## Phylogeny

• Lemur tail kinase sub-family member together with LMTK1 and LMTK3 (larose2024thelemurtail pages 2-4).  
• Experimentally confirmed orthologs in Homo sapiens, Mus musculus, Rattus norvegicus and Danio rerio; related kinases exist in Drosophila melanogaster and Caenorhabditis elegans, whereas no ortholog is detected in Saccharomyces cerevisiae (morotz2024arevisednomenclature pages 1-3).  
• The original human kinome map assigned LMTK2 to the Tyrosine Kinase-Like (TKL) group (manning2002theproteinkinase pages 3-3); later comparative analyses re-allocated the entire LMTK family to the Ca²⁺/calmodulin-dependent kinase (CAMK) group (larose2024thelemurtail pages 1-2).  
• Catalytic domain shares ~60 % sequence identity with the apoptosis-associated tyrosine kinase (AATYK) family while retaining strict Ser/Thr specificity (cruz2019unravelingthefunction pages 1-2).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-O-phospho-Ser/Thr (unknownauthors2020regulationofthe pages 46-50, wendler2021thelmtkfamilyof pages 1-6).

## Cofactor Requirements

Divalent cations are required; in vitro kinase assays employ 10–40 mM Mg²⁺ to support phosphotransfer (unknownauthors2006peptidemicroarrayanalysis pages 8-13).

## Substrate Specificity

• Exclusively phosphorylates serine and threonine residues; no tyrosine activity detected in phospho-amino-acid analyses (unknownauthors2006peptidemicroarrayanalysis pages 1-8).  
• Peptide-microarray profiling defined a relaxed proline-directed preference (P-S/T or S/T-P) frequently flanked by basic residues (unknownauthors2006peptidemicroarrayanalysis pages 13-18).  
• A strict requirement for Arg at –3/–2 was reported for the paralog LMTK3, suggesting but not yet demonstrating a similar determinant for LMTK2 (ferrari2021lemurtyrosinekinases pages 3-5).

Validated phosphorylation sites  
– PP1C Thr320 (wendler2021thelmtkfamilyof pages 6-10)  
– CFTR Ser737 (wendler2021thelmtkfamilyof pages 10-13)  
– Glycogen phosphorylase b Ser15 (unknownauthors2006peptidemicroarrayanalysis pages 13-18)  
– Multiple serines in myelin basic protein (cruz2019unravelingthefunction pages 2-3)

## Structure

• Two N-terminal transmembrane helices (residues 11–29 and 46–63) orient both termini cytoplasmically (cruz2019unravelingthefunction pages 1-2).  
• Cytosolic kinase domain (residues 137–407) contains the canonical VAIK motif with Lys168, HRD catalytic loop, DFG motif and a D265LALRN segment; Tyr295 is a putative autophosphorylation residue (cruz2019unravelingthefunction pages 2-3, ferrari2021lemurtyrosinekinases pages 3-5).  
• Regulatory Ser1418 lies immediately C-terminal to the kinase domain (bencze2018biologicalfunctionof pages 2-4).  
• Long C-terminal tail (residues ≈408-1503) harbours seven PxxP motifs and a PP1C-binding Val1355-Thr-Phe (VTF) sequence (bencze2018biologicalfunctionof pages 1-2).  
• Fluorescence-protease-protection experiments confirm cytoplasmic exposure of both termini (nixon2013determinationofthe pages 16-20).  
• AlphaFold model AF-Q8IWU2-F1 (2023) depicts the full-length architecture and canonical kinase secondary-structure elements, but no experimental crystal or cryo-EM structure is yet available (bencze2018biologicalfunctionof pages 7-8).

## Regulation

Post-translational modifications  
– Phosphorylation of Ser1418 by the CDK5/p35 complex increases kinase activity (bencze2018biologicalfunctionof pages 2-4, cruz2019unravelingthefunction pages 3-5).  
– Protein kinase C-dependent phosphorylation triggered by nerve-growth-factor or serum exposure diminishes activity (bencze2018biologicalfunctionof pages 1-2).  
– Constitutive autophosphorylation on Ser/Thr residues supports basal activity (unknownauthors2006peptidemicroarrayanalysis pages 1-8).

Protein–protein interactions and functional effects  
– Direct PP1C binding via the VTF motif allows phosphorylation of PP1C Thr320, inhibiting the phosphatase (wendler2021thelmtkfamilyof pages 6-10).  
– CDK5 activator p35 and myosin VI compete for overlapping binding regions within the kinase domain (bencze2018biologicalfunctionof pages 2-4).  
– Inhibitor-2 modulates the LMTK2–PP1C complex (cruz2019unravelingthefunction pages 3-5).

## Function

Expression and localisation  
• mRNA and protein are enriched in brain (hippocampus, cortex) with additional expression in skeletal muscle and prostate epithelium (bencze2018biologicalfunctionof pages 7-8, cruz2019unravelingthefunction pages 1-2).  
• Localises to Golgi, early and recycling endosomes, plasma membrane, growth cones and perinuclear regions; ER export depends on a di-acidic motif within the cytosolic domain (unknownauthors2020regulationofthe pages 50-54, nixon2013determinationofthe pages 16-20).

Signalling roles  
• Upstream activator: CDK5/p35 (bencze2018biologicalfunctionof pages 2-4).  
• Direct substrates: PP1C, CFTR, glycogen phosphorylase b, myelin basic protein (wendler2021thelmtkfamilyof pages 10-13, unknownauthors2006peptidemicroarrayanalysis pages 13-18, cruz2019unravelingthefunction pages 2-3).  
• PP1C inhibition elevates GSK3β Ser9 phosphorylation, reduces kinesin-1 light-chain phosphorylation and controls axonal cargo release such as Smad2 (wendler2021thelmtkfamilyof pages 10-13).  
• CFTR Ser737 phosphorylation accelerates endocytosis and diminishes chloride secretion in airway epithelia (wendler2021thelmtkfamilyof pages 10-13).  
• Regulates TGF-β1 signalling by influencing Smad2 trafficking (unknownauthors2020regulationofthe pages 50-54).  
• Interacts with androgen receptor, suppressing its transcriptional activity (ferrari2021lemurtyrosinekinases pages 7-8).

## Other Comments

• Lmtk2-knockout mice are viable but males are infertile due to azoospermia, indicating an essential role in spermatogenesis (bencze2018biologicalfunctionof pages 7-8).  
• Reduced LMTK2 expression is observed in Alzheimer-related models and is linked to neurodegenerative pathways (bencze2018biologicalfunctionof pages 7-8).  
• Down-regulation of LMTK2 in prostate cancer correlates with heightened androgen receptor signalling and disease progression (ferrari2021lemurtyrosinekinases pages 7-8).  
• Excessive LMTK2-mediated phosphorylation of CFTR contributes to cystic-fibrosis-related defects in chloride transport (wendler2021thelmtkfamilyof pages 10-13).

References

1. (bencze2018biologicalfunctionof pages 1-2): János Bencze, Gábor Miklós Mórotz, Woosung Seo, Viktor Bencs, János Kálmán, Christopher Charles John Miller, and Tibor Hortobágyi. Biological function of lemur tyrosine kinase 2 (lmtk2): implications in neurodegeneration. Molecular Brain, Apr 2018. URL: https://doi.org/10.1186/s13041-018-0363-x, doi:10.1186/s13041-018-0363-x. This article has 36 citations and is from a peer-reviewed journal.
2. (bencze2018biologicalfunctionof pages 2-4): János Bencze, Gábor Miklós Mórotz, Woosung Seo, Viktor Bencs, János Kálmán, Christopher Charles John Miller, and Tibor Hortobágyi. Biological function of lemur tyrosine kinase 2 (lmtk2): implications in neurodegeneration. Molecular Brain, Apr 2018. URL: https://doi.org/10.1186/s13041-018-0363-x, doi:10.1186/s13041-018-0363-x. This article has 36 citations and is from a peer-reviewed journal.
3. (bencze2018biologicalfunctionof pages 7-8): János Bencze, Gábor Miklós Mórotz, Woosung Seo, Viktor Bencs, János Kálmán, Christopher Charles John Miller, and Tibor Hortobágyi. Biological function of lemur tyrosine kinase 2 (lmtk2): implications in neurodegeneration. Molecular Brain, Apr 2018. URL: https://doi.org/10.1186/s13041-018-0363-x, doi:10.1186/s13041-018-0363-x. This article has 36 citations and is from a peer-reviewed journal.
4. (cruz2019unravelingthefunction pages 1-2): Daniel F. Cruz, Carlos M. Farinha, and Agnieszka Swiatecka-Urban. Unraveling the function of lemur tyrosine kinase 2 network. Frontiers in Pharmacology, Jan 2019. URL: https://doi.org/10.3389/fphar.2019.00024, doi:10.3389/fphar.2019.00024. This article has 18 citations and is from a peer-reviewed journal.
5. (cruz2019unravelingthefunction pages 2-3): Daniel F. Cruz, Carlos M. Farinha, and Agnieszka Swiatecka-Urban. Unraveling the function of lemur tyrosine kinase 2 network. Frontiers in Pharmacology, Jan 2019. URL: https://doi.org/10.3389/fphar.2019.00024, doi:10.3389/fphar.2019.00024. This article has 18 citations and is from a peer-reviewed journal.
6. (cruz2019unravelingthefunction pages 3-5): Daniel F. Cruz, Carlos M. Farinha, and Agnieszka Swiatecka-Urban. Unraveling the function of lemur tyrosine kinase 2 network. Frontiers in Pharmacology, Jan 2019. URL: https://doi.org/10.3389/fphar.2019.00024, doi:10.3389/fphar.2019.00024. This article has 18 citations and is from a peer-reviewed journal.
7. (ferrari2021lemurtyrosinekinases pages 3-5): Elena Ferrari, Valeria Naponelli, and Saverio Bettuzzi. Lemur tyrosine kinases and prostate cancer: a literature review. International Journal of Molecular Sciences, 22:5453, May 2021. URL: https://doi.org/10.3390/ijms22115453, doi:10.3390/ijms22115453. This article has 5 citations and is from a peer-reviewed journal.
8. (ferrari2021lemurtyrosinekinases pages 7-8): Elena Ferrari, Valeria Naponelli, and Saverio Bettuzzi. Lemur tyrosine kinases and prostate cancer: a literature review. International Journal of Molecular Sciences, 22:5453, May 2021. URL: https://doi.org/10.3390/ijms22115453, doi:10.3390/ijms22115453. This article has 5 citations and is from a peer-reviewed journal.
9. (larose2024thelemurtail pages 1-2): Angelique Larose, Christopher C. J. Miller, and Gábor M. Mórotz. The lemur tail kinase family in neuronal function and disfunction in neurodegenerative diseases. Cellular and Molecular Life Sciences, Nov 2024. URL: https://doi.org/10.1007/s00018-024-05480-0, doi:10.1007/s00018-024-05480-0. This article has 1 citations and is from a domain leading peer-reviewed journal.
10. (larose2024thelemurtail pages 2-4): Angelique Larose, Christopher C. J. Miller, and Gábor M. Mórotz. The lemur tail kinase family in neuronal function and disfunction in neurodegenerative diseases. Cellular and Molecular Life Sciences, Nov 2024. URL: https://doi.org/10.1007/s00018-024-05480-0, doi:10.1007/s00018-024-05480-0. This article has 1 citations and is from a domain leading peer-reviewed journal.
11. (manning2002theproteinkinase pages 3-3): G. Manning, D. B. Whyte, R. Martinez, T. Hunter, and S. Sudarsanam. The protein kinase complement of the human genome. Science, 298:1912-1934, Dec 2002. URL: https://doi.org/10.1126/science.1075762, doi:10.1126/science.1075762. This article has 10728 citations and is from a highest quality peer-reviewed journal.
12. (morotz2024arevisednomenclature pages 1-3): Gábor M Mórotz, Neil A. Bradbury, O. Caluseriu, S. Hisanaga, Christopher C J Miller, Agnieszka Swiatecka-Urban, H. Lenz, Stephen J Moss, and G. Giamas. A revised nomenclature for the lemur family of protein kinases. Communications Biology, Jan 2024. URL: https://doi.org/10.1038/s42003-023-05671-8, doi:10.1038/s42003-023-05671-8. This article has 6 citations and is from a peer-reviewed journal.
13. (nixon2013determinationofthe pages 16-20): Alexander Nixon, Ying Jia, Carl White, and Neil A. Bradbury. Determination of the membrane topology of lemur tyrosine kinase 2 (lmtk2) by fluorescence protease protection. American Journal of Physiology-Cell Physiology, 304:C164-C169, Jan 2013. URL: https://doi.org/10.1152/ajpcell.00288.2012, doi:10.1152/ajpcell.00288.2012. This article has 31 citations.
14. (unknownauthors2006peptidemicroarrayanalysis pages 1-8): Peptide Microarray Analysis of Substrate Specificity of the Transmembrane
15. (unknownauthors2006peptidemicroarrayanalysis pages 13-18): Peptide Microarray Analysis of Substrate Specificity of the Transmembrane
16. (unknownauthors2006peptidemicroarrayanalysis pages 8-13): Peptide Microarray Analysis of Substrate Specificity of the Transmembrane
17. (unknownauthors2020regulationofthe pages 46-50): Regulation of the TGF-β1 signaling in cystic fibrosis: the role of LMTK2
18. (unknownauthors2020regulationofthe pages 50-54): Regulation of the TGF-β1 signaling in cystic fibrosis: the role of LMTK2
19. (wendler2021thelmtkfamilyof pages 1-6): Franz Wendler, Teodora-Maria Purice, Thomas Simon, Justin Stebbing, and Georgios Giamas. The lmtk-family of kinases: emerging important players in cell physiology and pathogenesis. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1867:165372, Sep 2021. URL: https://doi.org/10.1016/j.bbadis.2018.12.023, doi:10.1016/j.bbadis.2018.12.023. This article has 25 citations.
20. (wendler2021thelmtkfamilyof pages 10-13): Franz Wendler, Teodora-Maria Purice, Thomas Simon, Justin Stebbing, and Georgios Giamas. The lmtk-family of kinases: emerging important players in cell physiology and pathogenesis. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1867:165372, Sep 2021. URL: https://doi.org/10.1016/j.bbadis.2018.12.023, doi:10.1016/j.bbadis.2018.12.023. This article has 25 citations.
21. (wendler2021thelmtkfamilyof pages 6-10): Franz Wendler, Teodora-Maria Purice, Thomas Simon, Justin Stebbing, and Georgios Giamas. The lmtk-family of kinases: emerging important players in cell physiology and pathogenesis. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1867:165372, Sep 2021. URL: https://doi.org/10.1016/j.bbadis.2018.12.023, doi:10.1016/j.bbadis.2018.12.023. This article has 25 citations.