## Phylogeny

5′-AMP-activated protein kinase catalytic subunit α2 (PRKAA2; AMPKα2) is a member of the highly conserved AMP-activated protein kinase family within the CAMK group of serine/threonine kinases (Henriksson, 2012; Steinberg & Hardie, 2023). Orthologues are present across eukaryotes—from yeast SNF1 to plant SnRK1—indicating origin in the last eukaryotic common ancestor (Jain et al., 2018; Yan et al., 2018). Mammals encode two catalytic isoforms, AMPKα1 and AMPKα2, which form mutually exclusive heterotrimers with β and γ subunits and display overlapping yet distinct tissue-specific roles (Russo et al., 2013; Henriksson, 2012).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Hawley et al., 2023).

## Cofactor Requirements

Requires Mg²⁺ for coordination with ATP during phosphotransfer (Hawley et al., 2023).

## Substrate Specificity

AMPKα2 prefers Ser/Thr residues within motifs enriched in basic residues (often at –3/–4) and with hydrophobic residues at defined positions (Rana et al., 2015; Yan et al., 2018). Validated substrates include ACACA, ACACB, LIPE, CRTC2, FOXO3, TSC2, RPTOR and ULK1, spanning lipid, carbohydrate and autophagy pathways (Russo et al., 2013).

## Structure

AMPKα2 contains an N-terminal bilobal kinase domain with an activation loop harbouring Thr172, an α-C helix and catalytic spine (Li et al., 2015; Kurumbail & Calabrese, 2016). C-terminal regions mediate assembly with regulatory β/γ subunits; the γ subunit’s CBS domains bind AMP/ADP/ATP to allosterically modulate the catalytic core (Yan et al., 2018). Nucleotide binding induces conformational changes that stabilise the phosphorylated activation loop and promote activity (Kurumbail & Calabrese, 2016).

## Regulation

• Activating phosphorylation of Thr172 by upstream kinases LKB1, CaMKKβ and TAK1 increases activity up to 1000-fold (Lu et al., 2021; Steinberg & Hardie, 2023).  
• AMP or ADP binding to the γ subunit allosterically stimulates the enzyme (≈2–5-fold) and protects Thr172 from dephosphorylation (Ovens et al., 2021; Yan et al., 2018).  
• Inhibitory phosphorylation at Ser485/491 by Akt or PKA counteracts activation (Lu et al., 2021; Ovens et al., 2021).  
• Additional post-translational modifications (e.g., ubiquitination) influence stability and turnover (Ovens et al., 2021).  
• Small-molecule ligands can activate (A-769662, MK-8722) or inhibit (Bay-3827, SBI-0206965) activity through distinct allosteric or catalytic-site interactions (Hawley et al., 2023; Rana et al., 2015).

## Function

AMPKα2 is a master energy sensor that switches metabolism from anabolic to catabolic during energy stress. Activated AMPKα2:  
• inhibits fatty-acid synthesis and promotes β-oxidation via phosphorylation of ACACA/B (Hawley et al., 2023).  
• regulates glucose uptake by modulating IRS1 and GLUT4 trafficking (Russo et al., 2013).  
• suppresses mTORC1-driven anabolism through phosphorylation of RPTOR and TSC2 (Steinberg & Hardie, 2023).  
• promotes autophagy via ULK1 phosphorylation (Lu et al., 2021).  
• affects transcription (CRTC2, FOXO3, p53) and mitochondrial biogenesis, circadian rhythm (CRY1) and cytoskeletal dynamics (Steinberg & Hardie, 2023; Sukumaran et al., 2020).

## Inhibitors

ATP-competitive inhibitors Bay-3827 and SBI-0206965 decrease catalytic activity but paradoxically elevate Thr172 phosphorylation (Hawley et al., 2023). Additional direct activators/ligands include A-769662, MK-8722 and the anti-diabetic drug metformin, which elevate AMPKα2 signalling via distinct mechanisms (Rana et al., 2015; Russell & Hardie, 2020).

## Other Comments

Dysregulated AMPKα2 activity contributes to type 2 diabetes, obesity, cancer and cardiovascular disease. Pharmacological modulation (activators or inhibitors) is being explored for metabolic disorders and oncology (Russo et al., 2013; Steinberg & Hardie, 2023; Rana et al., 2015). Ubiquitin-mediated degradation pathways present additional therapeutic targets (Ovens et al., 2021).

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