## Phylogeny

UHMK1 is a serine/threonine kinase classified within the human kinome (manning2002theproteinkinase pages 1-2). One source classifies it within the AGC kinase family (arfelli2023uhmk1isa pages 19-20), while other sources suggest it aligns with the CMGC group (cyclin-dependent, MAP, GSK3, CDK-like kinases) based on its proline-directed substrate preference and functional roles (arfelli2023uhmk1isa pages 1-2, manning2002theproteinkinase pages 7-8, unknownauthors2008moleculargeneticsof pages 166-170). The protein is highly conserved evolutionarily; protein identity is >99% with primates and other mammals, 99.3% with rodents (*Mus musculus*, *Rattus norvegicus*), 88.2% with *Gallus gallus* (chicken), and 73.6% with *Danio rerio* (zebrafish) (arfelli2018uhmk1(u2afhomology pages 20-22). Its U2AF homology motif (UHM) is evolutionarily adapted from RNA recognition motifs (RRMs) to mediate protein-protein interactions (arfelli2023uhmk1isa pages 1-2).

## Reaction Catalyzed

UHMK1 catalyzes the ATP-dependent transfer of a γ-phosphate group to the hydroxyl group of serine or threonine residues on substrate proteins (manning2002theproteinkinase pages 1-2, arfelli2023uhmk1isa pages 19-20).

## Cofactor Requirements

The catalytic activity of UHMK1 is dependent on Mg²⁺ as a cofactor (arfelli2018uhmk1(u2afhomology pages 15-17, arfelli2023uhmk1isa pages 19-20, francone2010signalingfromthe pages 1-2, unknownauthors2008moleculargeneticsof pages 166-170).

## Substrate Specificity

UHMK1 preferentially phosphorylates proline-directed serine residues (arfelli2018uhmk1(u2afhomology pages 17-18, arfelli2023uhmk1isa pages 1-2, arfelli2023uhmk1isa pages 1-2, unknownauthors2008moleculargeneticsof pages 166-170). pLogo motif analysis of phosphoproteomic data identified a consensus phosphorylation motif of [R]-X(0,3)-S-P-[E/D/Q] (arfelli2023uhmk1isa pages 5-6). This analysis revealed proline at the +1 position in 41.67% of sites, with a significant enrichment of arginine (R) at position -3 and glutamic acid (E) at positions -4, +2, and +3 (arfelli23uhmk1isa pages 5-6). UHMK1 was among 303 human serine/threonine kinases whose substrate specificity was profiled using positional scanning peptide arrays, though a specific motif from this study is not detailed in the provided context (johnson2023anatlasof pages 1-2).

## Structure

UHMK1 consists of an N-terminal kinase core of 282 amino acids and a C-terminal U2AF homology motif (UHM) of 100 amino acids (arfelli2018uhmk1(u2afhomology pages 17-18). The kinase domain confers catalytic activity, for which Lysine 54 (K54) is essential (arfelli2018uhmk1(u2afhomology pages 17-18). The C-terminal UHM domain is a protein-protein interaction module that binds to UHM-ligand motifs (ULMs) found in substrates, particularly splicing factors (arfelli2018uhmk1(u2afhomology pages 17-18, arfelli2023uhmk1isa pages 5-6). No experimentally determined 3D structures from the Protein Data Bank (PDB) are mentioned in the context; computational models from AlphaFold are referenced (arfelli2023uhmk1isa pages 5-6, johnson2023anatlasof pages 1-2). Information regarding key catalytic and regulatory features such as the activation loop, C-helix, or hydrophobic spine is not available in the provided sources.

## Regulation

UHMK1 is regulated at the transcriptional and post-translational levels. Its transcription is activated by transcription factors GABP and FOXM1 and is promoted by WDR5, a component of the KMT2A/SETD1A methyltransferase complex that mediates H3K4 trimethylation at the UHMK1 promoter (arfelli2018uhmk1(u2afhomology pages 17-18). UHMK1 expression levels accumulate in the G1 phase and decrease during the S phase of the cell cycle (arfelli2018uhmk1(u2afhomology pages 17-18). Mitogenic stimulation activates UHMK1 via autophosphorylation (unknownauthors2008moleculargeneticsof pages 170-175).

Post-translational modifications (PTMs) identified on UHMK1 include phosphorylation at sites Y197, S283, and S290, and ubiquitination at lysines K190, K282, K383, and K387 (arfelli2018uhmk1(u2afhomology pages 17-18). However, the functional consequences of these specific phosphorylation and ubiquitination events on UHMK1 activity, localization, or stability are not clarified in the provided sources (arfelli2018uhmk1(u2afhomology pages 17-18). Upstream signaling pathways involving Akt, FGF-2, PI 3-kinase/Rac1, and ERK1/2 also regulate UHMK1 functions (arfelli2018uhmk1(u2afhomology pages 15-17, arfelli2018uhmk1(u2afhomology pages 22-23).

## Function

UHMK1 is a kinase that localizes to both the nucleus and cytoplasm and is ubiquitously expressed, with enriched levels in the nervous system (especially the hippocampus) and hematopoietic cells (arfelli2018uhmk1(u2afhomology pages 18-20, arfelli2018uhmk1(u2afhomology pages 17-18, francone2010signalingfromthe pages 1-2).

UHMK1’s functions are mediated by phosphorylation of specific substrates: \* **RNA Processing and Splicing:** It phosphorylates splicing factors SF1 and SF3B1 to enhance early spliceosome assembly and regulates over 270 alternative splicing events (arfelli2018uhmk1(u2afhomology pages 18-20, arfelli2023uhmk1isa pages 1-2). This phosphorylation of SF1 enhances its binding to U2AF65 (arfelli2018uhmk1(u2afhomology pages 22-23). Other substrates in this pathway include SUGP1, hnRNP M, and PRRC2B (arfelli2023uhmk1isa pages 9-11). \* **Cell Cycle Progression:** In response to mitogenic signals, UHMK1 phosphorylates the cyclin-dependent kinase inhibitor p27Kip1 (CDKN1B) on Ser10, leading to its nuclear export and subsequent proteasomal degradation, which facilitates progression through the G1 phase (arfelli2018uhmk1(u2afhomology pages 18-20, barbutti2018theu2afhomology pages 16-20, arfelli2023uhmk1isa pages 1-2). \* **Cytoskeletal Dynamics and Cell Migration:** UHMK1 phosphorylates the microtubule destabilizer Stathmin (STMN) on Ser38, which targets STMN for degradation, thereby impacting microtubule dynamics and negatively regulating cell migration (arfelli2018uhmk1(u2afhomology pages 18-20, arfelli2023uhmk1isa pages 1-2). \* **Neuronal and Secretory Function:** UHMK1 phosphorylates peptidylglycine α-amidating mono-oxygenase (PAM) on Ser949, a modification essential for proper protein trafficking in the secretory pathway and for regulating the nuclear localization of a PAM fragment (arfelli2018uhmk1(u2afhomology pages 20-22, unknownauthors2008moleculargeneticsof pages 170-175). In neurons, it associates with RNA granule components such as KIF3A and NONO and modulates the translation of transported mRNAs like β-actin (arfelli2018uhmk1(u2afhomology pages 18-20).

UHMK1 interacts with the proliferation marker PIMREG (FAM64A/CATS) and the transcription factor MYBL2 (arfelli2018uhmk1(u2afhomology pages 20-22, arfelli2023uhmk1isa pages 1-2). It also phosphorylates other kinases (PIK3C3, WNK1, NUCKS1, PRPF4B) and a phosphatase (PPP4R2), indicating a broader role in signaling networks (arfelli2023uhmk1isa pages 9-11).

## Inhibitors

No specific chemical inhibitors of UHMK1 are described in the provided context (arfelli2018uhmk1(u2afhomology pages 20-22, barbutti2018theu2afhomology pages 16-20, arfelli2018uhmk1(u2afhomology pages 22-23). UHMK1 expression is inhibited by the EGFR-targeting antibody trastuzumab (arfelli2018uhmk1(u2afhomology pages 20-22). The antipsychotic drug clozapine, but not haloperidol, downregulates UHMK1 expression in mice (unknownauthors2008moleculargeneticsof pages 170-175). Depletion of UHMK1 sensitizes EGFR-positive breast cancer cells to the kinase inhibitor erlotinib (arfelli2018uhmk1(u2afhomology pages 20-22).

## Other Comments

UHMK1 is associated with several human diseases. Higher UHMK1 transcript levels are observed in neurofibromatosis type 1-related tumors (arfelli2018uhmk1(u2afhomology pages 20-22). It is implicated in breast cancer, vascular remodeling, and neointima formation (arfelli2018uhmk1(u2afhomology pages 20-22). A genome-wide association study (GWAS) identified a single nucleotide polymorphism (SNP) in the UHMK1 locus linked to bone mineral density (arfelli2018uhmk1(u2afhomology pages 20-22, arfelli2018uhmk1(u2afhomology pages 22-23). An association with schizophrenia has been proposed but is considered controversial (arfelli2018uhmk1(u2afhomology pages 20-22).

No recurrent somatic mutations in UHMK1 have been identified in diseases like myelodysplastic syndrome (MDS) (barbutti2018theu2afhomology pages 16-20). The COSMIC database reports over 160 unique somatic mutations in various cancers, though their significance is not detailed (arfelli2018uhmk1(u2afhomology pages 20-22).

*Uhmk1* knockout mice exhibit disease-relevant phenotypes, including locomotor hyperactivity, reduced learning capacity, altered SF1 phosphorylation, and aberrant RNA splicing (arfelli2018uhmk1(u2afhomology pages 18-20).

References

1. (arfelli2018uhmk1(u2afhomology pages 18-20): Vanessa C. Arfelli and L. Archangelo. Uhmk1 (u2af homology motif kinase 1). Atlas of Genetics and Cytogenetics in Oncology and Haematology, Nov 2018. URL: https://doi.org/10.4267/2042/68931, doi:10.4267/2042/68931. This article has 0 citations and is from a peer-reviewed journal.
2. (arfelli2018uhmk1(u2afhomology pages 20-22): Vanessa C. Arfelli and L. Archangelo. Uhmk1 (u2af homology motif kinase 1). Atlas of Genetics and Cytogenetics in Oncology and Haematology, Nov 2018. URL: https://doi.org/10.4267/2042/68931, doi:10.4267/2042/68931. This article has 0 citations and is from a peer-reviewed journal.
3. (arfelli2023uhmk1isa pages 1-2): Vanessa C. Arfelli, Yun-Chien Chang, Johannes W. Bagnoli, Paul Kerbs, Felipe E. Ciamponi, Laíssa Paz, Serhii Pankivskyi, Jean de Matha Salone, A. Maucuer, K. Massirer, W. Enard, B. Kuster, P. Greif, and L. Archangelo. Uhmk1 is a novel splicing regulatory kinase. The Journal of Biological Chemistry, Feb 2023. URL: https://doi.org/10.1016/j.jbc.2023.103041, doi:10.1016/j.jbc.2023.103041. This article has 8 citations.
4. (barbutti2018theu2afhomology pages 16-20): Isabella Barbutti, J. Machado-Neto, Vanessa C. Arfelli, Paula de Melo Campos, F. Traina, S. T. Olalla Saad, and L. Archangelo. The u2af homology motif kinase 1 (uhmk1) is upregulated upon hematopoietic cell differentiation. bioRxiv, Sep 2018. URL: https://doi.org/10.1101/187385, doi:10.1101/187385. This article has 14 citations.
5. (unknownauthors2008moleculargeneticsof pages 170-175): Molecular genetics of the 1q23. 3 schizophrenia susceptibility locus
6. (arfelli2018uhmk1(u2afhomology pages 15-17): Vanessa C. Arfelli and L. Archangelo. Uhmk1 (u2af homology motif kinase 1). Atlas of Genetics and Cytogenetics in Oncology and Haematology, Nov 2018. URL: https://doi.org/10.4267/2042/68931, doi:10.4267/2042/68931. This article has 0 citations and is from a peer-reviewed journal.
7. (arfelli2018uhmk1(u2afhomology pages 17-18): Vanessa C. Arfelli and L. Archangelo. Uhmk1 (u2af homology motif kinase 1). Atlas of Genetics and Cytogenetics in Oncology and Haematology, Nov 2018. URL: https://doi.org/10.4267/2042/68931, doi:10.4267/2042/68931. This article has 0 citations and is from a peer-reviewed journal.
8. (arfelli2018uhmk1(u2afhomology pages 22-23): Vanessa C. Arfelli and L. Archangelo. Uhmk1 (u2af homology motif kinase 1). Atlas of Genetics and Cytogenetics in Oncology and Haematology, Nov 2018. URL: https://doi.org/10.4267/2042/68931, doi:10.4267/2042/68931. This article has 0 citations and is from a peer-reviewed journal.
9. (arfelli2023uhmk1isa pages 19-20): Vanessa C. Arfelli, Yun-Chien Chang, Johannes W. Bagnoli, Paul Kerbs, Felipe E. Ciamponi, Laíssa Paz, Serhii Pankivskyi, Jean de Matha Salone, A. Maucuer, K. Massirer, W. Enard, B. Kuster, P. Greif, and L. Archangelo. Uhmk1 is a novel splicing regulatory kinase. The Journal of Biological Chemistry, Feb 2023. URL: https://doi.org/10.1016/j.jbc.2023.103041, doi:10.1016/j.jbc.2023.103041. This article has 8 citations.
10. (arfelli2023uhmk1isa pages 5-6): Vanessa C. Arfelli, Yun-Chien Chang, Johannes W. Bagnoli, Paul Kerbs, Felipe E. Ciamponi, Laíssa Paz, Serhii Pankivskyi, Jean de Matha Salone, A. Maucuer, K. Massirer, W. Enard, B. Kuster, P. Greif, and L. Archangelo. Uhmk1 is a novel splicing regulatory kinase. The Journal of Biological Chemistry, Feb 2023. URL: https://doi.org/10.1016/j.jbc.2023.103041, doi:10.1016/j.jbc.2023.103041. This article has 8 citations.
11. (arfelli2023uhmk1isa pages 9-11): Vanessa C. Arfelli, Yun-Chien Chang, Johannes W. Bagnoli, Paul Kerbs, Felipe E. Ciamponi, Laíssa Paz, Serhii Pankivskyi, Jean de Matha Salone, A. Maucuer, K. Massirer, W. Enard, B. Kuster, P. Greif, and L. Archangelo. Uhmk1 is a novel splicing regulatory kinase. The Journal of Biological Chemistry, Feb 2023. URL: https://doi.org/10.1016/j.jbc.2023.103041, doi:10.1016/j.jbc.2023.103041. This article has 8 citations.
12. (francone2010signalingfromthe pages 1-2): V. Francone, Marius F Ifrim, Chitra Rajagopal, C. Leddy, Yanping Wang, J. Carson, R. Mains, and B. Eipper. Signaling from the secretory granule to the nucleus: uhmk1 and pam. Molecular endocrinology, 24 8:1543-58, Aug 2010. URL: https://doi.org/10.1210/me.2009-0381, doi:10.1210/me.2009-0381. This article has 51 citations.
13. (unknownauthors2008moleculargeneticsof pages 166-170): Molecular genetics of the 1q23. 3 schizophrenia susceptibility locus
14. (johnson2023anatlasof pages 1-2): Jared L. Johnson, Tomer M. Yaron, Emily M. Huntsman, Alexander Kerelsky, Junho Song, Amit Regev, Ting-Yu Lin, Katarina Liberatore, Daniel M. Cizin, Benjamin M. Cohen, Neil Vasan, Yilun Ma, Konstantin Krismer, Jaylissa Torres Robles, Bert van de Kooij, Anne E. van Vlimmeren, Nicole Andrée-Busch, Norbert F. Käufer, Maxim V. Dorovkov, Alexey G. Ryazanov, Yuichiro Takagi, Edward R. Kastenhuber, Marcus D. Goncalves, Benjamin D. Hopkins, Olivier Elemento, Dylan J. Taatjes, Alexandre Maucuer, Akio Yamashita, Alexei Degterev, Mohamed Uduman, Jingyi Lu, Sean D. Landry, Bin Zhang, Ian Cossentino, Rune Linding, John Blenis, Peter V. Hornbeck, Benjamin E. Turk, Michael B. Yaffe, and Lewis C. Cantley. An atlas of substrate specificities for the human serine/threonine kinome. Nature, 613:759-766, Jan 2023. URL: https://doi.org/10.1038/s41586-022-05575-3, doi:10.1038/s41586-022-05575-3. This article has 446 citations and is from a highest quality peer-reviewed journal.
15. (manning2002theproteinkinase pages 1-2): 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.
16. (manning2002theproteinkinase pages 7-8): 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.