## Phylogeny

Dual-specificity tyrosine-phosphorylation-regulated kinase 4 (DYRK4) belongs to the CMGC protein-kinase group and is classified as a class II DYRK. Orthologs have been reported in human, mouse, rat, chicken, zebrafish, fruit-fly and yeast (Boni et al., 2020; Lindberg & Meijer, 2021). Within the DYRK lineage, DYRK4 clusters with yeast Yak1p and Drosophila minibrain (Becker et al., 1998).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr ⇌ ADP + protein-O-phospho-L-Ser/Thr (Becker et al., 1998)  
ATP + DYRK4 (activation loop) ⇌ ADP + DYRK4-Tyr(P) (autophosphorylation on the YxY motif) (Papadopoulos et al., 2011)

## Cofactor Requirements

Catalysis by DYRK-family kinases requires divalent Mg²⁺ or Mn²⁺; DYRK4 itself has not yet been assayed separately (Soundararajan et al., 2013; Lindberg & Meijer, 2021).

## Substrate Specificity

• No consensus motif is reported in the 2023 serine/threonine kinase motif atlas (Kokkorakis et al., 2024).  
• Peptide-array profiling indicates preference for Pro at +1 and tolerance for the absence of Arg at –3/–2; DYRKtide is phosphorylated poorly (Papadopoulos et al., 2011).  
• The 2024 tyrosine-kinase specificity atlas contains no DYRK4 data (Kokkorakis et al., 2024).

## Structure

DYRK4 comprises an N-terminal autophosphorylation accessory (NAPA) domain, a DYRK-homology (DH) box, a bilobal kinase core and a variable C-terminal tail (Lindberg & Meijer, 2021). An AlphaFold model (AF-Q9NR20-F1) predicts a canonical kinase fold with an intact HRD motif, DFG motif, ordered αC-helix and continuous hydrophobic spine (Lindberg & Meijer, 2021). The activation segment harbours the conserved YxY autophosphorylation motif (Papadopoulos et al., 2011). A splice variant lacking the CLV triplet near helix H disrupts the H/F interface and abolishes catalytic activity (Papadopoulos et al., 2011). No experimental crystal or NMR structure is available.

## Regulation

• Autophosphorylation of the second Tyr within the YxY motif is essential for full activity (Papadopoulos et al., 2011).  
• Class II DYRKs, including DYRK4, are hydroxylated on Pro-4 by PHD1 before autophosphorylation (Lindberg & Meijer, 2021).  
• Alternative promoters and splicing generate isoforms with or without a classical nuclear-localisation signal, defining nuclear versus cytosolic localisation (Papadopoulos et al., 2011; Aranda et al., 2011).  
• Additional, unidentified Ser/Thr phosphorylations cause electrophoretic mobility shifts (Papadopoulos et al., 2011).

## Function

Expression: GTEx and the Human Protein Atlas show low overall expression with enrichment in selected brain regions and reproductive tissues; in rodents, expression peaks in step-8 spermatids (Correa-Sáez et al., 2020; Yoshida & Yoshida, 2023).  
Phenotype: Dyrk4-null mice are viable and fertile with no detectable spermatogenic defects, indicating DYRK4 is non-essential for male reproduction (Yoshida, 2008).  
Cellular role: Over-expression in neurons enhances dendritic branching, suggesting a role in cytoskeletal organisation (Lindberg & Meijer, 2021).  
Substrates/interactors: No validated downstream substrates or stable protein interactors have been reported (Schmitt, 2014).

## Other Comments

The DYRK4 gene maps to chromosome 12q14.2. No selective inhibitors, disease-associated mutations or strong disease links have been described (Correa-Sáez et al., 2020; Kokkorakis et al., 2024).

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