## Phylogeny

Class I DYRK kinase within the CMGC branch; closest paralog DYRK1B and related to Class II DYRK2-4 and HIPKs (soundararajan2013structuresofdown pages 1-2, aranda2011dyrkfamilyof pages 11-12).  
Orthologs: Saccharomyces cerevisiae Yak1, Drosophila melanogaster minibrain (mnb), Mus musculus Dyrk1a (widowati2018functionalcharacterizationof pages 9-10, lee2020anovelde pages 8-9).

## Reaction Catalyzed

1. ATP + protein-L-serine/threonine → ADP + protein-L-O-phosphoserine/threonine (soundararajan2013structuresofdown pages 1-2).
2. ATP + protein-L-tyrosine → ADP + protein-L-O-phosphotyrosine (deboever2022theomnipresenceof pages 3-4).

## Cofactor Requirements

Catalysis requires divalent cations; Mn²⁺ is more efficient than Mg²⁺ in vitro (aranda2011dyrkfamilyof pages 11-12, lee2020anovelde pages 8-9).

## Substrate Specificity

Consensus motif R-x(2)-S/T-P with strong selection for Arg at –3/–2 and Pro at +1 (ananthapadmanabhan2023insightsfromthe pages 3-4, widowati2018functionalcharacterizationof pages 9-10).  
Non-canonical sites accepted when a small hydrophobic residue (Ala/Val) occupies +1 (ananthapadmanabhan2023insightsfromthe pages 3-4).  
Intrinsic cis autophosphorylation on Tyr321 within the YxY activation-loop motif is obligatory for catalytic maturation (aranda2011dyrkfamilyof pages 11-12).

## Structure

Modular arrangement: N-terminal DYRK-homology (DH) box required for folding/autophosphorylation; bilobal kinase domain; C-terminal region enriched in His, PEST and nuclear-localisation sequences (ananthapadmanabhan2023insightsfromthe pages 1-2, aranda2011dyrkfamilyof pages 11-12).  
Crystal structures of the catalytic domain (PDB 2WO6, 4YU2) show active DFG-in conformation, phosphorylated Tyr321 in a fully ordered activation loop, aligned hydrophobic spine and correctly positioned αC-helix (soundararajan2013structuresofdown pages 1-2, evers2017structuralanalysisof pages 6-7).  
The His-rich low-complexity tract targets the protein to nuclear speckles (ananthapadmanabhan2023insightsfromthe pages 2-3).

## Regulation

• Autophosphorylation: Tyr321—essential for activation (aranda2011dyrkfamilyof pages 11-12).  
• Additional phosphosites: Ser97 and Ser520 within regulatory regions influence activity/stability (widowati2018functionalcharacterizationof pages 9-10).  
• Ubiquitination: SCF-FBXW7 promotes proteasomal degradation (aranda2011dyrkfamilyof pages 11-12).  
• Proteolysis: Calpain-1 C-terminal cleavage generates a hyperactive fragment (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 18-19).  
• Protein partners: WD40 adaptor WDR68/DCAF7 associates with the N-lobe and modulates localisation; SRC-family kinases act upstream (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 16-18, lee2020anovelde pages 8-9).

## Function

Highly expressed in cerebral cortex, hippocampus and pancreatic islets; present in nucleus and cytoplasm with enrichment in nuclear speckles (deboever2022theomnipresenceof pages 3-4, ananthapadmanabhan2023insightsfromthe pages 1-2).  
Key substrates and pathways:  
– DNA-damage response: phosphorylates RNF169 to restrict TP53BP1 accumulation and promote homologous-recombination repair (ananthapadmanabhan2023insightsfromthe pages 1-2).  
– Transcription: functions as CTD kinase for RNA-polymerase II large subunit POLR2A (deboever2022theomnipresenceof pages 14-15).  
– mRNA splicing: phosphorylates splice factor SRSF6 and modulates alternative exon selection, including tau exon 10 (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 18-19).  
– Cell-cycle and neurogenesis: phosphorylates p27^Kip1 and Cyclin D1 to drive neuronal differentiation and G₀ exit (ananthapadmanabhan2023insightsfromthe pages 15-16).

## Inhibitors

Harmine – nanomolar ATP-competitive inhibitor widely used as chemical probe (aranda2011dyrkfamilyof pages 11-12).  
INDY – indirubin derivative with low-micromolar potency (deboever2022theomnipresenceof pages 14-15).  
Leucettine-41 – sub-micromolar leucettamine analogue, brain-penetrant (nguyen2017dualspecificitytyrosinephosphorylationregulated pages 15-16).

## Other Comments

Gene is located on chromosome 21; dosage increase contributes to cognitive deficits in Down syndrome, whereas haploinsufficiency causes autosomal-dominant intellectual-disability syndrome with microcephaly (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 18-19, widowati2018functionalcharacterizationof pages 9-10).  
Pathogenic missense variants H319Y and R467Q abolish activity; truncations produce loss-of-function phenotypes (lee2020anovelde pages 8-9).  
Hyperactivity promotes tau and APP phosphorylation linked to Alzheimer’s disease; context-dependent roles reported in several cancers and in β-cell regeneration paradigms (deboever2022theomnipresenceof pages 16-18, lindberg2021dualspecificitytyrosinephosphorylationregulated pages 18-19).

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