## Phylogeny

CAMKV (Q8NCB2) belongs to the Ca²⁺/calmodulin-dependent protein kinase (CAMK) group of the human serine/threonine kinome (Manning et al., 2002; Johnson et al., 2023; Simon et al., 2015). It is regarded as an atypical CAMK that has diverged from canonical CAMK1/2 members (Yu et al., 2024). Conservation of key Lys/Arg residues within its calmodulin-binding domain and the presence of orthologues from yeast to humans further support its evolutionary placement (Manning et al., 2002; Yu et al., 2024).

## Reaction Catalyzed

ATP + [a protein] ⇌ ADP + [a phosphoprotein] (Yu et al., 2024).  
(Note: Several studies report absent or very low intrinsic catalytic activity, describing CAMKV as a pseudokinase; others detect kinase activity in specific settings.)

## Cofactor Requirements

• Initial activation requires binding of Ca²⁺/calmodulin to a C-terminal calmodulin-binding domain; calmodulin is dispensable once activity is initiated (Yu et al., 2024).  
• A canonical DFG motif that normally coordinates Mg²⁺ is altered, potentially impairing Mg²⁺ binding in the inactive/pseudokinase state (Yu et al., 2024).

## Substrate Specificity

No consensus phosphorylation motif has been defined. Experimentally identified substrates include:  
– CREB Ser133 (Yu et al., 2024)  
– GATA2 Ser182/Ser192 (Yu et al., 2024)  
Phosphoproteomics also links CAMKV to regulation of STK10 and RIOK1 phosphorylation (Yu et al., 2024). Clustering by motif selectivity places CAMKV within the broader CAMK group (Johnson et al., 2023).

## Structure

CAMKV contains an N-terminal kinase-like domain and an intrinsically disordered ~200-residue C-terminal region that harbours a calmodulin-binding domain and seven tandem octapeptide repeats (D-X-X-X-T-P-A-T) critical for protein stability (Rozen et al., 2024). AlphaFold2 predicts a conventional bilobal kinase fold despite conflicting reports on catalytic competence (Yu et al., 2024).  
Key residues/features:  
– Lys53 essential for ATP binding in active models (Yu et al., 2024)  
– Thr183 autophosphorylation site required for activation (Yu et al., 2024)  
– Altered DFG motif, mis-positioned C-helix and locked activation loop cited as causes of pseudokinase behaviour (Rozen et al., 2024; Yu et al., 2024).

## Regulation

• Phosphorylation:  
– DYRK3 directly phosphorylates CAMKV at Thr387 and Thr427 within the C-terminal repeats, controlling liquid–liquid phase separation (Rozen et al., 2024).  
– Autophosphorylation on Thr183 activates CAMKV; T183E is constitutively active (Yu et al., 2024).

• Allosteric/conformational control:  
– Calmodulin binding is required for initial activation (Yu et al., 2024).  
– The C-terminal tail exerts autoinhibition; a splice isoform lacking 31 C-terminal residues (CAMKV-S) is more active than full-length CAMKV (Yu et al., 2024).

• Protein stability:  
– Seven tandem octapeptide repeats are necessary for steady-state expression (Rozen et al., 2024).

## Function

Expression/Localization: Highly expressed in neuroblastoma cells, embryonic neuroblasts and brain tissue (Rozen et al., 2023; Yu et al., 2024). Predominantly cytosolic; localizes to the mitotic spindle during division and forms aggregates when DYRK3 is inhibited (Rozen et al., 2023).

Signaling roles:  
– Direct transcriptional target of MYCN/MYC oncogenes (Yu et al., 2024).  
– In neuroblastoma, the DYRK3–CAMKV module regulates mitotic spindle dynamics and tumour cell proliferation (Rozen et al., 2023).  
– CAMKV phosphorylates CREB Ser133 and GATA2 Ser182/192, promoting proliferation (Yu et al., 2024).  
– Knockdown reduces proliferation and alters genes linked to neuronal function, translation and apoptosis (Yu et al., 2024).  
– Additional roles in dendritic spine maintenance and activity-dependent bulk endocytosis have been reported (Yu et al., 2024).

Interacting partners: DYRK3 (upstream kinase) and CREB (substrate) interact directly with CAMKV (Rozen et al., 2023; Yu et al., 2024).

## Inhibitors

ATP-competitive compounds, including K-252a and OTSSP167, dock into the CAMKV ATP-binding pocket and suppress neuroblastoma xenograft growth (Yu et al., 2024).

## Other Comments

High CAMKV expression correlates with advanced stage, high-risk disease and poor survival in neuroblastoma, and serves as a prognostic biomarker in endometrial carcinoma (Rozen et al., 2023; Yu et al., 2024). Two splice isoforms exist: full-length (501 aa) and CAMKV-S (Δ31 C-terminal aa), the latter displaying higher kinase activity and pro-proliferative capacity (Yu et al., 2024).

## References

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