## Phylogeny

Orthologs are documented in Caenorhabditis elegans (LIN-2), Drosophila melanogaster (CAKI/CMG), basal metazoans such as Trichoplax adherens, and throughout vertebrates including mouse, rat, zebrafish and human, underscoring deep conservation across Metazoa (laconte2013structuralconstraintsand pages 2-4).  
Vertebrate CASK acquired lineage-specific residues, e.g. Tyr268, that are absent in invertebrate paralogs, indicating functional specialization during chordate evolution (laconte2013structuralconstraintsand pages 5-6).  
Within the human kinome it belongs to the Ca²⁺/calmodulin-dependent kinase (CAMK) group, MAGUK-CAMK subfamily, as classified in the Manning 2002 framework referenced in contemporary analyses (laconte2018twomicrocephalyassociatednovel pages 16-17).  
The catalytic domain diverged from canonical CAMKs through motif replacements (DFG→GFG, Asn→Cys) that converted a primordial Mg²⁺-dependent enzyme into today’s Mg²⁺-inhibited kinase (mukherjee2010evolutionofcask pages 5-7).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr → ADP + protein-L-O-phospho-Ser/Thr (mukherjee2008caskfunctionsas pages 12-12).

## Cofactor Requirements

Catalysis proceeds without divalent cations; free Mg²⁺ binds the distorted active site and inhibits rather than stimulates phosphotransfer (mukherjee2008caskfunctionsas pages 9-10, hsueh2009calciumcalmodulin‐dependentserineprotein pages 2-3).

## Substrate Specificity

Physiological substrates include the presynaptic adhesion molecule neurexin-1 and the scaffold liprin-α2 (mukherjee2008caskfunctionsas pages 12-12, laconte2013structuralconstraintsand pages 5-6).  
A universal phosphoacceptor consensus is not defined; substrate selection relies on spatial recruitment via PDZ- or CaMK-mediated docking rather than primary-sequence preference (mukherjee2008caskfunctionsas pages 12-12).  
For CaMK-binding partners such as Caskin1 the recognition motif ζ-x-ψ-W-ψ-x-R has been delineated structurally (wang2022crystalstructureof pages 7-10).

## Structure

Domain organisation: N-terminal CaMK-like kinase, tandem L27A/L27B oligomerisation modules, class II PDZ domain, SH3 domain, 4.1-binding HOOK segment, and C-terminal guanylate-kinase-like (GK) domain (hsueh2009calciumcalmodulin‐dependentserineprotein pages 1-2).  
CaMK domain crystal structure (PDB 3C0H) shows a pre-activated fold with the non-canonical GFG motif and His145 occupying the metal pocket, explaining Mg²⁺ inhibition (mukherjee2008caskfunctionsas pages 9-10).  
Reversion of four active-site residues (CASK4M mutant) restores Mg²⁺ coordination and canonical catalytic geometry, confirming evolutionary rewiring (mukherjee2010evolutionofcask pages 5-7).  
An AlphaFold/experimental hybrid model (PDB 6G99) maps additional active-site substitutions linked to disease (laconte2018twomicrocephalyassociatednovel pages 16-17).  
The CaMK domain bound to Caskin1 CID peptide reveals a hydrophobic W376–I375 core engaging residues V117/H120/Y121 of CASK, exemplifying partner specificity (wang2022crystalstructureof pages 7-10).  
The PDZ–SH3–GK supramodule forms an integrated scaffold that stabilises intramolecular contacts and creates composite binding surfaces (wu2020structuralbasisfor pages 14-14).  
Catalytic and regulatory spines are pre-assembled, and the activation loop is ordered without phosphorylation, accounting for constitutive low-level activity (mukherjee2008caskfunctionsas pages 9-10).

## Regulation

• Autophosphorylation occurs constitutively because the canonical Ca²⁺/calmodulin autoinhibitory segment is degenerate (mukherjee2010evolutionofcask pages 5-7).  
• CDK5 phosphorylates Ser151 and Ser155 within the CaMK domain and sites in the L27 modules, enhancing presynaptic targeting and liprin-α interaction (hsueh2009calciumcalmodulin‐dependentserineprotein pages 1-2, laconte2013structuralconstraintsand pages 5-6).  
• Tyr72 is an additional regulatory phosphosite identified in cell-based analyses (laconte2013structuralconstraintsand pages 5-6).  
• SUMO-1 conjugates Lys679, weakening protein 4.1 binding and altering dendritic spine morphology (laconte2018twomicrocephalyassociatednovel pages 16-17).  
• The E3 ligase Mdm2 ubiquitinates CASK, implicating proteasomal turnover in abundance control (laconte2018twomicrocephalyassociatednovel pages 16-17).  
• Free Mg²⁺ or Mn²⁺ acts as an allosteric inhibitor by occupying the distorted nucleotide pocket (mukherjee2008caskfunctionsas pages 9-10).

## Function

Expression is highest in neuronal soma, axons, presynaptic terminals, dendritic spines and retinal ganglion cells, with lower levels in non-neural tissues (hsueh2009calciumcalmodulin‐dependentserineprotein pages 2-3, laconte2019ann‐terminalheterozygous pages 1-3).  
Presynaptically, CASK assembles a complex with neurexin-1, liprin-α2, Mint1 and Caskin1, coupling cell-adhesion to synaptic vesicle release (hsueh2009calciumcalmodulin‐dependentserineprotein pages 1-2, mukherjee2008caskfunctionsas pages 12-12).  
Postsynaptically, it links syndecan-2 to the actin/α-spectrin cytoskeleton via protein 4.1, shaping spine morphology (hsueh2009calciumcalmodulin‐dependentserineprotein pages 2-3).  
Within the LIN-10–LIN-2–LIN-7 complex it associates with KIF17 to transport NR2B-containing NMDA receptor vesicles along microtubules (unknownauthors2002identificationandcharacterization pages 30-35).  
In the nucleus, the GK domain binds TBR1 and co-activates transcription of developmental genes such as reelin and NR2B (unknownauthors2002identificationandcharacterization pages 39-44, hsueh2009calciumcalmodulin‐dependentserineprotein pages 2-3).  
Upstream regulator: CDK5; downstream phosphorylated substrates: neurexin-1 and liprin-α2 (hsueh2009calciumcalmodulin‐dependentserineprotein pages 1-2, laconte2013structuralconstraintsand pages 5-6).

## Other Comments

Loss-of-function or missense variants cause X-linked intellectual disability, microcephaly with pontocerebellar hypoplasia, FG syndrome and congenital nystagmus (hsueh2009calciumcalmodulin‐dependentserineprotein pages 6-6, laconte2013structuralconstraintsand pages 6-6).  
Pathogenic mutations include:  
– Y268H in the activation segment, abolishing a vertebrate-specific residue required for liprin binding (laconte2013structuralconstraintsand pages 5-6).  
– L209P in the αF helix, destabilising the CaMK domain and causing microcephaly with retinal dystrophy (laconte2019ann‐terminalheterozygous pages 17-20).  
– N299S in the catalytic core, associated with intellectual disability (laconte2013structuralconstraintsand pages 5-6).  
– PDZ mutation M519T and SH3 mutation G659D disrupt neurexin interaction and underlie pontocerebellar hypoplasia (laconte2018twomicrocephalyassociatednovel pages 1-3).

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