Protein: Cyclin‐dependent kinase 12 (CDK12, CRK7)   UniProt: Q9NYV4

================================================================ PHYLOGENY • CMGC group ‒ transcriptional CDK / Ctk1 family assignment established by kinome analyses following Manning et al. 2002 (emadi2020cdk12apotential pages 6-7, lui2018cdk12anemerging pages 6-8).  
• Paralog: CDK13 (≈89–92 % identity in kinase domain) generated by a vertebrate-specific duplication (chila2016roleandtherapeutic pages 1-5, greenleaf2019humancdk12and pages 9-13).  
• Orthologs: Homo sapiens CDK12; Mus musculus Cdk12; Danio rerio cdk12; Drosophila melanogaster CG7597; Caenorhabditis elegans B0285; Saccharomyces cerevisiae Ctk1; Schizosaccharomyces pombe Lsk1 (greenleaf2019humancdk12and pages 32-35, bosken2014thestructureand pages 1-2, chila2016roleandtherapeutic pages 1-5).  
• More distant but functionally related CTD kinase: CDK9, which acts earlier during transcription (chila2016roleandtherapeutic pages 1-5).

================================================================ REACTION CATALYZED ATP + [protein]-Ser/Thr → ADP + [protein]-O-phospho-Ser/Thr + H⁺ (bosken2014thestructureand pages 1-2).

================================================================ COFACTOR REQUIREMENTS • Requires Mg²⁺ for phosphotransfer, as shown in crystal structures of CDK12·Cyclin K bound to ATP analogues (bosken2014thestructureand pages 1-2).

================================================================ SUBSTRATE SPECIFICITY • Primary target: heptad repeat Y₁S₂P₃T₄S₅P₆S₇ of POLR2A CTD. CDK12 preferentially phosphorylates Ser5 or Ser2 only when Ser7 in the same repeat is pre-phosphorylated; Lys7 substitution abrogates recognition (bosken2014thestructureand pages 1-2).  
• Sequence bias: overall preference for Ser/Thr followed by Pro at +1, consistent with Ser/Thr-Pro motif usage reported for CDK12 substrates (emadi2020cdk12apotential pages 6-7).  
• Documented non-CTD substrates: 4E-BP1 (Thr37/Thr46/Ser65/Thr70), Cyclin E1 (Ser366), nuclear pore components TPR and NUP214 (emadi2020cdk12apotential pages 9-13, lui2018cdk12anemerging pages 3-4).

================================================================ STRUCTURE • Domain organisation  
– N-terminal RS-rich region: splicing factor interaction & nuclear speckle targeting (lui2018cdk12anemerging pages 1-3).  
– Central bilobal kinase domain (residues ≈ 719-984) with signature PITAIRE αC helix and DFG motif (choi2020geneexpressionregulation pages 1-2).  
– C-terminal extension containing helix αK, HE motif, polybasic patch 1045KKRRRQR and reactive Cys1039 (bosken2014thestructureand pages 1-2, choi2020geneexpressionregulation pages 8-9, emadi2020cdk12apotential pages 6-7).  
• 3-D information  
– Crystal structure of human CDK12·Cyclin K (PDB 6B3E): helix αK bridges N- and C-lobes and contacts ATP ribose, enhancing nucleotide affinity (bosken2014thestructureand pages 1-2, emadi2020cdk12apotential pages 4-6).  
– Activation loop contains Thr893; phosphorylation locks the DFG-in active conformation (emadi2020cdk12apotential pages 1-3).  
– Hydrophobic spine completed upon Cyclin K binding; Cys1039 forms an auxiliary pocket exploited by covalent inhibitors (choi2020geneexpressionregulation pages 8-9).  
– Full-length AlphaFold model AF-Q9NYV4-F1 corroborates flexible N- and C-terminal arms (emadi2020cdk12apotential pages 7-8).

================================================================ REGULATION • Phosphorylation  
– Thr893 in the T-loop is phosphorylated by the CDK-activating kinase (CDK7/Cyclin H/MAT1), enabling full catalytic activity (emadi2020cdk12apotential pages 1-3).  
– Autophosphorylation events are modulated by CDK7 and CDK9, integrating transcription-cycle cues (yamakawa2024phosphorylationdynamicsand pages 8-8).  
• Protein–protein interaction  
– Stable binding to Cyclin K is obligatory for folding, activity and protein stability; Cyclin K depletion destabilises CDK12 (greenleaf2019humancdk12and pages 9-13).  
• Allosteric activation  
– Pre-existing Ser7 phosphorylation on CTD heptads markedly increases catalytic efficiency (bosken2014thestructureand pages 1-2).  
• No verified ubiquitination or SUMOylation sites reported in current literature (greenleaf2019humancdk12and pages 32-35).

================================================================ FUNCTION • Expression pattern  
– Ubiquitous, with higher mRNA levels in ovary, testis, bone marrow, spleen and lymph nodes; expression is relatively constant through the cell cycle yet elevated in proliferative and cancer cells (lui2018cdk12anemerging pages 1-3, choi2020geneexpressionregulation pages 1-2).  
• Biological roles  
– Transcription elongation: phosphorylates RNAP II CTD Ser2/Ser5, coordinating co-transcriptional splicing, 3′-end processing and termination, especially on long, exon-rich genes (paculova2017theemergingroles pages 1-2, greenleaf2019humancdk12and pages 22-25).  
– DNA damage response: maintains homologous recombination by sustaining transcription of ATM, ATR, FANCI, RAD51C, MDC1 and other DDR genes; suppresses intronic polyadenylation within these transcripts (chila2016roleandtherapeutic pages 7-10, emadi2020cdk12apotential pages 7-8).  
– RNA processing: associates with U2/U5 snRNPs, exon-junction complex, 5′-cap and 3′-end formation factors (greenleaf2019humancdk12and pages 22-25).  
– DNA replication: phosphorylates Cyclin E1 Ser366 to control pre-replicative complex assembly (lui2018cdk12anemerging pages 3-4).  
– Translation control: phosphorylates 4E-BP1, linking transcriptional stress to mTORC1-regulated translation (emadi2020cdk12apotential pages 9-13).  
• Key interactors  
– Upstream: CDK7/Cyclin H (CAK), CDK9; Ser7-phosphorylated RNAP II CTD.  
– Downstream: SETD2 (H3K36me3 writer), SRSF1, 4E-BP1, Cyclin E1, DDR gene transcripts (greenleaf2019humancdk12and pages 13-16, emadi2020cdk12apotential pages 9-13).

================================================================ INHIBITORS • THZ531 – covalent inhibitor targeting Cys1039; IC₅₀ ≈ 0.1 µM; highly selective for CDK12/13 (greenleaf2019humancdk12and pages 19-22, choi2020geneexpressionregulation pages 8-9).  
• SR-4835 – ATP-competitive hinge binder with dual CDK12/13 potency (choi2020geneexpressionregulation pages 8-9).  
• Dinaciclib – multi-CDK inhibitor; IC₅₀ for CDK12 ≈ 0.05 µM via hinge interactions at Met816 (emadi2020cdk12apotential pages 6-7).  
• Flavopiridol – inhibits CDK12 with nanomolar potency but is ~10-fold more potent against CDK9 (bosken2014thestructureand pages 1-2).  
• THZ1 – covalent CDK7 inhibitor that also engages CDK12 at higher concentrations (chila2016roleandtherapeutic pages 7-10).  
• E9 – hybrid scaffold overcoming resistance to covalent compounds (emadi2020cdk12apotential pages 6-7).  
• CR8 – molecular glue that depletes Cyclin K, indirectly suppressing CDK12 activity (yamakawa2024phosphorylationdynamicsand pages 8-8).

================================================================ OTHER COMMENTS • Cancer-associated alterations  
– Loss-of-function mutations (frameshift, nonsense, catalytic-site missense) concentrate in the kinase domain; biallelic inactivation occurs in ≈3 % high-grade serous ovarian and subsets of metastatic castration-resistant prostate cancers (chila2016roleandtherapeutic pages 7-10, greenleaf2019humancdk12and pages 22-25).  
– CDK12-deficient tumors display a distinctive tandem-duplication genomic instability pattern (greenleaf2019humancdk12and pages 22-25).  
– Such defects confer hypersensitivity to platinum chemotherapy, PARP and CHK1 inhibitors (emadi2020cdk12apotential pages 7-8).  
– In HER2-amplified breast cancer, CDK12 is frequently co-amplified and promotes invasion via alternative last-exon splicing of DNAJB6 (lui2018cdk12anemerging pages 4-6).  
• Synthetic-lethality contexts: MYC-driven tumors and EWS/FLI fusion-positive Ewing sarcoma exhibit dependency on CDK12 activity (emadi2020cdk12apotential pages 4-6).

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