## Phylogeny

– Vertebrate-restricted paralog that arose from duplication of an ancestral NRBP locus; orthologs are present in bony fish (e.g., Danio rerio), amphibians, reptiles, birds and mammals, whereas invertebrates retain a single NRBP1-like gene (yang2024targetingtheparalog).  
– NRBP2 sequences form a well-supported monophyletic clade that is evolutionarily distinct from NRBP1 and display a higher amino-acid substitution rate (yang2024targetingtheparalog).  
– Classified within the NRBP pseudokinase family; central domain is a truncated Ser/Thr kinase-like fold lacking catalytic motifs and is placed in the “Other/Unaffiliated” group of the kinome (kerr2013nuclearreceptorbindingprotein, larsson2008nuclearreceptorbinding, jacobsen2017thesecretlife).

## Reaction Catalyzed

– No phosphoryl-transfer reaction; essential VAIK, HRD and DFG motifs are absent (yang2024targetingtheparalog, jacobsen2017thesecretlife).

## Cofactor Requirements

– Not applicable; divalent-metal or nucleotide binding has not been demonstrated (jacobsen2017thesecretlife).

## Substrate Specificity

– Enzymatic substrate specificity not determined; no consensus motifs reported (kerr2013nuclearreceptorbindingprotein).

## Structure

– Single-chain protein of ~500 amino acids, predicted mass 55–60 kDa (larsson2008nuclearreceptorbinding).  
– Domain organisation:  
– N-terminal low-complexity region with predicted NLS and NES signals (yang2024targetingtheparalog).  
– Central pseudokinase domain retaining the bilobal kinase scaffold but lacking catalytic residues (yang2024targetingtheparalog).  
– C-terminal region containing a BC-box and NRB (LXXLL) motif; sufficient for homo/heterodimerisation and for targeting NRBP1 to the proteasome (yang2024targetingtheparalog).  
– AlphaFold modelling preserves the core kinase topology yet shows an incomplete hydrophobic spine and shortened activation loop, consistent with pseudokinase status (xiao2024tsc22dwnkand, amnekar2024nrbp1pseudokinasebinds).

## Regulation

– No post-translational modifications have been mapped in large-scale proteomics surveys (yang2024targetingtheparalog).  
– Protein stability: the C-terminal NRB motif promotes proteasome-dependent degradation of NRBP1; NRBP1 reciprocally limits NRBP2 levels. This process is independent of the Elongin B/C E3 ligase complex (yang2024targetingtheparalog).  
– Transcriptional control: promoter DNA methylation and histone deacetylation silence NRBP2 in medulloblastoma; demethylating agents or HDAC inhibitors restore expression (xiong2020nuclearreceptorbinding).

## Function

– Expression: high in embryonic ventricular zones and hippocampus; in adults enriched in cerebellar Purkinje cells and hippocampal CA3 neurons (larsson2008nuclearreceptorbinding). Present in distal convoluted tubule of kidney where it localises to WNK bodies (maganaavila2024nrbp1andtsc22d).  
– Subcellular localisation: predominantly cytoplasmic; forms perinuclear or punctate foci, especially upon co-expression with NRBP1 (larsson2008nuclearreceptorbinding, yang2024targetingtheparalog).  
– Interacting partners: NRBP1 (heterodimerisation/degradation target), LINE-1 ORF1, UPF1, MOV10, G3BP1, YBX1, WNK1, WNK4, SPAK, Elongin B/C (yang2024targetingtheparalog, maganaavila2024nrbp1andtsc22d).  
– Pathway roles:  
– Suppresses LINE-1 retrotransposition by destabilising NRBP1 and disrupting ORF1–RNA association (yang2024targetingtheparalog).  
– Enhances WNK4–SPAK signalling in kidney, increasing NCC phosphorylation and contributing to electrolyte balance (maganaavila2024nrbp1andtsc22d).  
– Supports neural progenitor survival; siRNA knock-down increases apoptosis during differentiation (larsson2008nuclearreceptorbinding).  
– Over-expression in medulloblastoma cells decreases viability, elevates apoptosis and impairs migration/invasion (xiong2020nuclearreceptorbinding).  
– Knock-down up-regulates innate immune and type I interferon genes (yang2024targetingtheparalog).

## Other Comments

– Disease associations: down-regulated in paediatric medulloblastoma (xiong2020nuclearreceptorbinding); somatic mutation in pseudokinase domain reported in glioma (larsson2008nuclearreceptorbinding); reduced transcript levels in rheumatoid arthritis synovial tissue (yang2024targetingtheparalog).