## Phylogeny

CDK11A belongs to the eukaryotic protein kinase (ePK) superfamily, CMGC group, and Cyclin-Dependent Kinase (CDK) family (Manning et al., 2002a, 2002b). It is the closest vertebrate paralogue of CDK8, sharing ~91 % sequence identity, created by a vertebrate-specific gene duplication of an ancestral CDK8/CDK11 gene (Manning et al., 2002a). Single CDK8/CDK11 orthologues exist in Drosophila, C. elegans and yeast, while vertebrates possess both CDK8 and CDK11A/B; murine orthologues are present (Manning et al., 2002a, 2002b).

## Reaction Catalyzed

ATP + protein → ADP + phosphoprotein (Johnson et al., 2023).

## Cofactor Requirements

Catalysis requires a divalent metal, typically Mg²⁺ or Mn²⁺, to coordinate ATP in the active site (Karimbayli et al., 2024; Wood & Endicott, 2018).

## Substrate Specificity

CDK11A is a Ser/Thr, proline-directed kinase that preferentially phosphorylates motifs containing S/T-P; flanking sequence preferences differ from classical cell-cycle CDKs and were mapped by peptide-library/PSSM analyses (Johnson et al., 2023).

## Structure

The kinase domain displays the canonical bi-lobed fold: an N-terminal β-sheet-rich lobe (housing the glycine-rich loop and αC-helix) and a C-terminal α-helical lobe containing the activation (T)-loop; the ATP pocket lies in the inter-lobe cleft (Karimbayli et al., 2024; Wood & Endicott, 2018). A crystal structure of CDK11 bound to the inhibitor OTS964 adopts an active-like configuration and highlights a unique Gly at the xDFG position (Gly223) critical for inhibitor binding (Kelso et al., 2022).

## Regulation

• Cyclin binding: activity depends on association with Cyclin L1 or L2 (Loyer & Trembley, 2020).  
• Phosphorylation: activation requires phosphorylation of Thr229 within the activation segment; CHK2 and CK2 have been reported as upstream kinases (Kelso et al., 2022; unknown authors, 2020).  
• Isoforms: full-length CDK11p110 is constitutive; CDK11p58 is translated from an IRES during G₂/M; apoptotic cleavage generates the active p46 and mitochondrial p60 fragments (Loyer & Trembley, 2020).

## Function

A ubiquitously expressed nuclear kinase that:  
1. Couples transcription and pre-mRNA splicing by associating with hyper-phosphorylated RNA polymerase II and phosphorylating its CTD, as well as splicing factors SF3B1 and SFRS7 (Blazek, 2023; Loyer & Trembley, 2020). Interactors include RNPS1, RNAPII, TFIIF, TFIIS and ELL2 (Loyer & Trembley, 2020).  
2. Promotes G₂/M progression; depletion causes G₂/M arrest, while the p58 isoform contributes to sister-chromatid cohesion, spindle formation and cytokinesis (Li et al., 2022; unknown authors, 2023).  
3. Participates in apoptosis: caspase-generated p46 inhibits translation via eIF3, whereas p60 relocates to mitochondria (Loyer & Trembley, 2020).  
4. Has reported roles in autophagy (Blazek, 2023).

## Inhibitors

• OTS964: ATP-competitive inhibitor; KD ≈ 40 nM for CDK11B, >10-fold selectivity over other CDKs; disrupts spliceosome assembly (Blazek, 2023; Kelso et al., 2022; Lin et al., 2019).  
• ZNL-05-044: diaminothiazole scaffold, less potent than OTS964 (Kelso et al., 2022; Li et al., 2022).  
• Resistance mutations include G223S/A, E89G and M160F, which impair OTS964 binding (Kelso et al., 2022).

## Other Comments

CDK11A is overexpressed in numerous cancers (osteosarcoma, breast, multiple myeloma, ovarian, liposarcoma, colon, melanoma, oesophageal SCC) and high expression correlates with poor prognosis; many tumour cell lines are CDK11-dependent (Blazek, 2023; Kelso et al., 2022). FBXW7-deficient cells display synthetic lethality upon CDK11 inhibition (Kelso et al., 2022). CDK11 has also been linked to neuroblastoma, AIDS and Alzheimer’s disease (unknown authors, 2020).

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