## Phylogeny

Cyclin-dependent kinase 11B (CDK11B; UniProt P21127) belongs to the CMGC group, CDK family of the human kinome (Manning et al., 2002). A recent segmental duplication on chromosome 1 produced the closely related paralogue CDK11A; the two proteins differ by only 16 amino acids (Malumbres et al., 2009). Sequence-based clustering positions CDK11B closest to CDK11A and, within the CDK subfamily, to CDK8 and CDK9 (Varjosalo et al., 2013). Single-copy orthologues are found in mouse, rat, frog, zebrafish, fly and yeast, highlighting the broad evolutionary conservation of PITSLRE kinases (Malumbres et al., 2009).

## Reaction Catalyzed

ATP + protein-L-Ser/Thr ⇌ ADP + protein-L-Ser/Thr-phosphate (Loyer et al., 2005).

## Cofactor Requirements

Catalysis requires a divalent cation, preferentially Mg²⁺, for ATP coordination in the active site (Scheeff & Bourne, 2005).

## Substrate Specificity

In vitro and cellular mapping reveal a preference for Ser/Thr-Pro motifs with a basic residue at +3; consensus sequence: S/T-P-X-K/R (Anonymous, 2020).

## Structure

CDK11B is a 912-residue protein organised into four main regions:  
• N-terminal regulatory segment (≈ 1–400) containing multiple nuclear-localisation signals and a canonical 14-3-3 docking site (Anonymous, 2006).  
• Central arginine/glutamic acid-rich (RE) domain (≈ 400–560) that recruits spliceosomal factors (Anonymous, 2006).  
• Poly-glutamic acid (poly-E) domain (≈ 560–650) harbouring an internal ribosome entry site required for translation of the mitotic p58 isoform (Zhou et al., 2016).  
• C-terminal kinase domain (≈ 700–912) displaying the canonical bilobal CDK fold, including the PSTAIRE helix, Lys-Glu ion pair, C-helix, DFG motif and activation-loop Thr (Loyer & Trembley, 2020; Scheeff & Bourne, 2005).

Distinctive features include multiple caspase cleavage sites within the regulatory segment that generate catalytically active p46 and p60 fragments during apoptosis (Anonymous, 2006). No experimentally determined PDB structure is available; an AlphaFold model (AF-P21127-F1) depicts the folded kinase domain (Loyer & Trembley, 2020).

## Regulation

Post-translational modification  
– CK2 phosphorylates N-terminal Ser residues, enhancing transcription/splicing activity (Anonymous, 2006).  
– CHK2 phosphorylates CDK11p110, favouring homodimerisation and global splicing (Anonymous, 2020).  
– Autophosphorylation of the activation-loop Thr is required for full catalytic activity (Loyer & Trembley, 2020).

Proteolytic control  
– Caspase-1 and caspase-3 cleave p110 and p58 to yield p46 and p60, redirecting substrate specificity (Anonymous, 2006).

Translation control  
– An IRES within the poly-E domain restricts p58 synthesis to G2/M and is modulated by eIF2α phosphorylation and Unr binding (Anonymous, 2006).

Protein interactions  
– Kinase activation requires binding to Cyclin L1 or Cyclin L2; the mitotic p58 isoform can also engage Cyclin D3 (Zhou et al., 2016).  
– 14-3-3γ and the chaperones Hsp70/Hsp90 associate with specific isoforms to regulate localisation and stability (Anonymous, 2006).

## Function

Expression and isoforms  
– p110 is constitutively nuclear; p58 accumulates only at G2/M; p46 and p60 arise after caspase cleavage during apoptosis (Anonymous, 2006).

Transcription and splicing  
– p110 phosphorylates the RNA polymerase II C-terminal domain and SR splicing factors RNPS1 and 9G8, cooperating with ELL2 to couple transcription with 3′-end processing (Anonymous, 2006).

Mitosis  
– p58 promotes centrosome maturation, bipolar spindle assembly and sister-chromatid cohesion by recruiting PLK1, PLK4 and Cep192 (Anonymous, 2020).

Apoptosis and translation control  
– p46 phosphorylates PAK1, NOT2, RanBPM and eIF3f to inhibit translation and promote anoikis; p60 translocates to mitochondria to trigger cytochrome c release (Anonymous, 2006).

Cytoskeleton  
– Interactions with vimentin, α/β-tubulin and lamin A link CDK11B to microtubule dynamics (Anonymous, 2006).

## Inhibitors

OTS964 is a potent, selective small-molecule inhibitor of CDK11 (biochemical IC₅₀ ≈ 10–100 nM) that blocks spliceosome activation; resistance-conferring mutations in CDK11 emerge upon chronic exposure (Hluchý et al., 2022; Loyer & Trembley, 2020). No approved clinical inhibitors are currently available.

## Other Comments

High CDK11B expression is required for the survival of breast cancer, multiple myeloma, osteosarcoma and melanoma cells and correlates with poor prognosis (Loyer & Trembley, 2020). The CDC2L1 gene lies within the 1p36.3 region, a hotspot for chromosomal alterations in cancer (Zhou et al., 2016).

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