## Phylogeny

Human LMTK1 (UniProt Q6ZMQ8) defines the Lemur Tail Kinase sub-family that also comprises LMTK2 and LMTK3 (larose2024thelemurtail pages 2-4).  
Orthologous genes have been reported in mouse (Lmtk1a/Lmtk1b), rat, chicken, zebrafish, Drosophila and C. elegans, indicating conservation from vertebrates to invertebrates (wei2020isoformdependentsubcellularlocalization pages 22-23).  
Within the human kinome, AATK/LMTK1 is placed in the tyrosine-kinase–related branch (“Lemur Tail Kinase family”) as catalogued by the comprehensive kinome analysis of Manning et al. (manning2002theproteinkinase pages 3-3).

## Reaction Catalyzed

ATP + protein L-Ser/Thr → ADP + protein O-phospho-L-Ser/Thr + H⁺ (woods2022epigeneticallysilencedapoptosisassociated pages 9-10).

## Cofactor Requirements

No peer-reviewed biochemical study has yet quantified divalent-cation dependence; cofactor requirement therefore remains experimentally undetermined (wei2020isoformdependentsubcellularlocalization pages 11-12).

## Substrate Specificity

A global consensus phosphorylation motif for LMTK1 has not been defined; iPTMnet contains no annotated substrates (hamoud2024illuminatingthedark pages 5-7).  
Johnson 2023 serine/threonine kinome atlas did not report an LMTK1 motif (ferrari2021lemurtyrosinekinases pages 3-5).  
Experimentally validated substrate: TP53 is phosphorylated on serine/threonine residues after UV stress in multiple cancer cell lines (woods2022epigeneticallysilencedapoptosisassociated pages 9-10).

## Structure

Domain organisation (isoform LMTK1B):  
– N-terminal signal peptide followed by two transmembrane helices (~residues 1-60) anchoring the kinase to membranes (larose2024thelemurtail pages 4-5).  
– Protein kinase domain (~residues 60-360) containing the catalytic Lys within the β3-strand (Lys131-139 region) and an HRD motif with catalytic Asp263; Asp263→Val abolishes activity (ferrari2021lemurtyrosinekinases pages 3-5, wei2020isoformdependentsubcellularlocalization pages 27-28).  
– DFG motif at the start of the activation loop and a conserved C-helix complete the canonical kinase core (larose2024thelemurtail pages 2-4).  
– A proline-rich C-terminal tail (~1000 aa) with multiple PxxP motifs provides docking sites for SH3-domain proteins (larose2024thelemurtail pages 4-5).

Isoform LMTK1A lacks the transmembrane segment and attaches to recycling endosomes via palmitoylation of Cys4/Cys6/Cys7 (wei2020isoformdependentsubcellularlocalization pages 27-28).  
No crystallographic structure is available; an AlphaFold2 model (AF-Q6ZMQ8) captures an active-state kinase fold with correctly positioned activation loop and catalytic motifs (faezov2023alphafold2modelsof pages 14-16).

## Regulation

Phosphorylation  
– Cdk5/p35 phosphorylates Ser34, suppressing tyrosine phosphorylation of LMTK1 and modifying growth-cone localisation (tsutsumi2010phosphorylationofaatyk1 pages 8-9).  
– Cdk5-dependent phosphorylation further regulates LMTK1 control of Rab11-positive recycling endosomes during neuronal morphogenesis (takahashi2020hyperactiveandimpulsive pages 12-12).  
Autophosphorylation  
– Weak but detectable autophosphorylation has been observed in vitro (hisanaga2020lmtk1anovel pages 2-3).  
Lipidation  
– Palmitoylation of Cys4/Cys6/Cys7 is essential for LMTK1A endosomal targeting (wei2020isoformdependentsubcellularlocalization pages 27-28).  
Transcriptional/Post-transcriptional control  
– Intronic microRNA-338 modulates AATK mRNA abundance during neuronal differentiation (hisanaga2020lmtk1anovel pages 2-3).  
Epigenetic regulation  
– Promoter hypermethylation leads to silencing of AATK in several cancers (woods2022epigeneticallysilencedapoptosisassociated pages 11-12).

## Function

Expression  
High mRNA and protein enrichment in brain tissue is documented by HPA and GTEx datasets, with uniform distribution across multiple brain regions (hamoud2024illuminatingthedark pages 5-7, larose2024thelemurtail pages 4-5).

Interactors and signalling modules  
– Direct binding to Cdk5/p35 couples LMTK1 to the neuronal Cdk5 pathway (tsutsumi2010phosphorylationofaatyk1 pages 8-9).  
– Complex formation with PP1Cα, SPAK, Src, and Rab-GAPs TBC1D9B/TBC1D11 situates LMTK1 within endosomal-trafficking networks (larose2024thelemurtail pages 4-5).  
– The LMTK1–TBC1D9B–Rab11A cascade restricts Rab11-dependent vesicle motility, thereby limiting axon elongation, dendritic branching and spine density (wei2020isoformdependentsubcellularlocalization pages 23-24).  
– Phosphorylation of TP53 links LMTK1 to DNA-damage response pathways and cell-cycle control in non-neuronal contexts (woods2022epigeneticallysilencedapoptosisassociated pages 9-10).

Physiological roles  
Knockout mice exhibit increased axon outgrowth, elevated spine number and hyperactive/impulsive behaviour, demonstrating a role in neural-circuit maturation (takahashi2020hyperactiveandimpulsive pages 12-12).

## Other Comments

Disease associations  
– Epigenetic silencing of AATK correlates with reduced TP53 activation and radio-resistance in lung, melanoma and pancreatic cancers (woods2022epigeneticallysilencedapoptosisassociated pages 11-12).  
– Behavioural phenotypes in Lmtk1-null mice resemble attention-deficit/hyperactivity disorder traits (takahashi2020hyperactiveandimpulsive pages 12-12).

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