1. Phylogeny  
   Cyclin-dependent kinase 15 (CDK15), also known as PFTK2 or ALS2CR7, belongs to the serine/threonine-protein kinase family within the CMGC branch of the human kinome. It is classified in the PFTAIRE subfamily, a group of atypical or postmitotic CDKs that share a conserved kinase domain and a distinct PFTAIRE motif in place of the classical PSTAIRE sequence found in many mitotic CDKs (malumbres2009cyclindependentkinasesa pages 1-2, alonso2021caracterizacióndecdk1418 pages 29-32, wood2018structuralinsightsinto pages 2-3). Orthologs of CDK15 are present in other mammalian species, consistent with the idea that its catalytic domain and regulatory features have been conserved since early eukaryotic evolution. Evolutionary studies position CDK15 alongside related kinases such as CDK14, CDK16, CDK17, and CDK18, which collectively form a distinct clade within the CDK family (malumbres2009cyclindependentkinasesa pages 1-2, kamkar2015pftaire1(cyclindependent pages 24-29).
2. Reaction Catalyzed  
   CDK15 catalyzes a phosphorylation reaction that transfers a phosphate group from ATP to a serine or threonine residue within substrate proteins. The generalized reaction is as follows: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(L-serine/threonine)-phosphate + H⁺. In the case of CDK15, one well-documented substrate is BIRC5 (Survivin), which is phosphorylated at threonine 34. This phosphorylation event contributes to the antiapoptotic function of CDK15 by counteracting apoptosis induced by TRAIL/TNFSF10 (ong2022ubiquitylationandphosphorylation pages 107-150).
3. Cofactor Requirements  
   The catalytic activity of CDK15 depends on the presence of divalent metal ions as cofactors. Consistent with other serine/threonine kinases, CDK15 requires Mg²⁺ for efficient ATP binding and phosphate transfer during the phosphorylation reaction (ong2022ubiquitylationandphosphorylation pages 107-150).
4. Substrate Specificity  
   As a serine/threonine-protein kinase, CDK15 is expected to phosphorylate substrates that present a serine or threonine residue followed by a proline residue, which is the minimal consensus motif (S/T-P) observed in many CDK substrates. Available data indicate that approximately 53% of CDK substrates contain phospho-SP or phospho-TP motifs, with some substrates additionally conforming to an extended motif such as (S/T)-P-X-(K/R) (errico2010identificationofsubstrates pages 15-16, amrhein2022discoveryof3amino1hpyrazolebased pages 1-3). Although direct substrate identification for CDK15 has been limited, its placement within the CDK family and the similarity of its catalytic domain to those of well‐characterized CDKs suggest that its substrate specificity aligns with these consensus sequences.
5. Structure  
   CDK15 contains a single, canonical kinase domain that spans amino acids 102 to 387 and is flanked by distinct N-terminal (residues 1–101) and C-terminal (residues 388–429) regions. The central kinase domain contains conserved catalytic motifs such as the DFG sequence, which is involved in Mg²⁺ coordination and ATP binding, and the HRD motif, which contributes to phosphate transfer. Furthermore, CDK15 exhibits a modified cyclin-binding motif known as PFTAIRE, setting it apart from classic CDKs that possess the PSTAIRE motif (ong2022ubiquitylationandphosphorylation pages 107-150, kamkar2015pftaire1(cyclindependent pages 29-34). A notable feature within the N-terminal segment is a canonical nuclear localization sequence (NLS) located between amino acids 67 and 73 (sequence KFKSKRP), which is critical for its nuclear import during interphase (ong2022ubiquitylationandphosphorylation pages 150-155). Although no experimentally resolved 3D structure specific to CDK15 currently exists, computational models and homology-based predictions suggest that its overall fold conforms to the conserved bilobal architecture characteristic of the CDK family. This organization includes an N-terminal lobe that typically harbors a glycine-rich loop and an αC-helix, and a larger C-terminal lobe that contains the activation loop and other elements essential for substrate binding and catalysis (wood2018structuralinsightsinto pages 9-10, kamkar2015pftaire1(cyclindependent pages 29-34).
6. Regulation  
   The activity of CDK15 is regulated via several mechanisms that are common among CDKs. Although full activation generally requires binding to a cyclin partner, the specific cyclin that associates with CDK15 has not been definitively identified. CDK15 interacts with several key mitotic regulators, including Mad2, Plk1, Aurora Kinase B, and Survivin, indicating that protein–protein interactions play a significant role in its regulatory network (ong2022ubiquitylationandphosphorylation pages 107-150). Binding to Plk1, for example, occurs through the kinase domain of Plk1 rather than its polo box domain, which suggests a specific regulatory interface distinct from that observed in other CDKs (ong2022ubiquitylationandphosphorylation pages 107-150). Additionally, nuclear localization is a regulated aspect of CDK15 function; the NLS between residues 67 and 73 ensures proper subcellular localization, likely influencing its access to substrates and regulatory proteins (ong2022ubiquitylationandphosphorylation pages 150-155). Post-translational modifications, particularly phosphorylation events, are expected to be critical for modulating CDK15 activity. While activation loop phosphorylation and potential autophosphorylation events have been noted in other CDKs, detailed mapping of such regulatory sites on CDK15 remains to be elucidated (kamkar2015pftaire1(cyclindependent pages 29-34, ong2022ubiquitylationandphosphorylation pages 107-150).
7. Function  
   CDK15 serves as an antiapoptotic protein kinase that is involved in counteracting apoptosis induced by TRAIL/TNFSF10. It exerts this function by phosphorylating the inhibitor of apoptosis protein BIRC5 (Survivin) at threonine 34, thereby enhancing cell survival signals (ong2022ubiquitylationandphosphorylation pages 107-150, amrhein2022discoveryof3amino1hpyrazolebased pages 1-3). In addition to its antiapoptotic activity, CDK15 is implicated in the regulation of mitotic processes. It binds to several components of the spindle assembly checkpoint—such as Mad2—and associates with kinases like Plk1 and Aurora Kinase B, which are essential for proper chromosome segregation and cell cycle progression (ong2022ubiquitylationandphosphorylation pages 107-150, kamkar2015pftaire1(cyclindependent pages 24-29). Expression patterns for CDK15 indicate that it is present in neural tissues, including the brain and testis, reflecting a tissue distribution pattern common among members of the PFTAIRE subfamily (kamkar2015pftaire1(cyclindependent pages 49-53, alonso2021caracterizacióndecdk1418 pages 29-32). Furthermore, functional studies have linked aberrant CDK15 activity with oncogenic processes, particularly in colorectal cancer, where its kinase activity is associated with enhanced proliferation and poor patient prognosis (ong2022ubiquitylationandphosphorylation pages 107-150, amrhein2022discoveryof3amino1hpyrazolebased pages 1-3).
8. Other Comments  
   Preliminary investigations into pharmacological targeting reveal that CDK15 may be inhibited by compounds based on 3-aminopyrazole scaffolds, although these inhibitors are not yet selective for CDK15 over other CDKs of the PFTAIRE family (amrhein2022discoveryof3amino1hpyrazolebased pages 3-4). In addition, certain PARP inhibitors have exhibited activity against CDK15, suggesting cross-reactivity among kinase inhibitors that target the ATP-binding pocket (amrhein2022discoveryof3amino1hpyrazolebased pages 3-4). Genetic association data from large-scale initiatives such as the Open Targets Platform have identified a link between CDK15 and depressive disorder, supported by credible genome-wide association evidence; however, the mechanistic basis for this association is not fully detailed in the current literature (OpenTargets Search: -CDK15,PFTK2,ALS2CR7). No significant disease-causing mutations have been well characterized to date, and the kinase is primarily recognized for its role in modulating apoptosis and mitosis rather than for direct mutation-driven pathogenesis (malumbres2009cyclindependentkinasesa pages 1-2, ong2022ubiquitylationandphosphorylation pages 107-150).
9. References  
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