## Phylogeny

• Orthologs: Saccharomyces cerevisiae Rad53p, Schizosaccharomyces pombe Cds1p and Drosophila melanogaster DmChk2/Loki confirm conservation of the checkpoint-kinase lineage across fungi, insects and vertebrates (gabant2008autophosphorylatedresiduesinvolved pages 1-2, pommier2005targetingchk2kinase pages 1-2).  
• Kinome placement: member of the CHEK (checkpoint kinase) sub-family within the CaMK-like group; closest human paralogue is CHK1, although domain polarity and activation mechanisms differ (pommier2005targetingchk2kinase pages 1-2).  
• Highest sequence conservation resides in the FHA domain and catalytic core; N- and C-terminal tails are poorly conserved and intrinsically disordered (cai2009structureandactivation pages 12-12).

## Reaction Catalyzed

• ATP + [protein]-Ser/Thr → ADP + [protein]-O-phospho-Ser/Thr (lountos2009crystalstructureof pages 1-2).

## Cofactor Requirements

• Catalysis requires ATP coordinated by Mg²⁺, as inferred from canonical kinase active-site architecture (cai2009structureandactivation pages 12-12).

## Substrate Specificity

• Preferred consensus: R/K-X-X-S/T with a basic residue at −3 and a hydrophobic residue at +1, exemplified by CDC25A Ser123 and CDC25C Ser216 (pommier2005targetingchk2kinase pages 11-11).  
• Phosphoproteomic refinement adds a Leu preference at −5, yielding L-X-R-X-X-S/T (black2024chk2sustainsplk1 pages 12-15).

## Structure

• Domain organisation: N-terminal SQ/TQ cluster (19-69), central FHA domain (113-175), C-terminal kinase domain (220-486) and nuclear localisation signal 515-522 (pommier2005targetingchk2kinase pages 2-4).  
• Crystal structures 3I6U/3I6W reveal kinase-domain dimers with activation-segment exchange positioning Thr383 for trans-autophosphorylation (cai2009structureandactivation pages 1-2, cai2009structureandactivation pages 11-12).  
• Catalytic core: Lys249 (VAIK), Asp368 (HRD) and DFG motif align with an ordered C-helix and hydrophobic spine in the active state (cai2009structureandactivation pages 11-12).  
• An auxiliary hydrophobic pocket adjacent to the ATP site accommodates selective inhibitors such as NSC 109555 (lountos2009crystalstructureof pages 1-2).  
• Ca²⁺-calmodulin binds bidentately across both lobes near Lys373, occluding the substrate cleft and dampening catalysis (horne2024unconventionalbindingof pages 4-7).

## Regulation

• Activation: ATM phosphorylation of Thr68 within the SQ/TQ cluster triggers FHA-mediated dimerisation and subsequent autophosphorylation at Thr383, Thr387 and Ser516 for full activity (cai2009structureandactivation pages 1-2, gabant2008autophosphorylatedresiduesinvolved pages 1-2).  
• Alternative upstream inputs: TTK/hMps1 (Thr68) links spindle-assembly signals, and JAK2 sustains mitotic CHK2-PLK1 signalling independently of DNA damage (wei2005ttkhmps1participatesin pages 1-2, black2024chk2sustainsplk1 pages 12-15).  
• Additional phosphosites: Ser19, Ser33, Ser35, Ser372, Thr378, Thr389 and Tyr390 form an interdependent T-loop network controlling activity and chromatin dynamics (guo2010interdependentphosphorylationwithin pages 1-1).  
• Negative regulation: PP2A dephosphorylates Thr68 to terminate checkpoint signalling (pommier2005targetingchk2kinase pages 9-11).  
• Ubiquitination: phosphorylation at Ser379 is prerequisite for ubiquitin conjugation; T-loop mutations modulate ubiquitylation efficiency (guo2010interdependentphosphorylationwithin pages 7-8).  
• Allosteric inhibition: Ca²⁺-calmodulin binding at Lys373 sterically blocks substrate access (horne2024unconventionalbindingof pages 9-12).

## Function

• Expression: stable nuclear protein expressed throughout the cell cycle (pommier2005targetingchk2kinase pages 1-2).  
• Upstream kinases: ATM, ATR, DNA-PK, TTK/hMps1 and JAK2 phosphorylate or modulate CHK2 (cai2009structureandactivation pages 1-2, wei2005ttkhmps1participatesin pages 1-2, black2024chk2sustainsplk1 pages 12-15).  
• Downstream substrates:  
– CDC25A/B/C phosphatases—phosphorylation inhibits CDK activation and enforces G1/S-G2/M arrest (pommier2005targetingchk2kinase pages 1-2).  
– p53 at Ser20/Thr18—stabilises the tumour suppressor and primes apoptotic transcription (pommier2005targetingchk2kinase pages 2-4).  
– BRCA1 Ser988 and BRCA2—promote RAD51 loading and homologous-recombination repair (pommier2005targetingchk2kinase pages 11-11, anderson2011cct241533isa pages 11-11).  
– PLK1—phosphorylation sustains mitotic fidelity (black2024chk2sustainsplk1 pages 12-15).  
• Interactors: Mus81 endonuclease, PP2A phosphatase and calmodulin integrate CHK2 into DNA repair, checkpoint and calcium-responsive networks (pommier2005targetingchk2kinase pages 9-11, horne2024unconventionalbindingof pages 9-12).

## Inhibitors

• CCT241533—ATP-competitive; IC₅₀ ≈ 3 nM (recombinant), Ki ≈ 1.2 nM; >80-fold selectivity over CHK1; potentiates PARP-inhibitor cytotoxicity in p53-defective lines (anderson2011cct241533isa pages 1-3, anderson2011cct241533isa pages 5-7).  
• NSC 109555—binds ATP site plus auxiliary hydrophobic pocket; crystal structure at 2.1 Å defines hinge hydrogen bonds (lountos2009crystalstructureof pages 1-2).  
• PV1019—cellular IC₅₀ ≈ 2.8–10 µM for Ser516 autophosphorylation; selective across a 53-kinase panel; abrogates CHK2-dependent apoptosis (jobson2009cellularinhibitionof pages 4-6).

## Other Comments

• Germline variants: 1100delC truncation, FHA I157T, kinase H371Y and S428F associate with elevated risks of breast, prostate, gastric, testicular and thyroid cancers (pommier2005targetingchk2kinase pages 4-5, mccarthyleo2024comprehensiveanalysisof pages 16-17).  
• High-throughput yeast complementation of 669 missense variants shows strong intolerance within the ATP pocket and activation loop (mccarthyleo2024comprehensiveanalysisof pages 7-9).  
• Somatic L355P mutation impairs kinase activity and confers hypersensitivity to PLK1 inhibitors (black2024chk2sustainsplk1 pages 12-15).  
• Loss-of-function alleles contribute to Li-Fraumeni-variant syndromes and osteosarcoma predisposition (cai2009structureandactivation pages 1-2).

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