## Phylogeny

CaMK1D is assigned to the CaMK1 subfamily within the multifunctional CaMK group of the human kinome, a placement derived from kinome-wide analyses that follow the framework of Manning et al. 2002 (akizuki2021biochemicalcharacterizationof pages 4-5).  
Within vertebrates, confirmed orthologs include Mus musculus Camk1d (splice variants mCaMKIδ-a, ‑b, ‑c, ‑d) (akizuki2021biochemicalcharacterizationof pages 11-12), Rattus norvegicus Camk1d (unknownauthors2012evaluationofprotein pages 42-48) and Danio rerio camk1d, whose knock-down causes developmental defects (akizuki2021biochemicalcharacterizationof pages 21-22).  
A Drosophila CaMK homolog that retains the conserved kinase core is considered an invertebrate ortholog, whereas no yeast counterpart has been detected (unknownauthors2012evaluationofprotein pages 36-42, ohmae2006molecularidentificationand pages 4-5).  
Phylogenetically, CaMK1D clusters with CaMK1A, PNCK/CaMK1B and CaMK1G, yet remains distinct from the CaMKII and CaMKIV branches (ohmae2006molecularidentificationand pages 4-5).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-Ser/Thr-PO₃²⁻ (unknownauthors2018structural&kinetic pages 7-16).

## Cofactor Requirements

Catalysis requires Mg²⁺ for ATP coordination in the active site and activation requires Ca²⁺-bound calmodulin (Ca²⁺/CaM) (unknownauthors2018structural&kinetic pages 7-16, unknownauthors2018structural&kinetic pages 26-30).

## Substrate Specificity

CaMK1D recognises the CaMK1 consensus ϕ-X-Arg-X-X-Ser/Thr-X-X-X-ϕ motif that places a basic residue at −3 and a hydrophobic residue at −5 relative to the phospho-acceptor (unknownauthors2012evaluationofprotein pages 54-58).  
Validated cellular substrates include CREB Ser133, CREMβ, eIF4GII and eIF5A (unknownauthors2012evaluationofprotein pages 42-48, unknownauthors2018structural&kinetic pages 26-30).

## Structure

Domain organisation comprises an N-terminal bilobal kinase domain (residues 1-303) followed by a helix-loop-helix autoinhibitory domain (AID) that overlaps a calmodulin-binding domain (CBD; residues ~303-320) (unknownauthors2012evaluationofprotein pages 245-254, unknownauthors2012evaluationofprotein pages 48-54).  
The 2.3 Å crystal structure of CaMK1D bound to the ATP-competitive inhibitor GSK-3 XIII (PDB 2JC6) shows a canonical kinase fold with Gly-rich P-loop, catalytic Lys52, HRD catalytic loop and a DFG-in motif; the activation loop (residues 164-185, Thr180) is unresolved, indicating flexibility (unknownauthors2012evaluationofprotein pages 245-254).  
Solution NMR and SAXS reveal that the protein is monomeric and that Ca²⁺/CaM binding generates an elongated tri-lobed complex with CaM docked against the C-lobe (unknownauthors2018structural&kinetic pages 70-76).  
Key regulatory features include αR1 of the AID occluding the substrate pocket, αR2 contacting the N-lobe, and a buried Trp306 in the CBD that is critical for high-affinity CaM binding, contrasting with the solvent-exposed tryptophan in CaMK1A (unknownauthors2012evaluationofprotein pages 277-285).  
The inhibitor-bound structure presents an intact hydrophobic spine and properly aligned αC helix, supporting a catalytically competent conformation when autoinhibition is relieved (unknownauthors2012evaluationofprotein pages 245-254).

## Regulation

Phosphorylation of Thr180 in the activation loop by upstream kinases CaMKK1/2 is required for full catalytic activation (unknownauthors2012evaluationofprotein pages 42-48).  
Thr313 within the CBD is phosphorylated; this event reduces CaM affinity and down-regulates activity (unknownauthors2018structural&kinetic pages 76-82).  
Mouse splice variants mCaMKIδ-b and ‑c are additionally phosphorylated by PKA at canonical RRXS sites, introducing cross-talk with cAMP signalling (akizuki2021biochemicalcharacterizationof pages 17-18).  
Autophosphorylation at Ser349 has been observed in variant c, creating a conformation resistant to dephosphorylation (akizuki2021biochemicalcharacterizationof pages 17-18).  
Conformationally, the kinase is held inactive by the AID; binding of Ca²⁺/CaM to the CBD triggers a three-step displacement of the AID, exposing the substrate groove without perturbing the catalytic cleft (unknownauthors2012evaluationofprotein pages 329-333).  
A secondary CaM docking surface on the C-lobe yields biphasic nanomolar binding that stabilises the active state (unknownauthors2018structural&kinetic pages 76-82).

## Function

CAMK1D mRNA and protein are abundant in brain, liver, pancreas, spleen, thymus, prostate, testis, ovary and colon (unknownauthors2012evaluationofprotein pages 42-48).  
Upon neuronal depolarisation the kinase translocates to the nucleus and phosphorylates CREB to drive gene transcription required for basal dendritic growth of hippocampal neurons (unknownauthors2022theroleof pages 28-33).  
In neutrophils, CaMK1D is indispensable for cytokine-induced proliferation and for activation of the NADPH-oxidase respiratory burst (unknownauthors2018structural&kinetic pages 26-30).  
Upstream regulation is provided by CaMKK1/2, which phosphorylate Thr180 after Ca²⁺/CaM binding, whereas downstream effectors include CREB, CREMβ, eIF4GII and eIF5A (unknownauthors2012evaluationofprotein pages 42-48, unknownauthors2018structural&kinetic pages 26-30).

## Inhibitors

The ATP-competitive inhibitor GSK-3 XIII binds the hinge region of CaMK1D, forming hydrogen bonds to Val101 and water-mediated contacts to Leu29; binding is confirmed by crystallography and thermal-shift assays (unknownauthors2012evaluationofprotein pages 245-254, unknownauthors2012evaluationofprotein pages 307-317).  
Additional chemotypes selective for CaM-kinases, including CaMK1D, have been reported in a medicinal-chemistry campaign aimed at restoring insulin sensitivity in vivo (fromont2020discoveryofhighly pages 57-60).

## Other Comments

The CAMK1D locus is recurrently amplified and over-expressed in basal-like/triple-negative breast cancer, where overexpression drives proliferation, epithelial–mesenchymal transition, migration and invasion (bergamaschi2008camk1damplificationimplicated pages 4-5).  
Genome-wide association studies link regulatory variants at CDC123/CAMK1D with type 2 diabetes through effects on hepatic glucose regulation (fogarty2014identificationofa pages 9-10).  
CAMK1D shows altered hydroxymethylation and SNP associations in late-onset Alzheimer’s disease brain tissue (unknownauthors2022theroleof pages 28-33).  
High-throughput RNAi screening identifies CAMK1D as a kinase conferring immune resistance in multiple myeloma, positioning it as a potential immunotherapeutic target (unknownauthors2023ascreeningfor pages 133-137).

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