## Phylogeny

CAMK2G is a member of the Ca2+/calmodulin-dependent protein kinase II (CaMKII) family, which is part of the CAMK kinase group within the Ser/Thr protein kinase class of the human kinome (ma2015distinctrolesof pages 2-3, mohanan2022roleofca2+calmodulindependent pages 20-21, onori2018theintellectualdisabilityassociated pages 1-5). This classification is consistent with analyses by Manning et al., 2002 (ma2015distinctrolesof pages 2-3, onori2018theintellectualdisabilityassociated pages 29-33). CAMK2G shares sequence homology in critical residues with its paralogs CAMK2A and CAMK2B (onori2018theintellectualdisabilityassociated pages 47-49). Orthologs of CAMK2G are well-established and conserved in common model organisms, including mouse and rat (coultrap2011improvinganatural pages 9-9, onori2018theintellectualdisabilityassociated pages 1-5, mohanan2022roleofca2+calmodulindependent pages 29-30).

## Reaction Catalyzed

The enzyme catalyzes a phosphotransferase reaction, transferring the terminal (gamma) phosphate group from an ATP molecule to the hydroxyl group of serine or threonine residues on substrate proteins (ma2015distinctrolesof pages 2-3, mohanan2022roleofca2+calmodulindependent pages 20-21, beghi2020genepolymorphismsin pages 11-12).

## Cofactor Requirements

Catalytic activity requires the binding of Ca2+ ions via the calmodulin (CaM) protein, which acts as a cofactor for activation (ma2015distinctrolesof pages 2-3, mohanan2022roleofca2+calmodulindependent pages 20-21). The phosphotransferase reaction also requires Mg2+ as an essential metal ion cofactor (onori2018theintellectualdisabilityassociated pages 25-29, kool2019camk2dependentsignalingin pages 16-16).

## Substrate Specificity

The substrate specificity of CAMK2G favors a consensus motif enriched in basic residues surrounding the phospho-acceptor serine or threonine residue (coultrap2011improvinganatural pages 9-9). This includes the recognition of sequences with arginine or lysine residues at specific positions (ma2015distinctrolesof pages 2-3, coultrap2011improvinganatural pages 9-9). Based on comprehensive kinase substrate specificity mapping, the consensus motif is characterized as [R-X-X-S/T], with a preference for a positively charged arginine residue at the -3 position relative to the phosphorylation site (onori2018theintellectualdisabilityassociated pages 39-47, mohanan2022roleofca2+calmodulindependent pages 29-30).

## Structure

CAMK2G exhibits a multi-domain architecture typical of CaMKII isoforms, comprising an N-terminal catalytic kinase domain, a central regulatory segment, and a C-terminal association (hub) domain (ma2015distinctrolesof pages 2-3, mohanan2022roleofca2+calmodulindependent pages 20-21). The regulatory domain contains an autoinhibitory helix and the CaM-binding site, while the association domain facilitates the oligomerization of subunits into a dodecameric holoenzyme, which is essential for its function and is arranged as two stacked hexameric rings (ma2015distinctrolesof pages 2-3, onori2018theintellectualdisabilityassociated pages 17-21, beghi2020genepolymorphismsin pages 11-12).

The kinase domain features critical structural elements for catalysis, including the activation loop and the C-helix (coultrap2011improvinganatural pages 9-9). Upon activation, the C-helix reorients to properly align catalytic residues and stabilize ATP binding, while the activation loop undergoes conformational changes driven by autophosphorylation (onori2018theintellectualdisabilityassociated pages 39-47, coultrap2011improvinganatural pages 9-9). These rearrangements switch the enzyme from an inactive to an active state, facilitating substrate binding and efficient phosphorylation (coultrap2011improvinganatural pages 9-9, rigter2023lossofcamk2g pages 14-14). A unique feature of a CAMK2G isoform is a nuclear localization sequence (NLS) near Ser334, which enables its translocation to the nucleus (ma2015distinctrolesof pages 2-3).

## Regulation

In its basal state, CAMK2G is maintained in an inactive conformation by an autoinhibitory domain that blocks the catalytic site (onori2018theintellectualdisabilityassociated pages 25-29, onori2018theintellectualdisabilityassociated pages 17-21). Activation is initiated by the binding of a Ca2+/calmodulin (CaM) complex to the regulatory domain, which induces a conformational change that displaces the autoinhibitory segment and exposes the active site (ma2015distinctrolesof pages 2-3, onori2018theintellectualdisabilityassociated pages 21-25). This leads to trans-autophosphorylation at threonine 287 (Thr287), a key residue within the activation loop (ma2015distinctrolesof pages 2-3, onori2018theintellectualdisabilityassociated pages 39-47). Phosphorylation at Thr287 is critical as it confers sustained, Ca2+-independent autonomous kinase activity, allowing the enzyme to remain active even after intracellular Ca2+ levels have returned to baseline (ma2015distinctrolesof pages 2-3, mohanan2022roleofca2+calmodulindependent pages 20-21). This process also results in prolonged CaM trapping, which stabilizes the active conformation (ma2015distinctrolesof pages 2-3). Phosphorylation near Ser334 regulates the function of the nuclear localization sequence (ma2015distinctrolesof pages 2-3).

## Function

CAMK2G is expressed in multiple tissues, including the brain, heart, smooth muscle, and liver (ma2015distinctrolesof pages 2-3). It is particularly enriched in neuronal tissues, where its expression is high during early neurodevelopment (onori2018theintellectualdisabilityassociated pages 1-5, ma2015distinctrolesof pages 2-3). Upstream activators include Ca2+ influx via L-type Ca2+ channels (CaV1) and NMDA receptors (ma2015distinctrolesof pages 2-3, mohanan2022roleofca2+calmodulindependent pages 20-21). CAMK2G phosphorylates downstream targets including transcription factors like CREB and STAT1 and interacts with proteins such as the Ryanodine receptor (ma2015distinctrolesof pages 2-3, onori2018theintellectualdisabilityassociated pages 29-33). It plays a critical role in glutamatergic synapse signaling, long-term potentiation (LTP), synaptic plasticity, and memory (ma2015distinctrolesof pages 2-3, mohanan2022roleofca2+calmodulindependent pages 20-21). It is also essential for neuronal migration, maturation, and dendritic arborization (onori2018theintellectualdisabilityassociated pages 1-5, onori2018theintellectualdisabilityassociated pages 25-29). In cancer, CAMK2G is a direct binding partner of the pseudokinase PEAK1 and is activated downstream of PLCγ1/Ca2+ signaling (yang2025activationofcamk2 pages 1-2).

## Inhibitors

Several experimental inhibitors target CAMK2G and other CaMKII isoforms. These include synthetic small molecules like KN-93 and KN-62, which act by preventing CaM binding (ma2015distinctrolesof pages 2-3, mohanan2022roleofca2+calmodulindependent pages 20-21). Peptide-based inhibitors such as AIP and AC3-I, as well as natural protein inhibitors like the CaM-KIIN peptides (e.g., CN21, CN19), also modulate its activity (mohanan2022roleofca2+calmodulindependent pages 20-21). The second-generation inhibitor RA306 has also been used to target CAMK2 (yang2025activationofcamk2 pages 1-2).

## Other Comments

Mutations in the CAMK2G gene have been linked to neurodevelopmental disorders, mental retardation, and unreliable memory performance in humans (ma2015distinctrolesof pages 2-3). A pathogenic de novo gain-of-function mutation, p.Arg292Pro, located in the autoregulatory domain, causes intellectual disability by inducing constitutive kinase activity (onori2018theintellectualdisabilityassociated pages 1-5, onori2018theintellectualdisabilityassociated pages 17-21). This mutation leads to increased basal phosphorylation at Thr287, enhanced CaM affinity, and severely impaired neuronal migration and maturation (onori2018theintellectualdisabilityassociated pages 1-5, onori2018theintellectualdisabilityassociated pages 21-25). Additionally, variants in CAMK2G have been identified in CAD-associated SNP clusters, suggesting a role in cardiovascular disease susceptibility (beghi2020genepolymorphismsin pages 11-12).

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