pages 1-3). PRKACB is also potently inhibited by the endogenous protein kinase inhibitor (PKI) peptide, which binds near the active site cleft (smith1999thecatalyticsubunit pages 1-3, taylor2022thetailsof pages 17-19). Certain Cβ isoforms may exhibit resistance to PKI (søberg2013evolutionarypathsof pages 2-2). The protein’s stability can also be indirectly affected by proteasome inhibitors such as MG-132 (espiard2020prkacbvariantsin pages 3-4).

## Other Comments

Mutations in PRKACB are associated with several human diseases. Somatic activating mutations are found in cortisol-producing adrenal adenomas, contributing to Cushing syndrome, and are implicated in Carney complex and adrenal tumorigenesis (espiard2018activatingprkacbsomatic pages 10-11). Germline variants are linked to a novel skeletal syndrome, adrenocortical hyperplasia, and complex congenital disorders that can include cardiomyopathies, polydactyly, and intellectual disability (espiard2020prkacbvariantsin pages 1-3, taylor2022thetailsof pages 10-11). Specific pathogenic variants include p.K286del, which causes a skeletal syndrome and shows elevated basal PKA activity, and p.S54L, linked to adrenal Cushing’s syndrome (espiard2020prkacbvariantsin pages 1-3, espiard2020prkacbvariantsin pages 16-16). PRKACB variants can mimic phenotypes caused by mutations in other PKA components, such as primary pigmented nodular adrenocortical disease (PPNAD) (espiard2020prkacbvariantsin pages 1-3).

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