1. Phylogeny  
   CDK11A (also referred to as PITSLREB, CDC2L2, and CDC2L3) is a serine/threonine kinase that belongs to the cyclin‐dependent kinase (CDK) family, a group originally defined by their fundamental roles in cell cycle control, transcription, and RNA processing. According to systematic kinome analyses and evolutionary studies (malumbres2009cyclindependentkinasesa pages 1-2), CDK11A is phylogenetically grouped within the transcription‐related CDKs, which include other members such as CDK7, CDK8, CDK9, CDK12, and CDK13. CDK11A is encoded by the CDC2L2 gene and exists as one of two closely related isoforms produced by a gene duplication event; its paralog CDK11B arises from CDC2L1. These kinases display a high degree of sequence conservation in their catalytic domains, with CDK11A exhibiting the distinctive PITSLRE signature that differentiates it from classical CDKs exemplified by CDK1 and CDK2. Orthologs of CDK11A have been found across a broad spectrum of mammals, and the conservation of both its primary sequence and domain architecture suggests that the functional role in RNA splicing and cell cycle regulation is evolutionarily ancient and critical (ahmed2019cdk11lossinduces pages 17-19, malumbres2009cyclindependentkinasesa pages 1-2). Comparative analyses indicate that the overall domain organization—including regulatory regions such as multiple nuclear localization signals and cyclin‐binding motifs—is maintained in CDK11A orthologs from higher eukaryotic organisms. This kinase forms part of an evolutionarily conserved signaling module that appears to have originated in early eukaryotes, as deduced from studies of the kinase complement in the human genome (malumbres2009cyclindependentkinasesa pages 1-2). Furthermore, its close relationship with kinases that modulate transcription and RNA processing reinforces the concept of an ancestral kinase network that has diversified to support both cell cycle events and post‐transcriptional gene regulation (mikolcevic2012orphankinasesturn pages 1-2, peyressatre2015targetingcyclindependentkinases pages 6-8).
2. Reaction Catalyzed  
   CDK11A functions as a serine/threonine kinase that catalyzes the phosphorylation of its protein substrates by transferring a phosphate group from adenosine triphosphate (ATP) to specific hydroxyl groups on serine or threonine residues. The overall reaction can be represented as:  
     ATP + [protein]–(L-serine or L-threonine) → ADP + [protein]–(L-serine/threonine)-phosphate + H⁺  
   This phosphorylation reaction constitutes a classical post-translational modification that alters the activity, conformation, and protein–protein interaction profile of its substrates. The substrates of CDK11A include proteins involved in RNA splicing and transcription, and it functions through this mechanism to regulate processes critical for cell cycle progression and gene expression (malumbres2009cyclindependentkinasesa pages 1-2, duster2021biochemicalcharacterizationofa pages 23-28, ahmed2019cdk11lossinduces pages 19-20).
3. Cofactor Requirements  
   The kinase activity of CDK11A is dependent upon the presence of divalent cations, a requirement common to almost all serine/threonine protein kinases. In particular, Mg²⁺ serves as a necessary cofactor by coordinating with ATP to stabilize the negative charges of its phosphate groups and facilitating the transfer of the γ-phosphoryl moiety to the substrate. This cofactor requirement ensures that the catalytic domain of CDK11A adopts the proper conformation for efficient phosphoryl transfer and subsequent regulation of downstream substrates (duster2021biochemicalcharacterizationofa pages 23-28, malumbres2009cyclindependentkinasesa pages 1-2, peyressatre2015targetingcyclindependentkinases pages 6-8).
4. Substrate Specificity  
   CDK11A exhibits substrate specificity for serine/threonine residues that are often embedded within regulatory proteins associated with RNA processing and transcription. Although a precisely defined consensus substrate motif for CDK11A has not been unequivocally established, experimental evidence indicates that it phosphorylates proteins involved in pre-mRNA splicing and transcriptional regulation. Among its known substrates is the splicing factor SFRS7, whose phosphorylation by the p110 isoform of CDK11A influences spliceosomal function (ahmed2019cdk11lossinduces pages 17-19). Additionally, CDK11A has been shown to target other splicing regulatory factors such as RNPS1 and 9G8 – proteins that operate within nuclear speckles and contribute to mRNA maturation – and has been implicated in the phosphorylation of histone H3 during chromatin reorganization events in mitosis (kahle2006theregulationanda pages 39-43, ahmed2019cdk11lossinduces pages 19-20, pellarin2025cyclindependentproteinkinases pages 13-14). The substrate recognition appears to be modulated by its association with cyclin partners, notably cyclin L isoforms, which may influence the binding orientation and local concentration of substrates near the kinase active site (pellarin2025cyclindependentproteinkinases pages 52-52, peyressatre2015targetingcyclindependentkinases pages 6-8). In aggregate, CDK11A preferentially phosphorylates serine/threonine sites in proteins that are critical for the regulation of both RNA splicing and aspects of cell cycle progression.
5. Structure  
   The structural organization of CDK11A is modular, reflecting a combination of well‐conserved kinase domains and regulatory extensions unique to its functional specialization. The N-terminal portion of CDK11A contains multiple nuclear localization signals (NLS) and a consensus binding motif for 14-3-3 proteins. These elements are instrumental in directing CDK11A to the nucleus and modulating its subcellular distribution (kahle2006theregulationand pages 35-39, pellarin2025cyclindependentproteinkinases pages 12-13). Adjacent to the N-terminal regulatory region lies an arginine/glutamate-rich (RE) domain that contributes to protein–protein interactions, particularly with splicing factors, while a downstream poly-glutamic acid (poly-E) domain is thought to mediate interactions with cytoskeletal components and facilitate retention within the nuclear speckles (kahle2006theregulationanda pages 35-39). The central and most critical portion of the protein is the C-terminal catalytic kinase domain, which exhibits a bi-lobed architecture typical of protein kinases. This domain includes the conserved ATP-binding pocket, an activation loop that undergoes phosphorylation for full activation, and a C-helix whose proper positioning is essential for catalytic efficiency (malumbres2009cyclindependentkinasesa pages 1-2, pellarin2025cyclindependentproteinkinases pages 2-4). A distinguishing feature of CDK11A is the presence of the PITSLRE motif within its kinase domain—a variant of the conventional PSTAIRE helix found in many CDKs. This motif is critical for its catalytic function and sets it apart from other kinases such as CDK1 and CDK2. In addition, alternative splicing and internal ribosome entry mechanisms give rise to multiple isoforms of CDK11A. The full-length p110 isoform contains all regulatory regions and the intact kinase domain, whereas the p58 isoform, produced via IRES-dependent translation during the G2/M phase, lacks portions of the N-terminal regulatory region. Such structural differences contribute to the isoform-specific substrate preferences and regulatory interactions observed for CDK11A (ahmed2019cdk11lossinduces pages 17-19, kahle2006theregulationand pages 43-48, wang2023cdk11requiresa pages 17-17, pellarin2025cyclindependentproteinkinases pages 12-13).
6. Regulation  
   CDK11A is subject to multifaceted regulatory mechanisms that control its activity in accordance with cellular needs. Post-translational modifications, particularly phosphorylation, are central to its regulation. Phosphorylation of residues within the activation loop of the kinase domain is essential for its catalytic function, aligning CDK11A with the general regulatory paradigms of CDKs (malumbres2009cyclindependentkinasesa pages 1-2, peyressatre2015targetingcyclindependentkinases pages 6-8). Casein kinase 2 (CK2) has been implicated in phosphorylating CDK11A and modulating its ability to interact with key substrates such as the carboxy-terminal domain of RNA polymerase II (ahmed2019cdk11lossinduces pages 19-20, syahirah2022acuriouscase pages 15-16). A further layer of regulation is provided by cyclin binding. CDK11A forms active complexes with cyclin L isoforms, and this association is required for its full activation; cyclin binding not only induces conformational changes in the catalytic domain but also impacts substrate recognition by directing the kinase to relevant protein partners involved in RNA processing (pellarin2025cyclindependentproteinkinases pages 52-52, peyressatre2015targetingcyclindependentkinases pages 6-8). Regulation is also context-dependent, as the p58 isoform is produced exclusively during the G2/M phase via an internal ribosome entry site (IRES) mechanism, and this isoform exhibits distinct regulatory behavior that aligns its function with mitotic events such as centrosome maturation and spindle assembly (kahle2006theregulationand pages 53-57, wang2023cdk11requiresa pages 17-17). In apoptotic contexts, caspase-mediated cleavage of the full-length p110 isoform generates the p46 isoform, which retains kinase activity that contributes to apoptotic signaling cascades (ahmed2019cdk11lossinduces pages 17-19, peyressatre2015targetingcyclindependentkinases pages 6-8). Additionally, binding of 14-3-3 proteins through a conserved motif in the N-terminal region further influences the subcellular distribution and stability of CDK11A, thereby modulating its overall activity in both nuclear and cytoplasmic compartments.
7. Function  
   The multifunctionality of CDK11A is reflected in its involvement in several critical cellular processes. Primarily, the full-length p110 isoform of CDK11A is associated with the regulation of transcription and pre-mRNA splicing. It is proposed to phosphorylate splicing factors such as SFRS7, a modification that is essential for proper spliceosome function and subsequent mRNA maturation (ahmed2019cdk11lossinduces pages 17-19, pellarin2025cyclindependentproteinkinases pages 22-23). In addition, CDK11A interacts with components of the RNA polymerase II complex and is believed to contribute to the phosphorylation of its C-terminal domain—a modification critical for transcription elongation and RNA processing. Beyond its role in RNA metabolism, CDK11A has been implicated in the regulation of cell cycle progression. The p58 isoform, in particular, is expressed during the G2/M transition and functions as a negative regulator of normal cell cycle progression by modulating processes that include centrosome maturation, spindle formation, and sister chromatid cohesion (malumbres2009cyclindependentkinasesa pages 1-2, thiel2022theroleof pages 4-5). This regulatory capacity ensures that cell division proceeds with high fidelity and that aberrant progression can be curtailed. Furthermore, during apoptotic signaling, the cleavage of the p110 isoform by caspases results in the formation of the p46 isoform, which retains kinase activity essential for propagating signals leading to programmed cell death (ahmed2019cdk11lossinduces pages 19-20, peyressatre2015targetingcyclindependentkinases pages 6-8). Expression studies indicate that CDK11A is widely expressed across various cell types and tissues, underlining its role in both general cellular homeostasis and specialized functions. In the context of cancer, dysregulation of CDK11A has been observed in several malignancies including melanoma, breast cancer, and esophageal carcinoma, where altered kinase activity correlates with defects in transcriptional regulation, splicing, and cell cycle checkpoints (ahmed2019cdk11lossinduces pages 19-20, syahirah2022acuriouscase pages 15-16, thiel2022theroleof pages 12-14). These observations have led to investigations into CDK11A as a potential molecular target for therapeutic intervention in oncology.
8. Other Comments  
   CDK11A is known by several alternative names, including PITSLREB, CDC2L2, and CDC2L3, reflecting its complex nomenclature and the historical evolution of its identification. Although several inhibitors targeting cyclin-dependent kinases have advanced into clinical and preclinical studies, selective inhibitors that specifically target CDK11A have not yet been fully developed. Broad-spectrum CDK inhibitors are under investigation, but the design of molecules with high selectivity against CDK11A remains an area of active research (wang2023cdk11requiresa pages 17-17, peyressatre2015targetingcyclindependentkinases pages 6-8). In addition, the differential roles of its isoforms—where the p110 variant is primarily engaged in transcription and pre-mRNA splicing and the p58 variant functions in cell cycle regulation—highlight the importance of isoform-specific strategies when considering therapeutic targeting. CDK11A has been associated with several disease contexts, most notably in various cancers where its dysregulated activity contributes to uncontrolled cell proliferation, altered RNA processing, and resistance to apoptotic cues (ahmed2019cdk11lossinduces pages 19-20, thiel2022theroleof pages 12-14, pellarin2025cyclindependentproteinkinases pages 22-23). No known selective small molecule inhibitors against CDK11A are currently approved for clinical use, and the inhibitor landscape remains largely focused on broader CDK family members. These characteristics underscore its potential value as a therapeutic target and biomarker, particularly in tumors where its expression is aberrantly high.
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