## Phylogeny

Member of the Ca²⁺/calmodulin-dependent protein kinase (CAMK) group, AMP-activated protein kinase (AMPK) family (kurumbail2016structureandregulation pages 19-20). Representative orthologs: Saccharomyces cerevisiae Snf1, Drosophila melanogaster AMPKα, Caenorhabditis elegans aak-2, Arabidopsis thaliana SnRK1α, and Mus musculus Prkaa2 (hawley2023bay3827andsbi0206965 pages 20-21).

## Reaction Catalyzed

ATP + protein-Ser/Thr-OH ⇌ ADP + protein-Ser/Thr-O-PO₃²⁻ + H⁺ (hawley2023bay3827andsbi0206965 pages 20-21).

## Cofactor Requirements

Requires Mg²⁺ for phosphoryl transfer; Mn²⁺ can substitute in some assays (willows2017phosphorylationofampk pages 1-2, kurumbail2016structureandregulation pages 19-20).

## Substrate Specificity

Prefers the AMPK consensus motif φ-x-β-x-x-S/T-x-x-φ, with a basic residue at −3, a bulky hydrophobic residue at +4, and proline disfavoured at +1 (hawley2023bay3827andsbi0206965 pages 20-21, arad2007ampactivatedproteinkinase pages 13-13).

## Structure

552-residue polypeptide comprising:  
• N-terminal kinase domain (1–312) containing catalytic Lys45-Glu64-Asp157 triad and activation loop Thr172 (kurumbail2016structureandregulation pages 19-20).  
• Autoinhibitory/α-hook segment (313–392) that contacts the γ-subunit (bringas2025mechanismandcellular pages 4-7).  
• C-terminal β-interaction domain (393–552) forming the heterotrimer core (kurumbail2016structureandregulation pages 19-20).  
Crystal and cryo-EM structures (PDB 4CFE, 4CFF, 6C9F) reveal: aligned hydrophobic spine and inward αC-helix in the pThr172-activated state, an allosteric drug-and-metabolite (ADaM) pocket at the kinase/β interface, and nucleotide-induced domain rotations (steinberg2023newinsightsinto pages 6-9).

## Regulation

Post-translational modifications  
• Activating phosphorylation: Thr172 by LKB1, CaMKK2 and TAK1 (bringas2025mechanismandcellular pages 4-7).  
• Inhibitory phosphorylation: Ser485 by Akt and PKA; Ser345/347 by PKA (zhao2014investigatingthecamkkβ pages 195-197).  
• Autophosphorylation: Ser491 within the ST-loop (smiles2025ampkphosphositeprofiling pages 1-2).  
• Ubiquitination: by E3 ligase MKRN1, promoting proteolysis (bringas2025mechanismandcellular pages 4-7).  
• Acetylation: by Tip60, modulating stability and activity (bringas2025mechanismandcellular pages 4-7).

Allosteric control  
AMP or ADP binding to γ-subunit CBS sites increases Thr172 phosphorylation and catalytic activity, whereas ATP binding favors the inactive conformation (rey2023fromkinasesto pages 1-2).

## Function

Expression enriched in heart and skeletal muscle, with appreciable levels in liver and other metabolically active tissues (arad2007ampactivatedproteinkinase pages 4-5). Upstream kinases LKB1, CaMKK2, TAK1 convey energetic or Ca²⁺ signals (bringas2025mechanismandcellular pages 4-7). Verified substrates: acetyl-CoA carboxylase isoforms ACACA and ACACB, HMG-CoA reductase HMGCR, glycogen synthase GYS1, Rab-GAP TBC1D1, and autophagy kinase ULK1 (bringas2025mechanismandcellular pages 4-7, hawley2023bay3827andsbi0206965 pages 20-21). Phosphorylation of these targets suppresses lipid, cholesterol and glycogen synthesis, enhances glucose uptake, and initiates autophagy; additional phosphorylation of TSC2/Raptor links energy status to mTORC1 suppression (arad2007ampactivatedproteinkinase pages 11-13).

## Inhibitors

• Dorsomorphin (Compound C): ATP-competitive inhibitor binding the kinase active site (bringas2025mechanismandcellular pages 4-7).  
• SBI-0206965 and BAY-87-2243: ATP-competitive inhibitors that paradoxically elevate pThr172 yet block downstream signaling (hawley2023bay3827andsbi0206965 pages 20-21).  
• BAY-3827: nanomolar ATP-competitive inhibitor characterized structurally (bringas2025mechanismandcellular pages 4-7).  
• PF-739: allosteric activator binding the ADaM pocket; at high concentrations behaves as a functional inhibitor of AMPK signaling (bringas2025mechanismandcellular pages 4-7).

## Other Comments

Whole-body or tissue-specific Prkaa2 knockout mice display glucose intolerance and reduced cardiac ischemic tolerance (arad2007ampactivatedproteinkinase pages 1-3). Gain-of-function complexes containing α2 underlie PRKAG2 glycogen-storage cardiomyopathy with hypertrophy and conduction defects (ahmad2005increasedα2subunit–associated pages 9-10). Elevated PRKAA2 expression supports CD8⁺ T-cell exhaustion and Treg expansion in hepatocellular carcinoma, illustrating context-dependent tumour-promoting roles, whereas other studies report tumour-suppressive functions, reflecting contradictory observations (yan2024ampkα2promotestumor pages 2-4, bringas2025mechanismandcellular pages 4-7).

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