1. Phylogeny  
   Serine/threonine‐protein kinase LMTK2, encoded by the LMTK2 gene and alternatively known as AATYK2, BREK, KIAA1079, KPI2, and LMR2, is a member of the lemur tail kinase (LMTK) family, a distinct subgroup within the human kinome that was originally predicted to function as a tyrosine kinase but has been conclusively demonstrated to phosphorylate only serine and threonine residues (bencze2018biologicalfunctionof pages 1-2, morotz2024arevisednomenclature pages 1-3). Orthologs of LMTK2 are found across mammalian species, and its evolutionary conservation is evident from its shared structural architecture with the other family members LMTK1 and LMTK3, which together define a small but evolutionarily ancient branch of membrane‐anchored serine/threonine kinases (wendler2021thelmtkfamilyof pages 1-6, larose2024thelemurtail pages 1-2). The phylogenetic relationship of LMTK2 to other eukaryotic kinases is underscored by its modular domain organization and functional attributes that highlight its divergence from the classical tyrosine kinases; instead, it shares common ancestry with many serine/threonine kinases that regulate intracellular signaling and trafficking (morotz2024arevisednomenclature pages 1-3, bencze2018biologicalfunctionof pages 2-4). This family of kinases is thought to have evolved early in eukaryotic history, tracing back to the common ancestors of modern mammals while maintaining specialized functions in neuronal and reproductive tissues (larose2024thelemurtail pages 1-2, wendler2021thelmtkfamilyof pages 1-6).
2. Reaction Catalyzed  
   LMTK2 catalyzes a classical kinase reaction that transfers a phosphate group from ATP to the hydroxyl group of serine or threonine residues on target substrate proteins, following the reaction: ATP + [protein]-(L-serine or L-threonine) → ADP + [protein]-(phosphorylated serine/threonine) + H⁺ (bencze2018biologicalfunctionof pages 1-2, cruz2019unravelingthefunction pages 1-2). This phosphorylation reaction is central to LMTK2’s role in modulating the function of its substrates, which include the catalytic subunit of protein phosphatase 1 (PPP1C), phosphorylase b, and the cystic fibrosis transmembrane conductance regulator (CFTR) (bencze2018biologicalfunctionof pages 1-2, ferrari2021lemurtyrosinekinases pages 5-7).
3. Cofactor Requirements  
   The catalytic activity of LMTK2 depends on the presence of ATP as the phosphate donor and requires the divalent cation Mg²⁺ as an essential cofactor to properly coordinate the phosphate transfer reaction. This dependency on ATP and Mg²⁺ is typical for serine/threonine kinases and aligns with the conserved biochemical mechanisms observed across the kinome (morotz2024arevisednomenclature pages 5-5).
4. Substrate Specificity  
   LMTK2 exhibits substrate specificity by phosphorylating serine and threonine residues exclusively, a specificity that distinguishes it from dual-specificity kinases. It is known to phosphorylate the catalytic subunit of protein phosphatase 1 (PPP1C) at threonine-320, thereby inhibiting its phosphatase activity, and it also phosphorylates phosphorylase b as well as CFTR, with phosphorylation of CFTR occurring, for example, at serine 737 (bencze2018biologicalfunctionof pages 1-2, cruz2019unravelingthefunction pages 5-6). Although a precise consensus motif has not been universally defined for LMTK2 substrates, studies indicate that its activity is confined to serine/threonine residues and it does not act on tyrosine residues despite previous predictions based on sequence homology (bencze2018biologicalfunctionof pages 1-2, morotz2024arevisednomenclature pages 1-3).
5. Structure  
   LMTK2 is an approximately 250 kDa protein that is organized into distinct structural regions essential for its function. The protein is an integral membrane enzyme containing two amino‐terminal transmembrane domains that anchor it into cellular membranes, with both the N- and C-termini exposed to the cytosol as demonstrated by fluorescence protease protection and digitonin-permeabilization assays (bencze2018biologicalfunctionof pages 1-2, nixon2013determinationofthe pages 16-20). Immediately following the transmembrane segments, LMTK2 contains a conventional serine/threonine protein kinase domain, which spans roughly residues 137 to 407, and includes key features such as the conserved ATP-binding motif, an essential catalytic lysine, an activation loop, and hydrophobic spine elements that are characteristic of serine/threonine kinases (cruz2019unravelingthefunction pages 1-2, morotz2024arevisednomenclature pages 3-4). In addition to the kinase domain, LMTK2 possesses a long carboxyl-terminal tail enriched with multiple proline-rich (PxxP) motifs; these motifs are proposed to mediate interactions with SH3 domain-containing proteins, providing a scaffold for additional regulatory and signaling complexes (bencze2018biologicalfunctionof pages 1-2, larose2024thelemurtail pages 2-4). Structural models, including those generated by AlphaFold2, support this domain organization and reveal that the overall three-dimensional conformation is consistent with a membrane-associated kinase that integrates catalytic activity with protein–protein interaction capabilities (faezov2023alphafold2modelsof pages 49-50, morotz2024arevisednomenclature pages 5-5).
6. Regulation  
   The activity of LMTK2 is tightly regulated by multiple phosphorylation events and protein–protein interactions. An important regulatory mechanism involves phosphorylation by the cyclin-dependent kinase 5 (CDK5) complexed with its activator p35; CDK5/p35 phosphorylates LMTK2 at serine-1418 (mouse sequence; corresponding to serine-1450 in human), resulting in enhanced kinase activity (bencze2019neuropathologicalcharacterizationof pages 4-6, cruz2019unravelingthefunction pages 3-5). Conversely, exposure to nerve growth factor (NGF) in PC12 cells triggers PKC-dependent phosphorylation of LMTK2 that leads to a reduction in its activity and an increase in neurite outgrowth (bencze2018biologicalfunctionof pages 1-2, cruz2019unravelingthefunction pages 6-7). LMTK2 also auto‐phosphorylates and forms complexes with protein phosphatase 1 (PPP1C); by phosphorylating PPP1C at threonine-320, LMTK2 inhibits PPP1C activity, thereby affecting downstream kinases such as glycogen synthase kinase 3β (GSK3β) whose inhibitory phosphorylation at serine-9 is increased as part of this cascade (manser2012lemurtyrosinekinase2 pages 2-4, cruz2019unravelingthefunction pages 6-7). These regulatory events establish a complex network in which LMTK2 acts both as a substrate and as a modulator of phosphorylation-dependent signaling pathways, particularly those involved in intracellular transport and neuronal function (bencze2018biologicalfunctionof pages 2-4, larose2024thelemurtail pages 10-11).
7. Function  
   LMTK2 is predominantly expressed in the brain, where it is enriched in regions such as the cerebral cortex, hippocampus, and cerebellum, although it is also present in other tissues like the prostate and testis (bencze2018biologicalfunctionof pages 1-2, larose2024thelemurtail pages 1-2). In neuronal cells, LMTK2 plays a central role in regulating intracellular trafficking; for example, it phosphorylates the catalytic subunit of protein phosphatase 1 (PPP1C) to modulate phosphatase activity, thereby influencing axonal transport and synaptic plasticity (manser2012lemurtyrosinekinase2 pages 1-2, cruz2019unravelingthefunction pages 2-3). LMTK2 also phosphorylates phosphorylase b and CFTR, contributing to the regulation of basic metabolic and ion transport processes. In the context of CFTR, LMTK2-mediated phosphorylation affects the endocytosis and recycling of the chloride channel, which is important for maintaining proper epithelial cell function (ferrari2021lemurtyrosinekinases pages 5-7, cruz2019unravelingthefunction pages 5-6). Beyond its roles in intracellular transport, LMTK2 is implicated in neuronal differentiation and survival; its modulation by NGF and CDK5/p35 links it to pathways that control neurite outgrowth and tau protein phosphorylation, thereby playing a potential role in the pathogenesis of neurodegenerative diseases such as Alzheimer’s disease (bencze2019neuropathologicalcharacterizationof pages 4-6, wendler2021thelmtkfamilyof pages 1-6). Additionally, knockout studies in mice have demonstrated that loss of LMTK2 results in male infertility due to defects in spermatogenesis, indicating that LMTK2 has critical functions in reproductive biology (bencze2018biologicalfunctionof pages 1-2, wendler2021thelmtkfamilyof pages 6-10). In cancer, particularly prostate cancer, reduced LMTK2 expression has been correlated with enhanced androgen receptor signaling and tumorigenic phenotypes, suggesting a role in suppressing oncogenic pathways (ferrari2021lemurtyrosinekinases pages 7-8, shah2015lemurtyrosinekinase pages 1-3).
8. Other Comments  
   At present, no selective and well‐characterized inhibitors of LMTK2 have been reported, although its involvement in key signaling cascades that regulate neuronal function, intracellular trafficking, and androgen receptor activity renders it an appealing target for therapeutic intervention (bencze2018biologicalfunctionof pages 1-2, wendler2021thelmtkfamilyof pages 20-24). The standardized nomenclature for LMTK2, which consolidates its numerous alternative names, has facilitated clearer communication within the scientific community and helped to distinguish its function among the diverse members of the kinome (morotz2024arevisednomenclature pages 1-3, larose2024thelemurtail pages 1-2). In addition to its roles in normal cell physiology, aberrant LMTK2 expression has been associated with neurodegenerative conditions such as Alzheimer’s disease as well as with certain cancers, notably prostate cancer, where decreased levels of LMTK2 may contribute to disease progression (bencze2019neuropathologicalcharacterizationof pages 4-6, ferrari2021lemurtyrosinekinases pages 8-9). Further studies are required to fully characterize its substrate specificity, regulatory mechanisms, and potential for targeted pharmacologic inhibition.
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