Phylogeny  
• CMGC kinase group → DYRK family → class II branch comprising DYRK2, DYRK3 and DYRK4 (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 1-2).  
• Orthologs are present from yeast to mammals; examples include C. elegans MBK-2 and Drosophila dDyrk3, both corresponding to mammalian DYRK2 (deboever2022theomnipresenceof pages 1-3).  
• Additional conservation extends to yeast, plants, unicellular algae and parasites (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 2-4).  
• The catalytic domain shares >90 % sequence identity with DYRK3, reflecting recent divergence within class II DYRKs (tandon2021emergingrolesof pages 1-2).

Reaction Catalyzed  
ATP + protein-L-Ser/Thr ⇌ ADP + protein-O-phospho-L-Ser/Thr (chowdhury2023cmgckinasesin pages 9-10).

Cofactor Requirements  
Activity requires divalent Mg²⁺ or Mn²⁺ ions (becker1998sequencecharacteristicssubcellular pages 10-11).

Substrate Specificity  
• Preferred consensus: R-x(0-2)-S/T-P, with an arginine at −2/−3 and a proline at +1 (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 4-7).  
• Johnson 2023 kinome atlas refines the motif to ‘Rx(x)S/TP’ for DYRK2 substrates (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 13-14).  
• Kinase frequently primes substrates for downstream GSK3β phosphorylation (chowdhury2023cmgckinasesin pages 9-10).  
• Peptide-library profiling indicates reduced tolerance for proline at the +1 position in selected substrates (soundararajan2013structuresofdown pages 1-2).

Structure  
• Domain organisation: N-terminal NAPA1/NAPA2 autophosphorylation accessory regions, nuclear localisation signal (aa 189-191), DYRK-homology (DH) box (aa 200-210), catalytic kinase domain (aa 222-535) containing the YxY activation loop, and a CMGC-specific insert (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 1-2).  
• Solved crystal structures: apo form PDB 3KL2, curcumin-bound PDB 5ZTN, inhibitor complex PDB 6K0J; all reveal the canonical bilobal fold with phosphorylated Tyr382 stabilising the activation loop (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 1-2).  
• Active-site elements: Lys251 (VAIK motif) anchors ATP, HRD-His functions as catalytic base, DFG-Asp coordinates Mg²⁺, and pTyr382 completes the regulatory hydrophobic spine (unknownauthors2022determinationofnew pages 35-38).

Regulation  
• Autophosphorylation on Tyr382 is obligatory for full activity (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 11-13).  
• ATM kinase phosphorylates Thr33 and Ser369 after DNA damage, prevents MDM2-mediated degradation and promotes nuclear retention (unknownauthors2022determinationofnew pages 35-38).  
• MAP3K10 phosphorylates Thr308 and Ser376, linking Hedgehog signalling to DYRK2 (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 4-7).  
• Prolyl-4-hydroxylation at Pro441 enhances subsequent Tyr382 autophosphorylation (lindberg2021dualspecificitytyrosinephosphorylationregulated pages 2-4).  
• Ubiquitination by SIAH2 and by the EDVP (EDD-DDB1-VprBP) E3 complex targets DYRK2 for proteasomal degradation; ATM-dependent phosphorylation counteracts this process (tandon2021emergingrolesof pages 1-2, unknownauthors2022determinationofnew pages 35-38).  
• Cep78 modulates EDVP complex assembly, thereby influencing DYRK2 stability (unknownauthors2022determinationofnew pages 35-38).

Function  
• Highest transcript levels occur in small intestine and heart muscle (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 1-2).  
• Protein is enriched in neuronal tissue and participates in neurodevelopmental processes (santosduran2022rolesofdual pages 7-8).  
• Upstream regulator ATM activates DYRK2 during DNA-damage signalling (chowdhury2023cmgckinasesin pages 9-10).  
• DYRK2 phosphorylates p53 at Ser46, triggering apoptosis (chowdhury2023cmgckinasesin pages 9-10).  
• Phosphorylates NFATC1, limiting its nuclear accumulation and transcriptional output (chowdhury2023cmgckinasesin pages 9-10).  
• Phosphorylates EIF2B5 at Ser544 to facilitate subsequent GSK3β-mediated inhibition (chowdhury2023cmgckinasesin pages 9-10).  
• Targets CRMP2 and CRMP4 to prime GSK3β during neuronal morphogenesis (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 4-7).  
• Inactivates glycogen synthase by phosphorylating GYS1 at Ser641 (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 4-7).  
• Promotes degradation of c-Myc, c-Jun and GLI2 via sequential GSK3β phosphorylation (chowdhury2023cmgckinasesin pages 9-10).  
• Acts as scaffold for the EDVP E3 ligase, directing proteasomal turnover of substrates such as TERT (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 14-15).  
• Modulates 26S proteasome activity to maintain proteostasis (tandon2021emergingrolesof pages 1-2).  
• Controls G2/M progression and spindle dynamics during mitosis (unknownauthors2022determinationofnew pages 35-38).

Inhibitors  
• LDN-192960: ATP-competitive, IC₅₀ ≈ 13 nM against DYRK2 (tandon2021emergingrolesof pages 11-12).  
• Harmine: pan-DYRK inhibitor, IC₅₀ ≈ 0.8 µM for DYRK2 (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 1-2).  
• Curcumin: non-selective inhibitor, nanomolar potency; co-crystallised in PDB 5ZTN (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 1-2).  
• AZ191, 7BIO and ID-8 exhibit micromolar inhibition in biochemical assays (correasaez2020updatingdualspecificitytyrosinephosphorylationregulated pages 11-13).

Other Comments  
• Reduced DYRK2 expression is associated with poor prognosis in colorectal, bladder and ovarian cancers, whereas over-expression promotes progression in certain breast and lung carcinomas (boni2020thedyrkfamily pages 23-25).  
• Cancer-specific mutations at the EDVP-interaction surface alter substrate selectivity, explaining context-dependent tumour-suppressor versus oncogenic roles (tandon2021emergingrolesof pages 12-13).

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