## Proposed EC/sub-subclass

2.7.11.– (protein‐serine/threonine kinases)

## Accepted name

Serine/threonine-protein kinase DCLK1

## Synonyms

Doublecortin-like kinase 1; DCAMKL1; DCDC3A; KIAA0369

## Phylogeny

DCLK1 is a member of the serine/threonine kinase superfamily that combines two N-terminal doublecortin (DCX) microtubule-binding domains with a C-terminal CaMK-related catalytic module (Burgess & Reiner, 2001; Burgess & Reiner, 2002; Ohmae et al., 2006). The DCX domains are evolutionarily conserved across vertebrates, while the kinase domain shares ~45 % sequence identity with CaMKI/IV family members, positioning DCLK1 as an intermediate within the CaMK clade (Burgess & Reiner, 2002; Ohmae et al., 2006). Orthologues are widespread in mammals, and alternative splicing generates multiple isoforms that fine-tune cytoskeletal binding and kinase activity in tissue- and stage-specific contexts (Burgess & Reiner, 2002; Reiner et al., 2006; Venkat et al., 2023).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Patel et al., 2016; Venkat et al., 2023)

## Cofactor Requirements

Mg²⁺ is required for coordination of ATP and efficient phosphotransfer (Patel et al., 2016).

## Substrate Specificity

Peptide studies indicate a preference for basic residues, especially Arg at the −3/−2 positions relative to the target Ser/Thr, which enhance phosphorylation efficiency (Burgess & Reiner, 2002; Ramkumar et al., 2018). A definitive consensus motif has not yet been established.

## Structure

DCLK1 consists of tandem DCX domains that adopt β-grasp folds for tubulin binding, a bilobal kinase domain containing conserved G-loop, HRD, and DFG motifs, and an intrinsically disordered C-terminal tail (Burgess & Reiner, 2001; Patel et al., 2016; Shang et al., 2003). Docking of the phosphorylated C-tail against the catalytic core stabilises the hydrophobic spine and occludes the ATP site, providing an autoinhibitory mechanism (Rogers et al., 2020; Venkat et al., 2023).

## Regulation

1. Autophosphorylation of specific Ser/Thr residues—particularly within the C-tail—promotes tail docking and autoinhibition of kinase activity (Rogers et al., 2020).
2. Phosphorylation of residues inside the DCX domains reduces microtubule binding (Rogers et al., 2020).
3. Alternative splicing alters DCX copy number and C-tail length, modulating ATP affinity and catalytic turnover among isoforms (Burgess & Reiner, 2002; Rogers et al., 2021).

## Function

• Neuronal development: DCX domains stabilise microtubules to support neuronal migration, axon guidance, and dendritic patterning, while kinase activity further modulates cytoskeletal dynamics (Burgess & Reiner, 2001; Ohmae et al., 2006; Ramkumar et al., 2018).  
• Mature neurons: contributes to dendritic architecture and synaptic plasticity (Chhetri et al., 2022).  
• Cancer biology: over-expression or aberrant splicing of DCLK1 isoforms correlates with enhanced tumor cell migration, invasion, and cancer stem-cell properties (Burgess & Reiner, 2002; Chhetri et al., 2022).

## Inhibitors

Structure-guided efforts are underway to design small-molecule ATP-competitive inhibitors and compounds that disrupt C-tail docking, but no specific inhibitors are detailed in the cited literature (Venkat et al., 2023).

## Other Comments

DCLK1 lacks a canonical calmodulin-binding region found in related CaMKI/IV kinases; consequently, autophosphorylation and C-tail docking dominate its regulatory landscape (Rogers et al., 2020; Rogers et al., 2021). The protein’s dual microtubule-binding and kinase activities, together with its cancer associations, make isoform-selective inhibition an active therapeutic research goal (Venkat et al., 2023; Carli et al., 2023).

## References

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