## Phylogeny

• CAMKK2 is placed in the CAMK group, CaMKK family, of the human kinome, closely paralogous to CAMKK1 (o’byrne2020indepthanalysis pages 14-15).  
• Orthologs: Homo sapiens Q96RR4; Mus musculus Q3UFV3; Rattus norvegicus Q63537; Danio rerio Q7SXW4; Drosophila melanogaster CG1491 (najar2021acompletemap pages 1-2, racioppi2012calciumcalmodulindependentproteinkinase pages 1-2).  
• Mammalian sequences share >90 % identity across the kinase core, whereas invertebrate orthologs conserve catalytic motifs but diverge in regulatory regions (santiago2018structuralanalysisof pages 1-2).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-O-phospho-Ser/Thr (najar2021acompletemap pages 1-2, marcelo2016theca2+calmodulincamkk2axis pages 1-3).

## Cofactor Requirements

• Ca²⁺/calmodulin binding is mandatory for activation (najar2021acompletemap pages 2-4).  
• Catalysis requires divalent Mg²⁺ or Mn²⁺ for phosphotransfer (langendorf2020camkk2isinactivated pages 11-12, profeta2019bindingandstructural pages 9-10).

## Substrate Specificity

• Consensus motif: [R/K]-X-[R/K]-X-S/T\*-Φ, favouring basic residues at –3/–2 and a hydrophobic residue at +1 relative to the phosphoacceptor (langendorf2020camkk2isinactivated pages 12-14).  
• Verified phospho-targets: CaMKI Thr177, CaMKIV Thr200, AMPKα Thr172, CaMK1D Thr180 (racioppi2012calciumcalmodulindependentproteinkinase pages 1-2, fujiwara2016differentialampactivatedprotein pages 7-7).

## Structure

• Domain organisation: N-terminal regulatory segment (1-≈125); bilobal kinase domain (≈125-400); C-terminal autoinhibitory/CaM-binding region (≈400-505) (najar2021acompletemap pages 2-4).  
• Crystal structures 6BKS and 6BYH depict the active kinase core bound to ATP-competitive inhibitors, showing an ordered activation loop with Thr200 oriented for phosphorylation (profeta2019bindingandstructural pages 1-2, marcelo2016theca2+calmodulincamkk2axis pages 11-13).  
• Catalytic motifs: VAIK Lys157 (ATP anchoring), HRD His301-Asp303 (catalysis), DFG Asp319 (Mg²⁺ coordination) (racioppi2012calciumcalmodulindependentproteinkinase pages 1-2).  
• Active conformation requires the Lys157–Glu175 salt bridge and an intact hydrophobic spine; the C-terminal segment blocks the substrate groove until displaced by Ca²⁺/CaM (santiago2018structuralanalysisof pages 9-10).

## Regulation

Post-translational modifications  
– Thr85 autophosphorylation: confers Ca²⁺-independent activity (langendorf2020camkk2isinactivated pages 11-12).  
– Thr200 autophosphorylation within the activation loop: mandatory for full catalysis (santiago2018structuralanalysisof pages 9-10).  
– Ser495 & Ser511 phosphorylated by PKA: create 14-3-3 docking sites, suppressing activity (langendorf2020camkk2isinactivated pages 12-14).  
– Ser129 phosphorylated by CDK5: decreases activity (racioppi2012calciumcalmodulindependentproteinkinase pages 1-2).  
– Thr287 phosphorylated by GSK3: inhibitory (santiago2018structuralanalysisof pages 9-10).

Allosteric control  
• Ca²⁺/calmodulin binding displaces the autoinhibitory tail, aligning αC for catalysis (najar2021acompletemap pages 2-4).  
• 14-3-3 adaptor proteins bind phospho-Ser495/Ser511, locking an inactive conformation; fusicoccins further stabilise this complex (santo2020stabilizationofprotein–protein pages 11-12).  
• cAMP-PKA signalling enhances 14-3-3 binding, linking Ca²⁺ and cAMP pathways (langendorf2020camkk2isinactivated pages 11-12).

## Function

• Expression enriched in brain (arcuate nucleus, hippocampus), heart, liver and osteoblast lineage (najar2021acompletemap pages 1-2, beghi2022calciumsignallingin pages 9-11).  
• Upstream trigger: intracellular Ca²⁺ rise activating CAMKK2 via Ca²⁺/CaM (marcelo2016theca2+calmodulincamkk2axis pages 1-3).  
• Downstream pathways  
– AMPK activation governs glucose uptake, fatty-acid oxidation, autophagy and cardioprotection (beghi2022calciumsignallingin pages 17-19, fujiwara2016differentialampactivatedprotein pages 7-7).  
– CaMKI/IV phosphorylation drives CREB-dependent transcription, supporting neurite outgrowth and synaptic plasticity (marcelo2016theca2+calmodulincamkk2axis pages 13-14, racioppi2012calciumcalmodulindependentproteinkinase pages 1-2).  
– Facilitates GLUT4 translocation during cardiac ischemic stress (beghi2022calciumsignallingin pages 9-11).

## Inhibitors

• STO-609: ATP-competitive, IC₅₀ ≈ 80 nM; co-crystalised with CAMKK2; limited by poor aqueous solubility and CYP1A2 metabolism (langendorf2020camkk2isinactivated pages 11-12, york2017pharmacologicalinhibitionof pages 12-13).  
• Screening of kinase-focused libraries identified nanomolar, enthalpy-driven scaffolds; structural data support selective optimisation (profeta2019bindingandstructural pages 1-2).  
• SGC-CAMKK2-1 disclosed as a selective chemical probe for CAMKK2 cellular studies (wells2023sgccamkk21achemical pages 1-2).

## Other Comments

• Disease associations: promotes prostate cancer growth and metastasis via AMPK-dependent metabolic reprogramming (marcelo2016theca2+calmodulincamkk2axis pages 13-14, o’byrne2020indepthanalysis pages 17-18).  
• Pharmacological or genetic inhibition regresses non-alcoholic fatty liver disease in mouse models (york2017pharmacologicalinhibitionof pages 12-13).  
• Cardiac knockout exacerbates pressure-induced hypertrophy and mortality, underscoring a cardioprotective role (beghi2022calciumsignallingin pages 17-19).

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