## Phylogeny

STK11/LKB1 is classified within the Ca²⁺/calmodulin-dependent protein kinase-like (CAMK) group and forms the LKB1/CaMKK subfamily of the human kinome (fan2009themolecularmechanisms pages 2-2). Orthologs are conserved in Mus musculus (Lkb1), Xenopus laevis (XEEK1), Drosophila melanogaster (Lkb1) and Caenorhabditis elegans (par-4); the human enzyme shares ≥ 92 % overall identity with its murine counterpart and retains near-complete conservation within the catalytic core (fan2009themolecularmechanisms pages 8-9).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-Ser/Thr-P (fan2009themolecularmechanisms pages 2-2).

## Cofactor Requirements

Catalysis requires a divalent metal ion; substitution of the metal-binding residue Asp194 with Ala abolishes activity by preventing Mg²⁺ coordination, demonstrating Mg²⁺ dependence (zeqiraj2009structureofthe pages 1-2).

## Substrate Specificity

LKB1 phosphorylates the invariant activation-loop threonine of 13 AMP-activated protein kinase (AMPK)-related kinases, including PRKAA1/2, MARK1-4, NUAK1/2, SIK1-3, BRSK1/2 and SNRK (fan2009themolecularmechanisms pages 2-2, hawley2003complexesbetweenthe pages 16-16). A broader linear consensus beyond this activation-loop threonine has not been defined in the cited studies.

## Structure

The 433-residue protein contains:  
• N-terminal segment with a nuclear localisation signal (residues 38–43)  
• Bilobal kinase domain (residues 49–309)  
• C-terminal regulatory tail (residues 310–433) terminating in a CAAX farnesylation motif at Cys430 (fan2009themolecularmechanisms pages 2-2)

A 2.65 Å crystal structure of the LKB1–STRADα–MO25α heterotrimer shows:  
– STRADα adopts a closed, pseudo-active conformation and positions the αC helix to form the catalytic Lys78–Glu98 salt bridge in LKB1 (zeqiraj2009structureofthe pages 2-4).  
– MO25α stabilises the ordered activation loop; Glu199 supplies the negative charge that replaces canonical activation-loop phosphorylation (zeqiraj2009structureofthe pages 2-4).  
– The proline-rich C-terminal flanking tail contacts STRADα; its deletion destabilises the complex and lowers turnover (zeqiraj2009structureofthe pages 2-4).  
– Asp194 coordinates Mg²⁺; its mutation disrupts catalysis without affecting heterotrimer assembly (zeqiraj2009structureofthe pages 1-2).

## Regulation

Activation requires heterotrimer formation with STRAD (α or β) and MO25 (α or β), which promotes cytoplasmic localisation and allosteric activation (baas2003activationofthe pages 8-9, fan2009themolecularmechanisms pages 2-2, hawley2003complexesbetweenthe pages 16-16).

Post-translational modifications:  
– Autophosphorylation: Thr185, Thr336, Thr363, Thr402 (baas2003activationofthe pages 8-9).  
– Additional phosphorylation: Ser31, Ser325, Thr336, Thr366 (sapkota2002identificationandcharacterization pages 10-10).  
– Ser428 phosphorylated by PKA, p90RSK and PKCζ (unknownauthors2017theroleof pages 20-25).  
– SUMOylation: Lys96, Lys178, Lys235; Lys178 modification is required for AMPK engagement (trelford2024lkb1biologyassessing pages 11-13).  
– Farnesylation at Cys430 drives membrane association; S-nitrosylation of the same residue triggers ubiquitin-mediated degradation (trelford2024lkb1biologyassessing pages 11-13).  
– Reversible acetylation by SIRT1-3 modulates localisation and stability (trelford2024lkb1biologyassessing pages 11-13).  
– Polyubiquitination by Skp2-SCF and RNF146 promotes proteasomal turnover (trelford2024lkb1biologyassessing pages 11-13).

## Function

LKB1 is the master upstream kinase of the AMPK pathway, enforcing an energy-stress checkpoint that inhibits mTORC1 through AMPK-dependent phosphorylation of TSC2 and raptor (shackelford2009thelkb1–ampkpathway pages 2-4). Activation of MARK/PAR-1 kinases controls epithelial polarity and microtubule dynamics (hawley2003complexesbetweenthe pages 16-16). During metabolic stress, LKB1-AMPK signalling enhances NADPH production, restricts reactive oxygen species and stimulates autophagy and mitophagy (ponstostivint2021stk11lkb1modulationof pages 2-4). Expression is ubiquitous but enriched in cerebral cortex, ovary, salivary glands, skeletal muscle, testis and tonsil (unknownauthors2017theroleof pages 20-25). Upstream cues include PKA, PKCζ and ATM, which phosphorylate LKB1 at defined sites (unknownauthors2017theroleof pages 20-25, sapkota2002identificationandcharacterization pages 10-10).

## Inhibitors

No selective small-molecule inhibitors have been reported; the protein’s tumour-suppressor role and complex regulation hinder direct inhibitor development (trelford2024lkb1biologyassessing pages 11-13).

## Other Comments

Germline loss-of-function mutations cause Peutz–Jeghers syndrome, characterised by gastrointestinal hamartomas and elevated cancer risk (fan2009themolecularmechanisms pages 8-9). Somatic inactivation through deletions, nonsense or frameshift mutations occurs in lung, pancreatic and cervical cancers (fan2009themolecularmechanisms pages 2-2). Recurrent missense variants W308C, L67P, L182P, G242V and R297S disrupt folding and abolish activity (trelford2024lkb1biologyassessing pages 1-2). Tumour-derived mutants such as R87K, Y49D, G135R and D194Y display differential effects on kinase activity, motility and localisation (granadomartinez2020stk11(lkb1)missense pages 7-8). Loss of LKB1 synergises with oncogenic KRAS to accelerate lung tumourigenesis and is associated with immune-cold tumour microenvironments (shackelford2009thelkb1–ampkpathway pages 20-23, ponstostivint2021stk11lkb1modulationof pages 1-2).

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