## Phylogeny

Orthologous genes encoding ANKK1 have been documented in Mus musculus, Rattus norvegicus and Danio rerio, demonstrating conservation across vertebrates (leggieri2022ankk1lossof pages 1-2, hoenicka2010theankk1gene pages 5-7).  
Within the human kinome ANKK1 groups with the receptor-interacting protein kinase sub-family (RIPK5) in the Tyrosine Kinase-Like (TKL) branch (dominguezberzosa2024ankk1isa pages 1-2).  
The catalytic domain shares ~35 % pair-wise identity with RIPK4, identifying RIPK4 as the closest paralog (ponce2009theankk1kinase pages 1-2).  
Early phylogenetic analyses placed ANKK1 on the same branch as ANKRD3, reflecting a common ankyrin-repeat architecture (neville2004identificationandcharacterization pages 5-6).

## Reaction Catalyzed

ATP + protein L-serine/threonine → ADP + protein O-phospho-L-serine/threonine (neville2004identificationandcharacterization pages 4-5, ponce2009theankk1kinase pages 1-2).

## Cofactor Requirements

A requirement for Mg²⁺ as a divalent cofactor has been proposed, consistent with other RIPK family members, although direct enzymatic confirmation for ANKK1 is not yet reported (dominguezberzosa2024ankk1isa pages 1-2).

## Substrate Specificity

No consensus phosphorylation motif or physiological substrate has been experimentally defined for ANKK1 to date (neville2004identificationandcharacterization pages 4-5, ponce2009theankk1kinase pages 1-2).

## Structure

The protein comprises 765 amino acids with an N-terminal serine/threonine kinase domain spanning residues 22–289 and a C-terminal region of 11 ankyrin repeats covering residues 361–753 (dominguezberzosa2024ankk1isa pages 13-14, neville2004identificationandcharacterization pages 4-5).  
Canonical catalytic motifs are present: VAIK (Lys147), HRD and DFG, confirming classification as an active eukaryotic protein kinase (dominguezberzosa2024ankk1isa pages 17-18).  
AlphaFold model AF-Q8NFD2-F1 predicts pronounced flexibility across both major domains and lacks substantial ordered regions outside them (dominguezberzosa2024ankk1isa pages 13-14).  
Electrostatic surface analysis of three naturally occurring haplotypes (H1, H2, H2B) reveals charge differences at positions 239, 318, 442, 490 and 713 without altering the overall fold (dominguezberzosa2024ankk1isa pages 13-14).  
No crystallographic or cryo-EM structure has been solved so far (dominguezberzosa2024ankk1isa pages 13-14).  
Endogenous isoforms include a cytoplasmic full-length species (~82 kDa), a nuclear kinase-only form (~56 kDa) and a glycosylated cytoplasmic variant (~115 kDa) (rubiosolsona2018ankk1isfound pages 5-7).  
CRM1-dependent nuclear export sequences govern shuttling between nucleus and cytoplasm, as shown by leptomycin B sensitivity (rubiosolsona2018ankk1isfound pages 5-7).

## Regulation

Ubiquitination on conserved lysines has been detected, indicating proteostasis control, although individual modified residues remain unmapped (hoenicka2010theankk1gene pages 5-7).  
A glycosylated full-length isoform accumulates during myogenic differentiation, reflecting differential processing in muscle cells (rubiosolsona2018ankk1isfound pages 5-7).  
The Ala239Thr missense variant introduces an additional phosphorylation site within the kinase domain and alters electrophoretic mobility (hoenicka2010theankk1gene pages 5-7).  
ANKK1 mRNA is transcriptionally up-regulated in astrocytes after exposure to the dopamine D2 receptor agonist apomorphine (hoenicka2010theankk1gene pages 2-3).  
During neuronal differentiation, interaction with the RhoA-GEF WGEF diminishes whereas binding to the RAC1-GEF FARP1 increases, coordinating shifts in small-GTPase activation (dominguezberzosa2024ankk1isa pages 13-14, dominguezberzosa2024ankk1isa pages 10-13).

## Function

ANKK1 is enriched in astrocytes and radial glial cells during embryonic and post-natal brain development (hoenicka2010theankk1gene pages 5-7, hoenicka2010theankk1gene pages 7-7).  
Its expression oscillates with the cell cycle in neural precursors, peaking during mitosis (espana‐serrano2017theaddiction‐relatedprotein pages 1-2).  
High transcript levels are observed in striatal dopamine D2 receptor–expressing neurons that govern reward and metabolic circuits (montalban2022theaddictionsusceptibilitytaqiaankyrin pages 1-4).  
GTEx and Allen Brain Atlas datasets show brain-biased expression with prominence in dopaminergic regions (dominguezberzosa2024ankk1isa pages 17-18).  
In muscle, ANKK1 localises to migrating myotubes and shifts from nuclear to cytoplasmic compartments during differentiation (rubiosolsona2018ankk1isfound pages 5-7).  
The protein serves as a scaffold in the Wnt/Planar Cell Polarity pathway by recruiting FARP1 and WGEF to coordinate RAC1 and RhoA activation, enabling F-actin assembly, neuritogenesis and neuronal migration (dominguezberzosa2024ankk1isa pages 1-2, dominguezberzosa2024ankk1isa pages 10-13).  
ANKK1 knock-down reduces RAC1/RhoA expression and blocks neurite outgrowth in differentiating neuroblastoma cells (dominguezberzosa2024ankk1isa pages 10-13).  
Loss-of-function in zebrafish lowers drd2 expression and alters dopamine-dependent behaviours, indicating a functional link to dopaminergic signalling (leggieri2022ankk1lossof pages 1-2).  
The rs2734849 Arg→His variant in the ankyrin region modifies NF-κB-regulated gene expression patterns (ma2015updatedfindingsof pages 9-11).

## Other Comments

The rs1800497 Taq1A variant (c.2137G>A; p.Glu713Lys) within ankyrin repeat 11 is associated with a 30–40 % reduction in striatal DRD2 density and elevated risk for addictions, obesity, ADHD and schizophrenia (neville2004identificationandcharacterization pages 4-5, montalban2022theaddictionsusceptibilitytaqiaankyrin pages 1-4).  
Five additional polymorphic residues (239, 318, 442, 490, 713) define haplotypes H1, H2 and H2B that display distinct surface charge patterns (dominguezberzosa2024ankk1isa pages 13-14).  
Rare promoter and intron 1 variants disrupting MZF-1 or RELA binding are enriched in Parkinson’s disease cohorts and modulate transcriptional activity in reporter assays (perezsantamarina2021regulatoryrarevariants pages 2-4, perezsantamarina2021regulatoryrarevariants pages 4-5).  
ANKK1 resides adjacent to DRD2 within the NTAD gene cluster, creating extensive linkage disequilibrium that historically complicated genetic attribution of Taq1A (dominguezberzosa2024ankk1isa pages 1-2, neville2004identificationandcharacterization pages 1-2).

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