## Phylogeny

DCLK3 is a member of the doublecortin-like kinase (DCLK) family. Reports differ on its kinome placement: one study assigns it to the CMGC group within the dual-specificity tyrosine-phosphorylation-regulated kinase (DYRK) family (Ohmae et al., 2006), whereas several others place it in the Ca²⁺/calmodulin-dependent protein kinase (CAMK) group, CAMK-like subfamily (Anonymous, 2014; Anonymous, 2018; Venkat et al., 2023). The catalytic domain shares ~56 % amino-acid identity with DCLK1 and ~53 % with DCLK2 (Anonymous, 2018). Outside the kinase region, sequence similarity to DCLK1/2 is limited, making DCLK3 an atypical DCX-family member (Song et al., 2021). Orthologues are present across vertebrates, deuterostomes, protostomes and several invertebrates (Venkat et al., 2023).

## Reaction Catalyzed

ATP + L-seryl/threonyl-[protein] ⇌ ADP + H⁺ + O-phospho-L-seryl/threonyl-[protein] (Dijkmans et al., 2010; Anonymous, 2014; Ohmae et al., 2006).

## Cofactor Requirements

Catalytic activity requires a divalent metal ion cofactor, typically Mg²⁺ or Mn²⁺, that coordinates ATP during phosphoryl transfer (Ohmae et al., 2006; Dijkmans et al., 2010; Anonymous, 2014).

## Substrate Specificity

A dedicated DCLK3 consensus motif has not been reported (Johnson et al., 2023). For the broader DCLK family, a proposed recognition sequence is Hyd-Arg-X-X-Ser*/Thr*-Hyd (Dijkmans et al., 2010). Family members phosphorylate peptide substrates that mimic established CaMK targets such as myelin basic protein, autocamtide-2 and syntide (Dijkmans et al., 2010).

## Structure

The protein contains two N-terminal, truncated doublecortin (DCX) domains that confer limited microtubule binding, followed by a C-terminal Ser/Thr kinase domain (Dijkmans et al., 2010; Galvan et al., 2018). AlphaFold models show conserved catalytic elements, including the C-helix, activation loop and hydrophobic spine (Dijkmans et al., 2010; Galvan et al., 2018; Anonymous, 2014). A lysine essential for catalysis (K543 in mouse DCLK3) lies in the β3 strand of the kinase core (Galvan et al., 2018).

## Regulation

• Autophosphorylation modulates microtubule affinity (Dijkmans et al., 2010).  
• Phosphorylation of the activation-loop threonine (T286; isoform-specific T457 in L-DCLK3 and T289 in S-DCLK3) is required for kinase activation and neuroprotective function (Galvan et al., 2018; Dijkmans et al., 2010; Anonymous, 2014).  
• Calpain cleavage yields fragments that retain catalytic activity (Anonymous, 2014).  
• Unlike DCLK1/2, DCLK3 escapes KLHL15-mediated ubiquitination owing to loss of the C-terminal FRY degron (Song et al., 2021).

## Function

DCLK3 is a neuronal kinase enriched in striatal medium spiny neurons, the dentate gyrus and cortical pyramidal neurons (Anonymous, 2014; Anonymous, 2025a). It localises to both cytoplasm and nucleus (Anonymous, 2014). Reported interaction partners include TADA3 of the SAGA co-activator complex, several zinc-finger proteins, and transcription factors such as CREB1 and CLOCK, linking DCLK3 to histone acetylation and BDNF-responsive transcription (Anonymous, 2025a; Galvan et al., 2018). Biological roles encompass regulation of synaptic plasticity, memory, neuronal survival and GABAergic neurotransmission (Anonymous, 2025a, 2025b).

## Inhibitors

No selective small-molecule inhibitors are known. A kinase-dead mutant (K543M) is widely used as an experimental loss-of-function tool (Galvan et al., 2018; Anonymous, 2014).

## Other Comments

DCLK3 expression is markedly reduced in Huntington’s disease (HD) brains and mouse HD models; restoring DCLK3 levels affords neuroprotection and motor improvement (Anonymous, 2014; Galvan et al., 2018). Lower expression or polymorphisms in DCLK3 are associated with increased risk of schizophrenia, bipolar disorder, obsessive–compulsive disorder and major depression (Anonymous, 2025b; Anonymous, 2025c). Genetic ablation in mice produces anxiety-like behaviour and memory deficits (Anonymous, 2025a).

## 9. References

Anonymous. (2014). A study of striatal markers as disease modifiers in Huntington’s disease (pp. 153–159, 161–164, 204–207).

Anonymous. (2018). Étude du rôle de la protéine kinase DCLK3 dans les mécanismes de neurodégénérescence dans la maladie de Huntington (pp. 59–63).

Anonymous. (2025a). Loss of the neuronal kinase DCLK3 leads to anxiety-like behaviour and memory deficits (pp. 3–4, 20).

Anonymous. (2025b). Loss of the neuronal kinase DCLK3 leads to anxiety-like behaviour and memory deficits (pp. 20–21).

Anonymous. (2025c). Loss of the neuronal kinase DCLK3 leads to anxiety-like behaviour and memory deficits (pp. 20).

Dijkmans, T., van Hooijdonk, L. W. A., Fitzsimons, C., & Vreugdenhil, E. (2010). The doublecortin gene family and disorders of neuronal structure. Central Nervous System Agents in Medicinal Chemistry, 10, 32–46. https://doi.org/10.2174/187152410790780118

Galvan, L., Francelle, L., Gaillard, M., de Longprez, L., Carrillo-de Sauvage, M., Liot, G., … Brouillet, E. (2018). The striatal kinase DCLK3 produces neuroprotection against mutant huntingtin. Brain, 141, 1434–1454. https://doi.org/10.1093/brain/awy057

Johnson, J. L., Yaron, T. M., Huntsman, E. M., Kerelsky, A., Song, J., Regev, A., … Cantley, L. C. (2023). An atlas of substrate specificities for the human serine/threonine kinome. Nature, 613, 759–766. https://doi.org/10.1038/s41586-022-05575-3

Ohmae, S., Takemoto-Kimura, S., Okamura, M., Adachi-Morishima, A., Nonaka, M., Fuse, T., … Bito, H. (2006). Molecular identification and characterization of a family of kinases with homology to Ca²⁺/calmodulin-dependent protein kinases I/IV. Journal of Biological Chemistry, 281, 20427–20439. https://doi.org/10.1074/jbc.M513212200

Song, J., Merrill, R. A., Usachev, A. Y., & Strack, S. (2021). The X-linked intellectual disability gene product and E3 ubiquitin ligase KLHL15 degrades doublecortin proteins to constrain neuronal dendritogenesis. bioRxiv. https://doi.org/10.1101/2020.10.02.324285

Venkat, A., Watterson, G., Byrne, D., O’Boyle, B., Shrestha, S., Gravel, N., … Kannan, N. (2023). Mechanistic and evolutionary insights into isoform-specific ‘supercharging’ in DCLK family kinases. eLife. https://doi.org/10.7554/eLife.87958