## Phylogeny

Ca2+/calmodulin-dependent protein kinase II β (CaMK2B) is a member of the CaMK group of serine/threonine protein kinases (Bhattacharyya et al., 2020; Johnson et al., 2023). The CaMK family relationship was defined phylogenetically by Manning and co-workers (Johnson et al., 2023; Rigter et al., 2024). Regulatory-feature-containing homologues occur as far back as unicellular choanoflagellates, illustrating deep evolutionary conservation (Bhattacharyya et al., 2020). Within mammals, mouse CaMK2A and CaMK2B share ~84 % sequence identity (Rigter et al., 2024).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Johnson et al., 2023; Prömer et al., 2025).

## Cofactor Requirements

Catalytic turnover requires Mg²⁺ (Johnson et al., 2023). Activation additionally needs Ca²⁺ and calmodulin (Bhattacharyya et al., 2020; Rigter et al., 2024).

## Substrate Specificity

CaMK2B phosphorylates serine or threonine, showing a slight preference for serine (Rigter et al., 2024). An in-vivo consensus motif is R/K-X-X-S/T with:  
• basic residue at –3,  
• hydrophobic residue (often Leu) at –5/–6 and +1,  
• optional acidic residue (Asp/Glu) at +2 that enhances catalysis for some substrates (Bhattacharyya et al., 2020; Johnson et al., 2023; Rigter et al., 2024).  
Negative selectivity (avoidance of disfavoured residues) also shapes site choice (Johnson et al., 2023).

## Structure

The protein is modular: N-terminal kinase domain, autoinhibitory regulatory segment, variable-length flexible linker, and C-terminal hub domain that mediates oligomerisation (Bhattacharyya et al., 2020; Yasuda et al., 2022; Mohanan et al., 2022). CaMK2B possesses a filamentous-actin-binding domain absent in CaMK2A (Nicole & Pacary, 2020).

Hub domains assemble 12- or 14-mer holoenzymes organised as two stacked hexameric/heptameric rings, yielding donut-shaped particles ~15–35 nm across (Bhattacharyya et al., 2020; Yasuda et al., 2022; Mohanan et al., 2022; Rigter et al., 2024). Multiple conformers (extended, compact, kinase-paired) are observed (Mohanan et al., 2022).

The kinase domain has the typical bilobed fold; its activation loop lacks conventional regulatory phosphosites. Instead, the regulatory segment acts as a pseudosubstrate that blocks the active site in the basal state (Takemoto-Kimura et al., 2017; Yasuda et al., 2022).

## Regulation

• Ca²⁺/calmodulin binding to the regulatory segment displaces the autoinhibitory peptide and activates the kinase (Bhattacharyya et al., 2020; Yasuda et al., 2022).  
• Inter-subunit autophosphorylation at Thr287 yields Ca²⁺/CaM-independent (autonomous) activity (~20 % of Ca²⁺/CaM-stimulated rate) and promotes “CaM-trapping” (Takemoto-Kimura et al., 2017; Bhattacharyya et al., 2020).  
• Subsequent autophosphorylation at Thr305/Thr306 prevents further Ca²⁺/CaM binding, thereby inhibiting reactivation (Bhattacharyya et al., 2020; Mohanan et al., 2022).  
• Activation can trigger subunit exchange between holoenzymes, potentially prolonging signals (Bhattacharyya et al., 2020).

## Function

Expression: highly enriched in brain—cerebellum, hippocampus, cortex—with presence in excitatory pyramidal neurons, oligodendrocytes and uniquely in inhibitory interneurons (Nicole & Pacary, 2020; Mohanan et al., 2022). The CaMK2B:CaMK2A protein ratio is ~0.8 in cerebellum and ~0.3 in forebrain (Nicole & Pacary, 2020).

Enzymatic roles: phosphorylates AMPA receptors, TARPs, Tiam1, SHANK3 and other synaptic substrates (Takemoto-Kimura et al., 2017; Yasuda et al., 2022; Rigter et al., 2024).

Non-enzymatic/structural roles:  
• Direct F-actin binding and bundling via FABD regulates dendritic spine morphology; activation causes actin release enabling spine enlargement (Nicole & Pacary, 2020).  
• Interacts with GluN2B, Arc/Arg3.1 and PCM1 (Yasuda et al., 2022; Nicole & Pacary, 2020).  
• Targets CaMK2A to synapses and participates in synaptic tagging, proteasome recruitment and long-term potentiation, underpinning learning and memory (Takemoto-Kimura et al., 2017; Nicole & Pacary, 2020; Rigter et al., 2024).

## Inhibitors

Experimental inhibitors include the small molecules KN-62 and KN-93; peptide inhibitors AIP, AC3-I and tatCN21; photo-inducible paAIP2; endogenous CaM-KIIN; antisense oligodeoxynucleotides; and γ-hydroxybutyrate analogues (Mohanan et al., 2022; Yasuda et al., 2022).

## Other Comments

Heterozygous CAMK2B variants (e.g., p.Arg29\*, p.Pro139Leu) cause intellectual disability, language delay, seizures and impaired neuronal migration (Mohanan et al., 2022). Elevated CaMK2B expression is reported in schizophrenia and depression (Nicole & Pacary, 2020).

## 9. References

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