## Phylogeny

ULK4 is one of five human Unc-51-like kinases (ULK1-4 and STK36) that form a distinct branch within the CAMK group of the human kinome described by Manning et al. 2002 (preuss2020nucleotidebindingevolutionary pages 20-21). Orthologs occur across metazoans, including mouse, rat, zebrafish and Drosophila, and extend to plants and protists such as Arabidopsis, where the ancestral active-site residues are retained (preuss2020nucleotidebindingevolutionary pages 6-9). Phylogenetic comparisons segregate ULK4 from the catalytically active ULK1-3 because ULK4 has lost the VAIK, HRD and DFG motifs and gained an extended activation segment unique to this lineage (preuss2020nucleotidebindingevolutionary pages 4-6). Among ULK family members, ULK4 clusters most closely with STK36 but diverges functionally as a pseudokinase (khamrui2019highresolutionstructureand pages 1-2).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-Ser/Thr-P  
No phosphotransferase activity has been detected for ULK4 despite tight nucleotide binding (khamrui2019highresolutionstructureand pages 1-2, preuss2020nucleotidebindingevolutionary pages 11-14).

## Cofactor Requirements

ATP binding is magnesium-independent; Mg²⁺ destabilizes the nucleotide complex (preuss2020nucleotidebindingevolutionary pages 11-14).

## Substrate Specificity

No consensus phosphorylation motif has been reported; the 2023 atlas of serine/threonine kinase specificities lists no detectable activity for ULK4 (preuss2020nucleotidebindingevolutionary pages 20-21).

## Structure

Domain organisation – N-terminal pseudokinase domain (~1–288) followed by five C-terminal HEAT/armadillo repeats (khamrui2019highresolutionstructureand pages 1-2, luo2022ulk4inneurodevelopmental pages 2-3).  
3D structures – Crystal structures with ATPγS (PDB 6TSZ) and a fragment-like inhibitor (PDB 6U5L) reveal a bilobal kinase fold with an αC-in conformation (khamrui2019highresolutionstructureand pages 1-2, preuss2020nucleotidebindingevolutionary pages 1-4).  
Catalytic features – VAIK lysine → leucine (L33); alternative K39 in β3 coordinates phosphates (preuss2020nucleotidebindingevolutionary pages 11-14). HRD → FCD and DFG → NFC substitutions abolish catalysis (preuss2020nucleotidebindingevolutionary pages 6-9).  
Regulatory elements – An extended helical activation segment (L150–E161) packs against αC and blocks the substrate pocket, stabilising the domain (preuss2020nucleotidebindingevolutionary pages 6-9).  
Unique aspects – Nucleotide binding occurs without metal coordination and confers structural stability; Mg²⁺ disrupts this interaction (preuss2020nucleotidebindingevolutionary pages 11-14).

## Regulation

No post-translational modifications have been reported (khamrui2019highresolutionstructureand pages 1-2, preuss2020nucleotidebindingevolutionary pages 1-4). High-affinity ATP binding stabilises the fold; N139L disrupts binding and destabilises ULK4, whereas the common K39R polymorphism tightens ADP binding without affecting ATP affinity (preuss2020nucleotidebindingevolutionary pages 11-14).

## Function

Expression – Highly expressed in embryonic ventricular and subventricular zones, maintained in cortical layers and adult neural stem cells (luo2022ulk4inneurodevelopmental pages 2-3). Localises to the cytoplasm with enrichment at centrosomes and microtubules (preuss2020nucleotidebindingevolutionary pages 14-16).  
Protein interactions – Binds PP2A and PP1α phosphatases (luo2022ulk4inneurodevelopmental pages 1-2); interacts with CAMSAP1/3, HAUS2/8, CCP110, CEP97, CSPP1, OFD1, kinesins, and kinases STK36, ROCK1, ROCK2, PTPN14 (preuss2020nucleotidebindingevolutionary pages 14-16, preuss2020nucleotidebindingevolutionary pages 24-30).  
Biological roles – Regulates α-tubulin acetylation, controlling neurite branching, elongation and neuronal migration (unknownauthors2017regulationofthe pages 63-67, luo2022ulk4inneurodevelopmental pages 3-4). Required for corticogenesis, neural stem-cell proliferation, ciliogenesis, oligodendrocyte maturation and white-matter integrity (luo2022ulk4inneurodevelopmental pages 3-4, luo2022ulk4inneurodevelopmental pages 4-6). Knockdown perturbs Wnt, PKC, p38 MAPK, ERK1/2 and JNK pathways (luo2022ulk4inneurodevelopmental pages 4-6).

## Inhibitors

A fragment-like small molecule was co-crystallised in the ATP pocket, demonstrating chemical tractability (khamrui2019highresolutionstructureand pages 1-2).

## Other Comments

Disease associations – Variants confer susceptibility to schizophrenia, autism spectrum disorder, bipolar disorder and depression (luo2022ulk4inneurodevelopmental pages 4-6, khamrui2019highresolutionstructureand pages 1-2). Genome-wide studies link ULK4 polymorphisms to hypertension and sporadic thoracic aortic dissection (preuss2020nucleotidebindingevolutionary pages 11-14). Loss-of-function in mice causes hydrocephalus, hypomyelination and anxiety-like behaviour (luo2022ulk4inneurodevelopmental pages 3-4).  
Notable mutations – K39R increases ADP affinity; N139L abolishes nucleotide binding and destabilises the domain (preuss2020nucleotidebindingevolutionary pages 11-14).

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