## Phylogeny

Orthologues of CASK are present from basal metazoans (e.g., Trichoplax adherens) through invertebrates such as Caenorhabditis elegans (LIN-2) and Drosophila melanogaster (CAKI/CMG) to all examined vertebrates, including mouse, rat, zebrafish and human, indicating deep conservation across Metazoa (LaConte & Mukherjee, 2013). In the human kinome CASK groups with Ca²⁺/calmodulin-dependent kinases, MAGUK-CAMK subfamily (LaConte et al., 2018). Vertebrate CASK has acquired lineage-specific residues (e.g., Tyr268) that are absent from invertebrate paralogues, suggesting functional specialisation during chordate evolution (LaConte & Mukherjee, 2013). The catalytic domain diverged from canonical CAMKs via motif swaps (DFG→GFG; Asn→Cys) that converted a primordial Mg²⁺-dependent enzyme into the present Mg²⁺-inhibited form (Mukherjee et al., 2010).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr ⇌ ADP + protein-L-O-phospho-Ser/Thr (Mukherjee et al., 2008).

## Cofactor Requirements

No divalent cation is required for activity; free Mg²⁺ (or Mn²⁺) binds the distorted active site and inhibits catalysis (Mukherjee et al., 2008; Hsueh, 2009).

## Substrate Specificity

Physiological substrates include neurexin-1 and liprin-α2 (Mukherjee et al., 2008; LaConte & Mukherjee, 2013). A universal sequence consensus is lacking; substrate choice depends mainly on spatial recruitment through PDZ or CaMK-mediated docking (Mukherjee et al., 2008). For CaMK-binding partners such as Caskin1, a ζ-x-ψ-W-ψ-x-R motif has been defined (Wang et al., 2022).

## Structure

Domain architecture: 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 (Hsueh, 2009).  
• 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 (Mukherjee et al., 2008).  
• Reversion of four active-site residues (CASK4M mutant) restores Mg²⁺ coordination and canonical geometry (Mukherjee et al., 2010).  
• Hybrid model (PDB 6G99) maps additional disease-linked substitutions (LaConte et al., 2018).  
• CaMK domain bound to Caskin1 CID peptide highlights hydrophobic W376–I375 core interactions (Wang et al., 2022).  
• The PDZ–SH3–GK supramodule forms an integrated scaffold that stabilises intramolecular contacts and generates composite binding sites (Wu et al., 2020).  
• Catalytic/regulatory spines are pre-assembled and the activation loop is ordered without phosphorylation, accounting for constitutive low-level activity (Mukherjee et al., 2008).

## Regulation

• Constitutive autophosphorylation because the canonical Ca²⁺/calmodulin autoinhibitory segment is degenerate (Mukherjee et al., 2010).  
• CDK5 phosphorylates Ser151 and Ser155 in the CaMK domain and sites within L27 modules, boosting presynaptic targeting and liprin-α binding (Hsueh, 2009; LaConte & Mukherjee, 2013).  
• Additional phosphosite: Tyr72 (LaConte & Mukherjee, 2013).  
• SUMO-1 conjugation on Lys679 weakens protein 4.1 binding and alters dendritic spine morphology (LaConte et al., 2018).  
• Mdm2-mediated ubiquitination targets CASK for proteasomal degradation (LaConte et al., 2018).  
• Free Mg²⁺/Mn²⁺ acts as an allosteric inhibitor by occupying the distorted nucleotide pocket (Mukherjee et al., 2008).

## Function

Highly expressed in neuronal soma, axons, presynaptic terminals, dendritic spines and retinal ganglion cells; lower expression in non-neural tissues (Hsueh, 2009; LaConte et al., 2019).  
Presynaptically, CASK assembles a complex with neurexin-1, liprin-α2, Mint1 and Caskin1 to couple cell adhesion to synaptic vesicle release (Hsueh, 2009; Mukherjee et al., 2008). Postsynaptically, it links syndecan-2 to the actin/α-spectrin cytoskeleton via protein 4.1, influencing spine morphology (Hsueh, 2009).  
Within the LIN-10–LIN-2–LIN-7 complex CASK associates with KIF17 to transport NR2B-containing NMDA receptor vesicles (Identification and Characterization, 2002).  
Nuclear GK domain binds TBR1 and co-activates transcription of genes such as reelin and NR2B (Identification and Characterization, 2002; Hsueh, 2009).  
Upstream kinase: CDK5; downstream substrates: neurexin-1 and liprin-α2 (Hsueh, 2009; LaConte & Mukherjee, 2013).

## Inhibitors

Free Mg²⁺ or Mn²⁺ functions as an intrinsic allosteric inhibitor by occupying the distorted active site (Mukherjee et al., 2008).

## Other Comments

Loss-of-function or missense variants cause X-linked intellectual disability, microcephaly with pontocerebellar hypoplasia, FG syndrome and congenital nystagmus (Hsueh, 2009; LaConte & Mukherjee, 2013). Reported pathogenic mutations include Y268H (activation segment), L209P (αF helix), N299S (catalytic core), PDZ M519T and SH3 G659D, each linked to distinct neurodevelopmental disorders (LaConte & Mukherjee, 2013; LaConte et al., 2018; LaConte et al., 2019).

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