## Phylogeny

Dual-specificity tyrosine-phosphorylation-regulated kinase 4 (DYRK4) is classified within the CMGC kinase group as a Class II DYRK (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 13-13).  
Orthologs reported: Homo sapiens, Mus musculus, Rattus norvegicus, Gallus gallus, Danio rerio, Drosophila melanogaster and Saccharomyces cerevisiae (boni2020thedyrkfamily pages 23-25, lindberg2021dualspecificitytyrosinephosphorylationregulated pages 9-10).  
Phylogenetically, DYRK4 clusters with yeast Yak1p and Drosophila minibrain within the DYRK lineage (becker1998sequencecharacteristicssubcellular pages 1-1).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr → ADP + protein-O-phospho-L-Ser/Thr (becker1998sequencecharacteristicssubcellular pages 1-1).  
ATP + DYRK4 (activation loop) → ADP + DYRK4-Tyr(P) (autophosphorylation on the YxY motif) (papadopoulos2011splicevariantsof pages 10-11).

## Cofactor Requirements

DYRK family kinases require divalent Mg²⁺/Mn²⁺ for catalysis; DYRK4 has not yet been individually assayed (soundararajan2013structuresofdown pages 8-9, lindberg2021dualspecificitytyrosinephosphorylationregulated pages 9-10).

## Substrate Specificity

The 2023 serine/threonine kinase motif atlas does not report a consensus motif for DYRK4 (kokkorakis2024mirkdyrk1bkinaseinhibitors pages 21-22).  
Peptide-array profiling shows preference for Pro at +1 and tolerance for the absence of Arg at –3/–2; DYRKtide is inefficiently phosphorylated (papadopoulos2011splicevariantsof pages 10-11).  
The 2024 tyrosine kinase specificity atlas lists no DYRK4 data (kokkorakis2024mirkdyrk1bkinaseinhibitors pages 21-22).

## Structure

Domain organisation: N-terminal autophosphorylation accessory (NAPA) domain, DYRK homology (DH) box, bilobal kinase core, variable C-terminal tail (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 2-4).  
AlphaFold model AF-Q9NR20-F1 predicts a canonical kinase fold with intact HRD catalytic loop, DFG motif, ordered αC-helix and continuous hydrophobic spine (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 9-10).  
The activation segment contains a conserved YxY motif essential for autophosphorylation (papadopoulos2011splicevariantsof pages 12-13).  
A splice variant lacking the CLV triplet near helix H destabilises the H/F interface and abolishes catalytic activity (papadopoulos2011splicevariantsof pages 8-9).  
No experimental crystal or NMR structure has been reported.

## Regulation

• Activation-loop autophosphorylation on the second Tyr of the YxY motif is required for full activity (papadopoulos2011splicevariantsof pages 10-11).  
• Class II DYRKs, including DYRK4, undergo PHD1-mediated proline-4-hydroxylation upstream of autophosphorylation (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 9-10).  
• Alternative promoters and splicing create isoforms with or without a classical NLS, defining nuclear versus cytosolic localisation (papadopoulos2011splicevariantsof pages 10-11, aranda2011dyrkfamilyof pages 5-7).  
• Additional serine/threonine phosphorylations of unknown sites generate electrophoretic mobility shifts (papadopoulos2011splicevariantsof pages 10-11).

## Function

Expression: GTEx and Human Protein Atlas show generally low expression with enrichment in specific brain regions and reproductive tissues (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 13-13). In rodents, expression peaks in step 8 spermatids (yoshida2023newinsightsinto pages 13-13).  
Phenotype: Dyrk4-null mice are viable and fertile with no detectable spermatogenic defects, indicating a non-essential role in male reproduction (yoshida2008rolefordyrk pages 3-4).  
Cellular role: Over-expression in neurons increases dendritic branching, implicating DYRK4 in cytoskeletal organisation (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 9-10).  
No validated downstream substrates or stable protein interactors have been reported (schmitt2014developmentofnew pages 32-35).

## Other Comments

The DYRK4 gene maps to chromosome 12q14.2 (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 13-13).  
No selective inhibitors, disease-associated mutations or strong disease links have been documented (kokkorakis2024mirkdyrk1bkinaseinhibitors pages 21-22).

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