Phylogeny  
CaMK1D belongs to the CaMK1 sub-family of multifunctional CaM kinases and clusters with CaMK1A, PNCK/CaMK1B and CaMK1G, but not with CaMKII or CaMKIV (Ohmae et al., 2006). Clear vertebrate orthologues are present in mouse (Camk1d splice variants a–d), rat and zebrafish; a conserved invertebrate homologue exists in Drosophila, whereas no yeast counterpart has been detected (Akizuki et al., 2021; Ohmae et al., 2006; “Evaluation…”, 2012).

Reaction Catalyzed  
ATP + [protein]-Ser/Thr → ADP + [protein]-Ser/Thr-PO₃²⁻ (“Structural & kinetic studies…”, 2018).

Cofactor Requirements  
Mg²⁺ for ATP coordination and Ca²⁺-bound calmodulin (Ca²⁺/CaM) for activation (“Structural & kinetic studies…”, 2018).

Substrate Specificity  
The kinase recognises the CaMK1 consensus ϕ-X-Arg-X-X-Ser/Thr-X-X-X-ϕ motif with a basic residue at ‑3 and a hydrophobic residue at ‑5 relative to the phospho-acceptor. Confirmed cellular substrates include CREB Ser133, CREMβ, eIF4GII and eIF5A (“Evaluation…”, 2012; “Structural & kinetic studies…”, 2018).

Structure  
Residues 1–303 form an N-terminal bilobal kinase domain followed by a helix-loop-helix autoinhibitory domain that overlaps a calmodulin-binding segment (~303–320) (“Evaluation…”, 2012).  
A 2.3 Å crystal structure with the ATP-competitive inhibitor GSK-3 XIII (PDB 2JC6) displays a canonical fold with a Gly-rich loop, catalytic Lys52, HRD motif and DFG-in activation segment; the activation loop (164–185, Thr180) is flexible and unresolved (“Evaluation…”, 2012).  
Solution NMR/SAXS show a monomeric protein that, on Ca²⁺/CaM binding, forms an elongated tri-lobed complex with CaM docked against the C-lobe (“Structural & kinetic studies…”, 2018).  
Regulatory elements include αR1 blocking the substrate pocket, αR2 contacting the N-lobe, and a buried Trp306 essential for high-affinity CaM binding; the inhibitor-bound structure retains an intact hydrophobic spine and aligned αC helix (“Evaluation…”, 2012).

Regulation  
• Full activation requires Thr180 phosphorylation by upstream CaMKK1/2 (“Evaluation…”, 2012).  
• Thr313 phosphorylation within the calmodulin-binding domain lowers CaM affinity and down-regulates activity (“Structural & kinetic studies…”, 2018).  
• Mouse splice variants b and c are additionally phosphorylated by PKA at RRXS motifs, and variant c undergoes autophosphorylation on Ser349 (Akizuki et al., 2021).  
• The autoinhibitory domain maintains inactivity; Ca²⁺/CaM binding displaces this domain in a multi-step process, and a secondary CaM site on the C-lobe yields biphasic, nanomolar-affinity binding that stabilises the active state (“Evaluation…”, 2012; “Structural & kinetic studies…”, 2018).

Function  
CAMK1D mRNA/protein is abundant in brain, liver, pancreas, spleen, thymus, prostate, testis, ovary and colon (“Evaluation…”, 2012).  
• Neurons: depolarisation prompts nuclear translocation and CREB phosphorylation, promoting dendritic growth (Unknown Authors, 2022).  
• Neutrophils: required for cytokine-driven proliferation and NADPH-oxidase respiratory burst (“Structural & kinetic studies…”, 2018).  
Upstream kinase: CaMKK1/2; downstream effectors: CREB, CREMβ, eIF4GII, eIF5A (“Evaluation…”, 2012; “Structural & kinetic studies…”, 2018).

Inhibitors  
GSK-3 XIII binds the hinge region (H-bonds to Val101, water-mediated contacts to Leu29) as confirmed by crystallography and thermal-shift assays (“Evaluation…”, 2012). Additional selective CaM-kinase chemotypes that improve insulin sensitivity in vivo have been reported (Fromont et al., 2020).

Other Comments  
CAMK1D is recurrently amplified and over-expressed in basal-like/triple-negative breast cancer, driving proliferation, EMT, migration and invasion (Bergamaschi et al., 2008). GWAS identify regulatory variants at CDC123/CAMK1D associated with type 2 diabetes (Fogarty et al., 2014). Altered hydroxymethylation and SNP associations are observed in late-onset Alzheimer’s disease brain tissue (Unknown Authors, 2022). High-throughput RNAi screens highlight CAMK1D as a kinase conferring immune resistance in multiple myeloma (Unknown Authors, 2023).

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