Phylogeny  
• Classified in the group G branch of the human kinome and designated a class 1 pseudokinase because the kinase-like domain lacks the canonical VAIK, HRD and DFG catalytic motifs (kerr2013nuclearreceptorbindingprotein pages 2-4, murphy2014arobustmethodology pages 7-9).  
• Forms a distinct NRBP1/NRBP2 clade within the “other/atypical” sector of the kinome (yang2024targetingtheparalog pages 44-48).  
• Orthologous conservation: Homo sapiens vs Mus musculus 98.3 % identity, Caenorhabditis elegans 60.7 %, Drosophila melanogaster 53.8 % (kerr2013nuclearreceptorbindingprotein pages 2-4).

Reaction Catalyzed  
NRBP1 does not catalyze the canonical protein-serine/threonine kinase reaction (ATP + protein-OH → ADP + protein-O-phosphate); no nucleotide binding or phosphoryl-transfer activity is detected (murphy2014arobustmethodology pages 7-9).

Cofactor Requirements  
No Mg²⁺, Mn²⁺ or other divalent cation requirement has been observed, consistent with absent nucleotide binding (murphy2014arobustmethodology pages 7-9).

Substrate Specificity  
A phosphorylation consensus motif is undefined because NRBP1 is catalytically inactive (murphy2014arobustmethodology pages 7-9).

Structure  
• Domain organisation: SH2-interaction segment (aa 1-70), nuclear export signal (aa 121-129), pseudokinase domain (aa 73-327), nuclear localisation signal (aa 163-181), BC-box for Elongin B/C binding (aa 332-341), LisH/Cullin interaction region, MLF1-binding segment (aa 406-479), two LXXLL nuclear-receptor motifs (aa 462-466; 507-511) and a TSC22-binding module (kerr2013nuclearreceptorbindingprotein pages 1-2, yang2023thepseudokinasenrbp1 pages 2-3).  
• AlphaFold models preserve the bilobal protein-kinase scaffold yet confirm degradation of the catalytic lysine in the β3-strand, the catalytic HRD aspartate and the DFG motif, eliminating the regulatory spine and C-helix salt bridge (yang2023thepseudokinasenrbp1 pages 14-14).  
• Thermal-shift screens show no binding to ATP, ADP or divalent cations, corroborating structural incompetence for catalysis (murphy2014arobustmethodology pages 7-9).  
• The BC-box forms an exposed surface for CRL5 assembly, a feature absent from canonical active kinases (kerr2013nuclearreceptorbindingprotein pages 2-4).

Regulation  
• Phosphorylation: multiple sites identified by phospho-proteomics; specific residues and responsible kinases are not yet mapped (yang2023thepseudokinasenrbp1 pages 14-14).  
• Ubiquitination: the BC-box recruits Elongin B/C and CUL5, positioning NRBP1 as the substrate-recognition module of a CRL5 E3 ligase; NRBP1 itself and bound substrates are ubiquitinated (kerr2013nuclearreceptorbindingprotein pages 2-4). Additional CRL2 and CRL4A assemblies promote NRBP1 turnover (maganaavila2024nrbp1andtsc22d pages 16-17).  
• Osmotic stress: binding to WNK kinases modulates CRL5 association during osmotic adaptation (amnekar2024nrbp1pseudokinasebinds pages 25-27).  
• Subcellular distribution is regulated by intrinsic NES and NLS signals allowing cytoplasm–nucleus shuttling (kerr2013nuclearreceptorbindingprotein pages 1-2).

Function  
• Expression is ubiquitous across mammalian tissues (kerr2013nuclearreceptorbindingprotein pages 1-2).  
• Development: Nrbp1-/- embryos die at E7.5, indicating an essential embryonic function (kerr2013nuclearreceptorbindingprotein pages 4-5).  
• Intestine: conditional knockout causes crypt elongation, elevated progenitor proliferation and increased expression of Wnt-responsive genes (kerr2013nuclearreceptorbindingprotein pages 4-5).  
• Ubiquitination adaptor: serves as the substrate-selector in CRL5 complexes (kerr2013nuclearreceptorbindingprotein pages 2-4).  
• Trafficking: binds activated Rac3 to influence ER-to-Golgi transport (kerr2013nuclearreceptorbindingprotein pages 2-4).  
• Oncogenic signaling: scaffolds P-Rex1 with Rac1/Cdc42, enhancing GTPase activation, ROS production, migration, invasion and metastasis in triple-negative breast cancer (yang2023thepseudokinasenrbp1 pages 7-8).  
• Osmoregulation: associates with WNK kinases to modulate distal convoluted tubule signaling (amnekar2024nrbp1pseudokinasebinds pages 25-27, maganaavila2024nrbp1andtsc22d pages 16-17).  
• Viral replication: interaction with dengue virus NS3 protein alters intracellular membrane architecture (yang2023thepseudokinasenrbp1 pages 14-14).  
• Transcriptional repression: binds JAB1, inhibiting AP-1 activity (kerr2013nuclearreceptorbindingprotein pages 5-5).

Inhibitors  
No small-molecule inhibitors have been reported.

Other Comments  
• Tumour biology is context-dependent: NRBP1 down-regulation correlates with poor survival in lung and colorectal adenocarcinomas and cooperates genetically with oncogenic KRAS (kerr2013nuclearreceptorbindingprotein pages 4-5). Conversely, elevated NRBP1 drives proliferation and invasion in triple-negative breast, bladder and prostate cancers (yang2023thepseudokinasenrbp1 pages 1-2, yang2023thepseudokinasenrbp1 pages 14-14).  
• NRBP1 promotes PI3K/AKT-dependent malignant phenotypes in glioblastoma (zhang2024nrbp1promotesmalignant pages 16-16).  
• Functional interplay with the paralogue NRBP2 governs LINE-1 retrotransposition, providing a mechanistic basis for tissue-specific phenotypes (yang2024targetingtheparalog pages 44-48).

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