## Phylogeny

Based on phylogenetic analyses of the human kinome, CDK17 is classified within the CMGC group of protein kinases, which includes cyclin-dependent kinases (CDKs), mitogen-activated protein kinases (MAPKs), and glycogen synthase kinases (GSKs) (mikolcevic2012orphankinasesturn pages 9-10, karimbayli2024insightsintothe pages 15-17, malumbres2009cyclindependentkinasesa pages 1-2). Within the CMGC group, CDK17 is a member of the CDK family, specifically belonging to the PCTAIRE subfamily along with CDK16 and CDK18 (karimbayli2024insightsintothe pages 17-17, mikolcevic2012orphankinasesturn pages 1-2). This subfamily is part of the atypical CDKs, which are distinct from cell cycle-regulatory and transcriptional CDKs (unknownauthors2022dissectingtherole pages 16-19, karimbayli2024insightsintothe pages 1-2). The PCTAIRE kinases are phylogenetically related to CDK5 (58% sequence similarity) and the PFTAIRE kinases CDK14 and CDK15 (42–46% similarity) (karimbayli2024insightsintothe pages 1-2). The PCTAIRE kinase subgroup is highly conserved in eumetazoans (mikolcevic2012orphankinasesturn pages 9-10).

## Reaction Catalyzed

CDK17 is a serine/threonine kinase that catalyzes the phosphorylation of serine and threonine residues on substrate proteins (unknownauthors2021caracterizacióndecdk1418 pages 29-32, amrhein2022discoveryof3amino1hpyrazolebased pages 1-3). It has demonstrated kinase activity towards substrates like Histone H1 (unknownauthors2022dissectingtherole pages 19-22).

## Cofactor Requirements

Like other CDKs, the catalytic activity of CDK17 requires divalent cations, such as Mg²⁺ or Mn²⁺, to coordinate ATP binding (amrhein2022discoveryof3amino1hpyrazolebased pages 1-3, dixonclarke2017structureandinhibitor pages 1-3, karimbayli2024insightsintothe pages 18-19).

## Substrate Specificity

The consensus phosphorylation motif for CDK17 remains uncharacterized, as it was not included in the substrate specificity profiling data from Johnson et al. (2023, Nature) (karimbayli2024insightsintothe pages 17-17, mikolcevic2012orphankinasesturn pages 1-2, unknownauthors2021caracterizacióndecdk1418 pages 114-118, unknownauthors2022dissectingtherole pages 16-19).

## Structure

CDK17 is a protein of approximately 500 amino acids composed of a conserved catalytic kinase domain flanked by N- and C-terminal extensions that are critical for its regulation (mikolcevic2012orphankinasesturn pages 1-2, unknownauthors2021caracterizacióndecdk1418 pages 29-32, karimbayli2024insightsintothe pages 1-2). The kinase domain features conserved motifs essential for catalysis, such as HRD and DFG, and a distinct PCTAIRE motif in its cyclin-binding region (karimbayli2024insightsintothe pages 1-2, unknownauthors2021caracterizacióndecdk1418 pages 29-32). The N-terminal extension contains a conserved PKA binding motif (R-R-X-S) (unknownauthors2022dissectingtherole pages 16-19, unknownauthors2022dissectingtherole pages 19-22). No experimentally resolved 3D structure for full-length CDK17 is available; however, structural models have been generated by AlphaFold (karimbayli2024insightsintothe pages 17-17, unknownauthors2021caracterizacióndecdk1418 pages 29-32). The only experimentally resolved structure for a PCTAIRE kinase is a partial structure of CDK16 (PDB ID: 5G6V), which lacks the N- and C-terminal extensions (unknownauthors2022dissectingtherole pages 19-22).

## Regulation

CDK17 activity is regulated by phosphorylation and interaction with cyclin partners (karimbayli2024insightsintothe pages 17-17). Unlike canonical CDKs that have a threonine at the activation phosphorylation site in the T-loop, CDK17 has a serine, suggesting a distinct regulatory mechanism (unknownauthors2022dissectingtherole pages 16-19). Cyclin Y has been identified as a potential activating partner, a mechanism suggested by studies on its Drosophila ortholog and the related kinase CDK16 (unknownauthors2021caracterizacióndecdk1418 pages 29-32, karimbayli2024insightsintothe pages 17-17). The kinase possesses potential phosphorylation sites for PKA, including the conserved R-R-X-S motif (unknownauthors2022dissectingtherole pages 16-19, unknownauthors2021caracterizacióndecdk1418 pages 29-32). CDK17 also interacts with proteins such as Cables and 14-3-3 proteins, which may modulate its activity and localization (karimbayli2024insightsintothe pages 17-17, unknownauthors2021caracterizacióndecdk1418 pages 114-118). The kinase activity of CDK17 immunoprecipitated from rat brain diminishes under high-salt conditions (karimbayli2024insightsintothe pages 7-9).

## Function

CDK17 is predominantly expressed in the brain, particularly in terminally differentiated, postmitotic neurons of the hippocampus and olfactory bulbs, where it is involved in neuronal differentiation and function (karimbayli2024insightsintothe pages 17-17, mikolcevic2012orphankinasesturn pages 1-2, karimbayli2024insightsintothe pages 7-9). Its subcellular localization is primarily cytoplasmic and membranous, with mitochondrial localization also reported in COS7 cells (karimbayli2024insightsintothe pages 7-9, unknownauthors2021caracterizacióndecdk1418 pages 32-35). Known interacting partners include Cables, EGFR, the endocytic adaptor proteins EPS15 and AP2A2, and the AP2 complex subunit AP2B1 (karimbayli2024insightsintothe pages 17-17, unknownauthors2022dissectingtherole pages 54-57). In epithelial ovarian cancer cells under cisplatin-induced stress, CDK17 phosphorylates EGFR to regulate its non-degradative endocytosis and recycling, which sustains EGFR signaling (unknownauthors2022dissectingtherole pages 54-57). Multi-omics analysis associates CDK17 activation with the induction of epithelial-mesenchymal transition (EMT) and suppression of the cell cycle (chen2022integrativemultiomicsanalysis pages 5-7). Genome-wide association studies have linked CDK17 to glycerophospholipid metabolism pathways (karimbayli2024insightsintothe pages 7-9).

## Inhibitors

Selective inhibitors for CDK17 are not yet well established (karimbayli2024insightsintothe pages 17-17). Small molecule inhibitors targeting the broader PCTAIRE family have been developed, such as 3-amino-1H-pyrazole-based compounds (amrhein2022discoveryof3amino1hpyrazolebased pages 1-3). Some small molecules in the Pharos database have a measured dissociation constant (Kd) of 13 nM for CDK17 (axtman2019cdk16thepick pages 1-1).

## Other Comments

CDK17 has been implicated in neurological disorders and cancer (karimbayli2024insightsintothe pages 17-17). Its expression is elevated in Alzheimer’s disease models and in patients with Alzheimer’s disease and Mild Cognitive Impairment, where it may promote neurodegeneration (amrhein2022discoveryof3amino1hpyrazolebased pages 1-3, karimbayli2024insightsintothe pages 7-9). There is also evidence suggesting its involvement in the phosphorylation of tau, which is relevant to Alzheimer’s disease pathogenesis (unknownauthors2021caracterizacióndecdk1418 pages 114-118). In cancer, CDK17 is overexpressed in approximately 45% of tumors, with the highest expression observed in Low-Grade Glioma (LGG) (karimbayli2024insightsintothe pages 10-13). Downregulation of CDK17 has been associated with a poorer prognosis in glioma (axtman2019cdk16thepick pages 1-1). Missense mutations at residues Arg474 and Arg504 have been reported in a few patients, and CDK17 mutations are significantly enriched in uterine endometrial carcinomas (UCEC) (karimbayli2024insightsintothe pages 10-13).

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