Phylogeny  
CAMK1 α is classified within the CaMKI sub-family of the Ca²⁺/calmodulin-regulated (CAMK) group of the human kinome (simon2015molecularmechanismsof pages 1-3). Orthologs are documented in Homo sapiens, Mus musculus, Rattus norvegicus, Danio rerio, Drosophila melanogaster and Caenorhabditis elegans, whereas Saccharomyces cerevisiae lacks a direct counterpart (simon2015molecularmechanismsof pages 1-3). The enzyme shares an evolutionary relationship—and the conserved catalytic/regulatory architecture—with CaMKII, CaMKIV and DAPK1, all members of the broader CAMK branch (soderling2001structureandregulation pages 2-3).

Reaction Catalyzed  
ATP + protein L-Ser/Thr ⇌ ADP + protein L-O-phospho-Ser/Thr (simon2015molecularmechanismsof pages 1-3).

Cofactor Requirements  
Catalysis requires Mg²⁺ for ATP coordination, and Ca²⁺-saturated calmodulin functions as an obligatory allosteric activator (bhattacharyya2020structuralinsightsinto pages 15-16, simon2015molecularmechanismsof pages 1-3).

Substrate Specificity  
Biochemical and structural data define a preferred consensus Hyd-X-Arg-X₂-Ser/Thr-X₃-Hyd, with hydrophobic residues (Met/Leu/Val/Ile/Phe) favoured at positions −5 and +4, and an invariant Arg at −3 (clapperton2002structureofthe pages 1-2). Proteome-scale motif profiling confirms enrichment of non-polar amino acids at −5, basic residues at −3/−2, and acidic residues immediately downstream (+1 to +3) of the phosphoacceptor (jha2025deeplearningcoupledproximity pages 11-12).

Structure  
The 42 kDa polypeptide comprises:  
• N-terminal bilobal catalytic domain (CD) harbouring Lys49, Asp146, Asp162 and Thr177 as essential catalytic residues (bhattacharyya2020structuralinsightsinto pages 15-16).  
• Autoinhibitory domain (AID) containing αR1 and αR2 helices that block the substrate cleft in the basal state (simon2015molecularmechanismsof pages 8-10).  
• Calmodulin-binding domain (CBD), overlapping the AID, which adopts an extended αR3 helix upon Ca²⁺/CaM binding (clapperton2002structureofthe pages 7-8).

Crystal structures resolve key conformations:  
– Autoinhibited kinase domain (PDB 1A06) shows αR1/αR2 inserted into the active site and αR3 lying along the nucleotide pocket (simon2015molecularmechanismsof pages 8-10).  
– CaM-bound peptide complex (PDB 1MXE) demonstrates picomolar-affinity wrapping of CaM around residues 294-318, anchored by Trp303 and Met316 in a 1-14 binding mode (clapperton2002structureofthe pages 1-2).  
– Phosphorylation-competent assemblies (PDB 4FG9, 4FGB) reveal a continuous hydrophobic spine and correctly positioned C-helix characteristic of the active kinase (stratton2013structuralstudieson pages 10-11, rellos2010structureofthe pages 8-10).

Regulation  
Post-translational modifications  
• Thr177 in the activation loop is phosphorylated by CaMKK1/2, producing a marked increase in catalytic turnover and reduced Ca²⁺ dependence (racioppi2012calciumcalmodulindependentproteinkinase pages 1-2).  
• Ser52 in the N-terminal segment is targeted by PKA, providing an additional layer of control (tokumitsu2022molecularmechanismsunderlying pages 12-13).  
• PKA also phosphorylates CaMKK at Thr108, indirectly limiting Thr177 phosphorylation of CAMK1 α (matsushita1999inhibitionofthe pages 4-5).

Allosteric and conformational control  
Ca²⁺/CaM binding to the CBD displaces the AID, unmasking ATP and substrate sites and activating the enzyme by >100-fold (soderling2001structureandregulation pages 2-3). Hydrophobic residues Ile286, Val290, Ile294 and Phe298 act as an intramolecular “clamp” stabilising autoinhibition and are released upon CaM engagement (clapperton2002structureofthe pages 7-8).

Function  
Expression is broad but pronounced in brain regions such as hippocampal and cerebellar neurons, with additional presence in peripheral and endocrine tissues (unknownauthors2019roleofca2+calmodulin pages 28-32). Documented roles include:  
• Regulation of axonal extension and growth-cone motility in developing neurons (unknownauthors2019roleofca2+calmodulin pages 28-32).  
• Promotion of dendritic growth and spine formation downstream of NMDA receptor-mediated Ca²⁺ influx (unknownauthors2019roleofca2+calmodulin pages 28-32).  
• Phosphorylation of transcription factors such as CREB, linking Ca²⁺ signals to gene expression (clapperton2002structureofthe pages 1-2).  
• Integration into the CaMKK→CaMK1→CaMKIV cascade controlling cell-cycle progression and differentiation (soderling2001structureandregulation pages 2-3).

Inhibitors  
• CaMKIp (residues 294-318) binds the active site and functions as a high-affinity competitive inhibitor (clapperton2002structureofthe pages 7-8).  
• KN-62 and KN-93 are Ca²⁺/CaM-competitive small molecules that inhibit CAMK1 α with low-micromolar potency (pellicena2014camkiiinhibitorsfrom pages 2-3).  
• STO-609 inhibits upstream CaMKKs, thereby indirectly suppressing Thr177 phosphorylation and CAMK1 α activation (brown2024studyingcamkiitools pages 17-18).

Other Comments  
No recurrent disease-linked missense variants in CAMK1 α have been reported; however, genetic variation within the upstream CaMKK node is associated with cardiovascular and neuropsychiatric phenotypes, underscoring pathway relevance (unknownauthors2022variantigenetichenel pages 27-31).

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