## Phylogeny

* Member of the NIMA-related kinase (NEK) family comprising eleven human paralogs (NEK1–NEK11) (dana2022nek2kinasesignaling pages 1-2).
* Catalytic domain shares ~42-44 % identity with the Aspergillus nidulans mitotic regulator NIMA, making NEK2 the closest human homolog of the founding fungal kinase (fry2002thenek2protein pages 1-3, dana2022nek2kinasesignaling pages 1-2).
* Documented orthologs include Pfnek-1 from Plasmodium falciparum, underscoring conservation of NEK-type cell-cycle kinases in apicomplexan parasites (dana2022nek2kinasesignaling pages 13-14).
* NEK kinases localise to microtubule-organising centres across eukaryotes, reflecting an evolutionarily conserved role in centrosome regulation (fry2017mitoticregulationby pages 1-2).

## Reaction Catalyzed

ATP + protein-Ser/Thr → ADP + protein-O-phospho-Ser/Thr (dana2022nek2kinasesignaling pages 1-2).

## Cofactor Requirements

Requires Mg²⁺ or Mn²⁺ for catalytic activity (dana2022nek2kinasesignaling pages 28-29).

## Substrate Specificity

* Prefers Ser/Thr residues in basic sequence contexts (fry2002thenek2protein pages 1-3).
* Experimentally confirmed substrates:  
  • CEP250/C-Nap1 and CROCC/Rootletin (dana2022nek2kinasesignaling pages 2-4, dana2022nek2kinasesignaling pages 28-29).  
  • CEP68 (dana2022nek2kinasesignaling pages 28-29).  
  • NDC80/Hec1 (dana2022nek2kinasesignaling pages 13-14).  
  • CDC20 and MAD2L1 (dana2022nek2kinasesignaling pages 28-29).  
  • PP1 catalytic subunit Thr320 (dana2022nek2kinasesignaling pages 6-7).  
  • NPM1 Ser70/Ser88 (dana2022nek2kinasesignaling pages 6-7, dana2022nek2kinasesignaling pages 7-9).  
  • β-Catenin, Dishevelled and TRF1 (dana2022nek2kinasesignaling pages 7-9).  
  • SGO1 and NECAB3 (dana2022nek2kinasesignaling pages 6-7).

## Structure

* 445-aa protein with an N-terminal bilobal kinase domain and a C-terminal regulatory segment containing two coiled-coils; the first coiled-coil forms a leucine-zipper that mediates homodimerisation and trans-autophosphorylation (fry2002thenek2protein pages 1-3).
* Crystal structures show the canonical Lys-Glu salt bridge, HRD catalytic triad, DFG motif and an activation loop phosphorylated at Thr175/Thr179 that stabilises the active conformation (rellos2007structureandregulation pages 10-11, fry2017mitoticregulationby pages 6-8).
* Possesses a non-conserved Cys22 in the Gly-rich loop exploited by reversible covalent inhibitors (dana2022nek2kinasesignaling pages 26-28).
* Unphosphorylated NEK2 adopts a DFG-out inactive state in complexes with aminopyrazine and benzimidazole inhibitors, illustrating activation-loop plasticity (byrne2020nek7conformationalflexibility pages 14-14).

## Regulation

Post-translational modifications  
- Activating autophosphorylation at Thr170/Ser171 and Thr175; Thr179 and Ser241 reduce activity (fang2016targetingnek2as pages 1-2, rellos2007structureandregulation pages 10-11).  
- Interphase complex with PP1 and MST2 keeps NEK2 inactive; Plk1 phosphorylation of MST2 at mitotic onset releases PP1, enabling NEK2 activation (dana2022nek2kinasesignaling pages 2-4).  
- CDK1 and Plk1 add further activating phosphorylations in G2/M (fry2017mitoticregulationby pages 6-8).  
- PP1 dephosphorylates and inhibits NEK2; ATM activation enhances PP1 after DNA damage, down-regulating NEK2 (dana2022nek2kinasesignaling pages 6-7).  
- APC/C targets KEN- and D-box motifs in NEK2A for ubiquitin-dependent degradation at mitotic exit (fang2016targetingnek2as pages 1-2, dana2022nek2kinasesignaling pages 7-9).

Allosteric and signalling inputs  
- EGFR–PI3K–Akt signalling promotes NEK2 activity via MST2 phosphorylation (fry2017mitoticregulationby pages 4-5).  
- CIP2A binds NEK2 and augments its activity independently of PP1 (dana2022nek2kinasesignaling pages 2-4).

Transcriptional control  
- FoxM1 up-regulates NEK2, whereas E2F4, p53 and microRNA-128 repress expression, yielding S/G2 phase accumulation (fang2016targetingnek2as pages 1-2).

## Function

* Localises to centrosomes and kinetochores; expression peaks in late S/G2 (dana2022nek2kinasesignaling pages 1-2, fry2002thenek2protein pages 1-3).
* Drives centrosome separation by phosphorylating CEP250, CROCC, CEP68 and related linker proteins (dana2022nek2kinasesignaling pages 2-4, dana2022nek2kinasesignaling pages 28-29).
* Stabilises kinetochore–microtubule attachments through NDC80 phosphorylation and modulates the spindle-assembly checkpoint via CDC20 and MAD2L1 (dana2022nek2kinasesignaling pages 13-14, dana2022nek2kinasesignaling pages 28-29).
* Prevents premature centrosome separation after DNA damage, a process reversed by ATM-PP1 signalling (dana2022nek2kinasesignaling pages 2-4, dana2022nek2kinasesignaling pages 6-7).
* Links to signalling pathways: PP1 Thr320 phosphorylation connects NEK2 to Akt, β-catenin/Dishevelled phosphorylation integrates NEK2 with Wnt signalling, and MST2 interaction places NEK2 within the Hippo network (dana2022nek2kinasesignaling pages 6-7, dana2022nek2kinasesignaling pages 7-9, fry2017mitoticregulationby pages 4-5).
* Promotes osteoclast differentiation and bone resorption through heparanase up-regulation (dana2022nek2kinasesignaling pages 6-7).

## Inhibitors

* ATP-competitive indolinone SU11652 and related purine analogues resolved in NEK2 crystal complexes (fry2017mitoticregulationby pages 6-8).
* Aminopyrazine and benzimidazole scaffolds stabilising a DFG-out inactive conformation (byrne2020nek7conformationalflexibility pages 14-14).
* Reversible covalent inhibitors targeting Cys22 (dana2022nek2kinasesignaling pages 26-28).
* Hec1/NEK2 disruptor T-1101 tosylate with improved oral exposure (dana2022nek2kinasesignaling pages 26-28).
* PROTAC degraders and activity-based probes are under development for selective NEK2 ablation (dana2022nek2kinasesignaling pages 26-28).

## Other Comments

* NEK2 is over-expressed in breast, ovarian, colon, uterine endometrial and lung adenocarcinomas, correlating with aneuploidy, tumour aggressiveness and chemotherapy resistance (dana2022nek2kinasesignaling pages 1-2, dana2022nek2kinasesignaling pages 13-14).
* Dysregulated NEK2 signalling is also implicated in bone disorders, ciliopathies, immune and kidney diseases, and NEK2 orthologs in Plasmodium spp. are emerging anti-malarial targets (dana2022nek2kinasesignaling pages 1-2, dana2022nek2kinasesignaling pages 13-14).

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