## Phylogeny

CAMK2A encodes the α-isoform of Ca2+/calmodulin-dependent protein kinase II (CaMKII), a serine/threonine kinase placed in the CaMK group and CaMKII family (Bhattacharyya et al., 2020; Baucum et al., 2015; Rostas & Skelding, 2023). In vertebrates the family comprises four closely related genes—CAMK2A, CAMK2B, CAMK2G and CAMK2D—whose products share ~95 % sequence identity in the catalytic domain and ~80 % in the hub domain, while diverging mainly in the kinase-hub linker (Bhattacharyya et al., 2020; Sun et al., 2024).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H+ + O-phospho-L-seryl/threonyl-[protein] (Baucum et al., 2015; Fujii et al., 2022; Rostas & Skelding, 2023).

## Cofactor Requirements

Catalysis requires (i) Ca2+/calmodulin, which binds the regulatory segment and activates the enzyme, and (ii) Mg2+, which coordinates ATP during phosphoryl transfer (Bhattacharyya et al., 2020; Fujii et al., 2022; Rostas & Skelding, 2023).

## Substrate Specificity

CAMK2A is a basophilic kinase that prefers Ser/Thr residues preceded by an arginine at the ­2 or ­3 position; optimal motifs are R-x-S/T and R-x-x-S/T (Johnson et al., 2023).

## Structure

Individual subunits consist of an N-terminal bilobed kinase domain, a central regulatory segment, a variable linker, and a C-terminal hub (association) domain. Twelve or fourteen subunits assemble into two stacked hexameric or heptameric rings to form the holoenzyme (Hell, 2014; Bhattacharyya et al., 2020; Yasuda et al., 2022). The regulatory segment contains (i) an autoinhibitory pseudosubstrate and (ii) an overlapping CaM-binding element. Unlike many kinases, CaMKII lacks a canonical activation-loop phosphosite (Bhattacharyya et al., 2020). Isoform diversity largely reflects differences in the flexible kinase-hub linker (Bhattacharyya et al., 2020).

## Regulation

In the basal state the autoinhibitory segment occludes the active site (Takemoto-Kimura et al., 2017; Hell, 2014). Binding of Ca2+/CaM displaces this segment, enabling inter-subunit autophosphorylation (Bhattacharyya et al., 2020; Yasuda et al., 2022).  
• Thr286 autophosphorylation generates Ca2+-independent (autonomous) activity and promotes “calmodulin trapping” (Baucum et al., 2015; Rostas & Skelding, 2023).  
• Thr305/306 autophosphorylation blocks CaM rebinding and is inhibitory (Bhattacharyya et al., 2020; Takemoto-Kimura et al., 2017).  
Protein phosphatase 1 and other phosphatases terminate signalling by dephosphorylating these sites (Bhattacharyya et al., 2020). The interplay of activating and inhibitory phosphorylation allows decoding of Ca2+ signal frequency and amplitude (Rostas & Skelding, 2023).

## Function

CAMK2A is highly expressed in excitatory neurons of the hippocampus and cortex and is enriched in the postsynaptic density (Baucum et al., 2015; Yasuda et al., 2022). It is pivotal for synaptic plasticity, learning and memory, acting downstream of Ca2+ influx during long-term potentiation (Fujii et al., 2022). Reported substrates include AMPA-receptor subunit GluA1, TARPs, and regulators of the actin cytoskeleton such as RAC/RHO GEFs (Yasuda et al., 2022). Interacting partners encompass the NMDA-receptor subunit GluN2B, PSD-95, Shank3, Homer, F-actin and BAIAP2, linking CAMK2A to signalling scaffolds that organise the postsynaptic density (Baucum et al., 2015; Yasuda et al., 2022).

## Inhibitors

Experimental tools include the small-molecule KN-93 (blocks CaM binding), the peptide tatCN21 (disrupts GluN2B interaction), and the photo-activatable peptide paAIP2 (Yasuda et al., 2022; Baucum et al., 2015; Kool et al., 2019).

## Other Comments

De novo CAMK2A mutations (e.g., P212L, F98S, A112V) are linked to intellectual disability, autism spectrum disorders, growth delay and seizures; several variants aberrantly enhance kinase activity (Fujii et al., 2022; Yasuda et al., 2022).

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