## Phylogeny

CAMK2A is a serine/threonine kinase that belongs to the CaMK group and the CaMK2 family of protein kinases, a classification established by Manning et al. 2002 and supported by subsequent literature (baucum2015quantitativeproteomicsanalysis pages 16-17, bhattacharyya2020flexiblelinkersin pages 2-4, bhattacharyya2020flexiblelinkersin pages 23-24, rostas2023calciumcalmodulinstimulatedproteinkinase pages 14-15). The CaMKII family consists of four isoforms in humans (α, β, γ, and δ) encoded by the genes CAMK2A, CAMK2B, CAMK2G, and CAMK2D, respectively (rostas2023calciumcalmodulinstimulatedproteinkinase pages 1-2, sun2024unveilingtherole pages 1-2). These isoforms share high sequence identity in the kinase (~95%) and hub (~80%) domains but have divergent kinase-hub linker regions (bhattacharyya2020structuralinsightsinto pages 5-6).

## Reaction Catalyzed

The enzyme catalyzes the ATP-dependent transfer of a gamma-phosphate group to the hydroxyl group of serine or threonine residues on target substrate proteins (rostas2023calciumcalmodulinstimulatedproteinkinase pages 1-2, fujii2022försterresonanceenergy pages 19-20, baucum2015quantitativeproteomicsanalysis pages 16-17).

## Cofactor Requirements

Catalytic activity requires the binding of Ca2+ ions complexed with calmodulin (Ca2+/CaM), which acts as a primary activator (kool2019camk2dependentsignalingin pages 16-16, bhattacharyya2020flexiblelinkersin pages 23-24). Additionally, Mg2+ ions are an essential cofactor required for coordinating ATP binding and facilitating the phosphoryl transfer reaction (baucum2015quantitativeproteomicsanalysis pages 16-17, fujii2022försterresonanceenergy pages 18-19, rostas2023calciumcalmodulinstimulatedproteinkinase pages 14-15).

## Substrate Specificity

CAMK2A is a basophilic kinase that preferentially phosphorylates serine or threonine residues preceded by an arginine (R) residue at the -2 or -3 position (johnson2023anatlasof pages 12-18). The consensus substrate motifs are R-x-S/T or R-x-x-S/T (johnson2023anatlasof pages 12-18).

## Structure

CAMK2A is a subunit of a large holoenzyme, typically a dodecamer (12 subunits) or tetradecamer arranged as two stacked hexameric or heptameric rings (hell2014camkiiclaimingcenter pages 1-2, bhattacharyya2020flexiblelinkersin pages 1-2, yasuda2022camkiiacentral pages 1-2). Each subunit has a modular domain organization consisting of an N-terminal kinase (catalytic) domain with a bilobed structure, a central regulatory domain, a variable linker region, and a C-terminal association (hub) domain that mediates oligomerization (rostas2023calciumcalmodulinstimulatedproteinkinase pages 1-2, yasuda2022camkiiacentral pages 1-2, takemoto‐kimura2017calmodulinkinasesessential pages 1-4). The regulatory domain contains an autoinhibitory segment that acts as a pseudosubstrate, blocking the active site in the basal state, and an overlapping calmodulin-binding element (hell2014camkiiclaimingcenter pages 1-2, rostas2023calciumcalmodulinstimulatedproteinkinase pages 1-2). The isoforms differ primarily in the length and sequence of the flexible kinase-hub linker (bhattacharyya2020flexiblelinkersin pages 2-4). Unlike many other kinases, CaMKII lacks a canonical phosphorylation site in its activation loop (bhattacharyya2020structuralinsightsinto pages 3-5, bhattacharyya2020structuralinsightsinto pages 5-6).

## Regulation

In its basal state, CAMK2A is autoinhibited by its regulatory segment, which occupies the substrate-binding site of the kinase domain (takemoto‐kimura2017calmodulinkinasesessential pages 4-6, hell2014camkiiclaimingcenter pages 1-2). Activation is initiated by the binding of Ca2+/calmodulin to the regulatory segment, which induces a conformational change that displaces the autoinhibitory segment and exposes the catalytic site (yasuda2022camkiiacentral pages 1-2, bhattacharyya2020structuralinsightsinto pages 1-3).

This initial activation enables trans-autophosphorylation between adjacent subunits within the holoenzyme at several key residues (hell2014camkiiclaimingcenter pages 1-2, bhattacharyya2020flexiblelinkersin pages 1-2). - **Thr286 Phosphorylation**: Autophosphorylation at Thr286 (in the alpha subunit) is a critical activating event that generates Ca2+-independent (autonomous) activity, allowing the kinase to remain active even after intracellular Ca2+ levels decrease (baucum2015quantitativeproteomicsanalysis pages 16-17, bhattacharyya2020flexiblelinkersin pages 1-2). This phosphorylation event also greatly increases the affinity for Ca2+/CaM, a mechanism known as “calmodulin trapping” (rostas2023calciumcalmodulinstimulatedproteinkinase pages 2-4). - **Thr305/306 Phosphorylation**: Autophosphorylation at Thr305 and Thr306, located within the calmodulin-binding domain, is inhibitory (bhattacharyya2020flexiblelinkersin pages 1-2). This modification prevents the rebinding of Ca2+/CaM, thereby modulating kinase activity and preventing further stimulation (takemoto‐kimura2017calmodulinkinasesessential pages 4-6, rostas2023calciumcalmodulinstimulatedproteinkinase pages 1-2).

The balance between these activating and inhibitory phosphorylation events allows CaMKII to decode the frequency and amplitude of calcium signals (bhattacharyya2020flexiblelinkersin pages 2-4, rostas2023calciumcalmodulinstimulatedproteinkinase pages 2-4). Termination of autonomous kinase activity is mediated by phosphatases, such as Protein Phosphatase 1 (PP1), which dephosphorylate the Thr286 site, leading to the inactivation of the kinase (takemoto‐kimura2017calmodulinkinasesessential pages 4-6, bhattacharyya2020structuralinsightsinto pages 1-3). Phosphorylation at Thr305/306 is also reversed by phosphatases (bhattacharyya2020flexiblelinkersin pages 2-4).

## Function

CAMK2A is a multifunctional kinase predominantly expressed in the brain, particularly in the excitatory neurons of the hippocampus and cortex (baucum2015quantitativeproteomicsanalysis pages 16-17, yasuda2022camkiiacentral pages 1-2). It is a central component of the postsynaptic density and plays a pivotal role in synaptic plasticity, learning, and memory (baucum2015quantitativeproteomicsanalysis pages 16-17, yasuda2022camkiiacentral pages 1-2).

* **Signaling and Substrates**: CAMK2A functions as a key mediator in calcium signaling pathways, particularly in long-term potentiation (LTP) (fujii2022försterresonanceenergy pages 18-19, baucum2015quantitativeproteomicsanalysis pages 9-11). It phosphorylates numerous synaptic proteins to regulate synaptic strength, including the AMPA receptor subunit GluA1, TARPs, and regulators of the actin cytoskeleton like RAC and RHO GEFs (yasuda2022camkiiacentral pages 13-14, fujii2022försterresonanceenergy pages 19-20).
* **Interacting Partners**: CAMK2A is part of the NMDA receptor signaling complex through its interaction with the GluN2B (NR2B) subunit, which is enhanced by Thr286 autophosphorylation (baucum2015quantitativeproteomicsanalysis pages 9-11, fujii2022försterresonanceenergy pages 18-19). It also interacts with scaffolding proteins such as PSD-95, Shank3, Homer, F-actin, and BAIAP2 (IRSp53) to modulate postsynaptic density composition and dendritic spine maintenance (baucum2015quantitativeproteomicsanalysis pages 16-17, baucum2015quantitativeproteomicsanalysis pages 9-11).

## Inhibitors

Several experimental inhibitors are used to study CAMK2A function: - **KN-93**: A pharmacological inhibitor that targets the calmodulin binding site, preventing kinase activation (baucum2015quantitativeproteomicsanalysis pages 9-11, kool2019camk2dependentsignalingin pages 16-16). - **tatCN21**: A peptide inhibitor that displaces CaMKII from its binding partner GluN2B (yasuda2022camkiiacentral pages 13-14). - **paAIP2**: A photoinducible inhibitor that allows for precise temporal and spatial inhibition of CaMKII activity (yasuda2022camkiiacentral pages 13-14).

## Other Comments

De novo mutations in the CAMK2A gene are associated with neurodevelopmental disorders, including intellectual disability, autism spectrum disorders (ASD), growth delay, and seizures (yasuda2022camkiiacentral pages 13-14, fujii2022försterresonanceenergy pages 19-20). Specific pathogenic mutations, such as P212L, F98S, and A112V, have been shown to aberrantly facilitate CaMKIIα activity, leading to dysregulated neuronal signaling (fujii2022försterresonanceenergy pages 18-19).

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