1. Phylogeny  
   CAMKV (CaM kinase‐like vesicle‐associated protein, gene symbol CAMKV, also known as VACAMKL, Uniprot Q8NCB2) belongs to the Ca²⁺/calmodulin‐dependent protein kinase (CaMK) family and is evolutionarily conserved among vertebrates, being predominantly expressed in brain and neural tissues. Comparative sequence analyses indicate that CAMKV shares significant homology with active CaMK family members such as CaMKIIα; however, key catalytic motifs required for enzymatic activity are not conserved in CAMKV. In particular, while the N‐terminal region of CAMKV aligns with the kinase domain of CaMKIIα (e.g., residues corresponding to S18–K314), substitutions in critical motifs—for example, the replacement of the conserved glycine in the DFG motif with a histidine—underscore its classification as a pseudokinase. This evolutionary divergence—from potentially active kinases to a catalytically inactive regulator found almost exclusively in neural tissues—suggests that CAMKV has been preserved for its non‐catalytic, scaffolding, or regulatory functions rather than for direct phosphoryl transfer reactions (barylko2022palmitoylationregulatedinteractionsof pages 1-2, liang2016thepseudokinasecamkv pages 1-2).
2. Reaction Catalyzed  
   Unlike classical protein kinases that catalyze the reaction ATP + [protein]‐(serine/threonine) → ADP + [protein]‐(phospho-serine/threonine) + H⁺, CAMKV does not exhibit detectable catalytic activity. Experimental studies have failed to demonstrate ATP binding or substrate phosphorylation by CAMKV; its kinase‐like domain lacks several critical residues that normally support phosphate transfer. Accordingly, no ATP‐dependent phosphorylation reaction has been observed for CAMKV in vitro, and the protein is functionally characterized as a pseudokinase that does not catalyze the canonical reaction associated with active serine/threonine kinases (barylko2022palmitoylationregulatedinteractionsof pages 1-2, liang2016thepseudokinasecamkv pages 1-2).
3. Cofactor Requirements  
   In conventional serine/threonine kinases, Mg²⁺ (or sometimes Mn²⁺) serves as an essential cofactor for ATP binding and catalytic activity. However, given that CAMKV does not demonstrate measurable kinase activity, no definitive cofactor requirements (such as the need for Mg²⁺) have been established for its catalysis. The inability of CAMKV to bind ATP in a productive manner renders the typical cofactor dependency moot, and experimental data have not provided any evidence that CAMKV requires such cofactors for its regulatory role in neurons (barylko2022palmitoylationregulatedinteractionsof pages 1-2, liang2016thepseudokinasecamkv pages 1-2).
4. Substrate Specificity  
   For active kinases, substrate specificity is defined by characteristic sequence motifs that are recognized and phosphorylated, for example, an Arg‐rich sequence or an RxRxxp[ST] motif in many CaMK family members. In the case of CAMKV, however, there is no detectable intrinsic kinase activity, and consequently, no consensus phosphorylation substrate motif has been determined for the protein. Although CAMKV shares structural features with active kinases, its inability to undergo ATP‐dependent phosphorylation precludes the identification of substrate specificity based on catalytic function. Rather than phosphorylating substrates, CAMKV functions through protein–protein interactions that modulate downstream signaling events in neurons (barylko2022palmitoylationregulatedinteractionsof pages 1-2, liang2016thepseudokinasecamkv pages 1-2).
5. Structure  
   CAMKV is organized into distinct structural regions that reflect its evolutionary origins and specialized function. The protein contains an N‐terminal kinase‐like domain that shows significant sequence alignment with the active regions of CaMK family members such as CaMKIIα; for instance, residues S18–K314 in CAMKV align well with the corresponding region in CaMKIIα, although this domain lacks key catalytic residues. Notably, a critical substitution—where a histidine replaces the glycine typically found in the canonical DFG motif—further confirms its status as a pseudokinase. In addition to the kinase‐like domain, structural predictions have identified an intrinsically disordered region (spanning approximately residues 325–351), which may confer conformational flexibility for protein–protein interactions and regulatory responses. A unique structural feature of CAMKV is its post‐translational modification by palmitoylation; specifically, palmitoylation at cysteine residue 5 is critical for its subcellular localization to the plasma membrane and for mediating its interactions with synaptic proteins such as Arc/Arg3.1. Although no high‐resolution crystal structure is currently available, homology modeling and AlphaFold predictions suggest that while CAMKV retains the overall fold typical of CaMK domains, the disruption of key catalytic motifs distinguishes its three-dimensional structure from that of enzymatically active kinases (barylko2022palmitoylationregulatedinteractionsof pages 2-4, barylko2022palmitoylationregulatedinteractionsof pages 4-5).
6. Regulation  
   The regulatory mechanisms governing CAMKV function are mediated primarily through post‐translational modifications and protein–protein interactions rather than by changes in catalytic activity. CAMKV is reversibly palmitoylated at cysteine residue 5, a modification that is essential for its localization to the plasma membrane and for facilitating interactions with other proteins involved in synaptic plasticity, such as Arc/Arg3.1. In addition, phosphorylation by external kinases plays a role in modulating CAMKV function; for instance, cyclin-dependent kinase 5 (Cdk5) phosphorylates CAMKV at threonine 345, which has been reported to inhibit its function in dendritic spine maintenance. Beyond these modifications, conformational changes induced by calcium and calmodulin binding may further regulate its role as a scaffolding protein in neurons, although these interactions do not lead to intrinsic catalytic activity. Collectively, these regulatory processes underscore that CAMKV’s functional output is controlled by dynamic post‐translational modifications and interaction‐driven conformational changes rather than through conventional kinase activation mechanisms (barylko2022palmitoylationregulatedinteractionsof pages 1-2, liang2016thepseudokinasecamkv pages 1-2, parfentev2019elucidationofprotein pages 110-112).
7. Function  
   CAMKV is predominantly expressed in the brain and neural tissues, where it plays a critical role in regulating synaptic structure and function. Although it belongs to the CaMK family based on its amino acid sequence and overall domain organization, CAMKV does not exhibit detectable catalytic activity and is classified as a pseudokinase. Rather than transferring phosphate groups to substrates, CAMKV functions as a regulatory protein, contributing to the maintenance of dendritic spine density and synaptic plasticity. Its biological role is chiefly mediated by protein–protein interactions, for example with the cytoskeletal regulator GEF-H1, whose inhibition can lead to decreased RhoA activity, a pathway important for actin cytoskeleton remodeling in dendrites. Additionally, CAMKV’s palmitoylation‐dependent membrane association is crucial for its interaction with synaptic proteins such as the immediate‐early gene product Arc/Arg3.1, linking it to activity‐dependent synaptic modifications. These functions highlight the role of CAMKV in the modulation of neuronal signaling pathways that influence the structural integrity and plasticity of dendritic spines, which are essential for proper synaptic transmission and neural network activity (barylko2022palmitoylationregulatedinteractionsof pages 1-2, liang2016thepseudokinasecamkv pages 1-2).
8. Other Comments  
   Despite its classification within the calmodulin‐dependent protein kinase family, CAMKV has not been shown to catalyze ATP‐dependent phosphorylation reactions, and multiple studies have consistently reported a lack of detectable kinase activity. Instead, CAMKV appears to function predominantly as a scaffold, contributing to synaptic regulation through its interactions with other proteins and its palmitoylation‐mediated subcellular localization. In the context of neuroblastoma and other neural pathologies, CAMKV expression has been correlated with measures of synaptic plasticity and, in some studies, with worse clinical outcomes; however, its role is attributed to its non‐catalytic, regulatory functions rather than to any intrinsic enzymatic activity. Furthermore, CAMKV has been identified as a substrate for phosphorylation by other kinases such as DYRK3, indicating that its activity may be modulated by extrinsic phosphorylation events, yet it does not function as an autonomous kinase (rozen2024anoveldruggable pages 2-3, rozen2024anoveldruggable pages 8-9).
9. References
10. barylko2022palmitoylationregulatedinteractionsof pages 1-2
11. barylko2022palmitoylationregulatedinteractionsof pages 2-4
12. barylko2022palmitoylationregulatedinteractionsof pages 4-5
13. liang2016thepseudokinasecamkv pages 1-2
14. rozen2024anoveldruggable pages 2-3
15. rozen2024anoveldruggable pages 8-9

References

1. (barylko2022palmitoylationregulatedinteractionsof pages 1-2): Barbara Barylko, Per Niklas Hedde, Clinton A. Taylor, Derk D. Binns, Yu-Kai Huang, Gemma Molinaro, Kimberly M. Huber, David M. Jameson, and Joseph P. Albanesi. Palmitoylation-regulated interactions of the pseudokinase calmodulin kinase-like vesicle-associated with membranes and arc/arg3.1. Frontiers in Synaptic Neuroscience, Jul 2022. URL: https://doi.org/10.3389/fnsyn.2022.926570, doi:10.3389/fnsyn.2022.926570. This article has 7 citations and is from a peer-reviewed journal.
2. (barylko2022palmitoylationregulatedinteractionsof pages 2-4): Barbara Barylko, Per Niklas Hedde, Clinton A. Taylor, Derk D. Binns, Yu-Kai Huang, Gemma Molinaro, Kimberly M. Huber, David M. Jameson, and Joseph P. Albanesi. Palmitoylation-regulated interactions of the pseudokinase calmodulin kinase-like vesicle-associated with membranes and arc/arg3.1. Frontiers in Synaptic Neuroscience, Jul 2022. URL: https://doi.org/10.3389/fnsyn.2022.926570, doi:10.3389/fnsyn.2022.926570. This article has 7 citations and is from a peer-reviewed journal.
3. (barylko2022palmitoylationregulatedinteractionsof pages 4-5): Barbara Barylko, Per Niklas Hedde, Clinton A. Taylor, Derk D. Binns, Yu-Kai Huang, Gemma Molinaro, Kimberly M. Huber, David M. Jameson, and Joseph P. Albanesi. Palmitoylation-regulated interactions of the pseudokinase calmodulin kinase-like vesicle-associated with membranes and arc/arg3.1. Frontiers in Synaptic Neuroscience, Jul 2022. URL: https://doi.org/10.3389/fnsyn.2022.926570, doi:10.3389/fnsyn.2022.926570. This article has 7 citations and is from a peer-reviewed journal.
4. (liang2016thepseudokinasecamkv pages 1-2): Zhuoyi Liang, Y. Zhan, Yang Shen, Catherine C L Wong, J. Yates, F. Plattner, Kwok-On Lai, and N. Ip. The pseudokinase camkv is required for the activity-dependent maintenance of dendritic spines. Nature Communications, Oct 2016. URL: https://doi.org/10.1038/ncomms13282, doi:10.1038/ncomms13282. This article has 58 citations and is from a highest quality peer-reviewed journal.
5. (parfentev2019elucidationofprotein pages 110-112): Iwan Parfentev. Elucidation of protein interactions in complex samples by protein-protein cross-linking of synaptosomes. PhD thesis, University Goettingen Repository, 2019. URL: https://doi.org/10.53846/goediss-7615, doi:10.53846/goediss-7615.
6. (rozen2024anoveldruggable pages 8-9): Esteban J. Rozen, Kim Wigglesworth, and Jason M. Shohet. A novel druggable dual-specificity tyrosine-regulated kinase3/calmodulin kinase-like vesicle-associated signaling module with therapeutic implications in neuroblastoma. Biomedicines, 12:197, Jan 2024. URL: https://doi.org/10.3390/biomedicines12010197, doi:10.3390/biomedicines12010197. This article has 1 citations and is from a peer-reviewed journal.
7. (rozen2024anoveldruggable pages 2-3): Esteban J. Rozen, Kim Wigglesworth, and Jason M. Shohet. A novel druggable dual-specificity tyrosine-regulated kinase3/calmodulin kinase-like vesicle-associated signaling module with therapeutic implications in neuroblastoma. Biomedicines, 12:197, Jan 2024. URL: https://doi.org/10.3390/biomedicines12010197, doi:10.3390/biomedicines12010197. This article has 1 citations and is from a peer-reviewed journal.