Phylogeny  
Orthologues have been reported in Mus musculus, Rattus norvegicus and Danio rerio, indicating conservation across vertebrates (Leggieri et al., 2022; Hoenicka et al., 2010). Within the human kinome ANKK1 clusters with the receptor-interacting protein kinase sub-family (RIPK5) of the Tyrosine-Kinase-Like branch; its catalytic domain shares ≈35 % identity with RIPK4, the closest paralogue (Domínguez-Berzosa et al., 2024; Ponce et al., 2009). Early analyses grouped ANKK1 with ANKRD3 on the basis of a common ankyrin-repeat architecture (Neville et al., 2004).

Reaction Catalyzed  
ATP + L-seryl/threonyl-[protein] ⇌ ADP + O-phospho-L-seryl/threonyl-[protein] (Neville et al., 2004; Ponce et al., 2009).

Cofactor Requirements  
A divalent Mg²⁺ ion is proposed to be required, in line with other RIPK family kinases; direct enzymatic confirmation for ANKK1 is not yet available (Domínguez-Berzosa et al., 2024).

Substrate Specificity  
No consensus phosphorylation motif or physiological substrate has been defined to date (Neville et al., 2004; Ponce et al., 2009).

Structure  
• 765-residue protein with an N-terminal Ser/Thr kinase domain (residues 22–289) and 11 C-terminal ankyrin repeats (361–753) (Domínguez-Berzosa et al., 2024; Neville et al., 2004).  
• Conserved catalytic motifs VAIK (Lys147), HRD and DFG confirm an active eukaryotic protein kinase fold (Domínguez-Berzosa et al., 2024).  
• AlphaFold model AF-Q8NFD2-F1 predicts high flexibility outside the two main domains (Domínguez-Berzosa et al., 2024).  
• Comparative modelling of haplotypes H1, H2 and H2B shows surface-charge differences at residues 239, 318, 442, 490 and 713 without altering the global fold (Domínguez-Berzosa et al., 2024).  
• No X-ray or cryo-EM structure is available.  
• Endogenous isoforms: full-length cytoplasmic (~82 kDa), nuclear kinase-only (~56 kDa) and glycosylated cytoplasmic (~115 kDa) forms (Rubio-Solsona et al., 2018).  
• CRM1-dependent nuclear-export signals mediate nucleo-cytoplasmic shuttling, as shown by leptomycin B sensitivity (Rubio-Solsona et al., 2018).

Regulation  
• Ubiquitination on conserved lysines suggests proteostatic control, though individual sites remain unmapped (Hoenicka et al., 2010).  
• A glycosylated full-length isoform accumulates during myogenic differentiation (Rubio-Solsona et al., 2018).  
• Missense variant Ala239Thr introduces an additional phosphorylation site and alters electrophoretic mobility (Hoenicka et al., 2010).  
• ANKK1 mRNA is up-regulated in astrocytes after dopamine D₂ agonist (apomorphine) exposure (Hoenicka et al., 2010).  
• During neuronal differentiation, binding to WGEF (RhoA-GEF) decreases while interaction with FARP1 (RAC1-GEF) increases, coordinating RhoA/RAC1 activation (Domínguez-Berzosa et al., 2024).

Function  
• Highly expressed in astrocytes and radial glial cells during embryonic and post-natal brain development (Hoenicka et al., 2010).  
• Transcript levels oscillate with the cell cycle in neural precursors, peaking in mitosis (España-Serrano et al., 2017).  
• Enriched in striatal dopamine D₂-expressing neurons that regulate reward and metabolism; brain-biased expression confirmed by GTEx and Allen Brain Atlas datasets (Montalban et al., 2022; Domínguez-Berzosa et al., 2024).  
• In skeletal muscle, localises to migrating myotubes and shifts from nucleus to cytoplasm during differentiation (Rubio-Solsona et al., 2018).  
• Acts as a scaffold in the Wnt/Planar Cell Polarity pathway, recruiting FARP1 and WGEF to coordinate RAC1 and RhoA activation, promoting F-actin assembly, neuritogenesis and neuronal migration (Domínguez-Berzosa et al., 2024).  
• Knock-down reduces RAC1/RhoA expression and blocks neurite outgrowth in neuroblastoma cells (Domínguez-Berzosa et al., 2024).  
• Loss-of-function in zebrafish decreases drd2 expression and disrupts dopamine-dependent behaviours (Leggieri et al., 2022).  
• Variant rs2734849 (Arg→His) in the ankyrin region alters NF-κB-regulated gene expression (Ma et al., 2015).

Inhibitors  
Not reported in the material provided.

Other Comments  
• rs1800497 (Taq1A, p.Glu713Lys) in ankyrin repeat 11 is linked to a 30–40 % reduction in striatal DRD2 density and increased risk for addictions, obesity, ADHD and schizophrenia (Neville et al., 2004; Montalban et al., 2022).  
• Five polymorphic residues (239, 318, 442, 490, 713) define haplotypes H1, H2 and H2B with distinct surface-charge patterns (Domínguez-Berzosa et al., 2024).  
• Rare promoter and intron 1 variants that disrupt MZF-1 or RELA binding are enriched in Parkinson’s disease cohorts and modulate transcription in reporter assays (Pérez-Santamarina et al., 2021).  
• ANKK1 lies adjacent to DRD2 within the NTAD cluster, creating extensive linkage disequilibrium that historically complicated genetic attribution of Taq1A (Domínguez-Berzosa et al., 2024; Neville et al., 2004).

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