## Phylogeny

Human NEK7 is assigned to the NEK sub-family within the CMGC group of the human kinome as defined by Manning et al. 2002 (bachus2022inmitosisyou pages 24-25).  
Within the NEK clade it is most closely related to NEK6 (≈86 % catalytic-domain identity) and operates downstream of the upstream activator NEK9 (liu2020nek7apotential pages 1-2).  
Experimentally verified orthologs exist in mouse, rat, zebrafish and Drosophila, and the Aspergillus nidulans NIMA kinase represents a conserved fungal counterpart (bachus2022inmitosisyou pages 24-25, oregan2007mitoticregulationby pages 6-8).

## Reaction Catalyzed

ATP + protein-Ser/Thr ⇌ ADP + protein-O-phospho-Ser/Thr (bachus2022inmitosisyou pages 29-30).

## Cofactor Requirements

Dependence on divalent cations has not been explicitly reported for NEK7 in the cited literature (bachus2022inmitosisyou pages 29-30).

## Substrate Specificity

Oriented peptide library screening defined a family consensus [L/M/F/W]-X-X-S/T-[no Pro+1] for NEKs; NEK7 adds a bias for acidic residues at −1 and hydrophobic residues (Leu/Phe) at +3 (kooij2019comprehensivesubstratespecificity pages 4-5).  
Additional preferences include phospho-tyrosine at −1 and tryptophan at +4, features validated by in vitro peptide phosphorylation (kooij2019comprehensivesubstratespecificity pages 5-6, kooij2019comprehensivesubstratespecificity pages 16-18).  
The Johnson 2023 kinome atlas does not report a NEK7 motif (kooij2019comprehensivesubstratespecificity pages 3-4).  
Cellular substrates that conform to these preferences include EML4-Ser146, TRF1-Ser114, kinesins KIF11/KIF14, Eg5-Ser1033 and RPS6KB1 (bachus2022inmitosisyou pages 14-15, bachus2022inmitosisyou pages 15-17).

## Structure

NEK7 is a 302-residue monomer composed of a short disordered N-terminus and a canonical bilobal serine/threonine kinase domain (liu2020nek7apotential pages 1-2).  
Crystal structures (PDB 2WQN, 5SY1) reveal a five-stranded β-sheet N-lobe and an α-helical C-lobe linked by a flexible hinge; Tyr97 protrudes into the active site, enforcing autoinhibition (byrne2020nek7conformationalflexibility pages 12-13).  
The regulatory spine (His159-Leu180-Leu86-Tyr97) is fully stacked only after Ser195 phosphorylation or engineered aromatic substitutions (byrne2020nek7conformationalflexibility pages 3-4).  
Key catalytic features include Lys81–Glu97 salt-bridge formation upon activation and an activation loop that harbours Thr169 and Ser195 (byrne2020nek7conformationalflexibility pages 12-13).  
Cryo-EM of the NEK7-NLRP3 complex (PDB 6NPY) shows the NEK7 C-lobe docking onto NLRP3 LRR and NACHT domains while the N-lobe remains flexible, explaining kinase-activity-independent licensing (sharif2019structuralmechanismfor pages 1-2, fu2023structuralmechanismsof pages 5-7).

## Regulation

• Ser195 phosphorylation by NEK9 stabilises the regulatory spine and activates the kinase (byrne2020nek7conformationalflexibility pages 12-13).  
• Thr169 undergoes autophosphorylation within the activation loop (kooij2019comprehensivesubstratespecificity pages 28-29).  
• Reactive-oxygen-species-induced phosphorylation enhances NLRP3 binding (shi2016nlrp3activationand pages 4-6).  
• Tyr97 mediates autoinhibition; Y97F mutation disengages this block (byrne2020nek7conformationalflexibility pages 3-4).  
• NEK9 promotes back-to-back dimerization that is mutually exclusive with NLRP3 engagement, providing an allosteric switch between mitosis and inflammasome licensing (sharif2019structuralmechanismfor pages 4-6).  
• Ubiquitination has been suggested but specific sites remain undefined (byrne2020nek7conformationalflexibility pages 15-15).

## Function

NEK7 is expressed in heart, brain, liver, lung and spleen and localises to centrosomes throughout the cell cycle, relocating to the spindle midzone and midbody during late mitosis (liu2020nek7apotential pages 1-2, oregan2007mitoticregulationby pages 8-9).  
Mitotic roles include pericentriolar material recruitment, centriole duplication, bipolar spindle assembly, chromosome congression and cytokinesis; depletion causes spindle defects, lagging chromosomes and cytokinesis failure (bachus2022inmitosisyou pages 14-15, fry2017mitoticregulationby pages 1-2).  
Upstream regulation: CDK1 and PLK1 activate NEK9, which in turn phosphorylates and activates NEK7 (liu2020nek7apotential pages 1-2).  
Documented downstream substrates: EML4-Ser146 (chromosome congression), KIF11 (spindle organisation), TRF1-Ser114 (telomere protection) and RPS6KB1 (growth signalling) (bachus2022inmitosisyou pages 14-15, bachus2022inmitosisyou pages 15-17).  
Inflammasome licensing: NEK7 binds NLRP3 LRR/HD2 interfaces, releases NLRP3 autoinhibition and enables ASC speck formation; kinase activity is dispensable for this scaffolding role (shi2016nlrp3activationand pages 4-6, sharif2019structuralmechanismfor pages 1-2).

## Inhibitors

Compound 51 is the first ATP-competitive inhibitor co-crystallised with NEK7 and serves as a structural template for probe development (byrne2020nek7conformationalflexibility pages 1-2).  
JNK-IN-1 inhibits NEK7 by >80 % at 10 µM with limited cross-NEK activity (wells2018indepthanalysis pages 13-15).  
GSK-3 Inhibitor XIII reduces NEK7 activity to ~46 % at 1.25 µM via a substrate-competitive mode (moraes2015kinaseinhibitorprofile pages 12-15).  
Additional low-micromolar hits have been identified in broad kinase screens but lack potency and selectivity (unknownauthors2021probingthefunctions pages 41-45, byrne2020nek7conformationalflexibility pages 13-14).

## Other Comments

Elevated NEK7 expression is linked to retinoblastoma, gallbladder carcinoma, hepatocellular carcinoma and head-and-neck squamous cell carcinoma (xu2016nek7anovel pages 1-1).  
Through control of NLRP3 activation, NEK7 contributes to inflammatory diseases such as gout, atherosclerosis, type 2 diabetes and Alzheimer’s disease (liu2020nek7apotential pages 1-2).  
A disease-linked R121H variant resides in the regulatory region and perturbs kinase regulation (bayliss2015theysand pages 20-25).

References

1. (bachus2022inmitosisyou pages 24-25): Scott Bachus, Drayson Graves, Lauren Fulham, N. Akkerman, Caelan Stephanson, Jessica Shieh, and P. Pelka. In mitosis you are not: the nima family of kinases in aspergillus, yeast, and mammals. International Journal of Molecular Sciences, Apr 2022. URL: https://doi.org/10.3390/ijms23074041, doi:10.3390/ijms23074041. This article has 12 citations and is from a peer-reviewed journal.
2. (byrne2020nek7conformationalflexibility pages 12-13): M. Byrne, N. Nasir, C. Basmadjian, C. Bhatia, R. Cunnison, K. Carr, C. Mas-Droux, S. Yeoh, Céline Cano, and R. Bayliss. Nek7 conformational flexibility and inhibitor binding probed through protein engineering of the r-spine. Biochemical Journal, 477:1525-1539, Apr 2020. URL: https://doi.org/10.1042/bcj20200128, doi:10.1042/bcj20200128. This article has 15 citations and is from a domain leading peer-reviewed journal.
3. (byrne2020nek7conformationalflexibility pages 13-14): M. Byrne, N. Nasir, C. Basmadjian, C. Bhatia, R. Cunnison, K. Carr, C. Mas-Droux, S. Yeoh, Céline Cano, and R. Bayliss. Nek7 conformational flexibility and inhibitor binding probed through protein engineering of the r-spine. Biochemical Journal, 477:1525-1539, Apr 2020. URL: https://doi.org/10.1042/bcj20200128, doi:10.1042/bcj20200128. This article has 15 citations and is from a domain leading peer-reviewed journal.
4. (kooij2019comprehensivesubstratespecificity pages 16-18): Bert van de Kooij, Pau Creixell, Anne E. van Vlimmeren, Brian A. Joughin, Chad J. Miller, N. Haider, R. Linding, V. Stambolic, B. Turk, and M. Yaffe. Comprehensive substrate specificity profiling of the human nek kinome reveals unexpected signaling outputs. eLife, Jan 2019. URL: https://doi.org/10.7554/elife.44635, doi:10.7554/elife.44635. This article has 53 citations and is from a domain leading peer-reviewed journal.
5. (kooij2019comprehensivesubstratespecificity pages 4-5): Bert van de Kooij, Pau Creixell, Anne E. van Vlimmeren, Brian A. Joughin, Chad J. Miller, N. Haider, R. Linding, V. Stambolic, B. Turk, and M. Yaffe. Comprehensive substrate specificity profiling of the human nek kinome reveals unexpected signaling outputs. eLife, Jan 2019. URL: https://doi.org/10.7554/elife.44635, doi:10.7554/elife.44635. This article has 53 citations and is from a domain leading peer-reviewed journal.
6. (liu2020nek7apotential pages 1-2): Ganglei Liu, Xueliang Chen, Qianqian Wang, and Lianwen Yuan. Nek7: a potential therapy target for nlrp3-related diseases. BioScience Trends, 14:74-82, Apr 2020. URL: https://doi.org/10.5582/bst.2020.01029, doi:10.5582/bst.2020.01029. This article has 59 citations and is from a peer-reviewed journal.
7. (moraes2015kinaseinhibitorprofile pages 12-15): Eduardo C. Moraes, G. Meirelles, R. Honorato, Tatiana de Arruda Campos Brasil de Souza, E. E. de Souza, M. Murakami, P. S. L. de Oliveira, and J. Kobarg. Kinase inhibitor profile for human nek1, nek6, and nek7 and analysis of the structural basis for inhibitor specificity. Molecules, 20:1176-1191, Jan 2015. URL: https://doi.org/10.3390/molecules20011176, doi:10.3390/molecules20011176. This article has 31 citations and is from a peer-reviewed journal.
8. (oregan2007mitoticregulationby pages 6-8): Laura O’Regan, Joelle Blot, and Andrew M Fry. Mitotic regulation by nima-related kinases. Cell Division, 2:25-25, Aug 2007. URL: https://doi.org/10.1186/1747-1028-2-25, doi:10.1186/1747-1028-2-25. This article has 273 citations and is from a peer-reviewed journal.
9. (sharif2019structuralmechanismfor pages 1-2): Humayun Sharif, Li Wang, Wei Li Wang, Venkat Giri Magupalli, Liudmila Andreeva, Qi Qiao, Arthur V. Hauenstein, Zhaolong Wu, Gabriel Núñez, Youdong Mao, and Hao Wu. Structural mechanism for nek7-licensed activation of nlrp3 inflammasome. Nature, 570:338-343, Jun 2019. URL: https://doi.org/10.1038/s41586-019-1295-z, doi:10.1038/s41586-019-1295-z. This article has 726 citations and is from a highest quality peer-reviewed journal.
10. (shi2016nlrp3activationand pages 4-6): Hexin Shi, Ying Wang, Xiaohong Li, X. Zhan, M. Tan, Maggy W Fina, L. Su, David Pratt, C. Bu, Sara Hildebrand, Stephen Lyon, L. Scott, Jiexia Quan, Qihua Sun, Jamie Russell, Stephanie M. Arnett, P. Jurek, Ding Chen, V. Kravchenko, J. Mathison, E. Moresco, N. Monson, R. Ulevitch, and B. Beutler. Nlrp3 activation and mitosis are mutually exclusive events coordinated by nek7, a new inflammasome component. Nature immunology, 17:250-258, Nov 2016. URL: https://doi.org/10.1038/ni.3333, doi:10.1038/ni.3333. This article has 765 citations and is from a highest quality peer-reviewed journal.
11. (wells2018indepthanalysis pages 13-15): C. I. Wells, N. R. Kapadia, R. M. Couñago, and D. H. Drewry. In depth analysis of kinase cross screening data to identify chemical starting points for inhibition of the nek family of kinases. MedChemComm, 9:44-66, Jan 2018. URL: https://doi.org/10.1039/c7md00510e, doi:10.1039/c7md00510e. This article has 25 citations.
12. (xu2016nek7anovel pages 1-1): Jin Xu, Liqun Lu, and Lanfang Li. Nek7: a novel promising therapy target for nlrp3-related inflammatory diseases. Acta Biochimica et Biophysica Sinica, 48:966-968, Oct 2016. URL: https://doi.org/10.1093/abbs/gmw080, doi:10.1093/abbs/gmw080. This article has 45 citations and is from a peer-reviewed journal.
13. (bachus2022inmitosisyou pages 14-15): Scott Bachus, Drayson Graves, Lauren Fulham, N. Akkerman, Caelan Stephanson, Jessica Shieh, and P. Pelka. In mitosis you are not: the nima family of kinases in aspergillus, yeast, and mammals. International Journal of Molecular Sciences, Apr 2022. URL: https://doi.org/10.3390/ijms23074041, doi:10.3390/ijms23074041. This article has 12 citations and is from a peer-reviewed journal.
14. (bachus2022inmitosisyou pages 29-30): Scott Bachus, Drayson Graves, Lauren Fulham, N. Akkerman, Caelan Stephanson, Jessica Shieh, and P. Pelka. In mitosis you are not: the nima family of kinases in aspergillus, yeast, and mammals. International Journal of Molecular Sciences, Apr 2022. URL: https://doi.org/10.3390/ijms23074041, doi:10.3390/ijms23074041. This article has 12 citations and is from a peer-reviewed journal.
15. (bayliss2015theysand pages 20-25): Richard Bayliss, Tamanna Haq, and Sharon Yeoh. The ys and wherefores of protein kinase autoinhibition. Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics, 1854:1586-1594, Oct 2015. URL: https://doi.org/10.1016/j.bbapap.2015.04.025, doi:10.1016/j.bbapap.2015.04.025. This article has 21 citations.
16. (byrne2020nek7conformationalflexibility pages 1-2): M. Byrne, N. Nasir, C. Basmadjian, C. Bhatia, R. Cunnison, K. Carr, C. Mas-Droux, S. Yeoh, Céline Cano, and R. Bayliss. Nek7 conformational flexibility and inhibitor binding probed through protein engineering of the r-spine. Biochemical Journal, 477:1525-1539, Apr 2020. URL: https://doi.org/10.1042/bcj20200128, doi:10.1042/bcj20200128. This article has 15 citations and is from a domain leading peer-reviewed journal.
17. (byrne2020nek7conformationalflexibility pages 15-15): M. Byrne, N. Nasir, C. Basmadjian, C. Bhatia, R. Cunnison, K. Carr, C. Mas-Droux, S. Yeoh, Céline Cano, and R. Bayliss. Nek7 conformational flexibility and inhibitor binding probed through protein engineering of the r-spine. Biochemical Journal, 477:1525-1539, Apr 2020. URL: https://doi.org/10.1042/bcj20200128, doi:10.1042/bcj20200128. This article has 15 citations and is from a domain leading peer-reviewed journal.
18. (byrne2020nek7conformationalflexibility pages 3-4): M. Byrne, N. Nasir, C. Basmadjian, C. Bhatia, R. Cunnison, K. Carr, C. Mas-Droux, S. Yeoh, Céline Cano, and R. Bayliss. Nek7 conformational flexibility and inhibitor binding probed through protein engineering of the r-spine. Biochemical Journal, 477:1525-1539, Apr 2020. URL: https://doi.org/10.1042/bcj20200128, doi:10.1042/bcj20200128. This article has 15 citations and is from a domain leading peer-reviewed journal.
19. (fry2017mitoticregulationby pages 1-2): Andrew M. Fry, Richard Bayliss, and Joan Roig. Mitotic regulation by nek kinase networks. Frontiers in Cell and Developmental Biology, Dec 2017. URL: https://doi.org/10.3389/fcell.2017.00102, doi:10.3389/fcell.2017.00102. This article has 105 citations and is from a peer-reviewed journal.
20. (fu2023structuralmechanismsof pages 5-7): Jianing Fu and Hao Wu. Structural mechanisms of nlrp3 inflammasome assembly and activation. Annual Review of Immunology, 41:301-316, Apr 2023. URL: https://doi.org/10.1146/annurev-immunol-081022-021207, doi:10.1146/annurev-immunol-081022-021207. This article has 647 citations and is from a highest quality peer-reviewed journal.
21. (kooij2019comprehensivesubstratespecificity pages 28-29): Bert van de Kooij, Pau Creixell, Anne E. van Vlimmeren, Brian A. Joughin, Chad J. Miller, N. Haider, R. Linding, V. Stambolic, B. Turk, and M. Yaffe. Comprehensive substrate specificity profiling of the human nek kinome reveals unexpected signaling outputs. eLife, Jan 2019. URL: https://doi.org/10.7554/elife.44635, doi:10.7554/elife.44635. This article has 53 citations and is from a domain leading peer-reviewed journal.
22. (kooij2019comprehensivesubstratespecificity pages 3-4): Bert van de Kooij, Pau Creixell, Anne E. van Vlimmeren, Brian A. Joughin, Chad J. Miller, N. Haider, R. Linding, V. Stambolic, B. Turk, and M. Yaffe. Comprehensive substrate specificity profiling of the human nek kinome reveals unexpected signaling outputs. eLife, Jan 2019. URL: https://doi.org/10.7554/elife.44635, doi:10.7554/elife.44635. This article has 53 citations and is from a domain leading peer-reviewed journal.
23. (kooij2019comprehensivesubstratespecificity pages 5-6): Bert van de Kooij, Pau Creixell, Anne E. van Vlimmeren, Brian A. Joughin, Chad J. Miller, N. Haider, R. Linding, V. Stambolic, B. Turk, and M. Yaffe. Comprehensive substrate specificity profiling of the human nek kinome reveals unexpected signaling outputs. eLife, Jan 2019. URL: https://doi.org/10.7554/elife.44635, doi:10.7554/elife.44635. This article has 53 citations and is from a domain leading peer-reviewed journal.
24. (oregan2007mitoticregulationby pages 8-9): Laura O’Regan, Joelle Blot, and Andrew M Fry. Mitotic regulation by nima-related kinases. Cell Division, 2:25-25, Aug 2007. URL: https://doi.org/10.1186/1747-1028-2-25, doi:10.1186/1747-1028-2-25. This article has 273 citations and is from a peer-reviewed journal.
25. (sharif2019structuralmechanismfor pages 4-6): Humayun Sharif, Li Wang, Wei Li Wang, Venkat Giri Magupalli, Liudmila Andreeva, Qi Qiao, Arthur V. Hauenstein, Zhaolong Wu, Gabriel Núñez, Youdong Mao, and Hao Wu. Structural mechanism for nek7-licensed activation of nlrp3 inflammasome. Nature, 570:338-343, Jun 2019. URL: https://doi.org/10.1038/s41586-019-1295-z, doi:10.1038/s41586-019-1295-z. This article has 726 citations and is from a highest quality peer-reviewed journal.
26. (unknownauthors2021probingthefunctions pages 41-45): Probing the functions of Nek family kinases using chemical inhibition: towards the development of potent and selective inhibitors of Nek7
27. (bachus2022inmitosisyou pages 15-17): Scott Bachus, Drayson Graves, Lauren Fulham, N. Akkerman, Caelan Stephanson, Jessica Shieh, and P. Pelka. In mitosis you are not: the nima family of kinases in aspergillus, yeast, and mammals. International Journal of Molecular Sciences, Apr 2022. URL: https://doi.org/10.3390/ijms23074041, doi:10.3390/ijms23074041. This article has 12 citations and is from a peer-reviewed journal.