Phylogeny  
• Orthologs are reported in mouse, zebrafish, Caenorhabditis elegans and Drosophila melanogaster, demonstrating broad metazoan conservation of NEK8 (quarmby2005caughtnekingcilia pages 2-3, roig2025nek8animafamily pages 2-4).  
• Phylogenetic analyses place NEK8 in the NIMA-related kinase subfamily and show it clusters most closely with NEK9 because both possess an RCC1-like domain (roig2025nek8animafamily pages 1-2).  
• According to kinome classifications derived from the Manning framework, NEK8 belongs to the CMGC group, NEK family of serine/threonine kinases (unknownauthors2012regulationofthe pages 79-82).

Reaction Catalyzed  
• ATP + protein-Ser/Thr → ADP + phosphoprotein-Ser/Thr (zalli2012thenek8protein pages 2-3).

Cofactor Requirements  
• No experimental study has defined divalent-cation dependence for NEK8; Mg²⁺/Mn²⁺ requirement remains undetermined (roig2025nek8animafamily pages 1-2).

Substrate Specificity  
• Oriented peptide library screening shows NEK8 prefers threonine as the phospho-acceptor within the consensus [L/M/F/W]-X-X-S/T-ϕ, where ϕ is any residue except Pro at +1, and favours hydrophobic or basic residues at flanking positions (kooij2019comprehensivesubstratespecificity pages 5-7).

Structure  
• The 703-residue protein comprises an N-terminal bilobal kinase domain linked by a flexible region to a seven-bladed RCC1-like β-propeller that mediates protein interactions and sub-cellular targeting (roig2025nek8animafamily pages 8-9).  
• Key catalytic motifs include VAIK Lys33 for ATP binding, HRD Asp128 for catalysis, and an activation-loop Thr162 whose phosphorylation is required for activity (roig2025nek8animafamily pages 14-15).  
• Full-length NEK8 immunoprecipitated from mammalian cells is catalytically active without additional treatment, indicating that the activation loop is already phosphorylated in cells (roig2025nek8animafamily pages 8-9).  
• No crystal structure is available; AlphaFold model AF-Q86SG6-F1 predicts independent folding of the kinase and RCC1 modules with a solvent-exposed activation loop (bachus2022inmitosisyou pages 3-7).  
• The RCC1 domain can undergo intramolecular autophosphorylation, suggesting an additional layer of structural regulation (roig2025nek8animafamily pages 8-9).

Regulation  
• Autophosphorylation of Thr162 within the activation loop enhances catalytic activity (roig2025nek8animafamily pages 8-9).  
• ANKS6 binds the kinase domain, stimulates NEK8 activity and is itself phosphorylated by NEK8, supporting assembly of the ciliary inversin complex (czarnecki2015anks6isthe pages 1-2).  
• Serum-induced ciliogenesis triggers NEK8 activation followed by ubiquitin-proteasome-dependent degradation, coupling kinase turnover to cilium formation (zalli2012thenek8protein pages 2-3).  
• Hypoxia up-regulates NEK8 transcription via HIF1α/HIF2α under pVHL control, linking environmental cues to kinase abundance (bachus2022inmitosisyou pages 18-20).

Function  
• NEK8 localises to centrosomes and to the proximal region of primary cilia where it forms the inversin (INV) compartment together with INVS, ANKS6 and NPHP3 (roig2025nek8animafamily pages 1-2).  
• The kinase maintains renal tubular architecture by controlling distribution of Polycystin-1 and Polycystin-2 and by regulating ciliary morphology (bachus2022inmitosisyou pages 17-18).  
• NEK8 modulates Hippo signalling by interacting with YAP/TAZ, and loss of its partner ANKS6 causes YAP deficiency in liver cells (bachus2022inmitosisyou pages 17-18, airik2020lossofanks6 pages 26-27).  
• It participates in DNA double-strand break repair by promoting RAD51 foci and limits replication stress through inhibition of cyclin A–CDK complexes (bachus2022inmitosisyou pages 17-18).  
• Highest mRNA expression is detected in thyroid, adrenal gland and skin, and the protein is over-expressed in primary human breast carcinomas (bachus2022inmitosisyou pages 17-18).

Other Comments  
• Recessive mutations in the RCC1 domain cause cystic kidney disease in jck mice and human nephronophthisis, often accompanied by renal-hepatic-pancreatic dysplasia and laterality defects (roig2025nek8animafamily pages 12-13, czarnecki2015anks6isthe pages 1-2).  
• Heterozygous missense variants within the kinase domain can produce autosomal dominant polycystic kidney disease in humans (claus2023certainheterozygousvariants pages 13-15).  
• Disease-linked mutations frequently disrupt kinase activity or ciliary localisation, leading to aberrant INV complex assembly and mis-expression of Polycystins (bachus2022inmitosisyou pages 17-18).  
• Aberrant NEK8 expression and consequent Hippo pathway dysregulation have been reported in breast and other carcinomas, implicating the kinase in tumorigenesis (flax2024illuminationofunderstudied pages 9-11).

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