## Phylogeny

Kinome classification of DCLK3 is contradictory across sources. According to Manning et al. 2002, DCLK3 is classified within the kinome group CMGC and the family of dual-specificity tyrosine-phosphorylation-regulated kinases (DYRKs) (ohmae2006molecularidentificationand pages 4-5). Other analyses, also referencing Manning et al. 2002, place DCLK3 in the CAMK (calcium/calmodulin-dependent protein kinase) group and the subfamily of CAMK-like kinases (unknownauthors2014astudyof pages 153-159, unknownauthors2018etudedurôle pages 59-63, venkat2023mechanisticandevolutionary pages 1-1). DCLK3 is a member of the DCLK (doublecortin-like kinase) family, which shows homology to Cam Kinases 2 and 1/4 (dijkmans2010thedoublecortingene pages 10-11). The kinase domain of DCLK3 has 56% amino acid sequence identity to DCLK1 and 53% to DCLK2 (unknownauthors2018etudedurôle pages 59-63). DCLK3 is considered an atypical member of the DCX family as its homology with DCLK1 and DCLK2 is mostly limited to the kinase domain (song2021thexlinkedintellectual pages 3-4). Orthologs of DCLK3 are found in vertebrates, deuterostomes, protostomes, and invertebrates (venkat2023mechanisticandevolutionary pages 1-1).

## Reaction Catalyzed

DCLK3 is a serine/threonine kinase that catalyzes the transfer of the γ-phosphate group from ATP to serine or threonine residues on substrate proteins (dijkmans2010thedoublecortingene pages 10-11, unknownauthors2014astudyof pages 153-159, ohmae2006molecularidentificationand pages 4-5).

## Cofactor Requirements

The catalytic activity of DCLK3 requires divalent metal ion cofactors, typically Mg²⁺ or Mn²⁺, to coordinate with ATP and facilitate the phosphoryl-transfer reaction (ohmae2006molecularidentificationand pages 4-5, dijkmans2010thedoublecortingene pages 10-11, unknownauthors2014astudyof pages 153-159).

## Substrate Specificity

In the atlas of substrate specificities for the human serine/threonine kinome by Johnson et al., 2023, the kinase DCLK3 is not explicitly mentioned or listed, and a consensus substrate motif for DCLK3 is not provided (johnson2023anatlasof pages 4-4). Other studies propose a substrate recognition motif for the DCLK family as Hyd-Arg-X-X-Ser*/Thr*-Hyd (dijkmans2010thedoublecortingene pages 10-11). DCLK family kinases phosphorylate substrates that mimic known CamK targets, including myelin basic protein, autocamtide 2, and syntide (dijkmans2010thedoublecortingene pages 10-11).

## Structure

DCLK3 is organized into two tandem N-terminal doublecortin (DCX) domains that are responsible for microtubule binding and a C-terminal serine/threonine kinase domain (dijkmans2010thedoublecortingene pages 10-11, galvan2018thestriatalkinase pages 5-9). The DCX domains are truncated and mediate limited microtubule binding compared to other DCLK family members (unknownauthors2018etudedurôle pages 59-63). AlphaFold 3D structural models reveal that the kinase domain contains key catalytic and regulatory features, including the activation loop, the C-helix involved in positioning ATP for catalysis, and a hydrophobic spine that stabilizes the active conformation of the kinase (dijkmans2010thedoublecortingene pages 10-11, galvan2018thestriatalkinase pages 5-9, unknownauthors2014astudyof pages 204-207). A conserved lysine residue (K543 in mouse DCLK3) within the kinase domain is essential for catalytic activity (galvan2018thestriatalkinase pages 9-11).

## Regulation

DCLK3 activity is regulated by post-translational modifications. Autophosphorylation is a feature of DCLK proteins that affects their affinity for microtubules (dijkmans2010thedoublecortingene pages 10-11). Phosphorylation at Threonine 286 (T286), a conserved residue in the activation loop, is essential for kinase activation and its neuroprotective function (galvan2018thestriatalkinase pages 5-9, dijkmans2010thedoublecortingene pages 10-11). Isoform-specific numbering identifies this threonine as T457 in L-Dclk3 and T289 in S-Dclk3 (unknownauthors2014astudyof pages 161-164). The protein also undergoes proteolytic cleavage by calpain, which produces fragments that retain kinase activity (unknownauthors2014astudyof pages 204-207). Unlike DCLK1 and DCLK2, DCLK3 is not targeted for ubiquitination by the E3 ligase adaptor KLHL15 because it lacks the conserved C-terminal FRY degron motif (song2021thexlinkedintellectual pages 3-4).

## Function

DCLK3 is a neuronal kinase preferentially expressed in the striatum, the dentate gyrus of the hippocampus, and pyramidal neurons in the cerebral cortex (unknownauthors2014astudyof pages 153-159, unknownauthors2025lossofthe pages 3-4). The protein localizes to both the cytoplasm and the nucleus (unknownauthors2014astudyof pages 153-159). DCLK3 interacts with the transcriptional activator adaptor TADA3, a component of the SAGA co-activator complex, linking it to histone acetylation and transcriptional regulation (unknownauthors2025lossofthe pages 20-20, galvan2018thestriatalkinase pages 15-19). It also interacts with zinc finger proteins (unknownauthors2025lossofthe pages 20-20). DCLK3 is implicated in BDNF signaling pathways and is associated with transcription factors such as CREB1 and CLOCK (unknownauthors2025lossofthe pages 20-20). Its biological roles include regulating synaptic plasticity, memory, neuronal survival, and GABAergic neurotransmission (unknownauthors2025lossofthe pages 20-20, unknownauthors2025lossofthe pages 20-21, unknownauthors2025lossofthe pages 3-4).

## Inhibitors

No specific experimental or pharmacological inhibitors of DCLK3 have been reported (galvan2018thestriatalkinase pages 15-19, unknownauthors2014astudyof pages 204-207). A kinase-dead version, created by mutating the essential catalytic lysine residue at position 543 to methionine (K543M), is used as an experimental tool to abolish its function (galvan2018thestriatalkinase pages 9-11, unknownauthors2014astudyof pages 153-159).

## Other Comments

DCLK3 expression is significantly reduced in Huntington’s disease (HD) patients and mouse models; its overexpression provides neuroprotection against mutant huntingtin (mHtt) toxicity and improves motor function in HD models (unknownauthors2014astudyof pages 153-159, galvan2018thestriatalkinase pages 15-19). Genetic polymorphisms and lower brain expression of DCLK3 are associated with an increased risk for psychiatric disorders, including schizophrenia, bipolar disorder, obsessive-compulsive disorder, and major depression (unknownauthors2025lossofthe pages 20-21, unknownauthors2025lossofthe pages 3-4). Loss of DCLK3 in mouse models leads to anxiety-like behavior and memory deficits (unknownauthors2025lossofthe pages 20-20).

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