## Phylogeny

CaMK2B belongs to the CaMK (calcium/calmodulin-dependent protein kinase) group of serine/threonine kinases (bhattacharyya2020structuralinsightsinto pages 16-17, johnson2023anatlasof pages 4-5). This classification was established phylogenetically by Manning et al. 2002 (johnson2023anatlasof pages 4-5, rigter2024simultaneouslossof pages 12-15). CaMK2B is highly conserved, with homologs possessing similar regulatory features found in unicellular choanoflagellates (bhattacharyya2020structuralinsightsinto pages 5-6). Within mammals, mouse CAMK2A and CAMK2B share 84.1% sequence identity (rigter2024simultaneouslossof pages 1-3).

## Reaction Catalyzed

The enzyme catalyzes the reversible transfer of a γ-phosphate group from ATP to the hydroxyl group of serine or threonine residues on substrate proteins (johnson2023anatlasof pages 4-5, promer2025muskisa pages 1-2).

## Cofactor Requirements

CaMK2B activation requires Ca2+ and calmodulin as cofactors (bhattacharyya2020structuralinsightsinto pages 16-17, rigter2024simultaneouslossof pages 12-15). The kinase reaction also requires Mg2+ (johnson2023anatlasof pages 4-4).

## Substrate Specificity

CaMK2B phosphorylates serine and threonine residues, with a slight preference for serine (rigter2024simultaneouslossof pages 8-10). The substrate specificity is characterized by a consensus motif R-X-X-S/T, with a preference for basic residues proximal to the phosphoacceptor site (bhattacharyya2020structuralinsightsinto pages 16-17, johnson2023anatlasof pages 4-4). A refined in vivo consensus motif includes Arg (or Lys) at the -3 position, hydrophobic residues (often Leucine) at positions -5 (or -6) and +1, and an acidic residue (Asp or Glu) at the +2 position (rigter2024simultaneouslossof pages 8-10). The hydrophobic residue at +1 (specifically Leucine) and a basic residue at -3 are key determinants (rigter2024simultaneouslossof pages 12-15, rigter2024simultaneouslossof pages 15-17). The acidic residue at +2 plays a conditional, substrate-specific role, enhancing catalytic efficiency for some substrates but not all (rigter2024simultaneouslossof pages 12-15). Substrate specificity is also driven by negative selectivity, which is the avoidance of certain amino acids near the phosphorylation site (johnson2023anatlasof pages 1-2).

## Structure

CaMK2B is a modular protein composed of an N-terminal kinase (catalytic) domain, an autoinhibitory regulatory segment, a variable-length linker region, and a C-terminal association or hub domain that mediates oligomerization (bhattacharyya2020structuralinsightsinto pages 1-3, yasuda2022camkiiacentral pages 1-2, mohanan2022roleofca2+calmodulindependent pages 2-4). The CaMK2B isoform is distinguished by the length and sequence of its flexible kinase-hub linker, which can be much longer than in other isoforms (bhattacharyya2020structuralinsightsinto pages 1-3, bhattacharyya2020structuralinsightsinto pages 5-6). It also contains a filamentous actin binding domain (FABD) that is absent in the CaMKIIα isoform (nicole2020camkiiβinneuronal pages 1-3).

The protein assembles into large dodecameric or tetradecameric holoenzymes, typically organized as two stacked hexameric or heptameric rings formed by the central hub domains (bhattacharyya2020structuralinsightsinto pages 1-3, yasuda2022camkiiacentral pages 1-2, rigter2024simultaneouslossof pages 17-19). These donut-shaped structures are approximately 15–35 nm in diameter (mohanan2022roleofca2+calmodulindependent pages 2-4). The holoenzyme can exist in different conformations, including extended, compact, and kinase-paired states (mohanan2022roleofca2+calmodulindependent pages 2-4).

The kinase domain has a typical bilobed structure (yasuda2022camkiiacentral pages 1-2). A key regulatory feature is the activation loop, which, unlike in many other kinases, lacks typical regulatory phosphorylation sites (bhattacharyya2020structuralinsightsinto pages 5-6, bhattacharyya2020structuralinsightsinto pages 3-5). Instead, activity is controlled by an autoinhibitory segment that acts as a pseudosubstrate, binding to the substrate docking groove and blocking the active site in the basal state (takemoto‐kimura2017calmodulinkinasesessential pages 1-4, yasuda2022camkiiacentral pages 1-2).

## Regulation

CaMK2B activity is primarily regulated by the binding of a Ca2+/calmodulin (Ca2+/CaM) complex to the regulatory domain (bhattacharyya2020structuralinsightsinto pages 1-3). This binding event induces a conformational change that displaces the autoinhibitory segment from the catalytic site, thereby relieving autoinhibition and activating the kinase (yasuda2022camkiiacentral pages 1-2).

Post-translational modifications, predominantly autophosphorylation, are critical for regulation. Upon activation, inter-subunit autophosphorylation occurs in trans at Thr287 (numbering for CaMKIIβ; homologous to Thr286 in CaMKIIα) located within the regulatory segment (bhattacharyya2020structuralinsightsinto pages 5-6, yasuda2022camkiiacentral pages 1-2). This phosphorylation event confers autonomous, Ca2+/CaM-independent activity, which constitutes about 20% of the Ca2+/CaM-stimulated activity (takemoto‐kimura2017calmodulinkinasesessential pages 4-6). Phosphorylation at Thr287 also increases the affinity for CaM, a process termed “CaM-trapping” (takemoto‐kimura2017calmodulinkinasesessential pages 4-6).

Subsequent inhibitory autophosphorylation can occur at Thr305 and Thr306 (human CaMKIIα numbering) (bhattacharyya2020structuralinsightsinto pages 1-3). Phosphorylation at these sites negatively regulates the kinase by preventing subsequent Ca2+/CaM binding and inhibiting reactivation (bhattacharyya2020structuralinsightsinto pages 5-6, mohanan2022roleofca2+calmodulindependent pages 2-4).

The holoenzyme can also undergo activation-triggered subunit exchange, which has implications for signal perpetuation (bhattacharyya2020structuralinsightsinto pages 1-3).

## Function

CaMK2B is predominantly expressed in the brain, with high levels in the cerebellum, hippocampus, and cortex (nicole2020camkiiβinneuronal pages 1-3). It is found in excitatory pyramidal neurons, oligodendrocytes, and uniquely among CaMKII isoforms, in inhibitory interneurons (nicole2020camkiiβinneuronal pages 1-3, mohanan2022roleofca2+calmodulindependent pages 2-4). The expression ratio of CaMKIIβ to CaMKIIα is approximately 80% in the cerebellum and 30% in the forebrain (nicole2020camkiiβinneuronal pages 7-9).

CaMK2B has both enzymatic and non-enzymatic functions crucial for synaptic plasticity (nicole2020camkiiβinneuronal pages 9-11). It phosphorylates substrates such as AMPA receptors, TARPs, the RAC/RHO GEF Tiam1, and SHANK3 (takemoto‐kimura2017calmodulinkinasesessential pages 6-8, yasuda2022camkiiacentral pages 13-14, rigter2024simultaneouslossof pages 8-10). It interacts directly with F-actin via its FABD, bundling actin filaments and regulating dendritic spine morphology (nicole2020camkiiβinneuronal pages 1-3, nicole2020camkiiβinneuronal pages 7-9). It also interacts with the NMDA receptor subunit GluN2B, Arc/Arg3.1, and PCM1 (yasuda2022camkiiacentral pages 13-14, nicole2020camkiiβinneuronal pages 1-3).

Functionally, CaMK2B is essential for long-term potentiation (LTP), learning, and memory (takemoto‐kimura2017calmodulinkinasesessential pages 4-6). It plays a non-enzymatic structural role by targeting CaMKIIα to synapses (rigter2024simultaneouslossof pages 17-19). Upon activation, it detaches from F-actin, allowing for actin remodeling and spine enlargement during structural plasticity (nicole2020camkiiβinneuronal pages 7-9). It is involved in synaptic tagging and mediates the recruitment of proteasomes to dendritic spines (nicole2020camkiiβinneuronal pages 7-9, takemoto‐kimura2017calmodulinkinasesessential pages 6-8).

## Inhibitors

Experimental inhibitors that target CaMKII activity have been identified. These include synthetic small molecules such as KN-62 and KN-93; peptide inhibitors like AIP (Autocamtide-2-related inhibitory peptide), AC3-I, and tatCN21; and photoinducible inhibitors like paAIP2 (mohanan2022roleofca2+calmodulindependent pages 20-21, yasuda2022camkiiacentral pages 13-14). Natural inhibitory proteins like CaM-KIIN, CaMKII antisense oligodeoxynucleotides, and analogs of γ-hydroxybutyrate also modulate CaMKII activity (mohanan2022roleofca2+calmodulindependent pages 20-21).

## Other Comments

Mutations in the *CAMK2B* gene are associated with neurodevelopmental disorders (rigter2024simultaneouslossof pages 17-19, yasuda2022camkiiacentral pages 13-14). Specific pathogenic mutations have been identified in individuals with intellectual disability (ID), language impairments, seizures, and behavioral anomalies (nicole2020camkiiβinneuronal pages 9-11). For instance, a heterozygous nonsense mutation, c.85C>T leading to p.(Arg29\*), is associated with mild ID, delayed speech, and seizures (mohanan2022roleofca2+calmodulindependent pages 20-21). A missense variant, c.416C>T resulting in p.(Pro139Leu), correlates with severe ID, global developmental delay, hypotonia, and microcephaly (mohanan2022roleofca2+calmodulindependent pages 20-21). These mutations are reported to disrupt kinase function and neuronal migration (mohanan2022roleofca2+calmodulindependent pages 20-21). Additionally, elevated CaMKIIβ expression has been observed in schizophrenia and depression (nicole2020camkiiβinneuronal pages 9-11).

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