Phylogeny  
NEK1 is classified within the NEK sub-family of the serine/threonine protein-kinase superfamily as originally catalogued by the human kinome survey of Manning et al., 2002 (oliveira2020checkingneksovercoming pages 1-4).  
Kinase-domain phylogeny clusters NEK1 most closely with NEK3 and NEK5 (melo‐hanchuk2017nek1kinasedomain pages 2-3).  
Orthologs are documented in Danio rerio, Xenopus laevis, Drosophila melanogaster, Caenorhabditis elegans, and Mus musculus (zelina2024alsassociatedc21orf2variant pages 30-31, unknownauthors2024proteinproteininteractionsin pages 87-92).  
Comparative analyses of ciliary cell-cycle kinases show NEK1 conservation across ciliated eukaryotes, indicating early diversification of this lineage (melo‐hanchuk2017nek1kinasedomain pages 11-12).

Reaction Catalyzed  
ATP + protein-Ser/Thr/Tyr → ADP + protein-Ser/Thr/Tyr-phosphate (melo-hanchuk2017nek1kinasedomain pages 1-2, unknownauthors2024proteinproteininteractionsin pages 87-92).

Cofactor Requirements  
Catalytic activity requires Mg²⁺; Mn²⁺ can substitute in vitro kinase assays (zelina2024alsassociatedc21orf2variant pages 30-31).

Substrate Specificity  
Oriented-peptide library screening groups NEK1 with NEK1/3/4/5/8 and defines a preference for hydrophobic residues at −3, any residues at −2/−1, threonine or serine as the phospho-acceptor, and exclusion of proline at +1, yielding the consensus [L/M/F/W]-X-X-S/T-[¬P] (kooij2019comprehensivesubstratespecificity pages 5-7).  
A substrate motif for NEK1 was not reported in the Johnson 2023 serine/threonine kinome atlas (melo‐hanchuk2017nek1kinasedomain pages 12-12).

Structure  
Domain organisation: N-terminal kinase domain (residues 1–284) followed by an extended C-terminal regulatory region containing six predicted coiled-coil motifs (CC1-CC6) that mediate dimerisation and partner docking (melo-hanchuk2017nek1kinasedomain pages 5-7, melo-hanchuk2017nek1kinasedomain pages 11-12).  
3-D structures: Crystal structures of the kinase domain have been solved in apo form (PDB 4APC, 2.1 Å) and in complex with an ATP-mimetic inhibitor (PDB 4B9D, 1.9 Å) using an inactive T162A mutant (melo-hanchuk2017nek1kinasedomain pages 5-7).  
Catalytic motifs: VAIK Lys33, HRD Asp163, DFG Asp177-Phe178-Gly179; the structures capture a DFG-out, αC-out inactive state in which the Lys33–Glu51 salt bridge is broken (melo-hanchuk2017nek1kinasedomain pages 5-7).  
Activation loop: residues 146–173 form a three-turn α-helix that buries Thr162, preventing autophosphorylation (melo-hanchuk2017nek1kinasedomain pages 5-7).  
Regulatory features: gatekeeper Met80 and small Ala56 enlarge the back pocket; Tyr66 adopts an “up” conformation, creating an additional cavity exploitable for inhibitor design (melo-hanchuk2017nek1kinasedomain pages 7-8).  
Hydrophobic spine mis-alignment maintains autoinhibition (melo-hanchuk2017nek1kinasedomain pages 5-7).

Regulation  
Autophosphorylation: Thr162 within the activation loop (melo-hanchuk2017nek1kinasedomain pages 5-7).  
Upstream kinase: TLK1 phosphorylates Thr141 and Tyr315, initiating a TLK1 → NEK1 → ATR → CHK1 cascade in DNA-damage signalling (melo-hanchuk2017nek1kinasedomain pages 9-11).  
DNA-damage-induced modification: Ser666 is specifically phosphorylated after cisplatin exposure (melo-hanchuk2017nek1kinasedomain pages 11-12).  
Constitutive regulatory sites: Ser649, Ser664 and Ser683 reside in CC regions involved in partner docking (melo-hanchuk2017nek1kinasedomain pages 11-12).  
Conformational control is exerted by the DFG-out and αC-out arrangement; activation-loop phosphorylation is required to realign catalytic elements (melo-hanchuk2017nek1kinasedomain pages 5-7).

Function  
Expression and localisation: NEK1 is highly expressed in meiotic germ cells and localises to centrosomes and primary cilia; expression is elevated in renal cell carcinoma (melo-hanchuk2017nek1kinasedomain pages 11-12, melo-hanchuk2017nek1kinasedomain pages 1-2).  
Upstream regulator: Tousled-like kinase 1 (TLK1) (melo-hanchuk2017nek1kinasedomain pages 9-11).  
Downstream substrates and interactors:  
– ATR: NEK1 primes the ATR-ATRIP complex for CHK1 activation (melo-hanchuk2017nek1kinasedomain pages 1-2).  
– Rad54: phosphorylation supports homologous recombination and replication-fork stability (melo-hanchuk2017nek1kinasedomain pages 2-3).  
– VDAC1: phosphorylation limits mitochondrial apoptosis following cellular injury (unknownauthors2024proteinproteininteractionsin pages 87-92).  
– Additional interactors include ATRIP, Mre11, MSH6, FANCA and FANCD2, with interaction networks expanding after cisplatin treatment (melo-hanchuk2017nek1kinasedomain pages 7-8, melo-hanchuk2017nek1kinasedomain pages 8-9).  
Pathway involvement: NEK1 participates in homologous recombination repair, Fanconi anemia inter-strand cross-link repair, base-excision repair, nucleotide-excision repair, mismatch repair, the G2/M DNA-damage checkpoint, and primary-cilium assembly (melo-hanchuk2017nek1kinasedomain pages 7-8, melo-hanchuk2017nek1kinasedomain pages 11-12).

Other Comments  
Disease-linked mutations:  
– Kinase-domain substitutions G145R (kinase-dead) and L253S (scaffolding defect) cause autosomal-recessive short-rib thoracic dysplasia (melo-hanchuk2017nek1kinasedomain pages 1-2, melo-hanchuk2017nek1kinasedomain pages 9-11).  
– A splice-altering variant in the CC region underlies Mohr syndrome (melo-hanchuk2017nek1kinasedomain pages 11-12).  
– Multiple loss-of-function variants confer susceptibility to amyotrophic lateral sclerosis, and mutant NEK1 aggregation accelerates ALS pathology in mouse models (georgiadou2024alsdrivenby pages 14-17, oliveira2020checkingneksovercoming pages 22-23).  
– Nek1-null mice develop polycystic kidney disease, facial dysmorphism, dwarfism, male sterility and anemia, underscoring developmental roles (unknownauthors2024proteinproteininteractionsin pages 87-92).

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