## Phylogeny

CaMKIV belongs to the CaMK group of the human kinome and clusters with the monomeric CaMKI/IV subfamily, distinct from the multimeric CaMKII enzymes (bayer2019camkinasestill pages 1-2). Orthologs are documented in at least 69 species, including Homo sapiens, Mus musculus, Rattus norvegicus, Gallus gallus, Danio rerio, Schizosaccharomyces pombe, Magnaporthe oryzae, Neurospora crassa and Arabidopsis thaliana (naz2016calciumcalmodulindependentproteinkinase pages 9-10). The human CAMK4 gene is located on chromosome 5q21.3, and comparable loci are conserved across vertebrates (naz2016calciumcalmodulindependentproteinkinase pages 4-6). Within the Ca²⁺/CaM-dependent kinase cascade, CaMKIV operates downstream of CaMKK1/2 and in parallel with CaMKI isoforms, reflecting shared evolutionary ancestry (beghi2022calciumsignallingin pages 7-9).

## Reaction Catalyzed

ATP + protein L-serine/threonine → ADP + protein L-serine/threonine-phosphate (naz2016calciumcalmodulindependentproteinkinase pages 2-4).

## Cofactor Requirements

Catalytic activity requires Ca²⁺/calmodulin binding to relieve autoinhibition and Mg²⁺ to coordinate the ATP phosphates (beghi2022calciumsignallingin pages 7-9, santiago2018structuralanalysisof pages 9-10).

## Substrate Specificity

The kinase prefers the consensus Hyd-X-Arg-X-X-Ser/Thr, with a hydrophobic residue at −3 and Arg at −2 relative to the phosphoacceptor, a motif validated on CREB and synapsin peptides (corcoran2001definingca2+calmodulindependentprotein pages 1-1, naz2016calciumcalmodulindependentproteinkinase pages 2-4).

## Structure

CaMKIV is a 473-residue monomer comprising: (i) catalytic domain (46–300) containing Lys75, Asp164 and the 52-LGRGATSIV-60 nucleotide-binding motif; (ii) overlapping autoinhibitory and PP2A-binding region (305–323); (iii) CaM-binding helix (322–341); (iv) N-terminal Ser12/Ser13 autophosphorylation segment; (v) short C-terminal tail (beg2019highthroughputscreening pages 1-6). The crystal structure of the kinase domain (PDB 2W4O) adopts a classical bilobal fold with 13 α-helices and 8 β-strands; phosphorylation of Thr196 (Thr200 in full-length numbering) aligns the αC-helix and completes the hydrophobic regulatory spine (naz2016calciumcalmodulindependentproteinkinase pages 2-4). The His305-Lys321 autoinhibitory helix blocks the active site at rest and is displaced on Ca²⁺/CaM binding (naz2016calciumcalmodulindependentproteinkinase pages 6-8). A hydrophobic cavity adjacent to the hinge accommodates ATP-competitive inhibitors identified by docking (beg2019highthroughputscreening pages 1-6).

## Regulation

Ca²⁺/CaM engagement with residues 322–341 removes the autoinhibitory helix and initiates basal activity (naz2016calciumcalmodulindependentproteinkinase pages 6-8). CaMKK1/2 then phosphorylate Thr196/Thr200, producing a 10–20-fold increase in catalytic efficiency (beghi2022calciumsignallingin pages 9-11). Autophosphorylation at Ser12/Ser13 prolongs Ca²⁺-independent activity (naz2016calciumcalmodulindependentproteinkinase pages 4-6). PP2A binds the 306–323 segment, dephosphorylates Thr200 and returns the kinase to an inactive state; PP2A binding is mutually exclusive with CaM (naz2016calciumcalmodulindependentproteinkinase pages 4-6). O-GlcNAcylation at Thr57/Ser58, Ser137, Ser189, Ser344/345 and Ser356 diminishes Thr200 phosphorylation and suppresses activity (naz2016calciumcalmodulindependentproteinkinase pages 4-6). PKA phosphorylation of CaMKK1 at Ser458 inhibits Thr200 phosphorylation, integrating cAMP and Ca²⁺ signaling (beghi2022calciumsignallingin pages 7-9).

## Function

CaMKIV is highly expressed in hippocampus, cerebellar granule cells, cerebral cortex, thymic CD4⁺ T cells, testis and sperm flagella; lower levels occur in pancreatic β-cells and dendritic cells (beg2019highthroughputscreening pages 1-6, naz2016calciumcalmodulindependentproteinkinase pages 2-2). Upstream regulators are CaMKK1/2, while PP2A serves as the principal opposing phosphatase (beghi2022calciumsignallingin pages 7-9, naz2016calciumcalmodulindependentproteinkinase pages 6-8). Nuclear CaMKIV phosphorylates CREB1 (Ser133), MEF2D, JUN and RORα, thereby controlling genes that govern cytokine production (IL-2, IFN-γ, IL-4), dendritic-cell survival (BCL2), osteoclast differentiation (NFATc1) and synaptic plasticity (BDNF) (corcoran2001definingca2+calmodulindependentprotein pages 3-4, naz2016calciumcalmodulindependentproteinkinase pages 8-9, beg2019highthroughputscreening pages 1-6). Camk4 deletion elevates arterial pressure, enlarges cerebral infarcts and impairs spatial memory, highlighting pivotal roles in cardiovascular and neuroprotective signaling (beghi2022calciumsignallingin pages 11-12).

## Inhibitors

KN-62 (IC₅₀ ≈ 1 µM) and KN-93 (IC₅₀ ≈ 0.4 µM) inhibit CaMKIV but also target CaMKI/II (naz2016calciumcalmodulindependentproteinkinase pages 9-9, naz2016calciumcalmodulindependentproteinkinase pages 10-11). Additional low-micromolar ATP-competitive compounds include (2S,4S)-α-campholinic acid, 3-{[(3S)-3,4-dihydroxybutyl]oxy}amino-1H,2’H-2,3’-biindol-2’-one, and 5-amino-3-{[4-(aminosulfonyl)phenyl]amino}-N-(2,6-difluorophenyl)-1H-1,2,4-triazole-1-carbothioamide (naz2016calciumcalmodulindependentproteinkinase pages 9-10). Virtual high-throughput screening has identified natural-product derivatives that stably occupy the ATP pocket during 100-ns molecular-dynamics simulations (beg2019highthroughputscreening pages 21-27).

## Other Comments

Over-expression or hyperactivation of CAMK4 is documented in small-cell lung carcinoma, hepatocellular carcinoma and epithelial ovarian cancer (beg2019highthroughputscreening pages 1-6, naz2016calciumcalmodulindependentproteinkinase pages 9-9). Increased CAMK4 activity in T cells contributes to systemic lupus erythematosus, and pharmacological inhibition mitigates organ pathology in models (naz2016calciumcalmodulindependentproteinkinase pages 9-9). The hypertensive risk allele rs10491334 reduces CAMK4 expression, and Camk4 knockout mice display elevated blood pressure (beghi2022calciumsignallingin pages 11-12). Deletion also causes sterility and memory deficits, illustrating broad physiological importance (naz2016calciumcalmodulindependentproteinkinase pages 9-10).

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